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8

Psychosocial Dimensions of COPD for the Patient and Family

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1. Introduction

This chapter will review our current understanding from the qualitative research literature on the experience of COPD for the patient and family. It will provide exemplars from the author's past research to ground these concepts within patient and family experience. Whilst research into symptom measurement, functional and biochemical measurements of lung function and pharmacological outcomes give important insights into the physiological dimensions of COPD, methodologies that explore the psychosocial dimensions are not always well understood. Research output is increasingly valued according to clearly definable 'Levels of Evidence' (National Health and Medical Research Council, 2009). This approach makes visible the rigour of processes that underpin clinical evidence and considers practices confirmed at one extreme by double-blinded, randomised, controlled trials, through to the accepted wisdom of experts in the field. Demonstrable rigour in research is particularly important when evaluating the safety and efficacy of new drugs and interventions. In this case, large sample-sizes, strict control of variables and meticulous monitoring of the research protocol to maintain objectivity means that clinicians can weigh up, with confidence, the therapeutic choices available to them. This quantitative approach to research relies on statistical methods to determine 'truth'.

Clinicians have sought ways to apply quantitative research methods to measure psychosocial dimensions of illness and treatments. Symptom and impact scales such as the Hospital Anxiety and Depression Scale (Zigmond et al., 1983) and the International Continence Society Sex Questionnaire (Blanker et al., 2001), are examples of instruments that can identify the presence and frequency of issues of importance to patients across the COPD population. Instruments like the SF-36 (Mahler & Mackowiak, 1995) and the Sickness Impact Profile (McDowell & Newell, 1987) allow us to determine the influence of disease and interventions on a person's quality of life. Measures of adaption to illness such as the Jalowiec Coping Scale (Jalowiec et al., 1984) quantify the behavioural and cognitive coping strategies people use to deal with social, physical end emotional stressors.

These quantitative measures of psychosocial aspects of COPD are useful in their ease of applicability to large research samples. They provide an aspect of evaluation that goes beyond the purely physiological concerns of health professionals to consider the patient-

perceived impacts of health problems and treatments. What they do not always achieve is firstly, the sensitivity necessary to reveal subtle but important changes in patient experience, and secondly, an explanation of the meanings behind results. Qualitative research methods have a different purpose to positivist, quantitative studies. Rather than seeking objective 'truth', they seek to gain an understanding of the meanings of illness and treatments for people. As such, there is an acceptance of the subjectivity of experience, and an acknowledgement of the context of an experience, rather than trying to control for context.

2. Understanding qualitative approaches in COPD research

Phenomenology is an example of a widely applied method in the qualitative COPD literature. Edmund Husserl, the founder of *descriptive* phenomenology sought a rigorous scientific method, grounded in the experience of people living within their world. Husserl's transcendental phenomenology attempted to strip away what we know and take for granted about a phenomenon to reveal and describe its fundamental essence (Husserl, 1936:1970). He called this the phenomenological reduction and suggested this process required us to suspend or *bracket* our prior knowledge of the subject being studied (Husserl, 1931:1960).

Husserl's student, existential philosopher Martin Heidegger, further developed Husserl's ideas around discovering the essence of an experience to create an *interpretative* phenomenology. He did not agree that we could separate ourselves objectively from phenomena in our world. He saw people, not as passive recipients of information about, and perceptions of, objects in the world, but rather believed that we exist *in-the-world* and are drawn towards and grasp things of significance for us that need to be taken care of (Heidegger, 1927:1996).

In Heideggerian phenomenology, the essence of the experience, for example 'breathlessness in a shrinking-life world' (Gullick & Stainton 2008), acts as a lens through which to view the participants' story. The story is interpreted through language (i.e. transcripts of in-depth interviews) against the background of their personal concerns (perhaps expression of masculinity, earning a wage, social connection), that are aspects of the person's history, culture and family and comprise their *being-in-the-world*. The result is a rich narrative that interprets experiences to describe the meaning behind them for the participants.

Another common approach to qualitative inquiry is Grounded Theory. First described by Glaser & Strauss (1967) and further developed by Strauss & Corbin (1998), this method may use both in-depth interviews and field observations. The resulting data is coded progressively from the first interview by a method of *constant comparison* according to a highly structured framework. During coding, the researcher memos their ideas and these may grow into theories about the phenomena. As these theories emerge they are tested by theoretical sampling; this is a type of purposive sampling that increases the diversity of the sample, seeking participants and pursuing questioning that tests the developing theory until that particular idea is 'saturated' with enough data to evidence it. Traditionally, literature is collected only as it becomes relevant to the data, rather than as a precursor to the study. Past literature is given the same status as data and is treated as data to support the new theory. Many studies use a modified approach to this method.

Good qualitative research is underpinned by a philosophical framework to strengthen the scholarly rigour of the interpretation. Examples include s*ymbolic interactionism* (Blumer,

1969), which is frequently used alongside Grounded Theory to find social explanations for behaviours. Symbolic interactionism sees people as 'pragmatic actors' who constantly adjust their own behaviour in response to others, and we can do this because we have the cultural and social understandings to interpret the meaning of those actions (McClelland, 2000). Maurice Merleau-Ponty's philosophy of the body (Merleau-Ponty, 1945:1962) is an example often applied to phenomenological studies that explore the embodied experience of illness. Merleau-Ponty describes people as perceiving the world through their body which acts spontaneously, in a *taken-for-granted* manner until something goes wrong.

Other modes of qualitative inquiry informing this review include, but are not limited to, content analysis (Krippendorff, 2004) and narrative analysis (Reissman, 1994). As with all research, findings from qualitative studies should be carefully considered according to the pre-determined criteria for rigour within the chosen methodology (Ezzy, 2002).

3. Loss of *taken-for-granted* breathing

Breathlessness is at the forefront of the experience of COPD, and breathing becomes a conscious focus of the person's life. COPD has been described as "a story with no beginning" (Pinnock et al., 2011); the changes in breathing are so slow and insidious that for a long time the decline is normalised; put down to getting older or being less fit. Eventually, the breathlessness begins to impact on the person's ability to conduct their day-to-day activities and is accompanied by other respiratory symptoms and poor exercise tolerance. Petra (63 yrs) had severe COPD before she sought advice from her doctor: *"… to go from my bed to the lavatory and back, I'm huffing and puffing. I thought 'This can't be right' ... I get out of breath all the time".*[1]

Distressing breathlessness can be precipitated by certain body positions, by activities such as walking and climbing stairs and by extremes of emotion. Environmental triggers such as excessive heat or cold, smoke or perfumes exacerbate breathlessness and people may need to anticipate and avoid these triggers. This avoidance of the triggers of breathlessness can isolate people from locations and activities that once that once afforded them pleasure (Gullick & Stainton, 2008). Chris (67 yrs) explained: *"There's lots of things I'd like to do but I just can't… Get out in the garage, make things. Well, I went out the other day to try and sand down our cutting board …there's all the dust, and … forget it!"*

Breathless people experience good days and bad days and this means that despite planning ahead, a bad day may rule out hoped for activities. Certain times of the day can be more problematic, with breathing often worse in the mornings, coinciding with the need to clear sputum and the need to attend to washing and dressing, and at night interfering with sleep. Certain times of the year can also worsen breathlessness due to extremes of temperature (Barnett, 2004). Williams (2011) reported that the person's perception of air movement made a difference to breathing, with fresh 'outdoor air' being easier to breathe.

Acute breathlessness is associated with panic, fear of suffocation, and fear of dying during an attack. People feel helpless and out of control of their bodies at these times (Williams et al., 2011, Avsar & Kasilkci, 2011, Elkington et al., 2005). Strategies can be taught that help

[1] Any unreferenced participant quotes in this chapter are sourced from unpublished interview data from research reported in Gullick (2008). All names are pseudonyms.

bring respiratory distress under control. Breathing techniques such as consciously slowing breathing, diaphragmatic breathing or purse-lipped breathing are reported widely by patients as effective ways to help manage frightening breathlessness (Fraser et al., 2006, Avsar & Kasilkci, 2011, Cicutto et al., 2004).

4. Losing control of the body's *taken-for-granted* functions

When our body works well its functions and understandings are *taken-for-granted*. For well people, the habitual functions of breathing, walking and moving the body in meaningful ways are unconsciously undertaken as the body moves purposefully towards its tasks. The existential philosopher Merleau-Ponty notes the sudden awareness of our bodies as task-orientated when function is disrupted:

> *"I am conscious of the world through the medium of my body. It is precisely when my customary world arouses in me habitual intentions that I can no longer, if I have lost a limb, be effectively drawn into it, and the utilisable objects, precisely insofar as they present themselves as utilisable, appeal to a hand which I no longer have… Our body comprises as it were two distinct layers, that of the habit-body, and that of the body at this moment..." (Merleau-Ponty, 1945:1962)*

Sputum production, uncontrolled coughing and wheezing and urinary urgency (Avsar & Kasilkci, 2011, Gullick & Stainton, 2008) are examples of changed body behaviours that signify a loss of control, displaying the body in socially unacceptable ways. Terry (77 yrs) confided, "*I cough, and I cough, and I cough and… all of a sudden it's on the table. It just comes out, no control* " (Gullick & Stainton, 2008). Because these behaviours draw attention to the person's unpredictable body, they detract from enjoyable participation in family and community activities. This has been described as the 'stigma' of COPD where the illness is visible, and is associated with disability and lack of control (Johnson et al., 2007). The visibility of the illness challenges the person's personal integrity and sense of effectiveness (Leidy & Haase, 1999, Gullick & Stainton, 2008). Marcia explained of her husband Pete (66 yrs): "*He goes to the club for the raffle …and meets a chap he went to school with, just for an hour and a half… But he's on to that oxygen the minute he gets home. See, he's stubborn that way. He wouldn't dare let anybody see him using a bottle, or a wheelchair*" (Gullick, 2008).

Other common manifestations of the failing body in COPD are weakness and fatigue, pain, insomnia, loss of appetite and difficulty with mobility (Elkington et al., 2005, Jones et al., 2004, Gullick & Stainton, 2008, Seamark et al., 2004). Fatigue is strongly linked to levels of breathlessness and depression and has major consequences for functional performance (Kapella et al., 2006). Fatigue is responsive to improved rest and sleep; however, sleep deprivation is part of the experience of living with COPD and the resulting constancy of fatigue makes it difficult to maintain daytime motivation. Focussing on patient perceptions of sleep, the qualitative report of Shackell et al (2007) revealed almost all participants waking more than three times per night to pass urine, and disturbances from pain and breathlessness were frequent. Some people were isolated from their daytime support structures and so felt vulnerable during the night, fearing nocturnal breathlessness and panic and wondering if they would "see the next morning". Those with poorer sleep had poorer lung function and quality of life scores and were more likely to be anxious and depressed. Daytime sleep or sleep whilst in hospital was seen as safer. It is notable that some patient strategies for insomnia actually function as barriers to good sleep including the comfort-seeking activities of drinking tea, late night TV and daytime napping. Whilst people

continue with low expectations for a good night's sleep and remain physically inactive, they remain prone to sleep problems (Shackell et al., 2007).

Anorexia & weight loss are found amongst many COPD sufferers and are associated with worsening breathlessness (Seamark et al., 2004, Jones et al., 2004). The study of Odencrants et al (2005) focussed on the experience of meals and their findings noted a number of barriers to sustainable eating. The problems began in obtaining food, with difficulty parking, breathlessness during shopping and difficulty transporting heavy groceries being contributors. Some people experienced physical challenges when preparing food, particularly if they were rushed, whilst others found it difficult to tolerate cooking odours. Some chose to smoke instead of eat.

The attraction of food is sometimes reduced due to a loss of taste sensation. Fungal infections or a dry mouth resulting from the use of puffers can make chewing painful. Coughing before or during meals can tire the person and reduce the focus on the meal, making food a real challenge during exacerbations (Odencrants et al., 2005). Keith (73 yrs) defended his poor eating to his wife Marcia, *"Do you want me to eat or do you want me to breathe? I can't do both together*!"(Gullick, 2008). People experience bloating, feel full before finishing meals and are often embarrassed by the food left on their plate. They report having their intake watched during mealtimes by family members and experienced feelings of failure, anger or sadness when they are not able to eat (Odencrants et al., 2005).

Eating smaller amounts more often and planning a number of meals in advance on a 'good day' is a common strategy to improve food availability and intake. Of concern was that Odencrants' et al's participants thought positively about their low body weight and this may be problematic given the association between low body mass index and higher mortality in COPD (Yang et al., 2010).

Pain is commonly reported in qualitative studies on COPD (Halpin et al., 2008, Elkington et al., 2005, Shackell et al., 2007) although authors do not tend to elaborate on the nature or location of pain. It is reasonable to assume this pain may in some part relate to reduced mobility, and perhaps, to age. Boueri et al (2001) noted that whilst their participants reported pain, levels were similar to healthy individuals in the community. Pain is particularly noted for people with COPD in the last year of life (Elkington et al., 2005).

5. Loss of the body's spontaneity

People with healthy bodies combine their movements and activities in a fluid manner. They spontaneously act in response to sensory stimuli, or to a perceived need to attend to a particular task, and this rarely requires a conscious appraisal of the body's capacity.

> *"The body is polarised by its tasks, of its existence towards them, of its collecting together of itself in pursuit of its aims". (Merleau-Ponty, 1945:1962)*

People with COPD lose this spontaneous application of the body to its tasks; in fact, a lack of forward planning can leave the person gasping for breath. Chris explained, "*… things you've done all your life, you don't think, and you go to do them again. Picking things up that I shouldn't pick up and carry*". Simple activities such as walking and talking become difficult to combine (Gullick & Stainton, 2009).

Breathlessness requires the person with COPD to consider the task, the steps they need to go through to undertake it and their particular physical effectiveness on that day. They may need to research how far they have to walk, whether there may be stairs and whether a toilet is close. People need to allow more time in order to avoid having to rush or keep up. The use of oxygen bottles takes considerable planning in relation to the cylinder's duration and portability. Even just walking from one room to the next may require rest stops. Patricia (63 yrs) lamented, *"Coming out to the lounge room where the nebuliser is, opening the blinds and curtains, then sitting down to get on my nebuliser. I have to stop about five times just doing that".*

Attending to day-to-day activities means pacing the body and spacing out activities that tax the body's breathing. Pacing of movement and activities with frequent breaks and aligning activities into sequential rather than combined tasks allows the person to recover their breathing along the way. Because of the daily variability in symptoms, people may need to take on a flexible approach to assessing, on the day, outings they have planned in advance (Barnett, 2004). Those who adjust most effectively to their bodily restrictions *listen* to their body, plan, pace, prioritise and balance their activity with capacity on that day, and try hard to achieve a certain level of contribution within realistic parameters (Lindqvist & Hallberg, 2010, Leidy & Haase, 1999, Gullick & Stainton, 2008, Fraser et al., 2006).

6. Changes in personal effectiveness

Leidy & Haase (1999) noted physical effectiveness as a core component of personal integrity that is challenged in COPD. Effectiveness is expressed as 'being able'; the body's predictability in doing what we expect or desire it to do. In sharp contrast, the failing body in COPD is nothing like what is presumed for, or wished of the body (Nicolson & Anderson, 2003). Physical effectiveness is just as much an interpersonal process that includes doing for others, as well as for one's self. This notion of contribution is an important one to most well-socialised adults. When the ability to contribute is lost to ineffectiveness and dependence, then people feel shame, self-blame and perceive the blame of others (Lindqvist & Hallberg, 2010, Barnett, 2004).

COPD symptoms often begin during a person's productive, working life. For many, there is an assumed level of physical adeptness and a physical and aesthetic appearance that has constituted their body as it is known to themselves in its predictability, and known to others in its apparent wholeness and application to visible tasks. Even though women are long established in the workforce, men still tend to perceive themselves as 'the breadwinner' and this forms an important part of their self-concept that becomes threatened in chronic illness. For men, heavier household tasks such as mowing lawns and managing gardens are frequently tied to their own and their family's perception of them in their gendered roles. Mary recalled of her husband Keith, *"…because he's always been the really strong one… He did marvellous things around the house… He doesn't do anything now… He can't, he gets too breathless. … and he's very conscious of this and it upsets him."* (Gullick, 2008).

For men, these heavier tasks are eventually taken over by another family member, or by paid help. For women with COPD, there tends to be a sense of ownership and obligation towards housework, and they will tolerate significant symptoms to retain these duties. As the disease progresses there are often visible changes such as development of the classic 'barrel chest', significant weight loss and for some, facial and postural changes from

prolonged steroid use. Norman described changes to his wife Catherine (58 yrs), a once, striking woman who ran an exclusive boutique, "*She had this sort of wheezy voice, and she was beginning to get hunched shoulders.*"

The net result of this changed capacity and appearance is that people lose a variety of modes of self-expression (Leidy & Haase, 1999). Andy, (57 yrs) explains: "*I had to give up sport, I'm a real sport nut. I had to give up walking… Of course sex was out of the question*". Each task is considered as to whether the reward, for themselves or others, will outweigh any distressing symptoms. If the real or anticipated discomfort is thought to be greater than the perceived benefit, that task will be avoided. Rewards include either personal pleasure and fulfilment, or a task that is to the benefit or welfare of others (Leidy, 2008, Shackell et al., 2007).

7. Losing independence with body care

Severe COPD sees people coming to terms with their diminishing ability to care for themselves. Early losses in independence may include difficulty with shopping or driving. As the disease progresses, people find that basic tasks such as showering and dressing may become insurmountable, making them feel almost child-like in their dependence on others (Gullick, 2008, Oliver, 2001, Barnett, 2004). Chris was sensitive to his wife's workload around body care. "*I'm nearly an invalid, aren't I? She has to help me up the stairs… shower me… help me get dressed. Basically the stupid things I should be able to do myself*" (Gullick, 2008).

This loss of independence with self care is an enormous threat to people's sense of hope (Milne et al., 2009). Showering causes particular problems because of the effect of steam on breathlessness. Pete explained, "*I panic a little bit when I get in the bath or shower, and then I've got to get out and get dried up. I'm pushing for my breath, … and I dry one leg down to my ankle and …stand there and hang on to something until I get my breath and then I put the other leg up*". Lifting arms to wash the hair, or bending to dry the feet are movements that cause considerable restriction to breathing, and so may be avoided. For people who live alone, this loss of self care may herald their movement into residential care. For people with family carers, it may alter the existing family relationship dynamics (Barnett, 2004, Gullick, 2008).

8. Changes in personality and mood

There is an important temporal framework to the experience of COPD with the visions of past, present and future selves being held in constant comparison to each other. Nicolson & Anderson (2003) describe how these gradual changes from independence to dependence lead to loss of self-esteem, loss of self-image and loss of power. The disease creates an otherness where the more visible 'medical self' is separate from the real self. Several studies reveal the nature of patient storytelling with past selves portrayed as athletic and vigorous, and present selves being barely able to walk (Bailey & Tilley, 2002, Gullick, 2008). Their future is seen in terms of loss: loss of anticipated retirement, loss of hoped for relationships with children and grandchildren (Nicolson & Anderson, 2003), and loss of 'possible selves' which are no longer conceivable (Gullick & Stainton, 2009).

This loss of independence and loss of family and community roles frequently lead to frustration, irritability and depression (Elkington et al., 2005, Seamark et al., 2004, Wilson et al., 2007). Those with advanced disease may see their life as meaningless. They communicate hopelessness, worthlessness and resignation and this can make death seem

like an attractive option (Ek & Ternestet, 2008, Oliver, 2001, Lindqvist & Hallberg, 2010). Terry (72) recounted: *"As true as I'm sitting here, … I go to bed and I say, 'Tonight would be a nice night to die. Take me.' … Really and truly, what good am I? I can't take my wife down to the shop, I can't walk from here to my barber who's just round the corner…"* (Gullick, 2008).

Despite the extremes of emotions, people try to contain their feelings as emotional turmoil can bring on exacerbations of breathlessness that are difficult to recover from. This has long been recognised and described as living within an 'emotional straight jacket' with both positive emotions such as laughter, and negative emotions such as anger, leading to distressing dyspnoea (Rabinowitz & Florian, 1992, Dudley et al., 1980, Diethorn, 1985). Partners of COPD patients tend to avoid discussing problems, or subjects that could lead to conflict with their ill spouses, for the same reason (Ring & Danielson, 1997, Sexton & Munro, 1985, Gullick, 2008).

Hypoxia may result in cognitive and personality changes that can further isolate people from family and others in the community. These may manifest as hallucinations, confusion, memory loss or unreasonable and unsociable behaviour (Gullick, 2008, Boyle, 2009b). Betty (73 yrs) explains of her husband, Terry: *"It's been hard… He gets very stressed and cranky over nothing… If anything goes wrong, I've done it… I know he's having trouble; he can't get about too much… It makes him more upset"*. For carers, the mood and personality changes of their loved one are often the hardest thing about living with COPD (Oliver, 2001, Wicks, 1997).

We know that rates of depression in COPD are reported at around 40% (Yohannes, 2005, Wilson, 2006) and up to 57% for those on home oxygen (Lacasse et al., 2001). Depression is further tied up in self blame and the perceived blame of others as people acknowledge the burden of their care and their ineffectiveness (Barnett, 2004). Anxiety is suffered by around a third of COPD sufferers, is a predictor of hospital admissions, and impacts significantly on the person's quality of life (Yohannes, 2000, Jones, 1991) Despite our awareness of anxiety and depression, there remains a lack of access to psychology services that could ameliorate these symptoms (Wilson et al., 2007).

9. The confining nature of COPD for the patient and family

People with COPD and their close family members live within a shrinking life-world (Gullick & Stainton, 2008). The physical boundaries of their life are diminished as the sick person begins to avoid taxing outings and spends the majority of their time within their own four walls. Mary explained of her husband, Keith: *"He could just walk on to the verandah and play with the dog a little bit, just in the confines of what you might loosely call the house. And then he just gradually stopped doing that"* (Gullick & Stainton, 2008).

People become socially isolated as they avoid environments and situations that may trigger breathlessness. Their consciousness of the socially unacceptable nature of their coughing and spitting makes them reluctant to enter new social situations. People reliant on home oxygen concentrators may be literally tied to an electrical power source and this increases isolation for the patient and the complexity of care for the family (Boyle, 2009b). People lose shared experiences with family and friends leading to loneliness, sadness and abandonment as they not only avoid social activities but feel they are avoided by others (Ek & Ternestet, 2008, Wilson et al., 2007, Leidy & Haase, 1999). Williams et al (2011) describe this experience as like living within a 'stagnant pool'. The physical stagnation

through loss of mobility is likened to an imprisonment; there is a stagnation and staleness of self that highlights the disparity between what the mind wants to do and what the body is able to do.

The confining nature of COPD extends to the family carer. As the physical effectiveness of the ill person declines, the workload of close family members increases. In the case of older couples, the primary carer may be facing their own health and ageing issues and the role of caring can seem overwhelming. The fear that something may happen to their loved one in their absence means that they become bound, physically to the home and psychologically to the role of caring due to a perceived need for increased vigilance. Their need to closely monitor their loved one leads to the use of phones and intercoms, listening to breathing during the night, watching for early signs of exacerbation and using the current level of breathlessness as a gauge of capacity for tasks (Boyle, 2009b, Gullick, 2008).

The experience of caring differs between spouses and other family members. The reciprocal nature of most marital relationships places caring in a framework of the historical give-and-take between partners and is sealed with the understanding of "for better or worse". Amongst younger caregivers, caring may be challenged by the competing roles of working and parenting and a different level of perceived reciprocity (Gullick, 2008, Nicolson & Anderson, 2003). Children and siblings are more likely to find the caring burdensome, and to note the lack of caring input from other family members (Gullick, 2008). Those carers with a higher level of education may find it more difficult to accept the loss of independence (Nordtug et al., 2010). Family enmeshment also makes adjustment to illness more difficult. When people weave their identities and activities around each another so completely it is difficult for any one member to function independently (Kanervisto et al., 2007).

Carers often feel weighed down by their multiple roles and feel similar losses of shared social experiences (Seamark et al., 2004). The caring role may coincide with a time of both declining health and fitness and increasing heaviness of the work of nursing. Women caregivers in particular are prone to somatic symptoms and anxiety, and although taken for granted, the frequent interruptions to sleep can be wearing (Bergs, 2002, Nordtug et al., 2010, Boyle, 2009b). Whilst some carers manage to integrate caring with employment to provide some personal time and space, others are forced into an unwelcomed, early retirement (Boyle, 2009b, Gullick, 2008). It is known that for people who are unable to leave the home for some sort of personal pursuit, there is a higher perceived burden of care (Boyle, 2009b). These losses of social participation for carers may contribute to a loss of self-identity with some women becoming unable to separate a sense of themselves from their husbands. Their future hopes for meaningful pursuits and achievements, a relaxed lifestyle and personal freedom become lost in the daily grind of their present reality (Boyle, 2009b).

The majority of social interaction for carers is with the ill person; however, males with COPD tend to isolate themselves from conversation, have a reduced interest in things, and as a consequence, have little to talk about (Bergs, 2002). This loss of intimacy through conversation is parallelled with a loss of physical intimacy, including sexual interaction (Gullick, 2008, Sexton & Munro, 1985). Where intercourse is attempted it may be frightening with distressing breathlessness distracting both partners from the

romanticism or eroticism of the moment. Whilst for many couples sex becomes less important, other forms of intimate physical contact is also avoided so that simple loving gestures such as cuddling or kissing may be lost to the caregiving spouse. Carer Claire, (55yrs) explained, *"you get used to not having those sort of things. You get used to being…not touched"* (Gullick, 2008).

Much of the caring literature on COPD focuses on female spouses. However, where both men and women are participants there appears to be a difference in caring styles and responses to caring. Women carers, in particular, take on a micro-management approach, arranging medical appointments and scrutinising diet, medication and exercise compliance and this differs from the more passive and delegatory style of male carers. Women try to play down the ineffectiveness of the sick person by secretly completing heavier jobs or slowing their pace whilst walking. They look for opportunities to promote a sense of effectiveness by leaving available the achievable jobs around the house, and only assisting with body care where it is absolutely necessary. Liz described her approach with her brother, Andy: *"I made every effort so that he didn't see a lot of the things that I did, so that he didn't know that he was incapable of doing it"* (Gullick, 2008). Women try to protect others in the family from seeing how bad things are. There is a sense of wifely duty reported, with women determined to 'walk the road' with their husband until the end. They can't imagine life without their partners after giving such intense care for so long. Women caregivers ignore their own health needs and become sad and worn out (Bergs, 2002).

There are a number of unmet needs amongst family carers in COPD, including the desire for better support with physical care and symptom control, and more useful information about the course of the illness (Currow et al., 2008, Bergs, 2002). Women carers are often too proud to ask for help from other family members (Bergs, 2002), whereas male carers more happily enlist outside help. Because of the intensity of carer engagement in COPD home-management, health professionals must seek the insights of carers during the patient assessment process, and educate and involve them when introducing new therapies. Carers may be the champions of patient motivation, but they are also known to actively eliminate treatment strategies they see as unnecessary or harmful (Boyle, 2009a).

10. COPD and smoking: The meanings of a 'self-inflicted' disease

In developing countries COPD is most often related to exposure to cooking fires. In a small group of people, an inherited alpha-1 antitrypsin deficiency can lead to early onset COPD. For the vast majority of people in the western world, however, COPD develops as a direct result of cigarette smoking (GOLD, 2010). Up to half of all smokers will die from a tobacco related disease (World Health Organisation, 2011). Whilst some manage to give up smoking easily when confronted with a diagnosis, many people continue to smoke. If the issue of smoking is to be dealt with collaboratively, clinicians need some insight into the meanings of smoking for the addicted person.

People with COPD are stigmatised by the self-inflicted nature of their disorder (Johnson et al., 2007). They experience enormous guilt and shame that may cause them to deny smoking as the cause of breathlessness, to hide their symptoms and to delay their engagement with medical services (Gullick & Stainton, 2006, Arne et al., 2007, Robinson, 2005, Earnest, 2002). Smokers have described reduced access to services because they either fear the judgement of

health professionals or because of the actual attitudes of health professionals (Johnson et al., 2007, Burrows & Carlislea, 2010, O'Neill, 2002). For example, current smoking is a contraindication for many elective surgical procedures, including lung volume reduction procedures for emphysema. People are known to have been excluded on this basis without receiving the smoking cessation support that could facilitate their access to such interventions (Gullick & Stainton, 2006). Smokers are less likely to have visited a doctor in the past year (Fisher & Hill, 1990), and smoking is associated with non-adherence to pulmonary rehabilitation (Young et al., 1999).

The context of self-infliction may create an underlying anger and resentment amongst family members, particularly where family have not struggled with an addiction of their own. This anger may make the caring burden harder to accept, but may also be intermingled with guilt over these emotions (Boyle, 2009b, Gullick & Stainton, 2006). Gary (38 yrs) explains of his father: *"They can hardly drag themselves across the room, but they'll still smoke. It makes it tough for families, you're doing everything you can, but you feel, 'What's the use of doing it if he's still smoking?' He tries to blame different things… infection in his lungs… exercise… which is so idiotic. If you had a tape, and … let him hear himself he'd probably go "Oh… Silly!"*

Those who accept the causative role of smoking in their illness experience regret and anger for their past inability to stop (O'Shea et al., 2007). However, only a small proportion of people with COPD attribute cigarettes as the primary cause of their lung disease (Hansen et al., 2007). In a large, early survey of older smokers with or without COPD, 47% didn't think quitting would improve their health and 45% did not believe smoking was harming them (Fisher & Hill, 1990). The fact that there may be COPD amongst other family members is usually explained away as a family predisposition rather than a shared family smoking addiction. Numerous studies demonstrate the widespread denial of smoking as the main cause of breathlessness. Rather, patients attribute occupational exposure, ageing, lack of fitness and 'bad luck' as major contributors (Wilson et al., 2007, Hansen et al., 2007, Burrows & Carlislea, 2010, Gullick & Stainton, 2006). The study of Boyle (2009b) demonstrated that spouses are also inclined to find explanations for the illness that externalise the responsibility from their partners to others. Knowing other smokers who do not have COPD reinforces their beliefs.

The self-talk around the impact of smoking sometimes extends from denial of harm to positive physical, social and psychological benefits (Schofield et al., 2007, Osman & Hyland, 2005). Some research participants report that smoking makes them feel better and eases their breathing and others recall shared social experiences around smoking with affection. The issue of the pure enjoyment of smoking to the addicted individual cannot be ignored. Cigarettes have been described as a 'best friend', providing comfort and companionship (Lindqvist & Hallberg, 2010). Research participant Terry recalls and craves the sensation of smoking: *"I enjoyed smoking, and even now… I'd love a cigarette. My son … goes outside and has a smoke. I say 'Sit in here and I can smell it.' I want the smell of his smoke."* (Gullick & Stainton, 2006).

Smoking is widely utilised tool for stress reduction. It is common for people who have succeeded in smoking cessation to later relapse due to extreme stress or bereavement (Schofield et al., 2007, Burrows & Carlislea, 2010, Gullick & Stainton, 2006). The findings that cessation does not automatically deliver better well-being adds to the problem. All ex-

smokers in the study of Burrows & Carlislea (2010) described feeling worse after quitting due to symptom exacerbation or weight gain. This was the case for Petra after her successful cessation attempt: *"I was under the impression if I stopped smoking I would get better, or I'd stay the same. And I thought, 'I'll give them up immediately' which I did, straight away … and I didn't get any better, I felt as though I was getting worse"*. Even clinicians are unable to give reassurance of disease reversal, with slowing of COPD progression the best outcome of cessation. The lack of conviction of smoking as the main cause of illness is profound in its influence on smoking cessation failure (Hansen et al., 2007).

Smokers experience smoking as a "need of their taken-for-granted-body". In long-term smokers, the need to smoke is an embodied and automatic function that is reinforced by triggers of daily routine such as completion of a meal, having a cup of coffee or talking on the telephone (Gullick & Stainton, 2006). For smokers, this places smoking within a framework of ritual behaviour rather than addiction (Lindqvist & Hallberg, 2010). Whilst ever the immediate embodied rewards of smoking are stronger than the longer-term and more abstract possibility of future health gains, cessation success amongst long-term smokers is unlikely (Osman & Hyland, 2005). In the context of denial, merely providing education around harmful effects of smoking is equally unlikely to make a difference. As disability progresses, for the person to continue to smoke whilst accepting smoking as the cause of their illness means they are confronted with ideas of their own inherent foolishness, selfishness or weakness, leading to self-harm and burden to loved ones, and they find this idea of themselves unacceptable. That health professionals understand these meanings of denial around smoking is central to supporting cessation attempts.

A US Clinical Practice Guideline for tobacco dependence (Fiore et al., 2000) proposes the acknowledgement of smoking addiction itself as a chronic disease. By presenting smoking in a disease framework, clinicians can move beyond the issue of patient accountability for cessation failure and create the permission to accept medical, psychological and social support. It may also reduce the anger and resentment of family members arising from the addiction.

A number of disease milestones can act as prompts to stop smoking including being confronted with a diagnosis, the threat of oxygen dependence and serious exacerbations leading to hospital admission. Patient stories frequently link periods of heavy smoking with sudden and life-threatening health events and this may strengthen the person's resolve to stop. Taking the opportunity to communicate the 'right words at the right time' during a period of perceived vulnerability can be a precipitant for the person's eventual decision for cessation (Gullick & Stainton, 2006). West & Sohal (2006) describe this as 'motivational tension', a point at which even small triggers may lead to an unplanned quit attempt, and supportive treatments may be most effective. In their survey of almost 2000 past and current smokers, nearly half the reported attempts at quitting were unplanned and these unplanned attempts succeeded for longer.

The approach clinicians take to smoking advice is important. It is known that smokers will resent 'being told what to do', and need to feel that they have reached the decision for their own reasons (Burrows & Carlislea, 2010). If clinicians seek a partnership with the patient in managing the chronic illness of smoking addiction then this may sit more comfortably in the guilt/shame milieu of smoking experience. Whilst a didactic approach to discussions is not

recommended, it must be noted that there is a strong dose-response association between the intensity of smoking cessation counselling and its effectiveness. Programs that provide person-to-person contact such as face-to-face individual or group counselling or telephone counselling have demonstrated their consistent effectiveness, and effectiveness increases with treatment intensity (Anderson et al., 2002).

11. Living with crises

COPD is often experienced as relatively quiet times interrupted by episodes of serious illness. Episodic crises create the essence of uncertainty that defines the experience of COPD (Boyle, 2009a, Oliver, 2001, Gruffyd-Jones et al., 2007). These episodes are often described by patients and carers as near-death experiences that leave people with a constant sense of their own possible death. This has been described as 'living in the proximity of death' (Lindqvist and Hallberg 2010) and from a Heideggerian perspective, 'being-towards-death' (Gullick, 2008).

Crises may be the result of panic attacks, acute chest infections, allergic reactions or acute emergencies related to comorbidities. The crisis events begin with dyspnoea that does not respond to the usual self-management strategies. Initially, people may feel the need to be on their own during acute breathlessness, sensing that others can't help bring dyspnoea under control and that there is a need to focus internally on breathing and maintaining calm (Fraser 2006). Although the onset of exacerbation is recognised with panic and dread (Leidy, 2008), people are often reluctant to seek help, hoping things will improve and hospital admission will be avoided. Professional assistance is sought only after people are convinced they can't self-manage the event (Gruffyd-Jones et al., 2007, Leidy & Haase, 1999, Bailey, 2001). Gary described his father Jack's frightening experience: "*… he got a bit worried and rang the ambulance and by the time they got there all his vital signs… were starting to break down… they ended up working on him to save his life in the garage.*"(Gullick, 2008).

As respiratory distress increases and panic rises, people may change in appearance, may be unable to speak and may experience choking and loss of bladder or bowel control (Bailey, 2001, Gullick, 2008). These understandably terrifying events usually lead to emergency hospital admission. These crises are watershed events that mark a 'before' and 'after' in the person and family's life from which other events are then measured (Bailey, 2001). These crises underline life with COPD as uncertain and unpredictable and people fear each attack could be their last (Boyle, 2009a, Oliver, 2001). The experience reinforces the conviction of carers that they must closely monitor the person for early signs of deterioration, and this vigilance thereafter binds them emotionally and practically to the task of caring (Gullick, 2008). People will often develop emergency protocols that may define triggers for help-seeking and roles for family members that require 'understanding and trustworthiness' amongst those individuals (Bailey, 2001, Leidy & Haase, 1999) .

12. Emotional coping strategies in COPD

COPD is an imposing illness in its effects on normal body functioning, daily management of the body and the home environment and on the lives of family members who give support. People find strategies around 'conscious management of self' to counter the impact of the unpredictability of the disease. Many of these strategies can be found across the literature of other chronic illnesses. These strategies include conscious control of emotions, comparing

oneself to others worse off and learning to 'go with the flow' and make the best of unpredictable symptoms (Gullick & Stainton, 2008, Seamark et al., 2004, Cicutto et al., 2004). For some people, religious faith and spirituality provide an important emotional support that can reduce feelings of powerlessness (Leidy & Haase, 1999, Bergs, 2002, Milne et al., 2009, Seamark et al., 2004, Boyle, 2009b). Coming to a point of acceptance of the disease is named by many, but elegantly articulated by Lindqvist & Hallberg (2010) who describe the process of embodying and making a relationship with the disease. This requires a conscious replacement of the previously known life structure with a new, adapted one. This allows a determination of a reframed identity and normality that includes COPD. Patricia explains "*I've just got to learn to live with it. I call it 'me and my friend'*." Part of this acceptance lies in finding different foundations upon which to build hope; from cure to coping; from old dreams to new, realistic goals; and by discovering hope in the 'rewards of the moment' (Milne et al., 2009). People find simple and meaningful pleasure in realising skills, in having a good day, in being able to achieve a walk in the park or a shopping trip or in remembering past experiences with affection (Milne et al., 2009, Ek & Ternestet, 2008, Seamark et al., 2004).

Perhaps the most significant recognition for both the carers and people with COPD is of their family as 'the best thing in life' (Gullick & Stainton, 2008). Family is not only a practical support structure, but a reason for surviving and enduring, and through children and grandchildren, embodies an important source of meaningful connectivity and joy (Leidy & Haase, 1999, Cicutto et al., 2004, Bergs, 2002, Barnett, 2004).

13. The impact of pulmonary rehabilitation for the patient and family

Pulmonary rehabilitation is a valuable treatment option in chronic lung disease and is directed towards reversing the downward spiral of disability. People with COPD tend to use their body within the limits of worsening breathlessness so that they gradually decrease their body's activity. Patricia confided: "*They say you should go out for a walk, but I just can't be bothered because I just get too tired. You know, to me it's not worth it*".

Pulmonary rehabilitation programmes aim to reduce symptoms and disability and to reduce the person's reliance on acute health care systems by improving their understanding of the disease and encouraging active involvement and self-management. Current clinical practice guidelines (Ries et al., 2007) advise a multidisciplinary team approach, individualised patient assessment and the setting of realistic, patient-centred goals. A well-rounded rehabilitation program pays attention to the psychological, emotional and social dimensions of the patient experience, whilst trying to optimise the person's physical function by monitoring best-practice medical therapy.

Programmes usually offer a mixture of upper and lower body strength and aerobic exercise and expose the person to 'safe' breathlessness. Education sessions are an important component and typically discuss use of puffers and spacers, management of exacerbations and panic attacks, access to services and benefits, psychosocial support and understanding of Advanced Care Directives and No Resuscitation orders (Milne et al., 2009, Wilson et al., 2007). The duration and intensity of pulmonary rehabilitation programmes seem to impact on outcomes. People with mild to moderate COPD may see benefits from short to medium term participation, whilst people with severe COPD do best with programmes of at least six

months (Salman et al., 2003). The physical effectiveness gains also appear to be tied to the frequency of sessions per week (Gullick, 2008).

Having a specific COPD class means participants are empathetic towards others with symptoms of breathlessness and sputum production, and so are less self-conscious about their bodies' unpredictable behaviours (Gullick, 2008, Arnold et al., 2006). Under supervision, people become more comfortable exerting their body and are less likely to become panicked by exertional dyspnoea (Williams et al., 2010). Chris learned to manage his panic through the classes: *"The most helpful was avoiding panic attacks… It changed my outlook… I probably looked at it from the aspect 'Well, Bugger it! I can do these things' and I'd have a go at whatever it might be."* The increased sense of disease control due to greater confidence with managing medications and breathing techniques leads to a reduced likelihood of presentation to hospital (Camp et al., 2000).

Perceived physical gains include improved muscle strength, balance and mobility, reduced breathlessness and fatigue, and an improvement in joint mobility and pain management for those with musculoskeletal comorbidities. The result is that daily tasks are more achievable and require less pacing to complete (O'Shea et al., 2007, Gullick, 2008). Pulmonary rehabilitation has led to improvements in health related quality of life even where no significant improvement in lung function is demonstrated (Haave et al., 2007, Camp et al., 2000). This is in part, due to the reduction in social isolation and improved opportunities for expression of 'self' (Gullick, 2008, Toms & Harrison, 2002); patients describe feelings of enhanced well-being and hope (Milne et al., 2009, O'Shea et al., 2007), have higher self-esteem and mood (Arnold et al., 2006) and, following rehabilitation, are more likely to talk about their abilities rather than their limitations (Williams et al., 2010). Pulmonary rehabilitation can lead to a change in physical appearance and in turn, body image, and creates a sense of pride, satisfaction and achievement (O'Shea et al., 2007).

The intrinsic motivation of the person with COPD is important in determining the most successful approach to exercise training. Home-based programs may not be so successful for people who live alone or who do not have high internal levels of motivation. The notion of locus of control (Rotter, 1966) is a useful construct to predict those who may be most successful. People with a higher internal locus of control are more likely to seek information about their circumstances. They perceive a greater power to influence events through their own activities and behaviours and are more likely to believe that their labours will be successful. Those with a lower internal locus of control tend to see events as influenced by their environment, powerful others or fate. People with COPD who describe a higher intrinsic drive demonstrate more active engagement with rehabilitation and seem more successful with continuing on a home-based maintenance routine. Petra had severe COPD, but was carrying on a home-based exercise program more than a year after her initial rehabilitation: *"I have a walker… I only have to look at that and I'm at it. Never, ever will I fail! But I have two days off … Wednesdays comes my cleaning lady… Sunday… I entertain… So all the other days, that's exercise. That's like going to a job"* (Gullick, 2008). Those whose motivation is linked to exercising with others are less likely to benefit from a home-based rehabilitation (Milne et al., 2009). Jim (60 yrs) found maintaining a home-based program challenging: *"It's pretty right what they say – 'In a group you'll do it', whereas a lot of times you'll put it off at home."*

Pulmonary Rehabilitation itself can foster subsequent patient empowerment and a higher internal locus of control by demonstrating to the participant, the positive effects of self monitoring and management of their clinical status (Cafarella & Frith, 2001). Whilst breathlessness is still a feature of the person's experience after rehabilitation, it is the change in the way breathlessness is perceived that is most important, resulting from increased confidence and a loss of fear of physical exertion. With an increased sense of control over breathing, people often find panic and anxiety are reduced or eliminated and they increase their activity levels as a result (Williams et al., 2010, O'Shea et al., 2007).

14. The impact of volume reduction interventions for the patient and family

The major limitation to exercise tolerance, and therefore to functional performance in COPD, is dynamic hyperinflation (O'Donnell & Webb, 2008). Surgical procedures, such as Lung Volume Reduction Surgery (LVRS) and Endobronchial Valve Insertion (EBV™) have expanded the therapeutic possibilities for people with emphysematous hyperinflation. The procedures aim to reduce the amount of space taken up by hyperinflated lung tissue to improve elastic recoil, and chest wall and diaphragm dynamics. LVRS is an invasive procedure that requires the resection of between 20-40% of the total volume of each lung. It is safest and most effective for people with an FEV_1 greater than 20% of predicted and a heterogenous rather than diffuse pattern of emphysema (NETT, 2001). LVRS is not a first-line treatment, but should be considered where optimal medical management and pulmonary rehabilitation fails to improve the person's clinical status (Ries et al., 2005). LVRS is known to result in significant improvements in quality of life, exercise performance and lung function, and the best results occur where surgery is complemented with an extended period of pulmonary rehabilitation (Criner et al., 1999).

In response to the potential morbidity and mortality following the major surgical procedure of LVRS, minimally invasive alternatives have been developed, and these are usually targeted towards upper zone, heterogenous emphysema. To date, the most commonly utilised approach is to insert one or more one-way endobronchial valves (EVB) to allow air to escape from hyperinflated zones and to prevent the return of air to those zones.

Whilst some patients are known to benefit from this procedure, only a minority (these tend to be those with the most hyperinflation at baseline) experience long term improvements in lung function (Kotecha et al., 2011). This improvement comes at a cost of more frequent hemoptysis, pneumonia distal to the valves and more frequent exacerbations of COPD in the few months after valve implantation (Sciurba et al., 2010). These results are confirmed in the only qualitative study of lung volume reduction procedures to date, demonstrating sustained wellness amongst most of the LVRS participants in contrast to a gradual decline in effectiveness for those who had endobronchial valve insertion (Gullick & Stainton, 2009).

Importantly, FEV_1 as the hallmark of COPD measurement, frequently does not predict the person-centred outcomes of surgery (Gullick & Stainton, 2009, Leyenson et al., 2000, Moy et al., 1999). Patients and families who accept surgical intervention for COPD feel the need to 'take a chance' on a procedure, even if they perceive that to be high-risk decision. Whilst COPD leads to shrinking of the boundaries of the self, for some, undergoing a surgical intervention allows an increase in physical effectiveness and a regaining of self. Gail

explained of her husband Jim after EBV insertion, *"He can dig in his garden…he's got a lovely veggie garden at the moment. There's lots of things he wouldn't have been able to do had he not had it done"*. Claire, (52 yrs) describes her husband Sam's regaining of self after LVRS: *"It was important for all of us to get back what he wanted; his mobility, his freedom, his right to choose what he wants... It was a chance for Sam to continue being Sam, and the surgery achieved that. He could go on being the same person that he was – he was able to continue being himself."*

15. COPD at end-of-life

End-of-life planning in COPD is an important concept that allows goal-setting for patients and families, and facilitates a peaceful and dignified death. Specialist referral to palliative care services, in combination with a partnership approach with patients and families, allows the person to retain control over aspects of the experience of dying in the context of an otherwise uncontrollable illness course.

One of the great difficulties of planning the timing of end-of-life discussions is the uncertain disease trajectory in chronic respiratory conditions. COPD has not only an insidious onset, but also, an unchartable end-stage. We know that compared to patients with lung cancer, COPD patients have more Emergency Department admissions, more anxiety & depression, and report a lower quality of life. Compared to cancer patients, financial support comes later in the disease process and patients feel in greater need of aids and appliances, and of information on services and benefits (Gore et al., 2000, Crawford, 2010). COPD patients are less likely to receive prognostic information, less likely to know they are dying, or know they are dying for less time and they are more likely than lung cancer patients to die in hospital. Relatives of COPD patients are less likely to be present at the time of death, although, we know most would like to be present (Edmonds et al., 2001).

Many General Practitioners (GPs) may not think about COPD as a terminal disease and so may not consider a palliative management plan (Halliwell et al., 2004). They do not tend to talk about what dying may be like or how long that may take (Curtis et al., 2004). The recently revised Initiative on Chronic Obstructive Pulmonary Disease guidelines (GOLD, 2010) gives brief mention of end-of-life discussions and advance directives, yet gives no strategies for these considerations or for palliative management of COPD.

A nurse participant in the study of Crawford (2010) described COPD patients as having *"nine lives… you see them sick and think they won't get through this and then they do."* This tendency for people to bounce back has led to practitioners considering how best to define the time for end-of-life discussions and interventions. For clinicians, the final phase of life may be suggested by an FEV_1 less than 30% of predicted, frequent exacerbations and admissions to hospital, and the presence of right heart failure. The need for mechanical ventilation and long-term oxygen therapy dependence also signal serious disease (Halpin et al., 2008). However, such markers are not always reliable predictors of the terminal phase of COPD (Seneff et al., 1995). Patients may have their own interpretation of the time when treatment is no-longer worth the burden that continued life presents. Scenarios that include prolongation of inevitable death, dependence on machinery, functional and cognitive impairment, unmanageable symptoms and a burden on loved ones have been noted as unacceptable by patients (Fried & Bradley, 2003).

Another complicating factor is that what is acceptable to patients may change over time as they adjust to severe illness and this may influence discussions and the willingness of GPs to initiate advance care planning (Halpin et al., 2008). It is typical of people to normalise their experience of even severe day-to-day symptoms and see themselves a sick only during acute exacerbations. This may be, in part, a coping strategy, but is also a result of the long illness trajectory. Whilst in cancer narratives, there is a definite beginning and developing plot to the 'cancer story', COPD is more likely to be insidious in its beginning and intertwined with the person's 'life story'. The unpredictability of exacerbations creates a chaotic component to the person's experience of illness, yet they may have a sense of relative wellness between these crises (Pinnock et al., 2011). Whilst people may feel that each acute exacerbation may be their last (Oliver, 2001) the threat of death recedes after a COPD crisis, or perhaps the threat of death is also normalised. The result is that death is less likely to be considered imminent and so wishes are rarely discussed with professional carers, friends or family (Pinnock et al., 2011). Where end-of-life discussions do occur, they may be poorly documented and so patient wishes may not be visible to family or other members of a multi-disciplinary team (Crawford, 2010).

Having end-of-life discussions with COPD patients and families constitutes significant emotional work for clinicians and requires 'conscious emotional management'. This comes with experience as professionals learn to feel their way with an individual, and apply emotional intelligence and empathetic skills in their discussions (Crawford, 2010). Some ways to approach these difficult conversations include beginning discussions early in the disease course, using the uncertain disease trajectory to ease discussions and building a caring and respectful relationship with patients. It is useful to have a team approach with recognition of the collective responsibility of GPs, respiratory nurses and physicians to proactively identify and use opportunities to talk about prognosis (Halliwell et al., 2004).

The aim of good end-of-life discussions is to inform without removing hope, and to bring to the forefront the wishes of the patient and family. Research participant, Mary, described how she appreciated the honesty and sensitivity of the discussions after her husband had an ICU admission: "*The doctor did tell us the dangers of intubation …then when he was moved to ward said, 'You've come through this okay…Perhaps in the future it might happen again…You need to think what you want done, you and your family.' Just nicely … And I thought this is great*".

Discussing prognosis broadly in terms of a diagnostic population rather than directing it at the individual leaves room for hopeful possibilities. Physicians can foster hope by giving a 'commitment to non-abandonment', by addressing people's fears, such as fear of pain at end-of-life, and by having a management plan that addresses their changing situation (Curtis et al., 2008). Helping people to identify realistic goals and discussing their concerns about day-to-day living can also be useful (Clayton et al., 2005). The ideal is for a formal Advance Care Plan to be documented early. Again, the uncertain disease course of COPD makes this more complex, and means physicians are less comfortable with initiating such plans (Halpin et al., 2008). Fins et al (2005) point out that the process can be simplified by creating possibilities for revision of the plan, and by trying to understand and be true to the patient's core values whilst remaining flexible around practical details such as where they would prefer to die.

One marker of the end-of life stage may be the point where maximal therapy no longer provides relief of symptoms. Symptoms in the last year of life are characterised by constant breathlessness, weakness and fatigue. Pain, insomnia, depression, anxiety and panic attacks also shape the patient experience at this stage (Elkington et al., 2005). This requires a change in priorities of care, with symptom management needing the greatest focus. For example, in late-stage disease opioids may be central to dealing with dyspnoea, dyspnoea-related anxiety and pain. Clinician concerns around respiratory depression may lead to the underutilisation of opoids (Halpin et al., 2008). This may require a change in our understanding of what is 'good' or 'safe' for patients at different stages of their illness experience.

The COPD journey is a long and consuming one both for the person with the disease, and for the family carer. Whilst this may set up challenges for clinicians in understanding and supporting psychosocial concerns, it also creates possibilities for true management partnerships with our patients and their families. If we embrace these possibilities we may achieve real meaning in the care we provide, and we are more likely to locate the humanity within our practice.

16. References

Anderson, J. E., Jorenby, D., Scott, W. & Fiore, M. (2002) Treating tobacco use and dependence: An evidence-based clinical practice guideline for tobacco cessation. *CHEST,* Vol. 121, No. 3. pp.932-41, ISSN 0012-3692.

Arne, M., Emtner, M., Janson, S., & Wilde-Larsson, B. (2007) COPD patients' perspectives at the time of diagnosis: A qualitative study. *Primary Care Respiratory Journal.,* Vol. 16, No. 4, pp.215-21, ISSN 1471-4418.

Arnold, E., Bruton, A. & Ellis-Hill, C. (2006) Adherence to pulmonary rehabilitation: A qualitative study. *Respiratory Medicine,* Vol. 100, No. 10, pp.1716-23, ISSN 0954-6111

Avsar, G. & Kasilkci, M. (2011) Living with chronic obstructive pulmonary disease: A qualitative study. *Australian Journal of Advanced Nursing,* Vol. 28, No. 28, pp.46-52, ISSN 0813-0531.

Bailey, P. (2001) Death Stories: Acute exacerbations of Chronic Obstructive Pulmonary Disease. *Qualitative Health Research,* Vol. 11, No. 3, pp.322-338, ISSN 1049-7323

Bailey, P. & Tilley, S. (2002) Storytelling and the interpretation of meaning in qualitative research. *Journal of Advanced Nursing,* Vol. 38, No. 6, pp.574–583, ISSN 0309-2402

Barnett, M. (2004) Chronic obstructive pulmonary disease: A phenomenological study of patients' experiences. *Issues in Clinical Nursing,* Vol. 14, No. 7, pp.805-12, ISSN 0962-1067.

Bergs, D. (2002) 'The Hidden Client'– Women caring for husbands with COPD: their experience of quality of life. *Journal of Clinical Nursing,* Vol. 11, No. 5, pp.613–21, ISSN 0962-1067.

Blanker, M., Bosch, J., Groeneveld, F., Bohnen, A., Prins, A., Thomas, S. & Hop, W. (2001) Erectile and ejaculatory dysfunction in a community-based sample of men 50 to 78 years old: Prevalence, Concern, and relation to sexual activity. *Urology,* Vol. 57, No. 4, pp.763-8, ISSN 1527-9995.

Blumer, H. (1969) *Symbolic Interactionism: Perspective and Method.,* University of California Press., ISBN 0520056760, Berkeley.

Boueri, F., Bucher-Bartelson, B., Glenn, K. & Make, B. (2001) Quality of life measured with a generic instrument (Short Form-36) improves following pulmonary rehabilitation in patients with COPD. *CHEST,* Vol.19, No.1, pp.77-84, ISSN 0012-3692.

Boyle, A. (2009a) An integrative review of the impact of COPD on families. *Southern Online Journal of Nursing Research.* Southern Nursing Research Society. Accessed 23/6/2011. Available at: <http://snrs.org/publications/SOJNR_articles2/Vol09Num03Art05.html>

Boyle, A. (2009b) Living with a spouse with chronic obstructive pulmonary disease: the meaning of wives' experiences. *Journal of Nursing and Healthcare of Chronic Illness,* Vol. 1, No. 4, pp.273–82. ISSN 1752-9816.

Burrows, J. & Carlislea, J. (2010) They don't want it ramming down their throats. Learning from the perspectives of current and ex-smokers with smoking-related illness to improve communication in primary care: a qualitative study. *Primary Health Care Research & Development,* Vol. 11, pp. 206-14.

Cafarella, P. & Frith, P. (2001) Pulmonary rehabilitation fosters more effective patient self-management through changes in locus of control. *Proceedings of European Respiratory Society Annual Congress,* Berlin.

Camp, P., Appleton, J. & Reid, W. (2000) Quality of life after pulmonary rehabilitation: Assessing change using quantitative and qualitative methods. *Physical Therapy,* Vol. 80, No. 10, pp.986-95, ISSN 0031-9023.

Cicutto, L., Brooks, D. & Henderson, K. (2004) Self-Care issues from the perspective of individuals with chronic obstructive pulmonary disease. *Patient Education & Counseling,* Vol. 55, No. 2, pp.168-76, ISSN 0738-3991.

Clayton, J., Butow, P. & Tattersall, M. (2005) When and how to initiate discussions about prognosis and end-of-life issues with terminally ill patients. *Journal of Pain & Symptom Management.,* Vol. 30, pp.132-44, ISSN 0885-3924.

Crawford, A. (2010) Respiratory practitioners' experience of end-of-life discussions in COPD. *British Journal of Nursing,* Vol. 19, No. 18, pp.1164-9, ISSN 0966-0461.

Criner, G., Cordova, F., Furukawa, S., Kuzma, A., Travaline, J., Leyenson, V. & O'Brien, G. (1999) Prospective randomised trial comparing bilateral Lung Volume Reduction Surgery to pulmonary rehabilitation in severe Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory and Critical Care Medicine,* Vol. 160, No. 6, pp.2018-27, ISSN 1073-449X.

Currow, D., Ward, A., Clark, K., Burns, C. & Abernathy, A. (2008) Caregivers for people with end-stage lung disease: Characteristics and unmet needs in the whole population. *International Journal of COPD,* Vol. 3, No. 4, pp.753-62, ISSN 1176-9106.

Curtis, J., Engelberg, E., Nielson, E., Au, D. & Patrick, D. (2004) Patient-physician communication about end-of-life care for patients with severe COPD. *European Respiratory Journal,* Vol. 24, No. 2, pp.200-5, ISSN 0903-1936.

Curtis, J., Engelberg, R., Yound, J., Pig, L., Reinke, L., Wenrich, M., McGrath, B., McCown, E. & Back, A. (2008) An approach to understanding the interaction of hope and desire for explicit prognostic information among individuals with severe Chronic Obstructive Pulmonary Disease or advanced cancer. *Journal of Palliative Medicine.,* Vol. 11, No. 4, pp.610-20, ISSN 1096-6218.

Diethorn, M. (1985) Prevention of sensory deprivation for the C.O.P.D. victim's spouse. *Topics in Clinical Nursing,* Vol. 6, No. 4, pp.64-71, ISSN 0164-0534.

Dudley, D., Glaser, E., Jorgenson, B. & Logan, D. (1980) Psychosocial concomitants to rehabilitation in Chronic Obstructive Pulmonary Disease. *CHEST,* Vol. 77, No. 5, pp.544-51, ISSN 0012-3692

Earnest, M. (2002) Explaining Adherence to Supplemental Oxygen Therapy: The patient's perspective. *Journal of General Internal Medicine,* Vol. 17, No. 10, pp.749–55, ISSN 0884-8734.

Edmonds, P., Karlsen, S., Kahn, S. & Addington-Hall, J. (2001) A comparison of the palliative care needs of patients dying of chronic respiratory diseases and lung cancer. *Palliative medicine,* Vol. 15, No. 4, pp.287-95, ISSN 0269-2163.

Ek, K. & Ternestet, B. (2008) Living with chronic obstructive pulmonary disease at the end of life: a phenomenological study. *Journal of Advanced Nursing,* Vol. 62, No. 4, pp.470-8, ISSN 1365-2648.

Elkington, H., White, P., Addington-Hall, J., Higgs, R. & Edmonds, P. (2005) The healthcare needs of Chronic Obstructive Pulmonary Disease Patients in the last year of life. *Palliative Medicine.,* Vol. 19, no. 6, pp.485-91,

Ezzy, D. (2002) *Qualitative Analysis: Practice and Innovation,* Routledge, ISBN 0415281261, London.

Fins, J., Maltby, B., Friedmann, E., Greene Mg, Norris, K., Adelman, R. & Byock, I. (2005) Contracts, covenants and advanced care planning: an empirical study of the moral obligations of patient and proxy. *Journal of Pain and Symptom Management,* Vol. 29, No. 1, pp.55-68, ISSN 0885-3924.

Fiore, M., Bailey, W., Cohen, S. & Rockville, M. (2000) US Public Health Service clinical practice guideline: Treating tobacco use and dependence. *Respiratory Care,* Vol. 45, No. 10, pp.1200-62, ISSN 0020-1324.

Fisher, E. & Hill, R. (1990) Perspectives on older smokers. *CHEST,* Vol. 97, No. 3, pp.517-8, ISSN 0012-3692.

Fraser, D., Kee, C. & Minick, P. (2006) Living with chronic obstructive pulmonary disease: insiders' perspectives. *Journal of Advanced Nursing,* Vol. 55, No. 5, pp.550-8, ISSN 0309-2402

Fried, T. & Bradley, E. (2003) What matters to seriously ill older persons making end-of-life treatment decisions? A qualitative study. *J Qualitative Medicine,* Vol. 6, No. 2, pp.237-44, ISSN 1096-6218.

Glaser, B. & Strauss, A. (1967) *Discovery of Grounded Theory. Strategies for Qualitative Research,* Sociology Press, ISBN 0202302601, Mill Valley, CA.

GOLD (2010). *Global strategy for diagnosis, management and prevention of COPD: 2010 update.* 13/6/2011, Available from: http://www.goldcopd.org/

Gore, J., Brophy, C. & Greenstone, M. (2000) How well do we care for end-stage chronic obstructive pulmonary disease (COPD)? A comparison of palliative care and quality of life in COPD and lung cancer. *Thorax,* Vol. 55, No. 12, pp.1000-6, ISSN 0040-6376.

Gruffyd-Jones, K., Langley-Johnson, C., Dyer, C., Badlan, K. & Ward, S. (2007) What are the needs of patients following discharge from hospital after an acute exacerbation of chronic obstructive pulmonary disease (COPD)? *Primary Care respiratory Journal,* Vol. 16, No. 6, pp.363-368, ISSN 1471-4418.

Gullick, J. (2008) *Conscious Body Management of breathlessness: Living with COPD and choosing surgery,* VDM Verlag, ISBN 3639050746, Saarbrücken.

Gullick, J. & Stainton, M. (2006) Smoking in Chronic Obstructive Pulmonary Disease: A need of the taken-for-granted body. *Journal of Smoking cessation,* Vol. 1, No. 1, pp.7-12, ISSN 1834-2612.

Gullick, J. & Stainton, M. (2008) Living with chronic obstructive pulmonary disease: developing conscious body management in a shrinking life-world. *Journal of Advanced Nursing,* Vol. 64, No. 6, pp.605-14, ISSN 1365-2648.

Gullick, J. & Stainton, M. (2009) Taking a chance: the experience of lung volume reduction procedures for chronic obstructive pulmonary disease. *Chronic Illness,* Vol. 5, No. 4, pp.293-304, ISSN 1745-9206.

Haave, E., Hyland, M. & Engvik, H. (2007) Improvements in exercise capacity during a 4-weeks pulmonary rehabilitation program for COPD patients do not correspond with improvements in self-reported health status or quality of life. *International Journal of Chronic Obstructive Pulmonary Disease.,* Vol. 2, No. 3, pp.355–359, ISSN 1176-9106.

Halliwell, J., Mulcahey, P., Buetow, S., Bray, Y., Coster, G. & Osman, L. (2004) GP discussion of prognosis with patients with severe chronic obstructive pulmonary disease: a qualitative study. *Br J Gen Pract,* Vol. 54, No. 509, pp.904-8, ISSN 0960-1643.

Halpin, D., Seamark, C. & Seamark, D. (2008) End-of-life care for patients with COPD in the community setting. *British Journal of General Practice,* Vol. 58, No. 551, pp.390-392, ISSN 0960-1643.

Hansen, E., Walters, J. & Wood Baker, R. (2007) Explaining chronic obstructive pulmonary disease (COPD): perceptions of the role played by smoking. *Sociology of Health and Illness,* Vol. 29, No. 5, pp.730-49, ISSN 0141-9889.

Heidegger, M. (1927:1996) *Being and Time,* Harper & Brothers, ISBN 0791426777, New York.

Husserl, E. (1936:1970) *The crisis of European sciences and transcendental phenomenology: An introduction to phenomenological philosophy,* Northwestern University Press, Evanston, IL. ISBN 0810102552.

Husserl, E. (1931:1960) *Cartesian meditations: An introduction to phenomenology,* Martinus Nijhoff, ISBN 9024702143, The Hague.

Jalowiec, A., Murphy, S. & Powers, M. (1984) Psychometric assessment of the Jalowiec Coping Scale. *Nursing Research,* Vol. 33, No. 3, pp.157-1961, ISSN 0029-6562

Johnson, J., Campbell, A., Bowers, M. & Nichol, A. (2007) Understanding the social consequences of Chronic Obstructive Pulmonary Disease: The effects of stigma and gender. *The Proceedings of the American Thoracic Society.* ISSN 1546-3222

Jones, I., Kirby, A., Ormiston, P., Loomba, Y., Chan, K., Rout, J., Nagle, J., Wardman, L. & Hamilton, S. (2004) The needs of patients dying of chronic obstructive pulmonary disease in the community. *Family Practice.,* Vol. 21, No. 3, pp.310-3, ISSN 0263-2136.

Jones, P. (1991) Quality of life measurement for patients with diseases of the airways. *Thorax,* Vol. 46, No. 9, pp.676-82, ISSN 0040-6376.

Kanervisto, M., Paavilainen, E. & Heikkila, J. (2007) Family dynamics in families of severe COPD patients. *Journal of Clinical Nursing,* Vol. 16, No. 8, pp.1498-505, ISSN 0962-1067.

Kapella, M., Larson, J., Patel, M., Covey, M. & Berry, J. (2006) Subjective fatigue, influencing variables, and consequences in Chronic Obstructive Pulmonary Disease. *Nursing Research,* Vol. 55, No. 1, pp.10-17, ISSN 0029-6562.

Kotecha, S., Westall, G., Holsworth, L., Pham, A., Williams, T., Snell, G. & (2011) Long-term outcomes from bronchoscopic lung volume reduction using a bronchial prosthesis. *Respirology,* Vol. 16, No. 1, pp.167-73, ISSN 1440-1843.

Krippendorff, K. (2004) *Content analysis: an introduction to its methodology,* Sage, ISBN 9780761915454, Thousand Oaks.

Lacasse, Y., Rousseau, L. & Maltais, F. (2001) Prevalence of depressive symptoms and depression in patients with severe oxygen dependent Chronic Obstructive Pulmonary Disease. *Journal of Cardiopulmonary Rehabilitation.,* Vol. 21, No. 2, pp.80-6, ISSN 0883-9212.

Leidy, N. (2008) Addressing behavioural and emotional aspects of COPD. *Advanced Studies in Medicine,* Vol. 8, No. 13, pp.463-8.

Leidy, N. & Haase, J. (1999) Functional status from the patient's perspective: The challenge of preserving personal integrity. *Research in Nursing & Health,* Vol. 22, No. 1, pp.67-77, ISSN 0160-6891.

Leyenson, V., Furukawa, S., Kuzma, A., Cordova, F., Travaline, J. & Criner, G. (2000) Correlation of changes in quality of life after Lung Volume Reduction Surgery with changes in lung function, exercise, and gas exchange. *CHEST,* Vol. 118, No.3, pp.728-35, ISSN 0012-3692.

Lindqvist, G. & Hallberg, L. (2010) Feelings of guilt due to self-inflicted disease: A grounded theory of suffering from Chronic Obstructive Pulmonary Disease (COPD). *Journal of Health Psychology,* Vol. 15, No. 3, pp.456-466, ISSN 1461-7277.

Mahler, D. & Mackowiak, J. (1995) Evaluation of the Short-Form 36-Item Questionnaire to measure health-related quality of life in patients with C.O.P.D. *CHEST,* Vol. 107, No. 6, pp.1585-9, ISSN 0012-3692.

McClelland, K. (21/2/2000). *Symbolic Interactionism: Theoretical perspectives in sociology*, 13/6/2011, Available from: <http://web.grinnell.edu/courses/soc/s00/soc111-01/IntroTheories/Symbolic.html>

McDowell, I. & Newell, C. (1987) *Measuring health: A guide to rating scales and questionnaires,* Oxford University Press, ISBN 0195041011, Oxford.

Merleau-Ponty, M. (1945:1962) *Phenomenology of Perception,* Routledge and Kegan Paul, ISBN 0415045568, London.

Milne, L., Moyle, W. & Cooke, M. (2009) Hope: a construct central to living with chronic obstructive pulmonary disease. *International Journal of Older People Nursing,* Vol. 4, No. 4, pp.299-306.

Moy, M., Ingenito, E., Mentzer, S., Evans, R. & Reilly, J. (1999) Health-related quality of life improves following pulmonary rehabilitation and Lung Volume Reduction Surgery. *CHEST,* Vol. 115, No. 2, pp.383-9, ISSN 0012-3692.

National Health and Medical Research Council (2009) NHMRC levels of evidence and grades for recommendations for developers of guidelines. Australian Government. Accessed 20/7/2011, Available at: <http://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/evidence_statement_form.pdf>

NETT (2001) National Emphysema Treatment Trial Research Group. Patients at high risk of death after lung-volume-reduction surgery. *New England Journal of Medicine,* Vol. 345, No. 15, pp.1075-83, ISSN 0028-4793.

Nicolson, P. & Anderson, P. (2003) Quality of life, distress and self-esteem: A focus group study of people with chronic bronchitis. *British Journal of Health Psychology,* Vol. 8, No. 3, pp.251-70, ISSN 1359-107X.

Nordtug, B., Krokstad, S. & Holen, A. (2010) Personality features, caring burden and mental health of cohabitants of partners with chronic obstructive pulmonary disease or dementia. *Aging & Mental Health,* Vol. 15, No. 3, pp.318 - 326, ISSN 1364-6915.

O'Donnell, D. & Webb, K. (2008) The major limitation to exercise performance in COPD is dynamic hyperinflation. *Journal of Applied Physiology,* Vol. 105, No. 2, pp.753-5, ISSN 8750-7587.

O'Neill, E. (2002) Illness representations and coping of women with Chronic Obstructive Pulmonary Disease: A pilot study. *Heart and Lung,* Vol. 31, No. 4, pp.295-302, ISSN 0147-9563.

O'Shea, S., Taylor, N. & Paratz, J. (2007) Qualitative outcomes of progressive resistance exercise for people with COPD. *Chronic Respiratory Disease,* Vol. 4, No.3, pp.135-42, ISSN 1479-9723.

Odencrants, S., Ehnfors, M. & Grobe, S. (2005) Living with chronic obstructive pulmonary disease: Part I. Struggling with meal-related situations: experiences among persons with COPD. *Scandinavian Journal of Caring Sciences,* Vol.19, No. 3, pp.230-9, ISSN 0283-9318.

Oliver, S. (2001) Living with failing lungs: The doctor-patient relationship. *Family Practice,* Vol. 18, No. 4, pp.430-3, ISSN 0263-2136.

Osman, L. & Hyland, M. (2005) Patient needs and medication styles in COPD. *European Respiratory Journal.,* Vol. 14, No. 96, pp.89-92, ISSN 1600-0617.

Pinnock, H., Murray, S., Worth, A., Levack, P., Porter, M., Macnee, W., & Sheikh, A. (2011). Living and dying with COPD. *BMJ,* Vol. 342. pp.d142, ISSN 1468-5833.

Rabinowitz, B. & Florian, V. (1992) Chronic Obstructive Pulmonary Disease: Psychosocial issues and treatment goals. *Social Work in Health Care,* Vol. 16, pp.69-86, ISSN 0098-1389.

Reissman, C. (1994) *Narrative Analysis,* Sage, ISBN 9780857020116, Thousand Oaks.

Ries, A., Bauldoff, G., Carlin, B., Casaburi, R., Emery, C., Mahler, D., Make, B. & Rochester, C. (2007) Pulmonary rehabilitation: Joint ACCP/AACVPR evidence-based clinical practice guidelines. *CHEST,* Vol. 131, No. 5, pp.4S-42S, ISSN 0012-3692.

Ries, A., Make, B., Lee, S., Krasna, M., Bartels, M., Crouch, R. & Fishman, A. (2005) The effects of pulmonary rehabilitation in the National Emphysema Treatment Trial. *CHEST,* Vol. 128, No.6, pp.3799-809, ISSN 0012-369.

Ring, L. & E, D. (1997) Patients experiences of long term oxygen therapy. *Journal of Advanced Nursing,* Vol. 26, No. 2,pp.337-44, ISSN 0309-2402.

Robinson, T. (2005) Living with severe hypoxic COPD: the patients' experience. *Nursing Times,* Vol. 101, No. 7, pp.38-42, ISSN 0954-7762.

Rotter, J. (1966) Generalized expectancies of internal versus external control of reinforcements. *Psychological Monographs,* Vol. 80, No. 1, pp.609, ISSN 0096-9753.

Salman, G., Mosier, M., Beasley, B. & Calkins, D. (2003) Rehabilitation for patients with chronic obstructive pulmonary disease: meta-analysis. *Journal of General and Internal Medicine,* Vol. 18, No. 3, pp.213-21, ISSN 0884-8734.

Schofield, I., Kerr, S. & Tolson, D. (2007) An exploration of the smoking-related health beliefs of older people with chronic obstructive pulmonary disease. *Journal of Clinical Nursing,* Vol. 16, No. 9, pp.1726-35, ISSN 0962-1067.

Sciurba, F., Ernst, A., Herth, F., Strange, C., Criner, G., Marquette, C., Kovitz, K., Chiacchierini, R., Goldin, J., McLennan, G. & Vent Study Research Group (2010) A randomized study of endobronchial valves for advanced emphysema. *New England Journal of Medicine,* Vol. 363, No. 13, pp.1233-44, ISSN 1533-4406.

Seamark, D., Blake, S., Seamark, C., & Halpin, M. (2004) Living with severe chronic obstructive pulmonary disease (COPD): perceptions of patients and their carers: An interpretative phenomenological analysis. *Palliative Medicine,* Vol. 18, No. 7, pp.619-25, ISSN 0269-2163.

Seneff, M., Wagner, R., Zimmerman, J. & Knaus, W. (1995) Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. *JAMA,* Vol.274, No. 23, pp.1852-57, ISSN 0098-7484.

Sexton, D. & Munro, B. (1985) Impact of husband's chronic illness (COPD) on the spouse's life. *Research in Nursing and Health,* Vol. 8, No. 1, pp.83-90, ISSN 0160-6891.

Shackell, B., Jones, R., Harding, G., Pearse, S. & Campbell, J. (2007) 'Am I going to see the next morning?' A qualitative study of patient's perspectives of sleep in COPD. *Primary Care Respiratory Journal,* Vol. 16, No. 6, pp.378-383,

Strauss, A. & Corbin, J. (1998) *Basics of qualitative research techniques and procedures for developing Grounded Theory (2nd edition),* Sage, ISBN 0803959400, London.

Toms, J & Harrison, K. (2002) Living with Chronic Lung Disease and the effect of pulmonary rehabilitation: Patients perspectives. *Physiotherapy*, Vol.88, pp.605-19, ISSN 1471-4418.

West, R. & Sohal, T. (2006) "Catastrophic" pathways to smoking cessation: findings from a national survey. *BMJ,* Vol. 332, No. 7539, pp.458-460, ISSN 1468-5833.

Wicks, M. (1997) A test of the Wicks Family Health Model in families coping with Chronic Obstructive Pulmonary Disease. *Journal of Family Nursing,* Vol. 3, pp.189-212, ISSN 1074-8407.

Williams, V., Bruton, A., Ellis-Hill, C. & McPherson, K. (2010) The effect of pulmonary rehabilitation on perceptions of breathlessness and activity in COPD patients: a qualitative study. *Prim Care Respir J,* Vol. 19, No. 1, pp.45-51, ISSN 1475-1534.

Williams, V., Bruton, A., Ellis-Hill, C. & McPherson, K. (2011) The importance of movement for people living with Chronic Obstructive Pulmonary Disease. *Qualitative Health Research.* Vol. 21, No. 9, pp.1239-1248, ISSN 1049-7323.

Wilson, I. (2006) Depression in the patient with COPD. *International Journal of Chronic Obstructive Pulmonary Disease.,* Vol. 1, No. 1, pp.61-64, ISSN 1176-9106.

Wilson, J., O'Neill, B., Reilly, J., MacMahon, J. & Bradley, J. (2007) Education in pulmonary rehabilitation: The patient's perspective. *Archives of Physical Medicine and Rehabilitation,* Vol. 88, No. 12, pp.1704-9, ISSN 1532-821X.

World Health Organisation (2011) *WHO report on the global tobacco epidemic*, 24/7/2011, Available from: http://www.who.int/tobacco/global_report/2011/en/

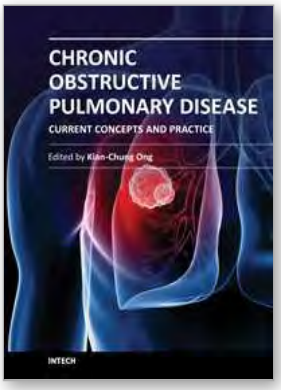
Yang, L., Zhou, M., Smith, M., Yang, G., Peto, R., Wang, J., Boreham, J., Hu, Y. & Chen, Z. (2010) Body mass index and chronic obstructive pulmonary disease-related mortality: a nationally representative prospective study of 220,000 men in China. *International Journal of Epidemiology,* Vol. 39, No. 4, pp.1027-36, ISSN 1464-3685.

Yohannes, A. (2005) Depression and COPD in older people: a review and discussion. *British Journal of Community Nursing,* Vol. 10, No. 1, pp.42-6, ISSN 1462-4753.

Yohannes, A., Baldwin, R. And Connolly, M. (2000) Depression and anxiety in elderly outpatients with Chronic Obstructive Pulmonary Disease: Prevalence, and the validation of the B.A.S.D.E.C. screening questionnaire. *International Journal of Geriatric Psychiatry,* Vol. 15, No. 12, pp.1090-96, ISSN 1462-4753.

Young, P., Dewse, M. & J., F. K. (1999) Respiratory rehabilitation in chronic obstructive pulmonary disease; predictors of non-adherence. *European Respiratory Journal,* Vol. 13, No. 4, pp.855-9, ISSN 0903-1936.

Zigmond, A., & Snaith, R. (1983) The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica,* Vol. 67, No. 6, pp.361-370, ISSN 0001-690X.



Chronic Obstructive Pulmonary Disease - Current Concepts and Practice

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A decade or so ago, many clinicians were described as having an unnecessarily 'nihilistic' view of COPD. This has certainly changed over the years... This open access book on COPD provides a platform for scientists and clinicians from around the world to present their knowledge of the disease and up-to-date scientific findings, and avails the reader to a multitude of topics: from recent discoveries in the basic sciences to state-of-the-art interventions on COPD. Management of patients with COPD challenges the whole gamut of Respiratory Medicine - necessarily pushing frontiers in pulmonary function (and exercise) testing, radiologic imaging, pharmaceuticals, chest physiotherapy, intensive care with respiratory therapy, bronchology and thoracic surgery. In addition, multi-disciplinary inputs from other specialty fields such as cardiology, neuro-psychiatry, geriatric medicine and palliative care are often necessary for the comprehensive management of COPD. The recent progress and a multi-disciplinary approach in dealing with COPD certainly bode well for the future. Nonetheless, the final goal and ultimate outcome is in improving the health status and survival of patients with COPD.

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Chapter 4

Neurocognitive Impairment as Systemic Effects of COPD

Cristian Oancea, Emanuela Tudorache and Voicu Tudorache

Additional information is available at the end of the chapter

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Abstract

Mild cognitive impairment (MCI), also known as incipient dementia, is characterized by the decline of cognitive function greater than expected for a certain age and educational level of the individual but not severe enough to interfere with their daily activities. However, this mild cognitive impairment affects several areas: visuospatial, memory, attention and fluency and it is a significant concern because it decreases the quality of life and treatment adherence of these patients. On the other hand, evidence suggests that individuals with Chronic obstructive pulmonary disease (COPD) also present an important risk of falls: 46% of these patients experience a fall/year, sometimes with fatal consequences. Standard clinical balance measures can predict the risk of falls in this population. Moreover, increased inflammatory biomarkers are associated with the decrease of cognitive functions and a higher risk of falls in this population. Patients with COPD have a higher balance and cognitive impairment than their healthy peers Therefore, it is important to identify, assess and understand the relevance of these comorbidities in order to characterize the full clinical spectrum of COPD and adjust prevention strategies, given the devastating consequences of these problems.

Keywords: balance, falls, dementia, cognition, COPD

1. Introduction

COPD is recognized as a disease with many systemic components [1]. Among them, the neuro-psychical component (anxiety/depression), has already been recognized. Besides this, in the last decade, research has been initiated on the neuromorphological substrate to explain whether certain manifestations such as cognition alteration, the occurrence of balance disorders, etc. could also be due to the impact of COPD, or would only be manifestations

related to age and/or other comorbidities. This paper presents an overview of the state of knowledge in this last field.

1.1. Summary

- Cognition – domain and modulating factors.
- Balance disorders: nosology, prevalence, clinical consequences.
- COPD: fundamental pathophysiological mechanisms susceptible to alter cerebral function.
- Clinical consequences of affected cognition; measure methods.
- Therapeutic implications; preventive strategies.

2. Cognition: domain and modulating factors

There are multiple classifications of cognition, of which that proposed by Dal Negro seems the most appropriate for the purpose of this chapter. According to that, its domains and subdomains are: (a) executional function with the subdomains: attention, problem solving, planning and reasoning; (b) language, with the subdomains: comprehension and verbal fluency; (c) memory, with the subdomains: memory-based tagging and work memory; (d) praxis, with the subdomains: motor-ideative, ideative and visual constructive [2].

The distinction between any cognitive impairment and mild cognitive impairment (MCI) should be clarified. The latter refers to a brain function syndrome involving the onset and evolution of cognitive impairments other than those age and education related, but that are not significant enough to interfere with daily activities [3]. To date (2017), one of the most comprehensive meta-analyses that have specifically investigated prevalence MCI in the context of COPD, included 23,116 people with COPD, and showed MCI prevalence of 25%, raising up to 32% if any cognitive impairment is assessed [4].

Compared to the prevalence of MCI in the general population, which is in the range of 10–20% in older adults, a rate of 25–32% present in patients with COPD is more than worrying [5].

But equally important is the relationship between the various cognitive domains affected in COPD patients and the disease itself. This is because the prevalence of impairment varies among the different cognitive domains. What is more, the psychometric profile impairment would be associated with the variable components of COPD such as hypoxemia, hypercapnia, lung function, exacerbations or disease severity.

Although one cannot speak about a specific profile encountered in “pure” COPD, that is, the one without comorbidities, the most frequently affected subdomains are attention, naming, visuospatial, memory, motor and executive function and mood decrements (fear and antinociception) [6–10].

We must be aware that COPD severity (hypoxemia/hypercapnia, pulmonary obstruction and exacerbations), factors typically present (age and smoking) as well as various combinations (comorbidities, education level, physical activity, nutritional status, etc.) make up in a complex mosaic. Assigning cognition alterations to the underlying disease (COPD), implies for this reason, an extremely laborious and unlikely effort to distinguish among these factors. An example, in a prospective study of 62 patients with COPD, it was possible to see how cognitive impairment varied depending on the stage of the disease: exacerbation, at discharge or when the stable phase was reached; unlike other studies, this research followed the same patient at all 3 different stages of his disease. Cognitive assessment was measured by Montreal cognitive assessment (MoCA) test. From exacerbation to stable COPD, all the clinical variables improved step-by-step: visual-constructional, attention, language, abstraction, delayed recall and orientation (from exacerbation to discharge), visual-constructional and naming (from discharge to stable phase) and taken as a whole, from exacerbation to stable COPD: naming, attention, language, abstraction and delayed recall [11].

Thus, differences in studies such as (a) various study designs and methodological limitations: lack of clinical assessment of airflow impairment, severity of COPD, heterogeneity of assessment moment (stable phase, exacerbation and long-term oxygen therapy [LTOT]), small sample size, lack of appropriate referent group, diagnostic criteria for cognitive impairment (psychometric tools and neuroimaging), (b) the use of different definition, (c) lack confounder adjustment procedures: comorbidities, age, active smokers, level of education, etc., may explain the wide range of prevalence rates of cognitive impairment in COPD from 5.5% up to 77% [12, 13].

2.1. Balance disorders: nosology, prevalence, clinical consequences

Chronic illnesses in general as the disease progresses develop debilitating features, and COPD is no exception. Age and other features may include lower limb muscle weakness, overall fatigue, dizziness, different functional impairment, body imbalance and others [14].

Among them we will refer to balance impairment, which can lead to the loss of coordination and implicitly to falls.

Involuntary falls are incidents that can occur at any age, more frequently in the elderly, with possible devastating consequences. Individuals aged over 65 would experience at least one fall per year [15]. In a prospective study, the incidence of falls was more than four times higher in patients with COPD, than in healthy individuals with respect to gender and age [16].

Due to comorbidities, elderly patients are often polymedicated: anxiolytics/sedatives, antihypertensives, corticosteroids, etc., medications that can be responsible for balance disturbances. According to a research conducted by Roig, the use of corticosteroid therapy in COPD population has been estimated to be ~61.5% for inhaled and ~8.3% for oral corticosteroids [17]. Corticosteroid therapy interferes with the production of contractile proteins (increase intracellular proteolysis) resulting in muscle weakness conducing to falls. Thus, in order to

relate falls to COPD we must exclude other confounders: polypharmacy, decreased vision, impaired mobility (arthrosis) and multiple other comorbidities.

Two other factors, such as sedentary life style and systemic inflammation, should not be neglected either: the former is almost constantly encountered and the latter in about 30% of cases [18].

Severe COPD stages as well as exacerbations are accompanied by an increased risk of falls [19].

Dispnoea, muscle mass loss (especially in the thighs) and decreased exercise endurance will reduce the ability of COPD patients to perform daily activities and limit their exercise tolerance, creating a downward spiral that will lead to generalized immobility [20].

Difficulties in achieving day-to-day activities and related instrumental activities contribute to a reduced quality of life, but in the event of falls, devastating effects may arise on global function and even on life expectancy. Except for a major physical trauma event, the disorder is resulting in loss of functional independence and social interaction.

Several studies have shown that the history of falls in the previous year is predictive of relapse [21].

Repeated falls will lead to insecurity, fear and lack of confidence in performing daily domestic activities. In a recent study, that included 93 patients with COPD, 32% had a degree of body balance impairment during the performance of dynamic activities, compared to 5% in the control group ($p = .0005$) [22].

Fear and lack of confidence in performing everyday domestic activities will develop a chronic status of loss of movement autonomy which can lead to muscle deconditioning, higher global fatigue and greater loss of body balance. As a consequence, the adherence to treatment will decrease, especially to rehabilitation programs [19].

The most common used tests are: the Berg Balance Scale (BBS), Falls Efficacy Scale-International (FES-I), Timed Up and Go (TUG), single-leg stance test (SLS) and activities balance confidence (ABC).

Studies that tried to ascertain whether there is a correlation between COPD phenotypes and nutritional status have generated contradictory results. Some of them have found that the cachectic/emphysematous phenotype would be more prone to falls, considering that loss of skeletal muscle and weakness would be the main cause [23]. Others, by contrast, mention that the bronchitis/obese phenotype would have a higher risk of falls, due to the fact that the obese patients would record the intensity of fear more than the cachectic phenotype [24].

The overall conclusion is that patients with COPD have greater balance impairment than their healthy peers.

2.2. COPD: fundamental pathophysiological mechanisms susceptible to alter cerebral function

Cognitive impairment is multifactorial, but a history of cigarette smoking, aging and educational level are recognized as major determinants [25, 26]. The origin of the cerebral dysfunction

in patients with COPD is still unknown, assuming the interference of several pathological relays: hypoxemia, oxidative stress, systemic inflammation, smoking, comorbidities, vascular-mediated brain pathology, neurotransmitter metabolism in the central nervous system (CNS), a decrease in physical functioning, genetic and epigenetic factors.

Hypoxia. In 1919, Haldane had a deep insight: "partial anoxia means not an appreciable slowing of life, but progressive, and perhaps irreparable damage to human structure." This "irreparable damage to human structure" can also include brain damage [27]. After half a century, Krop and colleagues observed the neuropsychological benefits of continuous oxygen therapy in COPD [28]. However, the first major randomized clinical trial (Nocturnal Oxygen Therapy Trials – NOTT), appeared in 1980, when the effects of continuous or nocturnal oxygen therapy on hypoxemic in COPD were investigated [29]. After the re-examination of the NOTT, it was possible to see that 42% of patients with COPD had moderate-to-severe cognitive impairment compared to 14% among controls [30]. In a follow-up of the NOTT cohort, it was observed that the neuropsychological deficit parallels the degree of hypoxia: 27% of those with mild hypoxemia to 62% in those with severe hypoxemia [31].

It is worthwhile discussing the mechanisms of response of the brain to hypoxemia. There is a very interesting mechanism for counteracting cerebral hypoxemia, the so-called cerebrovascular oxygen reactivity, which ensures blood flow up to 200% in the conditions of oxygen desaturation produced by chronic hypoxemia, nocturnal or exercise induced. For this reason, cerebral blood flow is much higher in hypoxemic than in non-hypoxemic COPD patients and even healthy controls [32, 33]. The same mechanism also explains that during rapid eye movement (REM) sleep, which accounts for about 13% of total sleep time in COPD patients, there is no cerebral hypoxemia. Surprisingly, during nonrapid eye movement (NREM) sleep, it is not known why, cerebrovascular oxygen reactivity is missing [34].

Nocturnal desaturation events are commonly met in 38–70% non-hypoxemic COPD patients [35]. Under these conditions, when the cerebrovascular oxygen reactivity mechanism is inoperative, the effect of night-time desaturation should injure the central nervous system (CNS). This was also the goal of a study of 115 non-hypoxemic COPD patients grades 2 and 3, without sleep apnoea, to which it was dosed a serum surrogate marker, namely S100B (a calcium binding protein produced in brain damage), and at the same time neuromuscular function via motor cortex activation and excitability and maximal voluntary quadriceps strength measurement was assessed. Absence of cerebrovascular reactivity would be the mechanism leading to brain injury formation during NREM sleep desaturations, which was found in approximately 50% of non-hypoxemic COPD patients [36].

The effort in daily activities would be likely to cause brain damage in severe COPD hypoxemic patients; emphasizing desaturations, inducing increase of frontal lobes choline (which is a reliable marker of myelin destruction with alteration of neuronal membrane turnover) corresponding to white matter hyperintensities on magnetic resonance imaging (MRI) [7].

In a study that enrolled younger patients (45–65 years) with COPD, low baseline oxygen saturation (≤88%) was strongly related to cognitive impairment (adjusted OR = 5.45). But what is more relevant is that in the same study, regular use of supplemental oxygen therapy in home setting

decreased the risk for cognitive impairment (OR = 0.14; $P < 0.0001$) [37]. It is a recognized fact that long-term oxygen therapy (LTOT) is able to protect significantly ($p < 0.022$) the cognitive functions from COPD-induced deterioration. Another fact is that the patients with mild cognitive impairment COPD induced are unaware of the risk that involves repetitive desaturations to produce conversion from mild cognitive impairment to dementia, if nothing is done with LTOT [38, 39].

Therefore, continuous or even intermittent hypoxia (efforts, daily activities and sleep) may cause changes in brain perfusion, transient deficits in neurotransmitter metabolism in the central nervous system with changes in brain neurochemistry and structure [7, 36, 40–42].

Although hypoxia is *per se* a damaging factor, it mostly acts in an additive manner in the development of structural abnormalities in the brain [43].

Chronic systemic inflammation. Inflammation as a driving force to the central pathology of the disease, in very recent years has been subjected to doubts and contestations [44]. Even in the definition of COPD, GOLD 2017 no longer mentions the contribution of chronic inflammation to the pathophysiological process [1].

However, patients with COPD, particularly when the disease is severe and during exacerbations have evidence of systemic inflammation: increased circulating cytokine, chemokine, and acute-phase protein levels or abnormalities in circulating cells. These mediators are derived from inflammatory and structural cells in the lung and interact with each other in a complex manner. Similar mediators that are found in the lungs of patients with COPD might also be increased in the circulation, presumed reached here through translocation or "spill-over"; this chronic low-grade systemic inflammation could underlie and potentiate comorbidities (muscle wasting/cachexia, cardiovascular diseases, osteoporosis, etc.) including central nervous system impairment [45, 46]. The chronic inflammatory status may contribute to vessel wall changes (endothelial dysfunction, stiffening of arteries and arterioles and impaired vascular reactivity) and may also have neurotoxic effects: synaptic dysfunction and neural cell apoptosis [46–49].

The inflammed endothelium overexpresses surface adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1), facilitating the adherence of white blood cells to damaged endothelial surfaces. Interleukin 6 (IL-6) can stimulate the release of acute-phase proteins by hepatocytes, including C-reactive protein (CRP), serum amyloid A, fibrinogen and procoagulant factors, which further promote or amplify the inflammatory process [50]. Moreover, CRP fosters the uptake of low-density lipoproteins (LDL) by macrophages, which contribute to the increased prevalence of arterial plaques containing a lipid core in patients with COPD [51]. Accelerated atherogenesis and impaired endothelial function, caused by a vascular inflammation status is assumed to lead to microvascular dysfunction and cerebral small vessel disease (microbleeds and lacunar infarcts) having as a consequence cognitive and functional impairment [52].

On the other hand, COPD is frequently associated with cardiovascular diseases, obesity or metabolic syndrome, the contribution of comorbidities into the systemic elevation of IL-6

levels is difficult to disentangle. Some authors described an inflammatory-prone COPD phenotype, patients with an increased risk of exacerbations (OR = 3.7) and simultaneously more severe cardiovascular and cerebral abnormalities [53, 54].

Acute exacerbations of COPD. These patients had significantly poorer cognitive function compared with control participants 3 months after discharge from hospital [55]. During a severe exacerbation, in the context of hypoxemia, paroxysmal inflammation (increased platelet activity and coagulation) and a pre-existing endothelial dysfunction, plaque rupture can occur and consequences will be coronary obstruction and stroke. However, other studies have shown that cognitive impairment during the exacerbation period recovers during periods of stability [56].

Smoking. Smoking has pleiotropic disastrous effects: promotes atherosclerosis (endothelial changes), direct effect of neurotoxicity (heavy metal, nicotine and constituents of smoke), exacerbates hypoxia brain due to chronically elevated carbon monoxide causing a left shift of the oxyhaemoglobin dissociation curve, deteriorates lung function, favors the development of comorbidities which have a negative effect on cognitive processes. Chronic smoking is also involved in the production of pathogenic changes (decrease in the gray matter density) in areas where Alzheimer's disease develops (inferior parietal lobule and precuneus). Moreover, its deleterious action can continue even after smoking cessation [57–59].

Comorbidities. It is a recognized fact that general morbidity and the burden of disease increases with both age and cumulative pathology, and COPD is no exception.

In a study of 52 stable non-hypoxic COPD patients, Ersel Dag et al., found that subjects with better functional capacity and lower comorbidity had better cognitive function; according to this study, the MoCA would be superior to Mini Mental Status Examination (MMSE) in detecting cognitive decline [60]. A higher Charlson Comorbidity Index and a reduced functional level have induced cognitive decline; this is also the conclusion of another similar study with 1 year follow-up of patients with COPD, which at baseline hospitalization lacked cognitive impairment [61]. Cleutjens et al. in a cross-sectional observational study on 90 stable COPD patients compared to 90 matched non-COPD controls, analyzed general cognitive impairment and domain-specific cognitive impairment using a complex battery of 6 psychometric tests, after correction for comorbidities using multivariate linear and logistic regression models. They found a prevalence rate of 56.7% for general cognitive impairment, which meant four times higher compared to matched non-COPD controls. The most prevalent affected domains were planning and cognitive flexibility, where abnormal planning was observed in 16.7% of patients without comorbidities but in none of the controls without comorbidities, and abnormal cognitive flexibility was observed in 44.4 and 11.6% of patients and controls without comorbidities, respectively [9].

Diseases accompanied by hypoxemia and vascular damage (coronary heart disease, cardiac failure, hypertension and stroke) have a proven risk of developing neural damage that is amplified if active smoking is also associated [4].

Another comorbidity present in over 20% of COPD cases is Obstructive Sleep Apnoea Syndrome (OSAS), a disease that underlies many common pathological pathways. Through recurrent hypoxia, moderate–severe forms of OSAS are able to affect cognitive performance, especially by focusing on attention, complex thinking, learning and memory [62, 63].

Depression and anxiety are among the most common comorbidities of COPD, reaching over 70% in oxygen-dependent cases, and much more important is that onset of depression was predictive of cognitive decline among COPD patients [64].

COPD was associated with baseline and incident disability which progresses over time and cognitive impairment was found to have an additive effect on this disability [64–66].

Therefore, cognitive comorbidities may contribute to a substantial burden of COPD-related morbidity, especially by impairing quality of life, reducing physical activity, reducing adherence to treatment and increasing the frequency of hospital admission.

Oxidative stress. An increase in the level of reactive oxygen species (oxygen ions, free radicals and peroxides) leads to oxidative stress, which would alter the neuronal signals that produce neuro-inflammation with neuro-degeneration and implicitly with cognitive impairment [67]. The most important triggers for the development of oxidative stress in patients with COPD are cigarette smoke and systemic inflammation.

Other possible mechanisms. In a highly laborious study in 55 patients with moderate-severe COPD in stable period were determined: (i) cognitive ability (through a battery of 6 psychometric tests), (ii) structural brain abnormalities using 3T MRI to seek signs of small vessels disease (white matter hyperintensities, lacunes, cerebral microbleeds and enlarged perivascular spaces) and (iii) hippocampal volume as an area involved in memory process. The 55 patients were divided into 2 subgroups, cognitively high (25 patients) and low-performing (30 patients), having comparable demographics, clinical characteristics and comorbidities. No structural changes were found between COPD patients with low or high cognitive performance, demonstrating that small vessels disease would not represent a pathological pathway [68]. On the contrary, other authors provided evidence of significant white and gray matter abnormalities associated with cognitive dysfunction in patients with COPD without arterial hypoxemia or hypercapnia. Given the paucity in current evidence, more research is needed to evaluate the impact of cerebral small vessel disease on stroke and cognitive functioning in patients with COPD [69, 70].

Mitochondria are the intracellular organelles that provide aerobic respiration and cellular energy. As a result, mitochondrial diseases have as expression and localization the most oxygen-consuming tissues: skeletal muscles, central nervous system and heart. Depending on the load of mutant mitochondrial genomes, neurological expression ranges from mild cognitive impairment to dementia, or epilepsy, stroke-like episodes, ataxia, etc. In COPD, there are approximately 20% of cachexia cases in which a mitochondrial component might be involved [71, 72].

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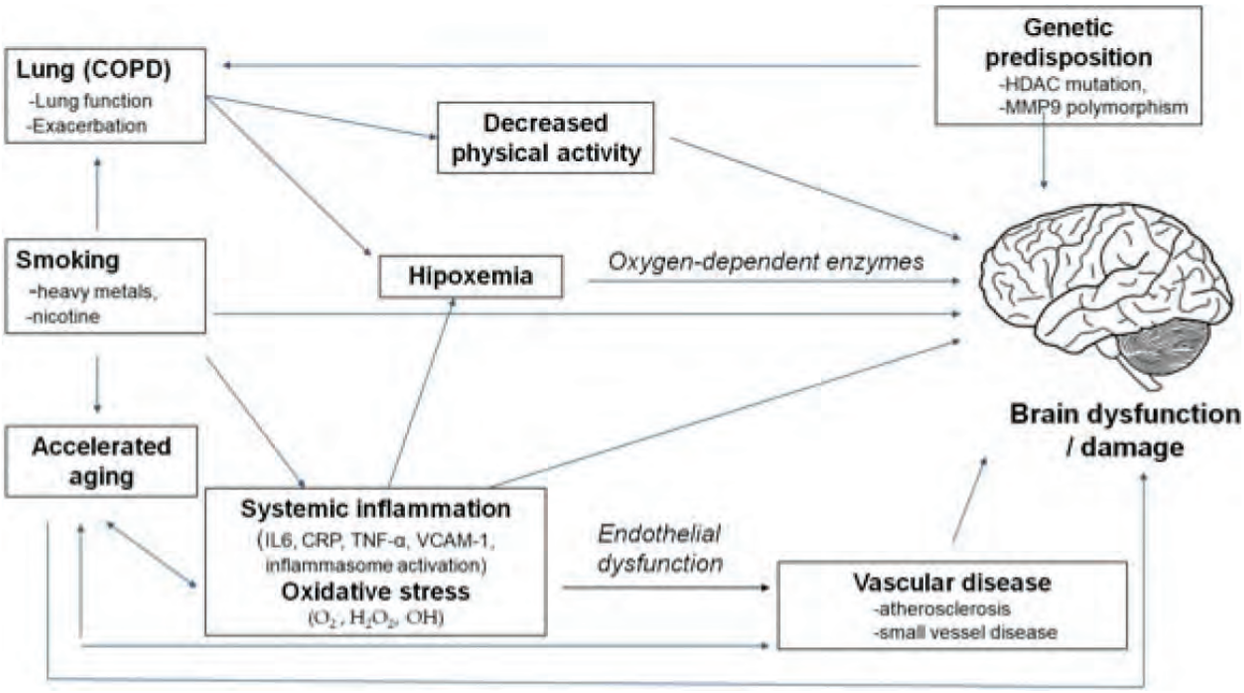

Figure 1. Potential mechanisms contributing to brain dysfunction and/or damage in elderly subjects with COPD. HDAC: histone deacetylase, MMP9: matrix metalloproteinase 9, IL-6: interleukin 6, CRP: C-reactive protein, TNF-α: tumor necrosis factor, VCAM-1: vascular cell adhesion molecule-1.

Many factors, generated by, or interconnected with COPD, could contribute to brain dysfunction and/or damage (**Figure 1**).

2.3. Clinical consequences of an affected cognition; measure methods

In order to diagnose MCI, besides the clinical and anamnestic examination, psychometric tests as well as neurochemistry and neuroimaging assessment are available.

Torres-Sánchez et al., in their meta-analysis listed more than 40 psychometric tests that were used [73]. The most used psychometric questionnaires are: the Mini Mental Status Examination (MMSE), the Clock Drawing test, the Trail Making test (TMT) A, the TMT B, Memory Impairment Screen (MIS); Montreal Cognitive Assessment test (MoCA) [74]. It is advisable to use a battery of tests, not a single one, to improve the result accuracy [75, 76].

Neuroimaging studies showed there are significantly lowered gray matter volumes in several brain regions as hippocamp [7], limbic and paralimbic structures [77], precuneus, bilateral calcarine, right superior temporal gyrus/middle temporal gyrus, bilateral fusiform, right inferior parietal lobule [78], cingulate and amygdala [8], dorsolateral prefrontal cortex [77] etc., evidenced by different neuroimaging techniques based on magnetic resonance imaging (MRI). Performance accuracy has increased by introducing voxel-based morphometry analysis also based on MRI. Using this technique, it was possible to show for the first

time gray matter volume alterations in stable COPD patients, even to those with subclinical cognitive impairment [79].

Passing over the slight contradictions or discrepancies between the results offered by these and other neuroimaging studies, what is common is heterogeneity and broad distribution of the lesions. Another important finding of neuroimaging studies is inferior parietal lobule and precuneus that are two regions altered also in COPD and Alzheimer disease.

Chronic airway involvement can be perceived as a strong aging factor leading to an early deterioration of cognition with a 10–15 years advanced age [2]. In a study on 301 stable moderate-severe COPD patients conducted by Schure et al. showed that cognitive functioning (especially, psychomotor speed and executive control) present in approximately 30% of cases would be associated with greater disease severity and poorer physical functioning (as measured by the six-minute walk test, total steps per day and grip strength). And these results are more relevant as patients were "healthier" COPD, namely the patients without comorbidities known underlying inflammation (Charlson Index = 0.9–1.2) [80].

Due to the non-homogeneous distribution on the brain mapping, patients will experience various and multiple disorders, most of which are reflected by difficulties in naming, memory, visuospatial, executive function and mood decrements.

COPD-related dyspnoea is a strong driver to anxiety, panic or/and depression and reduced quality of life. But, development of a secondary cognitive impairment component may contribute to increased behavioral disturbances; these may distress much more the family caregivers which need to cope with behavioral changes.

In a study on 88 patients with COPD, Turan et al. showed a positive correlation between declining of cognitive function, assessed by MMSE questionnaire, and suboptimal inhalation adherence, increasing hospitalizations and emergency visits [81]. In another study of 265 patients with COPD, adherence was measured using a tool incorporating sophisticated electronic devices to mark time and correctness of the technique; adherence over the study was 22.9% of what would be expected if all the doses had been taken correctly and on time, but more important adherence was negatively influenced by impairment in cognitive function [82].

According to statistics, 41% of patients with stable COPD who undergo rehabilitation would suffer from any cognitive impairment. Inclusion and completion of a pulmonary rehabilitation program is however affected by the presence of cognitive impairment, the drop-out number being higher in those with cognitive impairment. However, the comparison of the different parameters (functional status, health status and psychological well-being) to the patients able to complete the program does not differ between cognitive impairment patients and those with no cognitive impairment, this being an argument that patients suffering from cognitive impairment can benefit from the programs rehabilitation [83]. Do not forget to investigate factors related to balance changes in patients with COPD. Although the risk of falls may seem less important than the consequences of COPD itself, falls are associated with increased mortality, reduced independence, poorer quality of life and lower level of physical activity.

Depression and anxiety are found in high proportions (30–70%) and identifying the coping styles in patients with COPD represent an important aspect of the individualized treatment of the patient, because the coping style can be both adaptive, implying the stress reduction and maladaptive, situation in which the maintenance and the amplification of the current symptomatology are present or can determine the appearance of some new symptomatic elements and behaviors [84].

The fact that cognitive impairment would occur at younger age [2], would cross a subclinical period [79] and would present at least 30% of cases [80], all of which signals us that cognitive impairment may be an early indicator of emerging risk of frailty and poor overall mental functioning among COPD patients.

Cognitive impairment has also been reported to worsen over time due to both the aggravation of COPD and the increase in burden represented by the progression and/or complications of comorbidities [85]. Chang et al. reported that the co-occurrence of COPD and cognitive impairment in a 3-year prospective study was associated with increased rate of disability, hospital admission and mortality [86].

3. Therapeutic implications; preventive strategies

How to deal with a COPD patient who might be suffering from cognitive impairment? Based on growing evidence in recent years, it is reasonable that cognitive assessment in subjects suffering from chronic obstructive disease should enter the routine of diagnostic procedures to grade the overall impact of patients' respiratory condition. Multiple areas of cognition being altered in varying degrees, may explain a poor awareness of the disease and may compromise the individual's ability to manage his or her own care and adherence to treatment. The clinician, who observes signs of forgetfulness, disorientation or balance trouble and/or even poor adherence to medical treatment, should prompt to conduct further assessments using screening tools (e.g. MMSE score).

Addressing comorbidities. The number of comorbidities increases with age progression. Specific attention must be focused on so-called cognitive comorbidities. They relate in particular to cardiovascular diseases, cerebrovascular diseases, diabetes mellitus and OSAS. These should be treated according to current guidelines.

Pulmonary rehabilitation. Balance training and fall prevention strategies are not included in international guidelines for PR, and very few programs include standardized balance assessment. Although exercise can improve balance and decrease fall risk in older adults, interventions that include exercise to challenge balance have greater effects on fall risk and balance. Physical exercise training involving balance, strength training, movement speed and coordination has improved balance and frailty markers in multiple randomized and nonrandomized studies [87, 88]. Past cross-sectional research has provided support for the hypothesis that greater levels of aerobic fitness may be associated with a lessening of the normal age-related declines in cognitive functioning [89, 90]. It is conceivable that improvements in

cognitive functions such as executive function might help to improve self-management skills and potentially assist in sustaining the other substantial benefits of pulmonary rehabilitation.

Cognitive training. Given the increased prevalence of cognitive impairment in COPD and potentially devastating effects, a structured assessment of cognitive function should be implemented as a routine component of the evaluation of COPD patients. Those identified with a screening tool as possibly having MCI should be referred for further assessment to a psychiatrist. Identifying the coping styles in patients with COPD represents an important aspect of the individualized treatment of the patient. Interventions aiming at enhancing the problem- or emotion-focused coping may improve COPD prognosis [91].

Oxygen therapy: to whom? when? There is debate whether screening for cognitive impairment should be routinely applied. From the point of view of the hypoxemia approach, the answer to this debate will have to consider the evidence: (1) one in four people with COPD have cognitive impairment and over time, cognitive decline will deepen (risking an evolution toward multi-infarct dementia or Alzheimer disease) [92–94]. (2) It is now recognized that not only continuous, but also intermittent hypoxia (efforts, daily activities and sleep) can by repetition cause changes in brain neurochemistry and structure [7, 36]. (3) Cognitive impairment goes along with the severity of COPD, age and type/number of cognitive comorbidities. (4) Regular use of supplemental oxygen therapy has been shown to decrease the risk for cognitive impairment in patients with COPD [37, 38, 95].

Therefore, even the detection of intermittent desaturation (effort, daily activity and sleep), will have to lead to establishing earlier oxygen supplementation in order to prevent irreversible brain damage.

4. Conclusions

At least 40% of COPD patients present irreversible neuronal damage or dysfunction that is separate from other comorbidities. That is why cognitive impairment has to be listed in the first line of extrathoracic manifestations. Not identifying cognitive impairment we miss the fact that this condition may be a precursor to develop dementia in about a third of cases, or even higher in the context of COPD associated with other comorbidities. Cognitive impairment has been shown to increase the risk of hospitalization, disability and death. Hypoxemia is a serious problem that, even under the conditions of intermittent occurrence, should be sanctioned as early as possible by establishing LTOT. Besides oxygen therapy, the most effective therapeutic actions and strategies to these particular populations include: addressing comorbidities, pulmonary rehabilitation and cognitive training.

Author details

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References

[1] Global Initiative for Chronic Obstructive Lung Disease, 2017. http://goldcopd.org/wp-content/uploads/2016/12/wms-GOLD-2017-Pocket-Guide.pdf page.2

[2] Roberto W, Negro D, Bonadiman L, Tognella S, et al. Extent and prevalence of cognitive dysfunction in chronic obstructive pulmonary disease, chronic non-obstructive bronchitis, and in asymptomatic smokers, compared to normal reference values. International Journal of COPD. 2014;**9**:675-683

[3] Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: Clinical characterization and outcome. Archives of Neurology. 1999;**56**:303-308

[4] Yohannes AM, Chen W, Moga AM, et al. Cognitive impairment in chronic obstructive pulmonary disease and chronic heart failure: A systematic review and meta-analysis of observational studies. JAMDA. May 1;**18**(5):451.e1-451.e11

[5] Langa KM, Levine DA. The diagnosis and management of mild cognitive impairment. A clinical review. JAMA. 2014;**32**:2551-2561

[6] Dodd JW, Getov SV, Jones PW. Cognitive function in COPD. The European Respiratory Journal. 2010;**35**:913-922

[7] Borson S, Scanlan J, Friedman S, et al. Modeling the impact of COPD on the brain. International Journal of COPD. 2008;**3**(3):429-434

[8] Roland W, Esser M, Stoeckel C, Kirsten A, et al. Structural brain changes in patients with COPD. Chest. 2016;**149**(2):426-434

[9] Cleutjens FAHM, Franssen FME, Spruit MA, et al. Domain-specific cognitive impairment in patients with COPD and control subjects. International Journal of COPD. 2017;**12**:1-11

[10] Kuo HK, Jones RN, Milberg WP, et al. Effect of blood pressure and diabetes mellitus on cognitive and physical functions in older adults: A longitudinal analysis of the advanced cognitive training for independent and vital elderly cohort. Journal of the American Geriatrics Society. 2005;**53**:1154-1161

[11] López-Torres I, Valenza MC, Torres-Sánchez I, et al. Changes in cognitive status in COPD patients across clinical stages. COPD: Journal of Chronic Obstructive Pulmonary Disease. Dec 2015;14 Jun;**13**(3):327-32. DOI: 10.3109/15412555.2015.1081883

[12] Thakur N, Blanc PD, Julian LJ, et al. COPD and cognitive impairment: The role of hypoxemia and oxygen therapy. International Journal of Chronic Obstructive Pulmonary Disease. 2010;**5**:263-269

[13] Grant I, Heaton RK, McSweeny AJ, Adams KM, Timms RM. Neuropsychologic findings in hypoxemic chronic obstructive pulmonary disease. Archives of Internal Medicine. 1982;**142**(8):1470-1476

[14] Tudorache E, Oancea C, Avram C, et al. Balance impairment and systemic inflammation in chronic obstructive pulmonary disease. International Journal of COPD. 2015;**10**:1847-1852

[15] Rubenstein LZ. Falls in older people: Epidemiology, risk factors and strategies for prevention. Age and Ageing. 2006;**35**:37-41

[16] Roig M, Eng JJ, MacIntyre DL, et al. Falls in people with chronic obstructive pulmonary disease: An observational cohort study. Respiratory Medicine. 2011;**105**(3):461-469

[17] Roig M, Eng JJ, MacIntyre DL, Road JD. Falls in patients with chronic obstructive pulmonary disease: A call for further research. Respiratory Medicine. 2009;**103**(9):1257-1269

[18] Agusti A, Calverley PM, Celli B, et al., Evaluation of COPD longitudinally to identify predictive surrogate endpoints (ECLIPSE) investigators. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respiratory Research. 2010, Sep 10;**11**:122. DOI: 10.1186/1465-9921-11-122

[19] Crişan AF, Oancea C, Timar B, Fira-Mladinescu O, Tudorache V. Balance impairment in patients with COPD. PloS One. 2015 March; 13;**10**(3):e0120573

[20] Wouters EF. Chronic obstructive pulmonary disease. 5: Systemic effects of COPD. Thorax. 2002;**57**:1067-1070

[21] Beauchamp MK, Hill K, Goldstein RS, et al. Impairments in balance discriminate fallers from non-fallers in COPD. Chest. 2012;**141**(6):1496-1503

[22] Porto EF, Pradella CO, Rocco CM, et al. Comparative postural control in COPD patients and healthy individuals during dynamic and static activities. Journal of Cardiopulmonary Rehabilitation and Prevention. 2017;**37**:139-145

[23] Ko S, Stenholm S, Ferrucci L. Characteristic gait patterns in older adults with obesity – Results from the Baltimore longitudinal study of aging. Journal of Biomechanics. 2010;**43**:1104-1110

[24] Voica AS, Oancea C, Tudorache E, et al. Chronic obstructive pulmonary disease phenotypes and balance impairment. International Journal of COPD. 2016;**11**:919-925

[25] Barnes JN. Exercise, cognitive function, and aging. Advances in Physiology Education. 2015;**39**(2):55-62

[26] Roncero C, Campuzano AI, Quintano JA, et al. Cognitive status among patients with chronic obstructive pulmonary disease. International Journal of COPD. 2016;**11**:543-551

[27] Haldane JS. Symptoms, causes, and prevention of anoxemia (Insufficient Supply of Oxygen to the Tissues), and the value of oxygen in its treatment. British Medical Journal. Jul 19;**2**(3055):65-72

[28] Krop HD, Block AJ, Cohen E. Neuropsychologic effects of continuous oxygen therapy in chronic obstructive pulmonary disease. Chest. 1973;**64**:317-322

[29] Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. Annals of Internal Medicine. 1980;**93**:391-398

[30] Heaton RK, Grant I, McSweeny AJ, et al. Psychologic effects of continuous and nocturnal oxygen therapy in hypoxemic chronic obstructive pulmonary disease. Archives of Internal Medicine. 1983;**143**(10):1941-1947

[31] Grant I, Prigatano GP, Heaton RK, et al. Progressive neuropsychologic impairment and hypoxemia. Relationship in chronic obstructive pulmonary disease. Archives of General Psychiatry. 1987;**44**:999-1006

[32] Albayrak R, Fidan F, Unlu M, et al. Extracranial carotid Dopplerultrasound evaluation of cerebral blood flow volume in COPD patients. Respiratory Medicine. 2006;**100**:1826-1833

[33] Yildiz S, Kaya I, Cece H, et al. Impact of COPD exacerbation on cerebral blood flow. Clinical Imaging. 2012;**36**:185-190

[34] Meadows GE, O'Driscoll DM, Simonds AK, et al. Cerebral blood flow response to isocapnic hypoxia during slow-wave sleep and wakefulness. Journal of Applied Physiology. 2004;**97**:1343-1348

[35] Lacasse Y, Series F, Vujovic-Zotovic N, et al. Evaluating nocturnal oxygen desaturation in COPD--revised. Respiratory Medicine. 2011;**105**:1331-1337

[36] Alexandre F, Heraud N, Sanchez AMJ, et al. Brain damage and motor cortex impairment in chronic obstructive pulmonary disease: Implication of nonrapid eye movement SLEEP desaturation. Sleep. 2016;**39**(2):327-35

[37] Thakur N, Blanc PD, Julian LJ, et al. COPD and cognitive impairment: The role of hypoxemia and oxygen therapy. International Journal of Chronic Obstructive Pulmonary Disease. 2010;**5**:263-269

[38] Karamanli H, Ilik F, Kayhan F, et al. Assessment of cognitive impairment in long-term oxygen therapy-dependent COPD patients. International Journal of COPD. 2015;**10**:2087-2094

[39] Dal Negro RW, Bonadiman L, Bricolo FP, Tognella S, Turco P. Cognitive dysfunction in severe chronic obstructive pulmonary disease (COPD) with or without long-term oxygen therapy (LTOT). Multidisciplinary Respiratory Medicine. 2015 Apr 19;**10**(1):17

[40] Ortapamuk H, Naldoken S. Brain perfusion abnormalities in chronic obstructive pulmonary disease: Comparison with cognitive impairment. Annals of Nuclear Medicine. 2006;**20**(2):99-106

[41] Gibson GE, Pulsinelli W, Blass JP, Duffy TE. Brain dysfunction in mild to moderate hypoxia. The American Journal of Medicine. 1981;**70**(6):1247-1254

[42] Maccioni RB, Rojo LE, Fernandez JA, Kuljis RO. The role of neuroimmunomodulation in Alzheimer's disease. Annals of the New York Academy of Sciences. 2009;**1153**:240-246

[43] Huppert FA. Memory impairment associated with chronic hypoxia. Thorax. 1982;**37**(11):858-860

[44] Eapen MS, Myers S, Walters EH, et al. Airway inflammation in chronic obstructive pulmonary diseases: a true paradox. Expert Review of Respiratory Medicine. DOI: 10.1080/17476348.2017.1360769

[45] Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. The European Respiratory Journal. 2009;**33**:1165-1185

[46] Barnes PJ. Mechanisms of allergic diseases. The Journal of Allergy and Clinical Immunology. 2016;**138**:16-27

[47] Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: A systematic review and a meta-analysis. Thorax. 2004;**59**(7):574-580

[48] Su B, Liu T, Fan H, et al. Inflammatory markers and the risk of chronic obstructive pulmonary disease: A systematic review and meta-analysis. PloS One. 2016;**11**:e0150586

[49] Gorska-Ciebiada M, Saryusz-Wolska M, Borkowska A, et al. Serum levels of inflammatory markers in depressed elderly patients with diabetes and mild cognitive impairment. PloS One. 2015;**10**:e0120433

[50] Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: Role ofncomorbidities. The European Respiratory Journal. 2006;**28**(6):1245-1257

[51] Sin DD, MacNee W. Chronic obstructive pulmonary disease and cardiovascular diseases: A "vulnerable" relationship. American Journal of Respiratory and Critical Care Medicine. 2013;**187**(1):2-4

[52] Lahousse L, Q. van den Bouwhuijsen, D.W. Loth, et al., Chronic obstructive pulmonary disease and lipid core carotid artery plaques in the elderly: The rotterdam study, American Journal of Respiratory and Critical Care Medicine. 2013;**187**(1):58-64

[53] Agusti A et al. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: A novel phenotype. PloS One. 2012;**7**(5):e37483

[54] Thomson M, Ingebrigtsen TS, Marrot JL, et al. Inflammatory biomarkers and exacerbations in COPD. JAMA. June, 12, 2013;**309**(22):2353-61

[55] Dodd JW, Charlton RA, van den Broek MD, Jones PW. Cognitive dysfunction in patients hospitalized with acute exacerbation of COPD. Chest 2013;**144**(1):119-127

[56] Ambrosino N, Bruletti G, Scala V, et al. Cognitive and perceived health status in patient with chronic obstructive pulmonary disease surviving acute on chronic respiratory failure: A controlled study. Intensive Care Medicine. 2002;**28**(2):170-177

[57] Krueger CE, Dean DL, Rosen HJ, et al. Longitudinal rates of lobar atrophy in frontotemporal dementia, semantic dementia, and Alzheimer's disease. Alzheimer Disease and Associated Disorders. 2010;**24**:43-48

[58] Jan Ankersmit H, Nickl S, Hoeltl E, et al. Increased serum levels of HSP27 as a marker for incipient chronic obstructive pulmonary disease in young smokers. Respiration. 2012;**83**:391-399

[59] Lahousse L, Tiemeier H, Ikram MA, Brusselle GG. Chronic obstructive pulmonary disease and cerebrovascular disease: A comprehensive review. Respiratory Medicine. 2015;**109**:1371-1380

[60] Dag E, Bulcun E, Turkel Y, et al. Factors influencing cognitive function in subjects with COPD. Respiratory Care. 01, March 2016; DOI: 10.4187/respcare.04403

[61] Helvik AS, Selbæk G, Engedal K. Cognitive decline one year after hospitalization in older adults without dementia. Dementia and Geriatric Cognitive Disorders. 2012;**34**(3):198-205

[62] Fletcher EC. Chronic lung disease in the sleep apnea syndrome. Lung. 1990;**168**:751-761

[63] Engleman HM, Douglas NJ. Sleep 4: Sleepiness, cognitive function, and quality of life in obstructive sleep apnoea/hypopnoea syndrome. Thorax. 2004;**59**:618-662

[64] Incalzi RA, Chiappini F. Fuso, et al., predicting cognitive decline in patients with hypoxaemic COPD. Respiratory Medicine. 1998;**92**(3):527-533

[65] Martinez C, Richardson C, Han M, Cigolle C, et al. Chronic obstructive pulmonary disease, cognitive impairment, and development of disability: The health and retirement study. Annals of the American Thoracic Society. 2014;**11**:1362-1370

[66] Pedone C et al. Drawing impairment predicts mortality in severe COPD. Chest. 2006; **130**(6):1687-1694

[67] Popa-Wagner A, Mitran S, Sivanesan S, et al. ROS and brain diseases: The good, the bad, and the ugly. Oxidative Medicine and Cellular Longevity. 2013;**963520**. DOI: 10.1155/2013/963520

[68] Cleutjens FAHM, Ponds RWHM, Spruit MA, et al. The Relationship between Cerebral Small Vessel Disease, Hippocampal Volume and Cognitive Functioning in Patients with COPD: An MRI Study. Frontiers in Aging Neuroscience. 1 March 2017;**9**(88):1-9. DOI: 10.3389/fnagi.2017.00088

[69] Pantoni L. Cerebral small vessel disease: From pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurology. 2010;**9**(7):689-701

[70] Cai Z, Wang C, He W, Tu H, Tang Z, Xiao M, et al. Cerebral small vessel disease and Alzheimer's disease. Clinical Interventions in Aging. 2015;**10**:1695-1704

[71] Mancuso M, Calsolaro V, Orsucci D, et al. Mitochondria, cognitive impairment, and Alzheimer's disease. International Journal of Alzheimer's Disease. 2009;**2009**(951548). DOI: 10.4061/2009/951548

[72] Cielen N, Maes K, Gayan-Ramirez G. Musculoskeletal disorders in chronic obstructive pulmonary disease. BioMed Research International. 2014;**2014**(965764):1-17. DOI: 10.1155/2014/965764

[73] Torres-Sánchez I, Rodríguez-Alzueta E, Cabrera-Martos I, et al. Cognitive impairment in COPD: A systematic review. Jornal Brasileiro de Pneumologia. 2015;**41**(2):182-190

[74] Crisan AF, Oancea C, Timar B, Fira-Mladinescu O, Crisan A, Tudorache V. Cognitive Impairment in Chronic Obstructive Pulmonary Disease. PloS One. July 2014;**9**(7): e102468. DOI: 10.1371/journal.pone.0102468

[75] Trzepacz PT, Hochstetler H, Wang S, et al. Alzheimer's Disease Neuroimaging Initiative. Relationship between the Montreal cognitive assessment and Mini mental state examination for assessment of mild cognitive impairment in older adults. BMC Geriatrics. 2015;**15**:107

[76] Cameron J, Worrall-Carter L, Page K, et al. Screening for mild cognitive impairment in patients with heart failure: Montreal Cognitive Assessment versus Mini Mental State Exam. European Journal of Cardiovascular Nursing. 2013;**12**:252-260

[77] Zhang H, Wang X, Lin J, et al. Reduced regional gray matter volume in patients with chronic obstructive pulmonary disease: A voxel-based morphometry study. American Journal of Neuroradiology. 2013;**34**:334-339

[78] Wang C, Ding Y, Shen B, et al. Altered Gray matter volume in stable chronic obstructive pulmonary disease with subclinical cognitive impairment: An exploratory study. Neurotoxicity Research, Published Online. 22 December 2016; DOI: 10.1007/s12640-016-9690-9

[79] Chen J, Lin IT, Zhang H, et al. Reduced cortical thickness, surface area in patients with chronic obstructive pulmonary disease: A surface-based morphometry and neuropsychological study. Brain Imaging and Behavior. 2016;**10**:464-476

[80] Schure MB, Borson S, Nguyen HQ, et al. Fan associations of cognition with physical functioning and health-related quality of life among COPD patients. Respiratory Medicine. 9 March, 2016;**114**:46-52. DOI: 10.1016/j.rmed.2016.03.005

[81] Turan O, Turan PA, Mirici A. Parameters affecting inhalation therapy adherence in elderly patients with chronic obstructive lung disease and asthma. Geriatrics & Gerontology International. 2016; Jun;**17**(6):999-1005. DOI: 10.1111/ggi.12823

[82] Sulaiman I, Cushen B, Greene G, et al. Objective assessment of adherence to inhalers by COPD patients. AJRCCM. Articles in Press. Published on 13-July-2016 May 15;**195**(10):1333-1343. DOI: 10.1164/rccm.201604-0733OC

[83] Cleutjens FAHM, Spruit MA, Ponds RWHM, et al. The impact of cognitive impairment on efficacy of pulmonary rehabilitation in patients with COPD. JAMDA. 2016;1-7

[84] Maes S, Leventhal H, de Ridder DTD. Coping with chronic illness. In: Zeidner M, Endler NS, editors. Handbook of Coping. New York: Wiley & Sons; May 1;**18**(5):420-426

[85] Fix AJ, Daughton D, Kass I, Bell CW, Golden CJ. Cognitive functioning and survival among patients with chronic obstructive pulmonary disease. The International Journal of Neuroscience. 1985;**27**(1-2):13-17

[86] Chang SS, Chen S, McAvay GJ, Tinetti ME. Effect of coexisting chronic obstructive pulmonary disease and cognitive impairment on health outcomes in older adults. Journal of the American Geriatrics Society. 2012;**60**:1839-1846

[87] Chin A Paw MJM, van Uffelen JGZ, Riphagen I., The functional effects of physical exercise TRaining in frail older people. A systematic review., Sports Medicine, 2008; **38**:781-793

[88] Binder EF, Schechtman KB, Ehsani AA, et al. Effects of exercise training on frailty in community-dwelling older adults: Results of a randomized, controlled trial. Journal of the American Geriatrics Society. 2002;**50**:1921-1928

[89] Clarkson-Smith L, Hartley AA. Relationships between physical exercise and cognitive abilities in older adults. Psychology and Aging. 1989;**4**:183-189

[90] Elsayed M, Ismail AH, Young RJ. Intellectual differences of adult men related to age and physical fitness before and after an exercise program. Journal of Gerontology. 1980;**35**:383-387

[91] Papava I, Oancea C, Enatescu VR, et al. The impact of coping on the somatic and mental status of patients with COPD: A cross-sectional study. International Journal of COPD. 2016;**11**:1343-1351

[92] Hung W, Wisnivesky JP, Siu AL, et al. Cognitive decline among patients with chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine. 2009;**180**(2):134-137

[93] Ma F, Wu T, Miao R, et al. Conversion of mild cognitive impairment to dementia among subjects with diabetes: A population-based study of incidence and risk factors with five years of follow-up. Journal of Alzheimer's Disease. 2015;**43**:1441-1449

[94] Gauthier S, Reisberg B, Zaudig M, et al. International psychogeriatric association expert conference on mild cognitive impairment: Mild cognitive impairment. Lancet. 2006;**367**(9518):1262-1270

[95] Long Term Oxygen Therapy (LTOT). Thomas L. Petty., Robert W. McCoy., Dennis E. Doherty, 6th Oxygen Consensus Conference Recommendations., 2006

Chapter 6

Pulmonary Rehabilitation in COPD: Current Practice and Future Directions

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Additional information is available at the end of the chapter

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Abstract

This chapter will review the rationale for and the need for pulmonary rehabilitation in patients with Chronic Obstructive Pulmonary Disease (COPD). Its clinical effectiveness will be considered, including the evidence supporting a role for rehabilitation in improving exercise tolerance in COPD as measured. While the influence of pulmonary rehabilitation on dyspnoea, exercise tolerance and quality-of-life is clear, evidence for the benefits of rehabilitation on reducing healthcare utilisation such as admission to hospital or attendance at out-of-hours services is limited. The chapter will provide guidance on the setting up of a pulmonary rehabilitation programme and clinical staff required and the suitability of patients to enter such programmes will be outlined. There will be discussion on the key components of a programme including education, nutritional advice and the management of dyspnoea. Exercise is the central component of pulmonary rehabilitation. Assessment of the patient and prescription of an exercise programme will be outlined as will assessing a patient's improvement. One key goal of pulmonary rehabilitation is ongoing lifestyle modification to encourage patients to undertake a more active lifestyle in the future. Ways of activating patients to do this will be discussed and the evidence for the use of telehealth in this area will be reviewed.

Keywords: pulmonary rehabilitation, COPD, exercise, physical activity

1. Introduction

COPD is a systemic disease associated with extra pulmonary effects such as osteopaenia, muscle wasting, cardiovascular disease and depression [1]. The symptoms of COPD make engagement in physical activity unpleasant. Air trapping and hyperinflation of the lungs

cause increased breathlessness due to the resultant inefficient breathing. The breathlessness itself provokes anxiety, which in turn leads to further breathlessness, exacerbations of COPD and episodes of panic. Due to this, activities that involve physical exertion are avoided, leading to muscle deconditioning and a further reduced capacity to engage in physical activity. Pulmonary rehabilitation improves symptoms, quality of life and health-care utilisation in patients with COPD [1, 2].

Pulmonary rehabilitation is defined as "an interdisciplinary programme of care for patients with chronic respiratory impairment that is individually tailored and designed to optimise each patient's physical and social performance and autonomy. Programmes comprise individualised exercise programmes and education" [3]. Physical inactivity is a key predictor of mortality in COPD and consequently all major guidelines highlight the importance of exercise in the treatment and management of COPD. There is now high quality evidence for improved exercise capacity, health-related quality of life and decreased breathlessness, fatigue and health-care utilisation following pulmonary rehabilitation [1].

Pulmonary rehabilitation is focussed on an interdisciplinary and holistic approach to the management of COPD, emphasising behavioural change as a key component. It fits very well with the concept of integrated care, with its cornerstone being individually tailored exercise training. Patient assessment, education, psychosocial support and nutritional counselling are also included in the standard pulmonary rehabilitation programme. Overall, the focus of a pulmonary rehabilitation programme is to alleviate the physiological effects of the disease process and decrease the psychosocial effects of the illness on the individual.

2. Historical development

The effects of exercise in patients with chronic respiratory diseases have been a subject for study for some time. By the middle of the 20th century, accepted wisdom was that dyspnoea on exertion should be avoided [4]. Dr. Alvan Barach was the first to offer a contrary opinion in the 1950s, with his advice to "remember to cure the patient as well as the disease". Thomas L. Petty was the first to establish an out-patient programme of pulmonary rehabilitation in the 1960s, despite the conventional wisdom of not exerting patients with respiratory limitations. This programme included individualised instruction, bronchial hygiene, breathing retraining, physical reconditioning and individualised pharmacologic therapy. Rehabilitation programmes were set up throughout the USA, and Petty noted improved exercise tolerance, reduced hospitalisations and a return to gainful employment in the majority of his patients [4]. Subsequently, in the 1980s a view became prevalent that as exercise conditioning did not improve lung function, pulmonary rehabilitation was unlikely to provide physiological benefit to patients. It was felt that if physiological benefit was not demonstrated, the programme design was not particularly important. Finally, in the 1990s, physiologic benefit was proven by using exercise at a higher intensity and the concept of pulmonary rehabilitation was reinvigorated [4, 5].

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3. Rationale for pulmonary rehabilitation

Pulmonary rehabilitation is designed to reduce the symptoms of COPD, improve health related quality of life (HRQoL), improve and re-establish functional ability, enhance participation in everyday life and promote patient autonomy. The exercise component of pulmonary rehabilitation increases inspiratory volume and reduces dynamic hyperinflation, both of which reduce dyspnoea when a person is performing tasks. Exercise also increases muscle function, which delays fatigue and results in increased exercise tolerance. The educational component focuses on self-management and behaviour change. Providing information and knowledge, skills such as goal setting, problem solving and decision making, along with action plans to better recognise and manage their disease are all integral parts of the programme. Modifying nutritional intake and smoking patterns, medication adherence and utilising effective energy-saving strategies and breathing techniques are part of the education component [1].

The exercise capacity of patients with COPD is often impaired and limited by dyspnoea. The reasons for this are complex and multifactorial, including defective gas exchange, dynamic hyperinflation, peripheral muscle dysfunction, respiratory muscle dysfunction, the effects of physical deconditioning, the presence of co-morbidities and the natural age-related decline in exercise capacity [6]. Physical exercise in pulmonary rehabilitation is the best method of improving muscle function and skeletal muscle adaption in patients with COPD [5, 7–10]. The benefits pulmonary rehabilitation produces are explained by improvements in muscle function and the oxidative capacity and efficiency of skeletal muscles, despite the absence of any changes in lung function [11, 12]. Other related improvements include increased motivation, improved mood and improved cardiovascular functioning, which result in ongoing participation in exercise beyond the rehabilitation programme [13].

Even those patients with severe chronic respiratory disease can often sustain the necessary training intensity and duration for skeletal muscle adaptation. Skeletal muscle adaptation following exercise training leads to gains in exercise capacity despite the absence of changes in lung function. In addition, the improved oxidative capacity and efficiency of the skeletal muscles leads to a reduced ventilator requirement for a given submaximal work rate. This could reduce dynamic hyperinflation, adding to the reduction in exertional dyspnoea [6]. Medical therapy should be optimised prior to exercise training beginning and a patient assessment is required prior to beginning an exercise programme.

4. The clinical effectiveness of pulmonary rehabilitation

4.1. Physiological

One of the first studies to show an improvement in exercise tolerance following exercise training in COPD was Casaburi et al. in 1991 [14]. They showed a statistically significant improvement in exercise tolerance and reduced blood lactate and ventilatory requirement

post exercise. These findings have been supported by others [5] and a Cochrane review in 2009 [2] showed a statistically significant improvement in exercise capacity in people who underwent a pulmonary rehabilitation programme. Results of a further Cochrane review in 2015 strongly supported the benefits of pulmonary rehabilitation [1]. They found clinically and statistically significant improvements in important domains of health-related quality of life, including dyspnoea, fatigue, emotional function and mastery, as well as the 6 minute walk test: a measure of functional exercise [1]. Also noted was a small but statistically significant improvement in physical activity levels. Physical activity has become more important in COPD management as it has been shown that inactivity is linked with reduced survival, poorer quality of life and increased healthcare utilisation [15].

4.2. Quality of life

The benefits of pulmonary rehabilitation on dyspnoea and health status have been supported by a Cochrane review [1]. The Chronic Respiratory Questionnaire was used in a number of studies and showed an improvement in dyspnoea that was statistically significant and clinically relevant. Improvement was also noted in the other CRQ domains of fatigue, emotional function and patient's sense of control. The St. Georges Respiratory Questionnaire Scores were also subject to a meta-analysis in the same Cochrane review and found to show significant improvement following pulmonary rehabilitation [16].

4.3. Reduction of healthcare utilisation

Several studies have investigated whether pulmonary rehabilitation leads to a decrease in the number of caregiver or physician visits, hospital days, and medication use [3, 6]. In general, some benefit is shown in this important area. Several randomised studies comparing pulmonary rehabilitation with usual care found a trend towards reduced hospital admissions and hospital days. Studies comparing healthcare use before and after pulmonary rehabilitation show that pulmonary rehabilitation significantly reduced emergency room visits and physician visits [3, 6].

4.4. Psychosocial

In a Cochrane review published in 2015, participants allocated to rehabilitation had significantly greater changes in HRQoL [17]. A Cochrane review in 2009 had previously shown moderate to large effects of rehabilitation on health-related quality of life and exercise capacity [2].

4.5. Self-efficacy

Self-efficacy refers to the level of belief someone has in their ability to complete a chosen task or goal. Overall, self-efficacy scores improve with pulmonary rehabilitation [1].

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4.6. Survival

There is limited evidence for increased survival to date, however only one randomised controlled trial has looked at survival: the control group received education and the intervention group received rehabilitation and education. The study was unlikely to be powered to detect mortality [18]. A prospective observational study of 1218 patients showed no mortality benefit from pulmonary rehabilitation [19]; however, another study did show improved mortality in patients where exercise capacity and dyspnoea improved after rehabilitation only [9].

4.7. Nutrition

In an underweight population, some small weight gain was noted following exercise training; however, in general the effect of pulmonary rehabilitation on nutritional status does not appear to be significant. Nutritional outcomes at the start of a rehabilitation programme do not affect outcomes such as exercise capacity or health status [6].

5. Setting up a pulmonary rehabilitation Programme

5.1. Duration

There remains no consensus internationally on the optimum duration of a pulmonary rehabilitation programme. However, pulmonary rehabilitation programmes of 6–12 weeks are recommended and demonstrate a significant benefit in health status, dyspnoea and exercise in patients with chronic respiratory diseases limited by breathlessness. An attendance at a minimum of 12 exercise sessions is recommended to successfully complete the programme. Programmes of less than 6 weeks have been shown to provide some benefits in health status and exercise capacity in individuals with COPD; however, these programmes should be individualised and measures of benefit should be in place prior to the patient concluding the programme. The ongoing benefits of a pulmonary rehabilitation programme of longer than 3 months duration has been shown, including changes in daily physical activity levels, but the cost benefit of these remains unclear [3, 6, 20–22].

5.2. Frequency

The recommended frequency of exercise classes also differs internationally. The general consensus supports a minimum of two supervised exercise sessions per week, and either a third supervised session or formalised unsupervised session depending on the resources available. This is in contrast with the WHO recommendation of 5 sessions of 30 minutes exercise per week. However, to date the key improvement outcomes in pulmonary rehabilitation are based on at least two supervised sessions per week. Pulmonary rehabilitation

programmes should therefore encompass a minimum of twice weekly supervised exercise sessions, a third session of prescribed unsupervised exercise and encouragement of regular physical activity for 30 minutes five days per week in line with standard healthy living advice [3, 6, 20–22].

5.3. Staffing

There is no consensus on staffing levels for a pulmonary rehabilitation programme. The staffing of the programmes varies globally, with physical therapists coordinating programmes in Australia, South America and Europe, while respiratory therapists coordinate programmes in the United States. There is no one best staffing structure. Optimal staff-patient ratios also differ: the American Association of Cardiovascular and Pulmonary Rehabilitation recommends ratios of 1:4 for exercise training, 1:8 for educational sessions and 1:1 for complex patients; the British Thoracic Society recommends ratios of 1:8 for exercise training and 1:16 for educational sessions. These ratios are not evidence based and are designed based on experience and opinion [3, 6, 20–22].

It is recommended and accepted that for patients to gain optimum benefit from a pulmonary rehabilitation programme, a multidisciplinary approach should be taken [13, 23]. Availability of resources and staff will dictate the level of input the Multidisciplinary team will have but each member plays an important role in the rehabilitation programme:

- *Respiratory physician*: medical assessment; pharmacological management; referral; screening for oxygen and oxygen prescription.
- *Physiotherapist*: exercise testing, prescription and training; musculoskeletal assessment, treatment and advice; airway clearance education; strategies for the management of dyspnoea; inspiratory muscle training; assessment for ambulatory oxygen requirements.
- *Respiratory nurse*: Disease specific education; development of action plans; inhaler technique training.
- *Dietician*: Nutritional assessment and advice.
- *Occupational therapist*: Assessment and modification of home environment; energy conservation advice.
- *Pharmacist*: advice and education on respiratory education and inhaler use.
- *Social worker*: information and access to support services.
- *Psychologist:* psychosocial assessment and treatment for conditions including panic, anxiety and depression.

5.4. Rolling or cohort programme

Deciding on whether to administer a rolling or a cohort programme is dependent on local considerations, as there is no high-quality evidence to suggest the benefit of one over the other. The characteristics of a rolling and a cohort programme are outlined in **Table 1** [3]:

	Rolling	Cohort
Nature of programme	Continual cycle of sessions, where patients join when there is a space available and leave after completing the programme of sessions	All patients start and finish the programme at the same time
Waiting list	Patients enter the programme when a space arises, permits fast track access, potentially allows better capacity	An accumulative number of patients wait to start the programme, the waiting list may be distorted
Rehabilitation delivered at different locations by the same team	Not possible as the programme always runs in the same venue	Suitable
Education programme	The order of the talk is individual and governed by the point of entry	Can 'flow' in a logical order
Group dynamics	A new patient may be the sole new participant which may be a beneficial or a challenge	Patients all start together which permits group leaning of lifestyle changes
Assessments	Must perform pre and post assessments in parallel to the course	Dedicated assessment slots can be programmed for all subjects pre and post rehabilitation
Duration of programme	Allows lengthening the programme or early graduation as required	Fixed length for each programme

Table 1. Characteristics of Rolling and Cohort programmes.

5.5. Selection criteria for pulmonary rehabilitation programmes

Any person with a chronic lung condition who continues to be limited by breathlessness despite optimal medical management should be considered for a pulmonary rehabilitation programme [22]. Improvements following a pulmonary rehabilitation programme have been shown in patients with COPD irrespective of their age or gender [24–26] level of functional impairment [27–29] or disease severity [30, 31]. By promoting self-efficacy and behaviour change, improving exercise tolerance and physical activity and reducing exacerbations, pulmonary rehabilitation at an earlier stage of disease has the potential to markedly change the course of the disease [6]. Frequent reasons for referral to a pulmonary rehabilitation programme include:

- Dyspnoea/fatigue and chronic respiratory symptoms.
- Impaired health-related quality of life.
- Decreased functional status.
- Difficulty performing activities of daily living.
- Increased use of medical resources (e.g., frequent exacerbations, hospitalizations, emergency room visits).
- One of the primary indicators for referral to pulmonary rehabilitation is based on the modified Medical Research Council Breathlessness (mMRC) score (see **Table 2**) [3]. This scale

measures perceived respiratory disability, and allows patients to indicate the extent to which their breathlessness impacts their mobility. It is a 0–4 grade scale used to establish levels of perceived breathlessness [3, 6].

There is very strong evidence that patients with an mMRC dyspnoea score of 2–4 who are functionally limited by breathlessness should be referred for pulmonary rehabilitation. However, patients with an mMRC dyspnoea score of 1 who are functionally limited by breathlessness should also be referred for pulmonary rehabilitation. Patients with COPD who have an mMRC score of 4 but who are able to attend an outpatient pulmonary rehabilitation programme achieve similar benefits from the programme as those with a lower breathlessness score [28].

5.6. Exclusion criteria

The exclusion criteria for enrolment into a pulmonary rehabilitation programme are minimal, and in some cases participation in the programme by a patient can be facilitated by the attendance and support of a carer or relative. However, general exclusion guidelines would include [3, 6]:

- Patients with unstable cardiovascular disease or mobility problems which make exercising safely impossible (for example, severe arthritis, severe peripheral vascular disease, severe orthopaedic conditions).
- Patients with significant psychiatric or cognitive impairment who are unable to follow simple instructions safely in a group setting.
- Any further excluding factors are based on the assessor's own objective judgement or with a discussion with the referring physician, for example, a perceived lack of motivation to participate in the programme.

5.7. Referral process

Once a patient has been deemed suitable to attend a pulmonary rehabilitation programme by the healthcare professional, the referral should be used as an opportunity to educate the patient about the benefits of the programme, to explore their understanding of the programme

Grade	Degree of breathlessness related to activities
0	Not troubled by breathless except on strenuous exercise
1	Short of breath when hurrying or walking up a slight hill
2	Walks slower than contemporaries on level ground because of breathlessness or has to stop for breath when walking at own pace
3	Stops for breath after walking 100 metres or after a few minutes on level ground
4	Too breathless to leave the house, or breathless when dressing or undressing

Table 2. The modified Medical Research Council Breathlessness (mMRC) score.

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and to address the patients' concerns [3]. The programme should be presented to the patient as a core treatment for the management of their condition as opposed to an optional adjunct. Patients should be referred to the programme under the care of a respiratory physician, who should be available to the staff co-ordinating the programme to discuss any medical problems which may arise during the programme and to ensure that potential participants have been medically assessed for suitability for the programme and that their pharmacological management has been optimised [22].

5.8. Pulmonary rehabilitation post exacerbations of COPD

Exacerbations of COPD result in increased mortality and healthcare use, worsening symptoms and health-related quality of life, as well as impaired exercise capacity, reduced skeletal muscle function of the lower limbs and reduced physical activity levels [3, 6]. Studies have therefore been conducted to explore the merits and the safety of 'early' pulmonary rehabilitation both during a hospital admission and within 1 month of hospital discharge for an acute exacerbation of COPD. It is now known that early pulmonary rehabilitation post exacerbation [2]:

- Is not associated with any adverse events or increased mortality
- Reduces risk of hospital readmissions
- Improves health related quality of life
- Improves exercise capacity

It is therefore recommended unequivocally that patients with COPD who are hospitalised for an acute exacerbation should be referred for pulmonary rehabilitation at discharge, and should be enrolled into the pulmonary rehabilitation programme within 1 month of leaving the hospital.

6. Patient assessment

The initial assessment for the programme is an opportunity to outline a detailed description of the programme to the patient, to assess for co-morbidities, risk factors and contraindications for the programme, and to consider any appropriate onward referrals to maximise the benefit the patient will receive from the programme [3]. The essential information required for pulmonary rehabilitation includes:

- Known communication/language barriers.
- Current activity levels.
- Respiratory diagnosis: spirometry for those with COPD.
- Height, weight, BP and oxygen saturations at rest are desirable.
- Modified Medical Research Council breathlessness score.

- Smoking status (for those who continue to smoke, document details of previous attempts to quit; recent quitters may require support and/or counselling).
- Therapies: current list of medication.
- Use of oxygen: long-term oxygen therapy, short-burst oxygen therapy, ambulatory; oxygen saturations, use of domiciliary Positive Pressure Ventilation.
- Significant and relevant comorbidities (which may affect their ability to participate in the exercise programme or education sessions, including adequacy of literacy and vision).
- Transport needs: if applicable to that rehabilitation provider.
- Health care utilisation: including number of hospital admissions and length of stay in the previous 12 months.

6.1. Specific situations at assessment

When deciding on a patient's suitability for pulmonary rehabilitation, there are certain groups of patient characteristics which need further consideration during assessment for the programme including [3]:

6.1.1. Smoking status

There is currently no evidence that smokers benefit any less from pulmonary rehabilitation than non-smokers, and the rehabilitation programme can be an ideal opportunity to support and facilitate these patients in smoking cessation. Smokers should be offered smoking cessation advice and should be referred to smoking cessation programmes.

6.1.2. Chronic respiratory failure

Patients with chronic respiratory failure (PaO2 < 8 kPa, PO2 > 6 kPa or both) gain much benefit from pulmonary rehabilitation and should not be excluded from the programme for this reason alone. The use of oxygen and non-invasive ventilation for these patients during the programme should be discussed with the referring physician, and the safety of the patient with consideration to the skill mix of the staff in the programme and the programme setting should also be considered when accepting these patients onto the programme.

6.1.3. Cardiovascular disease

From a safety perspective, patients with unstable cardiovascular disease (e.g. unstable angina, unstable arrhythmias) should not commence a pulmonary rehabilitation programme until their cardiac condition is stabilised. However, patients with stable cardiovascular disease as well as a chronic respiratory disease do benefit from the programme, and should be referred if pulmonary rehabilitation is indicated. Patients with aortic aneurysms <5.5 cm can participate safely in moderate intensity aerobic exercise training as long as their blood pressure is monitored and controlled.

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6.1.4. Anxiety and depression

Patients with symptoms of anxiety and depression also benefit from the pulmonary rehabilitation programme, and should not be excluded from referral to the programme. The pulmonary rehabilitation programme allows an opportunity to detect these conditions and to consider onward referral for optimal management.

6.1.5. Obese subjects

Pulmonary rehabilitation may be an ideal setting in which to address the needs of obese patients with associated respiratory symptoms, including exercise training, nutritional education, psychological support and onward referral to specialists as required. Obese patients should not be excluded from the pulmonary rehabilitation programme; however, assessments for other cardiac and pulmonary comorbidities may need to be considered prior to commencing the pulmonary rehabilitation programme. Weight limits of equipment should be considered, low impact exercises may be more appropriate and specialised equipment may be required to accommodate these patients [6].

6.1.6. Co-morbidities

COPD is commonly associated with other medical co-morbidities, which may result from the common risk factors for COPD such as smoking as well as systemic inflammation. These can further impact on the patient's management, and can include cardiovascular disease (arrhythmias, congestive heart failure, hypertension, and coronary disease), metabolic conditions (diabetes mellitus, osteoarthritis, and hyperlipidaemia), infections, lung cancer, obstructive sleep apnoea, cognitive dysfunction, depression or anxiety. These co-morbidities must be considered in the assessment and management of COPD patients enrolled in a pulmonary rehabilitation programme, as early intervention may influence the course and prognosis of the disease and can have a beneficial effect on both COPD and the relevant co-morbidity. Pulmonary rehabilitation is very important for patients with COPD and co-morbidities as physical activity is well documented to not only benefit COPD but also many other chronic conditions including obesity, diabetes, cardiovascular disease, musculoskeletal disease and peripheral vascular disease [32–36].

The presence of co-morbidities does not preclude pulmonary rehabilitation in patients with COPD but they should be considered thoroughly when monitoring and prescribing exercise to allow these individuals to exercise safely. For patients with cardiac conditions, the need for pre-rehabilitation investigations (for example, echocardiography or stress testing) should be discussed with the referring physician to define safe exercise parameters. Anaemia, orthopaedic and neurological issues require further consideration of a safe exercise plan and the need for specialised equipment. The patient may also require further onward referrals (for example, dual energy X-ray absorptiometry (DEXA) scan, psychological review, and nutritional review) based on observations during the exercise programme.

6.2. Exercise testing

Prior to commencing the rehabilitation programme, an exercise assessment is essential to [6]:

- Ensure the patient is safe to participate
- Rule out cardiovascular morbidities
- Assess baseline capacity
- Individualise exercise prescription
- Assess for the need for supplementary oxygen
- Define the factors contributing to exercise limitation
- Evaluate the effectiveness of the intervention

Exercise tests can include field walking tests, or laboratory cycle ergometer or treadmill tests. Field walking tests are most commonly used, and are considered more reflective of daily living; they are low cost and are convenient in most settings. These include the 6-minute walk test (6MWT) and the incremental shuttle walk test (ISWT). The 6MWT is a valid, reliable and reproducible self-paced walk test once the established, recommended and standardised protocol is used. Performed over a minimum of 30 metres, patients are asked to walk as far as possible in 6 minutes along a flat corridor [37]. The ISWT is a symptom limited maximal exercise capacity, externally paced walk test performed over a 10-metre course. It is also valid and reliable. The walk speed continues until the participant can no longer continue, with a maximum duration of 20 minutes. The endurance shuttle walks test (ESWT) is a constant walking speed test performed at a set speed based on the ISWT [6].

The choice of test is usually decided based on objectives, time, cost and availability.

7. Exercise training in pulmonary rehabilitation

Lower limb weakness is commonly seen in patients with COPD, and is a poor prognostic indicator [12]. The exercise component of pulmonary rehabilitation therefore should primarily be delivered reflecting aerobic exercise and on lower limb endurance and resistance training. The general principles of exercise in COPD are no different than in exercising a healthy population: it must reflect the individuals own capacity, progress as improvement occurs and exceed normal loads encountered in daily life to improve aerobic capacity and muscle strength.

7.1. Aerobic/endurance training

A target intensity of 60% peak work rate, aiming for an accumulative time of 30–60 minutes of aerobic training per session is recommended, with 30 minutes of continuous aerobic

activity [3]. However, both interval and continuous training have been shown to be effective in patients with COPD, and should be selected based on both therapist and patient preference. Endurance exercise, most commonly delivered in the form of walking (treadmill or ground walking) or cycling, three to five times per week at a Borg dyspnoea or fatigue score of 4–6 (moderate to severe) is the recommended target training intensity [6].

7.2. Resistance training of the lower limbs

Resistance training of all major muscle groups, but particularly the quadriceps, should also be incorporated, not only for the improvements that are well documented for COPD symptoms, but also to reduce falls and to improve or maintain bone mineral density [6]. Resistance training should aim for 2–4 sets of 10–15 repetitions of each exercise, on 2–3 days of the week. The selected weight should be individualised for each patient, aiming for a prescribed weight of 60–70% of 1 repetition maximum for each individual patient. The weight should only have progressed once all sets can be completed with the selected weight [6]. Based on local resources, weight machines, elastic bands or free weights are all acceptable forms of resistance training.

7.3. Resistance training of the upper limbs

While it is suggested that upper limb training can improve upper limb function in patients with COPD, the optimal prescription of this training remains unclear, as do the improvements gained in broader outcomes for COPD patients. However, upper limb training may be incorporated based on individual needs to improve functional living. It could be assumed that starting loads and progression may follow the same prescription as for lower limb training [20].

7.4. Flexibility training

While minimal research has been done on flexibility training as part of the pulmonary rehabilitation programme or the optimal duration and intensity of stretching exercises, flexibility of the major upper and lower limb muscle groups on 2–3 days a week can be recommended [38]. Also, improved thoracic mobility and posture may improve vital capacity in COPD patients, and should be assessed and addressed in all COPD patients [6].

7.5. Generic vs. individualised exercise programmes

Generic exercise training is recommended for the pulmonary rehabilitation classes: all patients in the class should do all the same exercises as opposed to an individualised exercise programme for each patient. However, the prescription of exercise should be individualised to each patient to ensure the correct intensity for that patient. Goal setting should be addressed with each patient on the initial assessment to address any hurdles to exercise and to further address each patient's specific needs [3].

8. Education in pulmonary rehabilitation

Education on COPD and its management to both patient and family is an integral component of pulmonary rehabilitation programmes. Several studies show that patients instructed about the nature of their disease and the implications of therapy can better understand, recognise, and treat the symptoms of their disease [39]. The educational component acts as a support to lifestyle and behavioural change, and assists in the development of self-management skills. Patients are empowered to actively participate in their own healthcare, which can promote adherence to therapy and self-efficacy (i.e., the confidence in successfully managing one's health). The educational needs of each patient should be individualised and identified at the initial assessment and reassessed over the course of the programme. The style of teaching used in pulmonary rehabilitation is changing from traditional didactic lectures to a collaborative self-management approach, which may be more effective [6]. Education should run in conjunction with an exercise programme and should cover relevant topics associated with chronic lung disease. Different aspects should be delivered by different healthcare professionals involved in the programme, with the relevant expertise in that area.

Self-management includes core generic strategies, such as goal setting, problem solving, decision making, adherence to medication, maintaining regular exercise, nutritional advice, breathing techniques, bronchial hygiene and smoking cessation [40, 41]. Behavioural change strategies including the prevention, early recognition and treatment of exacerbations and advanced care directives are additional core educational issues incorporated in collaborative self-management programmes. The development of a patient-specific, collaborative self-management plan for COPD exacerbations including the recognition of symptoms, a personalised action plan and communication with a healthcare provider has been shown to be beneficial [41, 42].

8.1. Breathing strategies

Breathing strategies encompasses a range of breathing techniques, including active expiration, pursed lip breathing, diaphragmatic breathing, adapting certain body positions and coordinating paced breathing with activities. The aim of these techniques is to improve regional ventilation, gas exchange, respiratory muscle function, dyspnoea, exercise tolerance and quality of life [43].

The breathing strategies are tailored to the individual, with patients adopting the technique most effective in reducing symptoms [44].

8.2. Bronchial hygiene techniques

Excessive airway secretions secondary to mucus hypersecretion and impaired mucociliary clearance are distinctive features for some patients. Chest physiotherapy is used to aid removal of airway secretions, which involves teaching on importance of daily clearance and training in drainage techniques [45].

8.3. Smoking cessation

In approximately 90% of cases of COPD, cigarette smoking is the direct cause. The single most important intervention to retard the progression of air-flow limitation and improve survival is smoking cessation. For many patients smoking cessation may be difficult due to strong physiologic and psychological dependence. Long-term quit success rates of up to 25% can be achieved when sufficient reserves and time are dedicated to smoking cessation programmes [46]. The rehabilitation programme provides a forum for education and continued reinforcement, on risks of continued smoking, advice on nicotine replacement therapy and other pharmacotherapy, along with referral to smoking cessation programmes.

8.4. Advance care planning

The process of advance care planning is often inadequate in chronic respiratory diseases [47]. Anxiety and fear of death is well described in individuals with advanced COPD along with reluctance to discuss it with their treating physician [48]. The pulmonary rehabilitation programme has been identified as an appropriate setting for discussion on advance care planning and end of life care [49].

The idea is to allow both patient and family a unique opportunity to communicate goals of treatment and preferences regarding the use of life-sustaining treatments, such as cardiopulmonary resuscitation, mechanical ventilation, dialysis and feeding tubes, with the health care provider. Ideally, the discussion will facilitate better understanding of certain topics, such as the disease itself and prognosis, process of dying and end-of life care, advance directive documents (e.g. designating a health care proxy or enduring power of attorney).

8.5. Psychosocial support

Severe COPD is associated with increased risk for anxiety and depression, which can affect motivation levels and result in decreased participation in social activities [6, 46]. Episodes of dyspnoea often trigger fear and anxiety in patients with COPD and result in further anxiety in anticipation of repeat episodes [50]. Depression, feelings of hopelessness and an inability to cope are common in patients with COPD, with an approximate prevalence rate of 45% in patients with moderate to severe disease [51, 52]. Patients with depression have the tendency to withdraw from social interactions which can worsen feelings of isolation and loneliness. Sexual activity can be affected by depression and also the physical restrictions imposed by COPD itself, sexuality should be raised and discussed when necessary and appropriate counselling initiated.

Screening for anxiety and depression should be included at the initial assessment in a pulmonary rehabilitation programme. If possible interviewing and involving the caregiver is beneficial. Promotion of an adequate patient support system is an important component of pulmonary rehabilitation [53]. Psychological and social support provided within the pulmonary rehabilitation setting can facilitate adjustment the physiological impact of the disease by

encouraging adaptive thoughts and behaviours. These aid patients in diminishing negative emotions, provides a socially supportive environment and may improve compliance with rehabilitation. Multidisciplinary team members with the appropriate expertise to address these issues are most useful and referral to appropriate professional care may be necessary.

8.6. Nutrition

Nutrition counselling and education on weight management are particularly important in lung disease. Up to 20–30% of normal weight individuals with COPD show a shift in body composition to muscle wasting and relative increased fat mass, independent of spirometric severity [53]. Typically, underweight status and weight loss are more prevalent in advanced disease and emphysematous phenotype [54], while obesity is more prevalent in mild disease [53]. Patients with COPD are at risk of obesity and muscle wastage due to limitations in physical activity and adverse effects of glucocorticoids given for exacerbations. For patients with COPD there is an association between underweight status and lean muscle loss and increased mortality, again independent of FEV1 [55, 56], in addition underweight patients report a lower HRQoL status then normal weight patients with COPD [57].

Changes in body weight or BMI do not accurately reflect all the changes in body composition that occur in patients with COPD. Body weight is made up of fat mass and fat free mass (FFM), fat free mass consists of water and body cell mass (organ, muscles, bone). Muscle mass constitutes a major part of fat free mass. The loss of FFM is characteristic of chronic lung diseases such as COPD and in severe COPD low FFM and mid-thigh cross sectional area have been shown to be a better predictor of prognosis than BMI [58]. Patients with COPD and low FFM have a lower exercise tolerance and impaired respiratory muscle strength than patients with maintained FFM [59–61]. FFM can be estimated using skinfold anthrometry, bioimpedance analysis or dual energy X-ray absorptiometry (DEXA).

A comprehensive pulmonary rehabilitation programme should at a minimum include a simple nutritional screening, such as calculating patient's body mass index or BMI. The aetiology of weight loss and muscle wasting in COPD is complex and a number of different physiologic and pharmacologic interventions have been used to stop or even reverse the process. This includes simple nutritional supplementation with an emphasis on adequate protein intake in order to stimulate protein synthesis to maintain or restore FFM. The increased energy requirements during activity in pulmonary rehabilitation must also be met in both underweight and normal weight individuals. Nutritional supplementation alone has not been successful in achieving significant weight gain. However, a 6 month intervention of dietary counselling along with nutritional supplementation resulted in significant weight gain and maintenance of FFM compared with control group [62].

9. Post rehabilitation assessment

9.1. Patient-centred outcomes

Patient-centred outcomes are used as outcome measures in pulmonary rehabilitation to measure the change or impact the pulmonary rehabilitation programme has had on the patient's

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symptoms and quality of life [6]. Outcomes used during the programme should be valid, reliable and sensitive to change and have descriptions of relevant change, such as the minimally clinical important difference, which indicate a meaningful change of the condition for better or for worse.

Outcome measures used are generally generic or disease specific, and should assess quality of life (health related quality of life, symptoms and functional impairment), depression and anxiety, functional status and breathlessness.

Exacerbation history should also be documented as an outcome measure. The same exercise test used in the pre-rehabilitation assessment (6MWT or ISWT) should also be reassessed on completion of the programme to assess for improvements in exercise capacity. Quality of life measures are used to assess symptoms, physiological functioning, functional impairment and health related quality of life [55, 63, 64]. At least one of these questionnaires is advised and may include, for example, the Chronic Respiratory Disease Questionnaire [65, 66], the St. Georges Respiratory Questionnaire [16], or the COPD Assessment Test [67]. As outlined previously, up to 40% of COPD patients have symptoms of depression and anxiety [68]. All patients should be assessed both before and after the rehabilitation programme using, for example, the Hospital Anxiety and Depression Scale [68, 69], and an onward referral to a mental health professional considered if symptoms persist significantly on completion of the programme.

Patients who are attending pulmonary rehabilitation should have the outcome of their treatment in terms of dyspnoea, health status and exercise capacity measured. Objective measurements of a patient's baseline function and post-rehabilitation function, and reassessments in the months following completion of the rehabilitation programme allows the co-ordinator to assess the benefit obtained by the individual during the programme, to provide quality assurance for the rehabilitation services and to facilitate ongoing referrals if required. Other measures of outcome, such as muscle strength, nutritional status, physical activity levels and self-efficacy measures) may also be beneficial.

10. Unanswered questions in pulmonary rehabilitation

10.1. Where is the ideal location to carry out rehabilitation?

The ideal location to carry out rehabilitation is currently unclear. The settings for pulmonary rehabilitation programmes vary; most of the research to date has involved outpatient programmes; however pulmonary rehabilitation programmes may also be conducted in an inpatient hospital or home setting. In a recent international survey involving 400 centres in 40 countries, 85% of pulmonary rehabilitation programmes in Europe and North America were using an outpatient model [70]. Outpatient settings include hospital outpatient departments, community facilities and physiotherapy clinics.

Inpatient rehabilitation is offered in hospitals and can provide specialised rehabilitation care for individuals in a stable pulmonary state or after an exacerbation. It certain cases it can be initiated during inpatient acute care including the intensive care unit where ventilator limitations may limit aerobic exercise, but resistive muscle training can be well tolerated and is associated with improved 6-minute walk distance and muscle strength [6, 71]. Potential

disadvantages with inpatient rehabilitation include higher costs and lack of coverage by health insurance in certain countries.

Home based rehabilitation is an alternative model, which involves transferring the site of exercise training to the home. This could make the course more convenient and broaden the availability of the service. There is increasing evidence comparing home- and hospital-based programmes, including a recent large randomised equivalence study of home vs. outpatient rehabilitation. This demonstrated that important outcomes such as functional exercise capacity and health related quality of life were equivalent between both groups [72]. Fernandez and colleagues demonstrated that a home-based programme was safe and effective in a group of 50 patients with severe COPD on long-term supplemental oxygen [73]. There has been little uptake in clinical practice, with less than 5% of centres worldwide providing home based rehabilitation [70]. This is likely a result of limitations in some of the current studies, with many being underpowered or failing to provide all of the essential components of pulmonary rehabilitation.

The American Thoracic Society (ATS)/European Respiratory Society (ERS) Policy Statement on Pulmonary Rehabilitation identified the need to increase accessibility of pulmonary rehabilitation as a key priority, which includes investigating novel PR programme models that are more accessible and acceptable to patients [74]. Thus, when choosing a rehabilitation setting characteristics of both a particular healthcare system or setting and the patient as an individual need to be considered. Factors such as transportation, availability of various programme settings as described above and in certain countries, payment considerations and health insurance need also to be considered. In relation to patient specific factors, the severity of their disease is important, as is the haemodynamic stability of a patient often in the context of recent exacerbation, co-morbidities and extent of disability if any. These factors can influence the most appropriate setting and level of supervision a patient needs enrolling in a pulmonary rehabilitation programme.

10.2. What are the barriers to the uptake of pulmonary rehabilitation?

One key goal of pulmonary rehabilitation is ongoing lifestyle modification to encourage patients to undertake a more active lifestyle in the future. Despite the extensive evidence for its benefits, pulmonary rehabilitation is delivered to fewer than 10% with those with COPD who would benefit [52]. Accessibility is a major factor particularly in rural settings where programmes are not available or appropriate infrastructure to provide them does not exist. However, it has also been shown in metropolitan areas that up to 50% of those who are referred will never attend and of those who do present, up to a third will not complete the programme [75].

A systematic review in 2011 was carried out to identify barriers to uptake and factors affecting pulmonary rehabilitation adherence. The factors that influence whether people choose to attend their initial appointment can be different to the factors that influence programme completion [75]. A number of barriers to enrolment following referral were identified, including:

- Disruption to established routine, varying from concerns over missing social activities to work commitments or carer demands such as caring for other family members.
- Travel, transport and location, including distance to travel, available transportation or inability to travel independently.
- Influence of the referring physician – some patients declined to attend following referral by a doctor they did not know or if the perceived that their doctor did not think the rehabilitation programme would benefit them.
- Lack of perceived benefit, as some studies report patients perceiving their disease to be too severe to gain improvement or that the programme lacks guaranteed benefits.
- Inconvenient timing of the programme – patient preference on timing of rehabilitation sessions can vary between morning and afternoon, and given the limited capacity and availability not everyone's preference can be accommodated.

The definition of programme non-adherence varies in the literature from declining to participate in the programme to attending at least one session. A non-adherence rate ranging from 10 to 32% has been described and varies considerably from study to study [75]. Factors associated with non-adherence include illness and co-morbidities, travel, transportation, lack of perceived benefits, smoking, depressive symptoms and lack of support [27, 76]. Cigarette smoking at enrolment was the sole independent risk factor for non-completion of pulmonary rehabilitation, in the systematic review described above [75]. This highlights the importance of the educational component and facilitating behaviour change including programmes for strategies for smoking cessation.

10.3. How can the benefits of pulmonary rehabilitation be maintained?

Given the nature of COPD as a progressive chronic disease, it frequently results in a progressive loss of function over time. It is therefore reasonable that any benefits obtained from an initial programme are likely to regress over time [3]. The benefits of an initial pulmonary rehabilitation programme have been shown to persist to some degree for at least 12 months, with quality of life maintained better than the increased exercise capacity. Developing strategies to extend the effects of the rehabilitation programme is extremely important. The benefits of ongoing supervised maintenance exercise programmes beyond the completion of the initial cycle remains uncertain [6].

A repeat programme in those whose condition has deteriorated more than 1 year since completing the programme should be considered, and an earlier repeat programme may be warranted in those patients with a profound physiological decline within the initial 12 months of completing the programme. The benefits of a repeat programme of a patient who failed to benefit from the original programme are questionable. Ongoing exercise upon completing the programme should be encouraged in all patients, and opportunities for exercise upon completion of the programme should be provided to all patients.

Implementation of a home exercise programme at least twice a week at an early stage during the rehabilitation programme encourages the participant to exercise independently during the programme, but also improves adherence to regular exercise once the programme has been completed. Written material with an individualised description and prescription of each exercise, resembling those undertaken in the supervised classes should be provided to each participant. The programme coordinator should monitor the patients home exercise diary throughout the programme, and any barriers to exercise that the patient is experiencing should be addressed. Precautions and advice on exercise should also be addressed [20].

On completion of the programme, patients should be provided with a written, individualised, structured plan for ongoing exercise maintenance to encourage ongoing exercise. It should include aerobic and strength exercises, and information on local exercise amenities. Patients should be asked to reflect on the effect the programme has had on their daily physical activity and on their symptoms. Strategies to maintain their improvements and adherence to an ongoing exercise programme should be discussed. Regular assessments following completion of the initial programme can assist in maintaining the gains achieved during the programme [22].

10.4. Is there a role for new technology?

Pulmonary rehabilitation has rapidly established itself as a cornerstone in the comprehensive management of patients with COPD. As previously stated, a recent joint policy statement by the ATS and ERS has identified improved access and delivery of pulmonary rehabilitation to suitable patients as a priority in need of further research and development. As popularity and lack of capacity increase demand, other settings for effective rehabilitation will need to be found. These new settings would ideally maintain the quality and effectiveness of conventional programmes but be more convenient to patients [6].

New technology may play a part in improving services by telemonitoring or provision of remote rehabilitation to inaccessible regions. Telemedicine is the use of telecommunication and information technology to provide clinical health care from a distance. Telerehabilitation is the delivery of rehabilitation services over telecommunication networks and the internet, allowing point-to-point video conferencing between a central control unit and a patient at home. This is a promising way of delivering health services to individuals who may live in isolated areas without adequate access to transportation or have a level of disability which limits their ability to travel. A study carried out in 2008 used mobile phone based systems to remotely monitor an endurance exercise programme at home [77]. This programme provided a music component with an appropriate tempo to facilitate the correct intensity of training; adherence could also be monitored and appropriate feedback and support delivered. The study demonstrated good compliance and significant improvement, and was also associated with fewer exacerbations and hospitalisations [78].

There has also been evidence to support the delivery of a pulmonary rehabilitation programme from a large expert centre to smaller regional centres via videoconferencing [78]. In a

controlled trial, there were equivalent outcomes for exercise capacity and quality of life. One other small trial in individuals with moderate to severe COPD, who had completed at least 12 sessions of outpatient pulmonary rehabilitation, found that telemonitoring by health care professionals reduced primary care contacts for respiratory issues compared with usual care [79]. Neither demonstrated any differences between groups and hospital admissions, days in hospital or contact with COPD nurse specialists in the community.

Education, psychosocial support and counselling are components of a pulmonary rehabilitation programme which are critical to its success. A study in 2006 demonstrated that the combination of exercise counselling, stimulation of lifestyle change or adaption and the use of a pedometer is feasible and may improve outcome and maintenance of rehabilitation results [80]. Results of a systematic review comparing home telemonitoring with usual care showed that home telehealth (home telemonitoring and telephone support) decreased rates of hospitalisation and emergency department visits, whereas findings for hospital days varied between studies. There is a great deal of variability between studies in terms of interventions and approach [81].

11. Conclusion

Pulmonary rehabilitation is one of the most cost-effective therapies for individuals with chronic respiratory disease. Despite this, many programmes are not funded adequately due to a lack of knowledge and awareness of the benefits of pulmonary rehabilitation. Healthcare professionals in clinical practice are often not familiar with the benefits, science and process of pulmonary rehabilitation, and therefore do not offer it to suitable patients. The need for standardised formal training in pulmonary rehabilitation is clear. Interestingly, even when referred, uptake of pulmonary rehabilitation by suitable patients remains poor. This may be due to a perception of pulmonary rehabilitation as being difficult or frightening. Therefore, equally important is patient education regarding the proven benefits of pulmonary rehabilitation and the processes by which those benefits are attained. Given that pulmonary rehabilitation is an evidence-based, widely-accepted gold standard treatment for many respiratory patients, the disparity in access and availability results in unacceptable inequality of healthcare [82].

Author details

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References

[1] McCarthy B, et al. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews. 2015 Feb 23;(2):CD003793. DOI: 10.1002/14651858.CD003793.pub3

[2] Puhan M, et al. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews. 2009 Jan 21;(1):CD005305. DOI: 10.1002/14651858.CD005305.pub2

[3] Bolton CE, et al. British Thoracic Society guideline on pulmonary rehabilitation in adults. Thorax. 2013;**68**(Suppl 2):ii1-ii30

[4] Casaburi R. A brief history of pulmonary rehabilitation. Respiratory Care. 2008;**53**(9): 1185-1189

[5] Maltais F, et al. Skeletal muscle adaptation to endurancetraining in patients with chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine. 1996;**154**(2 Pt 1):442-447

[6] Spruit MA, et al. An official American Thoracic Society/European Respiratory Society statement: Key concepts and advances in pulmonary rehabilitation. American Journal of Respiratory and Critical Care Medicine. 2013;**188**(8):e13-e64

[7] Bernard S, et al. Aerobic and strength training in patients with chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine. 1999;**159**(3):896-901

[8] Griffiths TL, et al. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: A randomised controlled trial. Lancet. 2000;**355**(9201):362-368

[9] Ries AL, et al. Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. Annals of Internal Medicine. 1995;**122**(11):823-832

[10] Franssen FM, et al. Effects of whole-body exercise training on body composition and functional capacity in normal-weight patients with COPD. Chest. 2004;**125**(6):2021-2028

[11] Spruit MA, et al. Resistance versus endurance training in patients with COPD and peripheral muscle weakness. The European Respiratory Journal. 2002;**19**(6):1072-1078

[12] Swallow EB, et al. Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease. Thorax. 2007;**62**(2):115-120

[13] Ries AL, et al. Pulmonary rehabilitation: Joint ACCP/AACVPR evidence-based clinical practice guidelines. Chest. 2007;**131**(5 Suppl):4s-42s

[14] Casaburi R, et al. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. The American Review of Respiratory Disease. 1991;**143**(1):9-18

[15] Polkey MI, Rabe KF. Chicken or egg: Physical activity in COPD revisited. European Respiratory Journal. 2009;**33**(2):227-229

[16] Jones PW, et al. A self-complete measure of health status for chronic airflow limitation: The St. George's respiratory questionnaire. American Review of Respiratory Disease. 1992;**145**(6):1321-1327

[17] Kirshner B, Guyatt G. A methodological framework for assessing health indices. Journal of Chronic Diseases. 1985;**38**(1):27-36

[18] D-C Man W, et al. Community pulmonary rehabilitation after hospitalisation for acute exacerbations of chronic obstructive pulmonary disease: Randomised controlled study. British Medical Journal. 2004;**329**(7476):1209

[19] Ries AL, et al. The effects of pulmonary rehabilitation in the national emphysema treatment trial. Chest. 2005;**128**(6):3799-3809

[20] Garvey C, et al. Pulmonary rehabilitation exercise prescription in chronic obstructive pulmonary disease: Review of selected guidelines: An official statement from The American Association of Cardiovascular and Pulmonary Rehabilitation. Journal of Cardiopulmonary Rehabilitation and Prevention. 2016;**36**(2):75-83

[21] Medicine, A.C.o.S. ACSM's Guidelines for Exercise Testing and Prescription. Philadelphia PA: Lippincott Williams & Wilkins; 2013

[22] Jenkins S, Hill K, Cecins NM. State of the art: How to set up a pulmonary rehabilitation program. Respirology. 2010;**15**(8):1157-1173

[23] Nici L, et al. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. American Journal of Respiratory and Critical Care Medicine. 2006;**173**(12):1390-1413

[24] Trappenburg JC, et al. Psychosocial conditions do not affect short-term outcome of multidisciplinary rehabilitation in chronic obstructive pulmonary disease. Archives of Physical Medicine and Rehabilitation. 2005;**86**(9):1788-1792

[25] Haave E, Skumlien S, Hyland ME. Gender considerations in pulmonary rehabilitation. Journal of Cardiopulmonary Rehabilitation and Prevention. 2008;**28**(3):215-219

[26] Di Meo F, et al. Age does not hamper the response to pulmonary rehabilitation of COPD patients. Age and Ageing. 2008;**37**(5):530-535

[27] Garrod R, et al. Predictors of success and failure in pulmonary rehabilitation. European Respiratory Journal. 2006;**27**(4):788

[28] Evans RA, et al. Pulmonary rehabilitation is successful for COPD irrespective of MRC dyspnoea grade. Respiratory Medicine. 2009;**103**(7):1070-1075

[29] Sabit R, et al. Predictors of poor attendance at an outpatient pulmonary rehabilitation programme. Respiratory Medicine. 2008;**102**(6):819-824

[30] Berry MJ, et al. Exercise rehabilitation and chronic obstructive pulmonary disease stage. American Journal of Respiratory and Critical Care Medicine. 1999;**160**(4):1248-1253

[31] Chavannes N, et al. Effects of physical activity in mild to moderate COPD: A systematic review. The British Journal of General Practice. 2002;**52**(480):574-578

[32] Spruit MA, et al. Effects of moderate-to-high intensity resistance training in patients with chronic heart failure. Heart. 2009;**95**(17):1399-1408

[33] Tan KH, De Cossart L, Edwards PR. Exercise training and peripheral vascular disease. The British Journal of Surgery. 2000;**87**(5):553-562

[34] Bennell KL, Hinman RS. A review of the clinical evidence for exercise in osteoarthritis of the hip and knee. Journal of Science and Medicine in Sport. 2011;**14**(1):4-9

[35] O'Gorman DJ, Krook A. Exercise and the treatment of diabetes and obesity. Medical Clinics of North America. 2011;**95**(5):953-969

[36] Rees K, et al. Exercise based rehabilitation for heart failure. Cochrane Database of Systematic Reviews. 2010 Apr 14;(4):CD003331. DOI: 10.1002/14651858.CD003331.pub3

[37] Redelmeier DA, et al. Interpreting small differences in functional status: The six minute walk test in chronic lung disease patients. American Journal of Respiratory and Critical Care Medicine. 1997;**155**(4):1278-1282

[38] Munro PE, et al. Pulmonary rehabilitation following lung transplantation. Transplantation Proceedings. 2009;**41**(1):292-295

[39] Make B. Collaborative self-management strategies for patients with respiratory disease. Respiratory Care. 1994;**39**(5):566-579 discussion 579-83

[40] Bourbeau J, Nault D, Dang-Tan T. Self-management and behaviour modification in COPD. Patient Education and Counseling. 2004;**52**(3):271-277

[41] Rice KL, et al. Disease management program for chronic obstructive pulmonary disease: A randomized controlled trial. American Journal of Respiratory and Critical Care Medicine. 2010;**182**(7):890-896

[42] Bischoff EW, et al. Effects of written action plan adherence on COPD exacerbation recovery. Thorax. 2011;**66**(1):26-31

[43] Gosselink R. Breathing techniques in patients with chronic obstructive pulmonary disease (COPD). Chronic Respiratory Disease. 2004;**1**(3):163-172

[44] Lareau S, Larson JL. Ineffective breathing pattern related to airflow limitation. The Nursing Clinics of North America. 1987;**22**(1):179-191

[45] Jones AP, Rowe BH. Bronchopulmonary hygiene physical therapy for chronic obstructive pulmonary disease and bronchiectasis. Cochrane Database of Systematic Reviews. 2000;(2):CD000045

[46] From the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. www.goldcopd.org (cited July 2017)

[47] Spruit MA, et al. Rehabilitation and palliative care in lung fibrosis. Respirology. 2009;**14**(6):781-787

[48] Janssen DJA, et al. A call for high-quality advance care planning in outpatients with severe COPD or chronic heart failure. Chest. 2011;**139**(5):1081-1088

[49] Heffner JE. Advance care planning in chronic obstructive pulmonary disease: Barriers and opportunities. Current Opinion in Pulmonary Medicine. 2011;**17**(2):103-109

[50] Heim E, Blaser A, Waidelich E. Dyspnea: Psychophysiologic relationships. Psychosomatic Medicine. 1972;**34**(5):405-423

[51] Mills TL. Comorbid depressive symptomatology: Isolating the effects of chronic medical conditions on self-reported depressive symptoms among community-dwelling older adults. Social Science & Medicine. 2001;**53**(5):569-578

[52] Yohannes AM, Connolly MJ. Pulmonary rehabilitation programmes in the UK: A national representative survey. Clinical Rehabilitation. 2004;**18**(4):444-449

[53] Emery CF, et al. Psychological and cognitive outcomes of a randomized trial of exercise among patients with chronic obstructive pulmonary disease. Health Psychology. 1998;**17**(3):232-240

[54] Engelen MP, et al. Different patterns of chronic tissue wasting among patients with chronic obstructive pulmonary disease. Clinical Nutrition. 1999;**18**(5):275-280

[55] Schols AM, et al. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine. 1998;**157**(6 Pt 1):1791-1797

[56] Prescott E, et al. Prognostic value of weight change in chronic obstructive pulmonary disease: Results from the Copenhagen City heart study. The European Respiratory Journal. 2002;**20**(3):539-544

[57] Shoup R, et al. Body composition and health-related quality of life in patients with obstructive airways disease. European Respiratory Journal. 1997;**10**(7):1576-1580

[58] Marquis K, et al. Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine. 2002;**166**(6):809-813

[59] Mostert R, et al. Tissue depletion and health related quality of life in patients with chronic obstructive pulmonary disease. Respiratory Medicine. 2000;**94**(9):859-867

[60] Kobayashi A, et al. The relation of fat-free mass to maximum exercise performance in patients with chronic obstructive pulmonary disease. Lung. 2000;**178**(2):119-127

[61] Nishimura Y, et al. Relationship between respiratory muscle strength and lean body mass in men with COPD. Chest. 1995;**107**(5):1232-1236

[62] Weekes CE, Emery PW, Elia M. Dietary counselling and food fortification in stable COPD: A randomised trial. Thorax. 2009;**64**(4):326-331

[63] Taillefer M-C, et al. Health-related quality of life models: Systematic review of the literature. Social Indicators Research. 2003;**64**(2):293-323

[64] Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. Journal of the American Medical Association. 1995;**273**(1):59-65

[65] Guyatt GH, et al. A measure of quality of life for clinical trials in chronic lung disease. Thorax. 1987;**42**(10):773-778

[66] Williams JEA, et al. Health status measurement: Sensitivity of the self-reported chronic respiratory questionnaire (CRQ-SR) in pulmonary rehabilitation. Thorax. 2003;**58**(6):515

[67] Jones PW, et al. Development and first validation of the COPD assessment test. European Respiratory Journal. 2009;**34**(3):648

[68] Coventry PA. Does pulmonary rehabilitation reduce anxiety and depression in chronic obstructive pulmonary disease? Current Opinion in Pulmonary Medicine. 2009;**15**(2): 143-149

[69] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatrica Scandinavica. 1983;**67**(6):361-370

[70] Spruit MA, et al. Differences in content and organisational aspects of pulmonary rehabilitation programmes. European Respiratory Journal. 2014;**43**(5):1326-1337

[71] Troosters T, et al. Resistance training prevents deterioration in quadriceps muscle function during acute exacerbations of chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine. 2010;**181**(10):1072-1077

[72] Holland AE, et al. Home-based rehabilitation for COPD using minimal resources: A randomised, controlled equivalence trial. Thorax. 2016

[73] Fernandez AM, et al. Home-based pulmonary rehabilitation in very severe COPD: Is it safe and useful? Journal of Cardiopulmonary Rehabilitation and Prevention. 2009;**29**(5):325-331

[74] Rochester CL. An official American Thoracic Society/European Respiratory Society policy statement: Enhancing implementation, use, and delivery of pulmonary rehabilitation. Am J Respir Crit Care Med. 2015;**192**(11):1373-1386

[75] Keating A, Lee A, Holland AE. What prevents people with chronic obstructive pulmonary disease from attending pulmonary rehabilitation? A systematic review. Chronic Respiratory Disease. 2011;**8**(2):89-99

[76] Hogg L, et al. Effectiveness, attendance, and completion of an integrated, system-wide pulmonary rehabilitation service for COPD: Prospective observational study. Chronic Obstructive Pulmonary Disease. 2012;**9**(5):546-554

[77] Liu WT, et al. Efficacy of a cell phone-based exercise programme for COPD. The European Respiratory Journal. 2008;**32**(3):651-659

[78] Stickland M, et al. Using Telehealth technology to deliver pulmonary rehabilitation in chronic obstructive pulmonary disease patients. Canadian Respiratory Journal. 2011;**18**(4):216-220

[79] Lewis KE, et al. Does home telemonitoring after pulmonary rehabilitation reduce health-care use in optimized COPD? A pilot randomized trial. Chronic Obstructive Pulmonary Disease. 2010;**7**(1):44-50

[80] de Blok BM, et al. The effects of a lifestyle physical activity counseling program with feedback of a pedometer during pulmonary rehabilitation in patients with COPD: A pilot study. Patient Education and Counseling. 2006;**61**(1):48-55

[81] Polisena J, et al. Home telehealth for chronic obstructive pulmonary disease: A systematic review and meta-analysis. Journal of Telemedicine and Telecare. 2010;**16**(3):120-127

[82] Vogiatzis I, et al. American Journal of Respiratory and Critical Care Medicine

Chapter 7

Advances in Pulmonary Rehabilitation for Chronic Obstructive Pulmonary Disease and Associated Conditions

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Additional information is available at the end of the chapter

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Abstract

Pulmonary rehabilitation (PR) is an evidenced-based, proven treatment as mentioned recent guidelines in patients with chronic obstructive pulmonary disease (COPD). Exercise training is a cornerstone of PR programs, Inspiratory muscle training, neuromuscular electrical stimulation (NMES) are effective in selected patients. Water-based rehabilitation and tai chi are well tolerated recent modalities. Although there is an absence of a specific PR protocol for special conditions, PR is recommended before and also after endobronchial volume reduction (EBVR), lung volume reduction surgery (LVRS), both before and after lung transplantation periods, before, after surgery, during the intensive care unit (ICU) period, the chemotherapy period and as a component of palliative care. After COPD exacerbation, it is recommended within 3 weeks of hospital discharge. Modifying PR programs while considering comorbidities might lead to greater improvement in outcomes. After PR, the important points are to follow prescribed home exercise programs, control programs in the PR center/unit, and being more active in daily living life for the purpose of preserving improvements. Tele-PR is an alternative to conventional modalities due to similar improvements. Although PR is effective, it is an underutilized resource. The awareness of PR should be increased in patients and among health professionals.

Keywords: PR, exercise capacity, quality of life, perioperative lung transplantation, EBVR

1. Introduction

Chronic obstructive pulmonary disease (COPD), a systemic progressive disease that results in reduced exercise capacity and quality of life, progressive dyspnea, and mortality. It causes

health and economic burdens unless pharmacologic and nonpharmacologic treatments are optimized. One of the most important interventions is pulmonary rehabilitation (PR). It is a proven modality and is included in COPD treatment guidelines. The evidence-based benefits are improvement in exercise capacity and quality of life, recovery time after hospitalization, and survival; and reduction in perceived intensity of breathlessness, number of hospitalizations, and days in hospital; and enhancement of the effect of long-acting bronchodilators. Although most studies included patients with moderate-to-severe COPD and demonstrated evidence for these patients, PR is recommended for all patients who are symptomatic with reduced exercise capacity and quality of life, regardless of disease severity. PR is also an effective, feasible modality during the intensive care unit (ICU) period and early periods after exacerbation. The recommended time for PR is during the perioperative period in lung transplantation. Additionally, PR is required before endobronchial volume reduction (EBVR) and has shown to be beneficial before and after lung cancer surgery. This chapter outlines the pathophysiologies that give rise to indications for PR, the latest developments in PR, and PR modalities associated with COPD.

2. The definition of PR

PR is described as "a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behavior changes, that is designed to improve the physical and psychological conditions of people with chronic respiratory disease, and to promote the long-term adherence to health-enhancing behaviors [1]."

3. Pathophysiologies indicated for PR

3.1. Exercise limitation

Exercise intolarence is one of the most important and common symptoms experienced by patients with mild-to-severe COPD and are related to reduced health-related quality of life. Exercise intolerance in patients with COPD is primarily due to impaired ventilatory mechanics, but it is also associated with gas exchange limitation, cardiovascular factors, peripheral skeletal muscle dysfunction and a combination of these [2, 3]. Additionally, anxiety and poor motivation are other factors of exercise intolerance. Although the exact association has yet to be found, it is thought that anxiety and depression contribute to exercise intolerance [4], due to the effect that these have on increased symptom perception [5, 6].

Ventilatory limitation: Multiple factors determine ventilatory limitation, which consists of abnormalities in ventilatory mechanics and ventilatory muscle function. Other reasons for ventilatory limitation are increased ventilatory demands as a result of changes in gas exchange, and discordance in the neuroregulatory control of breathing. The most important pathophysiology in patients with COPD is expiratory flow limitation. During exercise, air becomes trapped, which results in dynamic lung hyperinflation (DH) above the already

increased resting volumes. Additionally, DH inhibits tidal volume expansion during exercise and contributes to cardiac dysfunction by increasing the positive intrathoracic pressures, which likely contribute to cardiac impairment [7].

Gas exchange limitation: Hypoxia is likely to limit exercise tolerance. Hypoxia increases pulmonary ventilation by enhancing output of peripheral chemoreceptors and production of lactic acid. Lactic acidemia results in increased pulmonary ventilation because of an increase in carbon dioxide production due to buffered lactic acid [8]. Above the lactic threshold, severe dyspnea correlates with increased work rates. Dyspnea may quickly increase. Furthermore, plasma norepinephrine and epinephrine also increase during exercise [9, 10].

Cardiovascular factors: In patients with COPD, the cardiovascular system is influenced by various mechanisms. The most important is an increase in right ventricular afterload through elevated pulmonary vascular resistance from direct vascular injury [11, 12], hypoxic vasoconstriction [13], and/or increases in effective pulmonary vascular resistance due to erythrocytosis [14]. In the course of time, the overloaded right ventricle leads to right ventricular hypertrophy, which could result in right ventricular failure [15]. During exercise, pulmonary vascular resistance is rapidly increased due to breathing at lung volumes close to total lung capacity [16, 17]. Lung hyperinflation and excessive expiratory muscle recruitment are likely to reduce venous return and right ventricular preload in COPD [18, 19]. Moreover, during exercise, large intrathoracic pressure swings for the purpose of overcoming the increased elastic and resistive loads, may result in left ventricular dysfunction by increasing left ventricular afterload [20, 21]. These right ventricular effects can also compromise left ventricular filling through septal shifts that further reduce the ability of the heart to meet exercise demands [22].

Peripheral skeletal muscle dysfunction: Skeletal muscle dysfunction in patients with COPD is characterized by remarkably decreased muscle strength and endurance. The mechanisms are reduction in muscle mass and proportion of oxidative fibers, increases in the proportion of glycolytic fibers and muscle atrophy, and also a detoriation of oxidative metabolic capacity due to reductions in mitochondrial enzyme activities and capillary density. Additionally, systemic inflammation; malnutrition; corticosteroid use; hypoxemia; aging; smoking; the production of reactive oxygen and nitrogen species; enhanced protein degradation inside muscle fibers; increased activities of the proteasomal and lysosomal pathways; and activation of calpains and caspases contribute to muscle dysfunction. Therefore, patients with COPD enter into a vicious circle owing to disuse and inactivity due to the aforementioned mechanisms [23].

3.2. Body composition disorders

Unexplained weight loss occurs in about 50% of patients with severe COPD and 15% of patients with mild-to-moderate COPD [24, 25]. The main cause of weight loss in COPD is the reduction in skeletal muscle mass rather than loss of fat mass. Based on the reduction of fat mass or fat-free mass index (FFMI), nutritional abnormalities in COPD have been categorized into four types. Normal body mass index (BMI) with normal FFMI is normal, low BMI with normal or above-normal FFMI is defined as semistarvation, normal or above-normal BMI with low FFMI is defined as muscle atrophy, and low BMI with low FFMI as cachexia [26]. There are several reasons for weight loss in patients with COPD, even if during a stable period. In patients

with stable COPD, there is an increased metabolic rate due to abnormal respiratory dynamics, chronic systemic inflammation, and drugs [27–31]. In malnourished mobile patients with COPD, although the basal metabolic rate is reduced, the resting energy expenditure is high. During exercise, inefficient muscle contractions due to increased consumption of adenosine triphosphate are added on. Also, there is an increase in the levels of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL) 1 in circulation. TNF-α and IL1 have been shown to contribute to weight loss even in healthy individuals [32].

3.3. Psychological status

Patients with COPD have a higher prevalence of depression and anxiety than the general population [33] and a higher risk for developing depression [34]. The etiology of the association between depression and COPD has not been revealed clearly. The most important risk factor for COPD is smoking. Depressed individuals are more likely to smoke [35], have a tendency to smoking [36, 37], and find smoking cessation more difficult [35, 38]. Conversely, smokers are more likely to be depressed [39], which could be caused by activation of nicotinic acetylcholine receptors [40], and the inflammatory effects of smoking [41]. Soluble tumor necrosis factor receptor-1 has shown to be associated with rates of depression in patients with COPD [42], but there is not exact relationship between TNF-α and COPD [43, 44]. Hypoxia is thought be an additional factor in the development of depression in COPD. Low arterial oxygen saturation has been shown to be associated with periventricular white matter lesions [45], which are found in patients with depression [46]. Other important risk factors are the severity of symptoms and reported quality of life [47]. Depression is found more frequently in support-bound patients with COPD [48].

4. Content of PR programs

4.1. Exercise training

Exercise training is a cornerstone of PR programs. Exercise training is shown to be the best approach for increasing muscle strength, is likely to improve motivation for exercise, reduce mood abnormalities [49, 50], decrease symptoms [51], and improve cardiovascular function [1]. As recent major guidelines recommend, the main components of exercise training programs for patients with COPD are endurance and resistance training, which should be included in PR programs. Although none of the guidelines make clear, specific, and accurate recommendations for whole exercise training, they agree on endurance training at least 3 to 5 times weekly >60% of the maximal work rate. However, there is no consensus of initial workloads or in increasing the exercise load or program duration; the duration of exercise is recommended for at least 20 minutes and a target program duration of up to 12 weeks [52].

Inspiratory muscle training (IMT): Respiratory muscle training is a part of rehabilitation in selected patients with COPD. Respiratory strength has been found to correlate with improved pulmonary function, reduction of dyspnea severity, improved exercise tolerance, and enhanced functionality and quality of life [53, 54]. IMT is thought to contribute to contraction of the diaphragm by increasing type II fibers [55], which results in reduced inspiratory time [56] and

subsequently increased expiratory time. Hyperinflation is expected to eventually diminish [57]; therefore, IMT is thought to impact on dyspnea without any significant change in inspiratory pressure [58, 59].

Neuromuscular electrical stimulation (NMES): NMES is one of the recent rehabilitation modalities that involve passive stimulation of contraction of the peripheral muscles through the application of an electric current via electrodes placed on the skin over the targeted muscles by depolarizing motor neurons. It aims to elicit beneficial training effects without causing dyspnea in patients who are unable to participate in PR programs. The stimulation-pulse duration is usually 250–400 μs, and stimulation frequency ranges from 8 to 120 Hz. Intensities range from 10 to 100 mA, and these are gradually increased throughout the entire stimulation according to the patient's individual tolerance. In a meta-analysis published in 2016, it was found that NMES improved quadriceps strength and exercise capacity; however, there was no statistically significant improvement in the degree of health-related quality of life in patients with moderate-to-severe COPD [60]. In several studies, it has been reported that NMES had an impact on the increase in type II fiber cross-sectional area with a decrease in type I fiber cross-sectional area of the muscle, and on the decrease in muscle oxidative stress in patients with COPD. Owing to the fact that NMES has a low impact on ventilation, heart rate, and dyspnea, it could be applied during periods of exacerbation, and during admission to the ICU for acute COPD exacerbation [61, 62].

Recent exercise training approaches: Besides conventional exercise trainings, there have been a few papers published recently about alternative exercise training modalities in patients with COPD. According to these studies, water-based rehabilitation [63] and tai chi were found as well tolerated and enjoyable [64, 65].

4.2. Other interventions

PR programs should be comprehensive and individualized according to patients' needs. Other interventions are breathing strategies, bronchial hygiene techniques, psychological and nutritional recommendations and support if needed, and education of patients and care givers. Body composition abnormalities, especially malnutrition, have already been found to increase risks of mortality among patients with COPD. A significant improvement has been shown in pulmonary function in patients with COPD who have a higher fat, lower carbohydrate diet than the traditional high-carbohydrate diet [66]. Omega-3 polyunsaturated fatty acids (PUFA) have been shown to have an antiinflammatory effect and be effective in patients with COPD [67]. It is also important to relapse any deficiency of vitamin D due to the association with early progression, myopathy/muscle weakness, and the immune-modulatory effect of vitamin D [27].

5. Outcomes and response to PR

It has been demonstrated that PR is the most effective therapeutic approach for improving dyspnea, health status, and exercise tolerance [68]. It is also one of the most cost effective

therapeutic strategies. Additionally, it reduces hospitalizations among patients who have had recent exacerbations [69]. Improvements are seen among all grades of COPD severity, but recommendations are stronger in moderate-to-severe COPD. In some studies, improvements of outcomes were seen regardless of baseline lung function, dyspnea, and exercise capacity [70].

5.1. Exercise capacity

Various exercise tests are used for evaluating exercise capacity, the mechanisms of main disruption, and the response to PR. Some are also strong independent prognostic factors in patients with COPD. There are several laboratory-based exercise tests that use either maximal incremental or constant workload protocols to evaluate exercise performance after PR. Field tests are more widely used and more practical to perform. The six-minute walk test (6MWT), incremental and endurance shuttle walk test (ISWT, ESWT) are standardized and have also been used in PR and various clinical trials. In COPD, endurance tests [constant work rate exercise test (CWRET) and ESWT] are more responsive to interventions than other types of tests. The cycle ergometer CWRET has been used more widely than ESWT. By using CWRET, the work rate, inspiratory capacity, and isotime responses, which verify potential mechanisms of improvement or deterioration, are accurately measured [71].

The ISWT is a significant predictor of survival, readmission, and is usually sensitive to PR in patients with COPD [72]. In a recent meta-analysis of nine trials, a mean improvement of 38 m was found [68]. After recovering from a stay in the ICU, ISWT was found to improve by a mean of 64 m after rehabilitation [72]. ESWT duration was found as moderately correlated with FEV1, but not with muscle mass or strength in patients with COPD [73]. ESWT is responsive to PR improving by 100–400 s. [71]. According to a meta-analysis of rehabilitative interventions in COPD, the mean effect of rehabilitation on 6MWD was 44 m when treatment and control groups were compared [74].

Peak oxygen uptake (V′O2peak) shows the highest oxygen uptake during incremental exercise tests by achieving the subject's limit of tolerance. With good subject effort, V′O2peak is closely reflective of the subject's "maximum" V′O2, the gold standard index of aerobic capacity [75]. There is very little information about what constitutes a minimal clinically important difference (MCID) in V′O2peak. In the National Emphysema Treatment Trial (NETT), 4 ± 1 W was considered the symptoms-anchored MCID in patients with severe COPD [76], with a V′O2peak change of ~0.04 ± 0.01 L·min^{-1}. In several studies including patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages 2–4 COPD V′O2peak has been shown to moderately significantly increase after lower limb endurance muscle training. After PR in patients with COPD, V′O2peak was found to be in the range 0.1–0.5 L·min^{-1} or ~10–40% of baseline, with a mean improvement of ~11% [77, 78].

5.2. Health-related quality of life daily living activities

In a recent study, it was aimed to determine the responsiveness of St. George's Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT), COPD Clinical Questionnaire (CCQ), and Hospital Anxiety and Depression Scale (HADS) to PR in 419 patients with COPD, and also estimate the MCID for CAT, CCQ, and HADS. It was demonstrated that SGRQ, CAT,

CCQ, and HADS were responsive to PR in patients with moderate-to-very-severe COPD. The calculated MCID ranges were −3.0 to −2.0 points for CAT; −0.5 to −0.3 points for CCQ; −1.8 to −1.3 points for HADS-A, and −1.7 to −1.5 points for HADS-D [79].

6. PR in special conditions

6.1. Before and after transplantation

Lung transplantation is a recommended intervention in patients with advanced-stage pulmonary disease who are unresponsive to pharmacologic and nonpharmacologic treatment. Factors such as chronic respiratory failure, cardiovascular risk factors, muscular and nutritional conditions, which are likely to influence the prognosis for a successful lung transplantation, usually accompany advanced chronic respiratory disorders. Therefore, PR is an important approach that modifies and controls potential risk factors. PR plays an important role for the maintenance of exercise tolerance and physical functioning [80] both before and after the lung transplantation because common extra pulmonary manifestations could be persistent or deteriorate. As such, PR is recommended both before and after lung transplantation. Although there is an absence of a specific PR protocol for patients for lung transplant, it was shown to improve maximal and functional exercise capacity, quality of life, and skeletal muscle function [81].

Before transplantation: The role of PR in preoperative patients is essential for quitting smoking, improving body composition, optimizing medical treatment, and restoring patients' independence for functioning, relieving symptoms, decreasing disability, and improving quality of life by increasing their participation in social and physical activities. It has been shown that the rate of success in lung transplantation was linked to exercise capacity and resting carbon dioxide in arterial blood values [82]. Those parameters were also found to predict hospital stay after surgery and mortality. Additionally, pretransplant PR was also found to be associated with decreased posttransplant ICU days, mechanical ventilation, and chest tube days and survey [83]. Multidisciplinary, comprehensive PR must be individualized and the modality and intensity of training must be selected for each patient. The duration of training can vary from 6 weeks to 6 months [84]. The program should consist of education (including the following topics: bronchial hygiene, breathing control techniques, relaxation, education about COPD, and education of relatives and energy conservation), exercise training (upper and lower limb aerobic exercise, resistance training, flexibility, inspiratory muscle training), psychological support, and nutritional support. The intensity of exercise is dynamically increased according to the progress of each individual patient.

After transplantation: Although pulmonary functions are improved after transplantation, limited exercise capacity is persistent due to different mechanisms. Persistent limited exercise capacity is not only associated with ventilatory or cardiovascular factors [85, 86], skeletal muscle dysfunction is the main problem. Skeletal muscle changes include impaired oxidative capacity, lactate threshold changes, and a lower proportion of type I muscle fibers [87]. A sedentary life style both before and after transplantation contributes to skeletal muscle weakness [88]. Hospitalizations due to

infections or acute rejections and the use of immunosuppressive medication further impact muscle function in lung recipients [89]. It was found that V'O2 peak was 45–52% predicted in patients after lung transplantation for up to 2 years. Patients stop exercise because of leg fatigue, rather than dyspnea [90]. Additionally, maximal cycle-work capacity correlates better with isokinetic cycling work capacity than with pulmonary function after lung transplantation [91]. PR should be started in the ICU with positioning of the patient, ventilation of all lung lobes, and mobilization of secretions by managing cough. Deep breathing exercises should be initiated because tachypnoea and pursed-lip breathing persist postoperatively and old breathing patterns must be overcome. Sitting and mobilization out of bed should then be performed. After all chest drains have been removed, walking or cycle ergometry should performed. Muscle strength and function, and endurance training should focus on lower extremities, and weights can be limited to 3 kg initially for upper extremities [92]. After discharge, patients should be referred to PR center/units as soon as possible. Although there is no consensus on optimal exercise training and education programs, aerobic and strength exercise training of the lower and upper extremities 2–3 times per week for 6–8 weeks, are recommended. The intensity of exercise can be increased according to patient tolerance. High-intensity aerobic exercise training at 60–80% of maximal work capacity has been found to be correlated with physiologic improvements in patients with stable COPD. Hence, high-intensity training is preferred. Interval training could be applied in patients who cannot sustain continuous high-intensity. Stretching, flexibility, and chest-mobility exercises may also be an important component of exercise after LVRS or transplantation [1, 82, 93]. Education of patients and care givers is also an important issue.

6.2. Lung volume resection surgery (LVRS)

Similar recommendations are valid for LVRS, which is not usually an effective intervention for exercise intolerance and functional disability. Baseline skeletal muscle dysfunction, time needed to achieve postoperative improvement in lung function (peak benefits are usually seen 6–12 months after surgery), and inactivity/immobility associated with the perioperative period are factors that reduce exercise capacity. Several studies compared the benefits of LVRS and several-weeks'–duration comprehensive PR in patients with severe emphysema. PR was found to significantly improve exercise tolerance, health status, and dyspnea, without significant changes in lung function as compared with PR and LVRS, even if highly selected patients showed significantly better improvement in lung function [94–97], exercise capacity [95–97], and quality of life [96, 97].

6.3. Endobronchial volume reduction (EBVR)

Endobronchial volume reduction interventions result in improved spirometric measures and 6MWD at 6 months, only if in correctly selected subjects. PR is recommended before and after EBVR, which is indicated in the presence of persistent dyspnea despite maximal medical therapy and PR, and reduced exercise capacity (6MWD ≥140 m after rehabilitation) [97].

6.4. Lung cancer

In patients with lung cancer, exercise limitations can be due to the effects of the cancer, coexisting morbidities, and/or the effects of treatment and surgery. Cancer-related anemia, and muscle atrophy and dysfunction contribute to limited exercise capacity. Inactivity due to

cancer and its comorbidities further compound this situation. In the pre- and postoperative period, quitting smoking, optimizing COPD medical treatment, educating patients, prophylaxis for thrombosis, and PR are the recommended approaches that decrease risks. PR is an effective and feasible intervention before and after surgery, during the chemotherapy period, and as a component of palliative care. Even though PR consists of an exercise program for lower and upper extremities, breathing, airway clearance techniques, oxygen therapy, bronchodilator optimization, and self-management training similar to other conditions, it should also be individualized and multidisciplinary in patients with cancer.

Even though surgical procedures have improved and patients are highly selected, morbidity and mortality rates are still increasing as a consequence of cardiopulmonary complications after surgery. Limited exercise capacity as a modifiable risk factor is the best independent predictor of postoperative complications. Multidisciplinary preoperative PR improves exercise capacity and postoperative recovery, and reduces hospital stay and pulmonary infections [98]. During the chemotherapy period, symptoms such as fatigue, breathlessness, and quality of life are likely to deteriorate. Exercise training improves fatigue, aerobic capacity, muscular strength, and physical and functional activity in patients with cancer, even though they are undergoing chemotherapy [99]. Breathing techniques and medications that result in reduced inflammation and opened airways in combination with exercise training have recently become a part of supportive care for patients undergoing chemotherapy and radiation therapy [100]. PR plays a role in the management of terminal cancer. Exercise training modalities include walking with/without assistance or device, passive or active strengthening exercises, continuous passive motion, passive or active range of motion, NMES, and pain management interventions such as massage and heating pads [101]. Oxygen therapy has an important role in palliative care because it both treats hypoxemia and reduces the sensation of dyspnea. Additionally, education about mobilization with assistive devices, environmental modification, energy conservation, and work simplification techniques are also beneficial. These interventions have been investigated and were shown to be effective in cancer-related fatigue in several studies [102–104]. In another study, it was shown that exercise training decreased anxiety, stress, depression, and there were improvements in pain, fatigue, shortness of breath, constipation, and insomnia in patients with cancer, even at advanced stages [105].

6.5. Exacerbation of COPD

COPD exacerbations are known to deteriorate life quality, disease progression, and mortality. The British Thoracic Society (BTS) recommends the initiation of PR within 1 month of hospital discharge after exacerbation, consisting of a minimum of twice-weekly supervised sessions lasting between 6 and 12 weeks [106]. Exercise should combine progressive muscle resistance and aerobic training [106]. Systematic reviews have shown that quality of life and daily functioning were improved with large and important clinical effects of PR [107, 108]. According to the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines of management of COPD exacerbations, PR added to medical treatment during hospitalization increases mortality [109]; however, NMES and resisted quadriceps exercises performed during hospitalization during exacerbation have been shown to improve muscle strength without increasing systemic inflammation. PR that is started within 3 weeks of discharge following a COPD exacerbation reduces hospital admissions, improves quality of life, and also

increases exercise capacity when implemented within 8 weeks of discharge. Although the best approach is indistinct and further investigations are necessary, a combination of regular exercise with breathing technique training has been shown to be superior [109].

6.6. PR in the intensive unit care

In the ICU, skeletal muscle mass is lost at a rate of 5% per week. This neuromuscular weakness has been found to be correlated with the duration of mechanical ventilation, and associated with functional disability and decreased quality of life for up to 5 years after hospitalization. Mobilization and rehabilitation of critically ill patients might improve physical functioning and decrease duration of mechanical ventilation and ICU length of stay [110, 111]. A meta-analysis was published in 2017 that consisted of studies with PR programs containing patient mobilization, walking, standing, breathing exercises, in-bed supine cycle ergometry, passive-active range of motion (ROM), and NMES. It was shown that early mobilization and physical rehabilitation of critically ill patients seemed to be safe, with a low risk of potential safety events, even if as a usual care. Although the definition of safety assessments was heterogeneous, it was emphasized that the awareness and implementation of existing recommendations should be increased [112].

6.7. Patients with hypercapnia

Hypercapnia is an indicator of alveolar hypoventilation due to an overload on the ventilatory pump that is greater than its capacity. In patients with COPD, diminished ventilatory response usually results in chronic retention of carbon dioxide. Chronic respiratory failure is frequently seen in the end stage of the progression of COPD. In the BTS guidelines, it is mentioned that patients with chronic respiratory failure gain as much benefit as those without chronic respiratory failure from PR with level 3 evidence [106]. A study showed that pCO2 levels were significantly more reduced in patients with COPD with pursed-lip and diaphragmatic breathing exercises during hospitalization period than in a control group. It was suggested that respiratory exercise training was quite effective in reducing pCO2 levels. As the guidelines recommend, patients with COPD should be referred for PR regardless of having chronic respiratory failure [113].

Noninvasive mechanical ventilation (NIMV): Noninvasive mechanical ventilation (NIMV) reduces breathlessness and increases exercise tolerance by reducing the acute load on the respiratory muscles. According to these mechanisms, the effect of NIMV on PR outcomes has been investigated in several studies in which NIMV was applied during exercise training or at night. In a review of the Cochrane Database in which the effect of NIMV was investigated during exercise training as a part of PR, it was shown that NIMV during exercise training improved exercise capacity of the lower limbs, and enabled exercise at higher training intensities. There was no definite evidence about quality of life and none of the studies investigated the effect of NIMV during exercise training on physical activity [114]. It has also been shown that exercise tolerance and quality of life were improved in patients with severe COPD using nocturnal NIMV after PR, presumably through resting the respiratory muscles at night [115]. As a recommendation of the ERS/ATS guidelines, NIMV could be an adjunctive therapy to

unload the respiratory muscles for the purpose of increasing the intensity of exercise training in selected patients with severe chronic respiratory disease who have a suboptimal response to exercise [1].

6.8. Comorbidities

The most common comorbidities associated with COPD are cardiovascular disease, orthopedic problems, metabolic disease, depression, and anxiety. It is expected that comorbidities may effect the outcomes of PR as an impact on COPD outcomes such as quality of life, health care costs, and mortality rate. Various comorbidities such as anxiety and depression, cardiovascular disease, metabolic disease, and osteoporosis affected PR outcomes in some studies [116–121]; a meta-analysis could not be performed according to the heterogeneous results. Only four studies investigated the influence of the number of comorbidities on PR outcomes. Three of which showed that the number of comorbidities was not related to PR outcomes [117, 119, 120]. A study showed that metabolic disease negatively influenced 6MWT distance, whereas cardiac disease negatively influenced the St. George's Respiratory Questionnaire [118]. A prior study of patients with COPD with osteoarthritis and neurologic problems who were assigned to water-based exercise training reported a greater improvement in outcomes compared with land-based exercise training [121]. Previous studies have identified that patients with psychiatric problems experienced a lesser improvement in dyspnea [117], and patients with metabolic disease demonstrated a greater improvement in dyspnea after PR compared with controls [118]. A study was published in 2017 that included 165 patients with COPD with exercise limitations. Comorbidity was classified as cardiac, metabolic, orthopedic, behavioral health problems, or other diseases. Comorbidities were found to have no effect on the maximal incremental exercise test and constant workload cycle endurance time after PR. Patients with cardiac disease were found to have greater improvements in dyspnea scores than those with no cardiac disease, and patients with orthopedic problems had a smaller but clinically significant improvement in dyspnea after PR [122]. Modifying PR programs with consideration to comorbidities might lead to greater improvement in outcomes, but how to structure programs according to comorbidities is still to be determined.

7. Follow-up programs of PR and Tele-PR

The best and the most effective follow-up program have not been found. After PR, the important points are to follow prescribed home exercise programs and follow-up programs in the PR center/unit, and to be more active in daily living life for the purpose of preserving improvements. Accordingly, family members have a role that is as important as that of the PR center staff in encouraging and motivating the patients. In a cohort of patients with COPD who completed a 10-week comprehensive PR program, a structured follow-up home program was prescribed and the patients were monitored for 1 year. At the 1-year follow-up evaluation, only the patients who continued with the home program had maintained the improvements of the initial PR program in endurance capacity, and psychological and cognitive functioning [123, 124]. Despite the clear benefits of PR, it is often an under-utilized resource. Limited

access and poor adherence result in <5% of eligible people with COPD receiving PR each year. Although the traditional models of inpatient and outpatient PR are suitable for many patients, alternative models may also be effective and may improve patient access, particularly in regions or healthcare systems where traditional models of PR are not feasible. For example, tele-rehabilitation, which links expert rehabilitation healthcare providers with others at a remote site or with patients in their homes, also has the potential to improve access [125]. A recent study showed that home-based maintenance tele-rehabilitation was equally as effective as hospital-based, outpatient, maintenance PR in reducing the risk for acute exacerbations of COPD and hospitalizations with lower risk for emergency department visits. It was suggested that tele-rehabilitation was likely to be an effective alternative strategy to hospital-
based, outpatient, maintenance PR. In addition, it had a potential economic advantage com-pared with standard PR [126]. Tele-PR has been developed to improve patients' participation and treatment adherence, but the most important point is awareness. The awareness of PR should be increased in patients and among health professionals.

Author details

References

[1] Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: Key concepts and advances in pulmonary rehabilitation. American Journal of Respiratory and Critical Care Medicine. 2013;**188**(8):13-64

[2] MacIntyre NR. Mechanisms of functional loss in patients with chronic lung disease. Respiratory Care. 2008;**53**(9):1177-1184

[3] European Respiratory Society Task Force. Clinical exercise testing with reference to lung diseases: Indications, standardization and interpretation strategies. The European Respiratory Journal. 1997;**10**(11):2662-2689

[4] Borak J, Chodosowska E, Matuszewski A, Zielinski J. Emotional status does not alter exercise tolerance in patients with chronic obstructive pulmonary disease. The European Respiratory Journal. 1998;**12**:370-373

[5] Janson C, Bjornsson E, Hetta J, Boman G. Anxiety and depression in relation to respiratory symptoms and asthma. American Journal of Respiratory and Critical Care Medicine. 1994;**149**:930-934

[6] Parekh PI, Blumenthal JA, Babyak MA, Merrill K, Carney RM, Davis RD, Palmer SM. Psychiatric disorder and quality of life in patients awaiting lung transplantation. Chest. 2003;**124**:1682-1688

[7] O'Donnell DE. Ventilatory limitations in chronic obstructive pulmonary disease. Medicine and Science in Sports and Exercise. 2001 Jul;**33**(7 Suppl):S647-S655

[8] Somfay A, Porszasz J, Lee SM, Casaburi R. Effect of hyperoxia on gas exchange and lactate kinetics following exercise onset in nonhypoxemic COPD patients. Chest. 2002;**121**:393-400

[9] Wasserman K, Hansen JE, Sue DY, Stringer W, Whipp BJ. Principles of Exercise Testing and Interpretation. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 41

[10] Weltman A, Wood CM, Womack CJ, Davis SE, Blumer JL, Alvarez J, et al. Catecholamine and blood lactate responses to incremental rowing and running exercise. Journal of Applied Physiology. 1994;**76**(3):1144-1149

[11] World Health Organization. Definition of chronic corpulmonale. Circulation. 1963;**27**: 594-615

[12] Santos S, Peinado VI, Ramirez J, Melgosa T, Roca J, Rodriguez-Roisin R, Barbera JA. Characterization of pulmonary vascular remodelling in smokers and patients with mild COPD. The European Respiratory Journal. 2002;**19**:632-638

[13] Voelkel NF, Tuder RM. Hypoxia-induced pulmonary vascular remodeling: A model for what human disease? The Journal of Clinical Investigation. 2000;**106**:733-738

[14] Chetty KG, Brown SE, Light RW. Improved exercise tolerance of the polycythemic lung patient following phlebotomy. The American Journal of Medicine. 1983;**74**:415-420

[15] Sietsema K. Cardiovascular limitations in chronic pulmonary disease. Medicine and Science in Sports and Exercise. 2001;**33**:S656-S661

[16] Ranieri VM, Dambrosio M, Brienza N. Intrinsic PEEP and cardiopulmonary interaction in patients with COPD and acute ventilatory failure. The European Respiratory Journal. 1996;**9**:1283-1292

[17] Oswald-Mammosser M, Kessler R, Massard G, et al. Effect of lung volume reduction surgery on gas exchange and pulmonary hemodynamics at rest and during exercise. American Journal of Respiratory and Critical Care Medicine. 1998;**158**:1020-1025

[18] Mahler DA, Brent BN, Loke J, et al. Right ventricular performance and central circulatory hemodynamics during upright exercise in patients with chronic obstructive pulmonary disease. The American Review of Respiratory Disease. 1984;**130**:722-729

[19] Miller JD, Pegelow DF, Jacques AJ, et al. Effects of augmented respiratory muscle pressure production on locomotor limb venous return during calf contraction exercise. Journal of Applied Physiology. 2005;**99**:1802-1815

[20] Oswald-Mammosser M, Apprill M, Bachez P, et al. Pulmonary hemodynamics in chronic obstructive pulmonary disease of the emphysematous type. Respiration. 1991;**58**:304-310

[21] Montes de Oca M, Rassulo J, Celli BR. Respiratory muscle and cardiopulmonary function during exercise in very severe COPD. American Journal of Respiratory and Critical Care Medicine. 1996;**154**:1284-1289

[22] MacNee W. Pathophysiology of corpulmonale in chronic obstructive pulmonary disease: Part one. American Journal of Respiratory and Critical Care Medicine. 1994;**150**:833-852

[23] Kim HC, Mofarrahi M, Hussain NA. Skeletal muscle dysfunction in patients with chronic obstructive pulmonary disease. International Journal of COPD. 2008;**3**(4):637-658

[24] Creutzberg EC, Schols AM, Bothmer-Quaedvlieg FC, Wouters EF. Prevalence of an elevated resting energy expenditure in patients with chronic obstructive pulmonary disease in relation to body composition and lung function. European Journal of Clinical Nutrition. 1998;**52**:396-401

[25] Choudhury G, Rabinovich R, MacNee W. Comorbidities and systemic effects of chronic obstructive pulmonary disease. Clinics in Chest Medicine. 2014;**35**:101-130

[26] Schols AM, Broekhuizen R, Weling-Scheepers CA, Wouters EF. Body composition and mortality in chronic obstructive pulmonary disease. The American Journal of Clinical Nutrition. 2005;**82**:53-59

[27] Vermeeren MA, Creutzberg EC, Schols AM, et al. Prevalence of nutritional depletion in a large out-patient population of patients with COPD. Respiratory Medicine. 2006;**100**: 1349-1355

[28] Agusti AG. Systemic effects of chronic obstructive pulmonary disease. Proceedings of the American Thoracic Society. 2005;**2**:367-370 discussion 371-372

[29] Vermeeren MA, Wouters EF, Geraerts-Keeris AJ, Schols AM. Nutritional support in patients with chronic obstructive pulmonary disease during hospitalization for an acute exacerbation; a randomized controlled feasibility trial. Clinical Nutrition. 2004;**23**:1184-1192

[30] Brug J, Schols A, Mesters I. Dietary change, nutrition education and chronic obstructive pulmonary disease. Patient Education and Counseling. 2004;**52**:249-257

[31] Creutzberg EC, Wouters EF, Mostert R, et al. Efficacy of nutritional supplementation therapy in depleted patients with chronic obstructive pulmonary disease. Nutrition. 2003;**19**: 120-127

[32] Sehgal S, Dhooria S, Agarwal R. Chronic obstructive pulmonary disease and malnutrition in developing countries. Current Opinion in Pulmonary Medicine. 2017;**23**:139-148

[33] Hynninen KM, Breitve MH, Wiborg AB, et al. Psychological characteristics of patients with chronic obstructive pulmonary disease: A review. Journal of Psychosomatic Research. 2005;**59**:429-443

[34] Atlantis E, Fahey P, Cochrane B, et al. Bidirectional associations between clinically relevant depression or anxiety and COPD: A systematic review and meta-analysis. Chest. 2013;**144**:766-777

[35] Glassman AH, Helzer JE, Covey LS, et al. Smoking, smoking cessation, and major depression. JAMA. 1990;**264**:1546-1549

[36] Fergusson DM, Lynskey MT, Horwood LJ. Comorbidity between depressive disorders and nicotine dependence in a cohort of 16-year-olds. Archives of General Psychiatry. 1996; **53**:1043-1047

[37] Patton GC, Hibbert M, Rosier MJ, et al. Is smoking associated with depression and anxiety in teenagers? American Journal of Public Health. 1996;**86**:225-230

[38] Glassman AH, Covey LS, Stetner F, et al. Smoking cessation and the course of major depression: A follow-up study. Lancet. 2001;**357**:1929-1932

[39] Wiesbeck GA, Kuhl HC, Yaldizli O, et al. Tobacco smoking and depression--results from the WHO/ISBRA study. Neuropsychobiology. 2008;**57**:26-31

[40] Mineur YS, Picciotto MR. Nicotine receptors and depression: Revisiting and revising the cholinergic hypothesis. Trends in Pharmacological Sciences. 2010;**31**:580-586

[41] Sinden NJ, Stockley RA. Systemic inflammation and comorbidity in COPD: A result of 'overspill' of inflammatory mediators from the lungs? Review of the evidence. Thorax. 2010;**65**:930-936

[42] Eagan TM, Ueland T, Wagner PD, et al. Systemic inflammatory markers in COPD: Results from the Bergen COPD cohort study. The European Respiratory Journal. 2010;**35**:540-548

[43] Al-shair K, Kolsum U, Dockry R, et al. Biomarkers of systemic inflammation and depression and fatigue in moderate clinically stable COPD. Respiratory Research. 2011;**12**:3

[44] Marinho PE, Castro CM, Raposo MC, et al. Depressive symptoms, inflammatory markers and body composition in elderly with and without chronic obstructive pulmonary disease (COPD). Archives of Gerontology and Geriatrics. 2012;**54**:453-458

[45] van Dijk EJ, Vermeer SE, de Groot JC, et al. Arterial oxygen saturation, COPD, and cerebral small vessel disease. Journal of Neurology, Neurosurgery, and Psychiatry 2004;**75**:733-736.

[46] Campbell JJ 3rd, Coffey CE. Neuropsychiatric significance of subcortical hyperintensity. The Journal of Neuropsychiatry and Clinical Neurosciences. 2001;**13**:261-288

[47] Dunlop DD, Lyons JS, Manheim LM, et al. Arthritis and heart disease as risk factors for major depression: The role of functional limitation. Medical Care. 2004;**42**:502-511

[48] Penninx BW, van Tilburg T, Boeke AJ, et al. Effects of social support and personal coping resources on depressive symptoms: Different for various chronic diseases? Health Psychology 1998;**17**:551-558

[49] Emery CF, Leatherman NE, Burker EJ, MacIntyre NR. Psychological outcomes of a pulmonary rehabilitation program. Chest. 1991;**100**:613-617

[50] Emery CF, Schein RL, Hauck ER, MacIntyre NR. Psychological and cognitive outcomes of a randomized trial of exercise among patients with chronic obstructive pulmonary disease. Health Psychology. 1998;**17**:232-240

[51] O'Donnell DE, McGuire M, Samis L, Webb KA. The impact of exercise reconditioning on breathlessness in severe chronic airflow limitation. American Journal of Respiratory and Critical Care Medicine. 1995;**152**:2005-2013

[52] Garvey C, Bayles MP, Hamm LF, Hill K, Holland A, Limberg TM, Spruit MA. Pulmonary rehabilitation exercise prescription in chronic obstructive pulmonary disease: Review of selected guidelines. Journal of Cardiopulmonary Rehabilitation and Prevention. 2016;**36**: 75-83

[53] Mota S, Güell R, Barreiro E, Solanes I, Ramírez-Sarmiento A, OrozcoLevi M, et al. Clinical outcomes of expiratory muscle training in severe COPD patients. Respiratory Medicine. 2007;**101**(3):516-524

[54] Weiner P, McConnell A. Respiratory muscle training in chronic obstructive pulmonary disease: Inspiratory, expiratory, or both? Current Opinion in Pulmonary Medicine. 2005;**11**(2): 140-144

[55] Ramirez-Sarmiento A, Orozco-Levi M, Guell R, et al. Inspiratory muscle training in patients with chronic obstructive pulmonary disease: Structural adaptation and physiologic outcomes. American Journal of Respiratory and Critical Care Medicine. 2002;**166**(11):1491-1497

[56] Villafranca C, Borzone G, Leiva A, et al. Effect of inspiratory muscle training with an intermediate load on inspiratory power output in COPD. The European Respiratory Journal. 1998;**11**(1):28-33

[57] O'Donnell DE, Webb KA. Exertional breathlessness in patients with chronic airflow limitation. The American Review of Respiratory Disease. 1993;**148**(5):1351-1357

[58] Mador MJ, Deniz O, Aggarwal A, et al. Effect of respiratory muscle endurance training in patients with COPD undergoing pulmonary rehabilitation. Chest. 2005;**128**(3):1216-1224

[59] Larson JL, Covey MK, Wirtz SE, et al. Cycle ergometer and inspiratory muscle training in chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine. 1999;**160**(2):500-507

[60] Chen R, Li X, Guan N, Guo B, Wu W, Zhou Z, Huo Y, Chen X, Zhou L. Effectiveness of neuromuscular electrical stimulation for the rehabilitation of moderate-to-severe COPD: A meta-analysis. Intl J COPD. 2016;**11**:2965-2975

[61] Abdellaoui A, Préfaut C, Gouzi F, Couillard A, Coisy-Quivy M, Hugon G, Molinari N, Lafontaine T, Jonquet O, Laoudj-Chenivesse D, et al. Skeletal muscle effects of electrostimulation after COPD exacerbation: A pilot study. The European Respiratory Journal. 2011;**38**: 781-788

[62] Dal Corso S, Nápolis L, Malaguti C, Gimenes AC, Albuquerque A, Nogueira CR, De Fuccio MB, Pereira RD, Bulle A, McFarlane N, et al. Skeletal muscle structure and function in response to electrical stimulation in moderately impaired COPD patients. Respiratory Medicine. 2007;**101**:1236-1243

[63] McNamara RJ, McKeough ZJ, McKenzie DK, Alison JA. Water-based exercise in COPD with physical comorbidities: A randomised controlled trial. The European Respiratory Journal. 2013;**41**(6):1284-1291

[64] Leung RW, McKeough ZJ, Peters MJ, Alison JA. Short-form sun-style t'ai chi as an exercise training modality in people with COPD. The European Respiratory Journal. 2013;**41**(5): 1051-1057

[65] Yan JH, Guo YZ, Yao HM, Pan L. Effects of tai chi in patients with chronic obstructive pulmonary disease: Preliminary evidence. PLoS One. 2013;**8**(4) e61806

[66] Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: Systematic review and meta-analysis. The European Respiratory Journal. 2006;**28**: 523-532

[67] Decramer M, Janssens W, Miravitlles M. Chronic obstructive pulmonary disease. Lancet. 2012;**379**:1341-1351

[68] McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease (review). Cochrane Database of Systematic Reviews. 2015;(2). DOI: 10.1002/14651858.CD003793.pub3

[69] The Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. http://goldcopd.org.

[70] Evans RA, Singh SJ, Collier R, Williams JE, Morgan MD. Pulmonary rehabilitation is successful for COPD irrespective of MRC dyspnoea grade. Respiratory Medicine. 2009;**103**: 1070-1075

[71] Puente-Maestu L, Palange P, Casaburi R, Laveneziana P, Maltais F, Neder J, O'Donnell DE, Onorati P, Porszasz J, Rabinovich R, Rossiter HB, Singh S, Troosters T, Ward S. Use of exercise testing in the evaluation of interventional efficacy: An official ERS statement. The European Respiratory Journal. 2016;**47**:429-460

[72] Ringbaek T, Martinez G, Brøndum E, et al. Shuttle walking test as predictor of survival in chronic obstructive pulmonary disease patients enrolled in a rehabilitation program. Journal of Cardiopulmonary Rehabilitation and Prevention. 2010;**30**:409-414

[73] Steiner MC, Singh SJ, Morgan MD. The contribution of peripheral muscle function to shuttle walking performance in patients with chronic obstructive pulmonary disease. Journal of Cardiopulmonary Rehabilitation. 2005;**25**:43-49

[74] Lacasse Y, Wong E, Guyatt GH, et al. Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease. Lancet. 1996;**348**:1115-1119

[75] Wasserman K, Hansen JE, Sue DY, et al. Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2011

[76] Puhan MA, Chandra D, Mosenifar Z, et al. The minimal important difference of exercise tests in severe COPD. The European Respiratory Journal. 2011;**37**:784-790

[77] Corhay JL, Nguyen D, Duysinx B, et al. Should we exclude elderly patients with chronic obstructive pulmonary disease from a long-time ambulatory pulmonary rehabilitation programme? Journal of Rehabilitation Medicine. 2012;**44**:466-472

[78] Troosters T, Casaburi R, Gosselink R, et al. Pulmonary rehabilitation in chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine. 2005;**172**:19-38

[79] Smid MSc E, Franssen F, Houben-Wilke S, Vanfleteren L, Janssen D, Wouters E, Spruit M. Responsiveness and MCID estimates for CAT, CCQ, and HADS in patients with COPD undergoing pulmonary rehabilitation: A prospective analysis. JAMDA. 2017;**18**:53e58

[80] Langer D. Rehabilitation in patients before and after lung transplantation. Respiration. 2015;**89**:353-362

[81] Wickerson L, Mathur S, Brooks D. Exercise training after lung transplantation: A systematic review. The Journal of Heart and Lung Transplantation. 2010;**29**:497-503

[82] Takaoka ST, Weinacker AB. The value of preoperative pulmonary rehabilitation. Thoracic Surgery Clinics. 2005;**15**:203-211

[83] Costache V, Chavanon O, St Raymond C, et al. Dramatic improvement in survival after lung transplantation over time: A single center experience. Transplantation Proceedings. 2009;**41**:687-691

[84] Troosters T, Demeyer H, Hornikx M, et al. Pulmonary rehabilitation. Clinics in Chest Medicine. 2014;**35**:241-249

[85] Van der Woude BT, Kropmans TJB, Douma KW, et al. Peripheral muscle force and exercise capacity in lung transplant candidates. International Journal of Rehabilitation Research. 2002;**25**:351-355

[86] Mathur S, Reid WD, Levy RD. Exercise limitation in recipients of lung transplants. Physical Therapy. 2004;**84**:1178-1187

[87] Wang XN, Williams TJ, McKenna MJ, Li JL, Fraser SF, Side EA, et al. Skeletal muscle oxidative capacity, fiber type, and metabolites after lung transplantation. American Journal of Respiratory and Critical Care Medicine. 1999;**160**(1):57

[88] Krieger AC, Szidon P, Kesten S. Skeletal muscle dysfunction in lung transplantation. The Journal of Heart and Lung Transplantation. 2000;**19**:392-400

[89] Pantoja JG, Andrade FH, Stokic DS, Frost AE, Eschenbacher WL, Reid MB. Respiratory and limb muscle function in lung allograft recipients. American Journal of Respiratory and Critical Care Medicine. 1999;**160**:1205-1211

[90] Williams TJ, Patterson GA, McClean PA, Zamel N, Maurer JR. Maximal exercise testing in single and double lung transplant recipients. The American Review of Respiratory Disease. 1992;**145**(1):101-105

[91] Lands LC, Smountas AA, Mesiano G, Brosseau L, Shennib H, Charbonneau M, Gauthier R. Maximal exercise capacity and peripheral skeletal muscle function following lung transplantation. The Journal of Heart and Lung Transplantation. 1999;**18**(2):113-120

[92] Schuurmans MM, Benden C, Inci I. Practical approach to early postoperative management of lung transplant recipients. Swiss Medical Weekly. 2013;**143**:137-173

[93] Downs AM. Physical therapy in lung transplantation. Physical Therapy. 1996;**76**(6): 626-642

[94] National Emphysema Treatment Trial Group. A randomized trial comparing lung volume-reduction surgery with medical therapy for severe emphysema. The New England Journal of Medicine. 2003;**348**(21):2059-2073

[95] Pompeo E, Marino M, Nofroni I, Matteucci G, Mineo TC. Reduction pneumoplasty versus respiratory rehabilitation in severe emphyse- ma: A randomized study. The Annals of Thoracic Surgery. 2000;**70**(3):948-954

[96] Criner GJ, Cordova FC, Furukawa S, Kuzma AM, Travaline JM, Leyenson V, O'Brien GM. Prospective randomized trial comparing bilateral lung volume reduction surgery to pulmonary rehabilitation in severe chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine. 1999;**160**(6):2018-2027

[97] Koegelenberg CF, Theron J, Dheda K, Bruwer JW, Allwood BW, Vorster J, Groote-Bidlingmaier F, Slebos DJ, Shah PL, Herth FJF. Recommendations for the use of endoscopic lung volume reduction in South Africa: Role in the treatment of emphysema. SAMJ. 2015;**105**:810-815

[98] Gao K, PM Y, JH S, He CQ, Liu LX, Zhou YB, Pu Q, Che GW. Cardiopulmonary exercise testing screening and pre-operative pulmonary rehabilitation reduce postoperative complications and improve fast-track recovery after lung cancer surgery: A study for 342 cases. Thorac Cancer. 2015 Jul;**6**(4):443-449

[99] Adamsen L, Midtgaard J, Andersen C, Quist M, Moeller T, Roerth M. Transforming the nature of fatigue through exercise: Qualitative findings from a multidimensional exercise programme in cancer patients undergoing chemotherapy. European Journal of Cancer Care. 2004;**13**(4):362-370

[100] Pasqua F, D'Angelillo R, Mattei F, et al. Pulmonary rehabilitation following radical chemoradiation in locally advanced non surgical NSCLC: Preliminary evidences. Lung Cancer. 2012;**76**(2):258-259

[101] Tarumi S, Yokomise H, Gotoh M, et al. Pulmonary rehabilitation during induction chemoradiotherapy for lung cancer improves pulmonary function. Journal of Thoracic and Cardiovascular Surgery. 2015;**149**(2):569-573

[102] Keays KS, Harris SR, Lucyshyn JM, MacIntyre DL. Effects of pilates exercises on shoulder range of motion, pain, mood, and upper extremity function in women living with breast cancer: A pilot study. Physical Therapy. 2008;**88**(4):494-510

[103] Clay CA, Perera S, Wagner JM, Miller ME, Nelson JB, Grrenspan SL. Physical function in men with prostate cancer on androgen deprivation therapy. Physical Therapy. 2007;**87**(10):1325-1333

[104] Bicego D, Brown K, Ruddick M, Storey D, Wong C, Harris SR. Exercise for women with or at risk for breast cancer-related lymphedema. Physical Therapy. 2006;**86**(10):1398-13405

[105] Albrecht TA, Taylor AG. Physical activity in patients with advanced-stage cancer: A systematic review of the literature. Clinical Journal of Oncology Nursing. 2012;**16**(3):293-300

[106] Bolton CE, Bevan- Smith EF, Blakey JD, et al. British Thoracic Society guideline on pulmonary rehabilitation in adults. Thorax. 2013;**68**:1-30

[107] Puhan M, Scharplatz M, Troosters T, Walters EH, Steurer J. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews. 2011;**1**:5305

[108] Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews. 2006;**4**:37-93

[109] Wedzicha JA, Miravitlles M, Hurst JR, Calverley P, Albert K, Anzueto A, Criner J, Papi A, Rabe KF, Rigau D, Sliwinski P, Tonia T, Vestbo J, Wilson KC, Krishnan JA. Management of COPD exacerbations: A European Respiratory Society/American Thoracic Society guideline. The European Respiratory Journal. 2017;**49**:1600791

[110] Ntoumenopoulos G. Rehabilitation during mechanical ventilation: Review of the recent literature. Intensive & Critical Care Nursing. 2015;**31**(3):125-132

[111] Sommers J, Engelbert RHH, Dettling-Ihnenfeldt D, Gosselink R, Spronk PE, Nollet F, van der Schaaf M. Physiotherapy in the intensive care unit: An evidence-based, expert driven, practical statement and rehabilitation recommendations. Clinical Rehabilitation 2015;**29**(11):1051-1063

[112] Nydahl P, Sricharoenchai T, Chandra S, Kundt FS, Huang M, Fischill M, Needham DM. Safety of patient mobilization and rehabilitation in the intensive care unit. Systematic review with meta-analysis. Annals of the American Thoracic Society. 2017 May;**14**(5): 766-777

[113] Hoff J, Tjonna AE, Steinshamn S, et al. Maximal strength training of the legs in COPD: A therapy for mechanical inefficiency. Medicine and Science in Sports and Exercise. 2007;**39**: 220-226

[114] Menadue C, Piper AJ, van 't Hul AJ, Wong KK. Non-invasive ventilation during exercise training for people with chronic obstructive pulmonary disease (review). Cochrane Data base of Systematic Reviews. 2014(5). Art. No.: CD007714

[115] Garrod R, Mikelsons C, Paul EA, Wedzicha JA. Randomized controlled trial of domiciliary noninvasive positive pressure ventilation and physical training in severe chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine. 2000;**162**:1335-1341

[116] Hornikx M, Van Remoortel H, Demeyer H, et al. The influence of comorbidities on outcomes of pulmonary rehabilitation pro- grams in patients with COPD: A systematic review. BioMed Research International. 2013;**2013**:146-148

[117] Carreiro A, Santos J, Rodrigues F. Impact of comorbidities in pulmonary rehabilitation outcomes in patients with chronic obstructive pulmonary disease. Revista Portuguesa de Pneumologia. 2013;**19**(3):106-113

[118] Crisafulli E, Costi S, Luppi F, et al. Role of comorbidities in a cohort of patients with COPD undergoing pulmonary rehabilitation. Thorax. 2008;**63**:487-492

[119] Crisafulli E, Gorgone P, Vagaggini B, et al. Efficacy of standard rehabilitation in COPD outpatients with comorbidities. European Respiratory Journal. 2010;**36**:1042-1048

[120] Walsh JR, McKeough ZJ, Morris NR, et al. Metabolic disease and participant age are independent predictors of response to pulmonary rehabilitation. Journal of Cardiopulmonary Rehabilitation and Prevention. 2013;**33**:249-256

[121] McNamara RJ, McKeough ZJ, McKenzie DK, Alison JA. Water- based exercise in COPD with physical comorbidities: A ran- domised controlled trial. European Respiratory Journal. 2013;**41**:1284-1291

[122] Tunsupon P, Lal A, Khamis MA, Mador MJ. Comorbidities in patients with chronic obstructive pulmonary disease and pulmonary rehabilitation outcomes. Journal of Cardiopulmonary Rehabilitation and Prevention. 2017;**00**:1-9

[123] Emery CF, Shermer RL, Hauck ER, Hsiao ET, MacIntyre NR. Cognitive and psychological outcomes of exercise in a 1-year follow-up study of patients with chronic obstructive pulmonary disease. Health Psychology. 2003;**22**(6):598-604

[124] Corhay J, Dang DN, Cauwenberge H, Louis R. Pulmonary rehabilitation and COPD: Providing patients a good environment for optimizing therapy. International Journal of COPD. 2014;**9**:27-39

[125] Rochester CL, Vogiatzis I, Holland AE, Lareau SC, Marciniuk DD, Puhan MA, et al. An official American Thoracic Society/European Respiratory Society policy statement: Enhancing implementation, use, and delivery of pulmonary rehabilitation. American Journal of Respiratory and Critical Care Medicine. 2015;**192**(11):1373-1386

[126] Vasilopoulou M, Papaioannou AI, Kaltsakas G, et al. Home-based maintenance tele-rehabilitation reduces the risk for acute exacerbations of COPD, hospitalisations and emergency department visits. The European Respiratory Journal. 2017;**49**:1602129

17

Noninvasive Positive-Pressure Ventilation Therapy in Patients with COPD

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1. Introduction

Noninvasive positive pressure ventilation (NPPV) refers to the administration of ventilatory support without using an invasive artificial airway (endotracheal tube or tracheostomy tube). The use of NPPV has markedly increased over the past two decades. Rudimentary devices that provided continuous positive airway pressure were described in the 1930s, but the negative-pressure ventilators were the predominant method of ventilatory support until the polio epidemics overwhelmed their capacity in the 1950s. In the 1980s, increasing experience with positive-pressure ventilation delivered through a mask in patients with obstructive sleep apnea led to this type of ventilatory support, initially in patients with neuromuscular respiratory failure. Success led to its adoption in other conditions, and NPPV became especially promising in the treatment of patients with exacerbations of chronic obstructive pulmonary disease (COPD).

NPPV is defined as ventilatory support delivered by a non-invasive interface such as mask or similar device, acting as an alternative to intubation or tracheostomy. Consequently, by avoiding tracheal intubation, NPPV presents several potential advantages, such as reduction in pulmonary infections, barotrauma and need for sedation (British Thoracic Society Standards of Care Committee 2002). As a result, NPPV should be considered a standard of care to treat COPD exacerbation in selected patients, since it markedly reduces the need for intubation and improves outcome by lowering complication and mortality rates, and shortening hospital stay (Brochard et al. 1995; Kramer et al. 1995; Celikel et al. 1998; Martin et al. 2000; Conti et al. 2002; Squadrone et al. 2004; Lightowler et al. 2003; Nava, Navalesi, & Conti 2006). Weaker evidence indicates that NPPV could allow earlier extubation, avoid re-intubation in patients who fail extubation, and assist do-not-intubate patients, and thus could be beneficial for COPD patients who are suffering respiratory failure precipitated by superimposed pneumonia or postoperative complications, and COPD patients with severe stable disease who have substantial daytime hypercapnia and superimposed nocturnal hypoventilation.

This chapter will examine the evidence pertaining to the use of NPPV for various applications in COPD and make recommendation on patient, ventilation mode and interface selection as well as technical aspects of NPPV application in COPD. The literature review

and consensus processes used to reach the recommendations presented here are the American College of Chest Physicians [ACCP] consensus report on clinical indications for NPPV in CRF due to restrictive lung disease, COPD and nocturnal hypoventilation published in 1999, the British Thoracic Society guidelines published in 2002, the Indian Society of Critical Care Medicine guidelines published in 2006, the guidelines from 12 German Medical Societies published in 2008 and the most recent guideline published in 2011 from Canadian Critical Care Trials Group/Canadian Critical Care Society Noninvasive Ventilation Guidelines Group.

2. Physiologic mechanism of NPPV effect in patients with COPD

Severe COPD places the respiratory muscles at a mechanical disadvantage (Rochester, Braun, & Arora 1979). During COPD exacerbation, this situation becomes catastrophic. Exacerbations of COPD increase the respiratory load in these patients, exceeding their ability to adequately ventilate through a variety of mechanisms, including increasing hyperinflation with decreased diaphragmatic excursion and strength, increasing intrinsic positive end-expiratory pressure (PEEP), changes in respiratory patterns and increased respiratory frequency leading to ineffective or inadequate tidal volume generation. NPPV effectively unloads the respiratory muscles by increasing tidal volume, decreasing the respiratory rate, and decreasing the diaphragmatic work of breathing, which translates into an improvement in oxygenation, a reduction in hypercapnia, and an improvement in dyspnea. NPPV treatment counterbalances auto-PEEP, assists inspiration, reduces transdiaphragmatic pressure, lowers respiratory rate, rests the accessory muscles, increases functional residual capacity, decreases respiratory load and work of breathing and leads to favorable changes in the ventilation/perfusion ratio as well as the respiratory center and the sensivity of chemoreceptors (Mansfield & Naughton 1999; de Miguel et al. 2002). Expiration positive airway pressure (EPAP) counterbalances intrinsic PEEP. Inspiration positive airway pressure (IPAP) is capable of increasing tidal volume and subsequently decreasing the elevated levels of PC02.

3. Indications of NPPV in patients with COPD

3.1 Acute respiratory failure/Exacerbation of COPD

Based upon the overwhelming evidence that NPPV reduces the need for intubation, reduces mortality and complications rates, and shortens the length of stay in both the intensive care unit (ICU) and hospital (Kramer et al. 1995; Brochard et al. 1995; Celikel et al. 1998; Martin et al. 2000; Carlucci et al. 2001; Mehta & Hill 2001) , NPPV should be considered as a standard of care in acute respiratory failure (ARF) due to COPD exacerbations (Keenan et al. 2011). Brochard et al. were the first to show that pressure-support ventilation administered via face mask significantly reduced the need for intubation, duration of mechanical ventilation, and ICU stay in patients with COPD exacerbations (Brochard et al. 1990). The patients with relatively mild COPD exacerbations are not likely to benefit from NPPV, which suggests that NPPV should be applied to selected patients who have moderate-to-severe COPD exacerbations. Though, patients with milder exacerbations appear to demonstrate a more rapid improvement in their level of dyspnea with NPPV treatment, the addition of NPPV to standard therapy for patients with milder exacerbations of COPD is not well tolerated (Keenan, Powers, & McCormack 2005). NPPV should be the first option for ventilatory

support in patients with either a severe exacerbation of COPD or cardiogenic pulmonary edema(Keenan et al. 2011). Furthermore, consensus groups of experts advocate the routine use of NPPV for selected patients with COPD exacerbations (British Thoracic Society Standards of Care Committee 2002). High quality studies have shown that NPPV is an effective treatment for moderate to severe COPD exacerbation (Kramer et al. 1995; Celikel et al. 1998; Martin et al. 2000). In patients with mild to moderate ARF, characterized by pH levels between 7.25 and 7.35, the rate of NPPV failure was ranging from 15% to 20% (Elliott 2002; Lightowler et al. 2003). In more severely ill patients (pH<7.25), the rate of NPPV failure was inversely related to the severity of respiratory acidosis, rising up to 52%-62% (Conti et al. 2002; Squadrone et al. 2004). In patients with ''mild'' exacerbations, not complicated by respiratory acidosis, the use of NPPV was investigated in few studies, including patients in large majority with pH>7.35, which failed to demonstrate a better effectiveness of NPPV than standard medical therapy in preventing the occurrence of ARF (Bardi et al. 2000; Keenan, Powers, & McCormack 2005). Guidelines recommend the use of NPPV in addition to usual care in patients who have a severe exacerbation of COPD (pH<7.35 and relative hypercarbia) (grade 1A recommendation) (Keenan et al. 2011). Based on that evidence, the authors of the meta-analyses and the participants in the consensus groups recommended that NPPV should be used early in the course of a COPD exacerbation, in addition to the standard medical care (Lightowler et al. 2003; Keenan et al. 2003; British Thoracic Society Standards of Care Committee 2002) . NPPV is not appropriate for all COPD patients with ARF and the selection of candidates is important. Most of the indications and contraindications for NPPV in ARF are listed in Table 1 (Brochard et al. 1995). There are no absolute contraindications to NPPV although a number have been suggested (Ambrosino et al. 1995; Soo Hoo, Santiago, & Williams 1994). In part, these contraindications have been determined by the fact that they were exclusion criteria for the controlled trials. It is therefore accurate to state that NPPV is not proven in these circumstances rather than stating that it is contraindicated.

3.2 Severe community-acquired pneumonia in patients with COPD

The presence of pneumonia has been associated with poor outcome in patients treated with NPPV (Ambrosino et al. 1995). However COPD exacerbation is still an appropriate indication for NPPV even when complicated by community-acquired pneumonia (Confalonieri et al. 1999). In one randomized trial with patients suffering severe community-acquired pneumonia, NPPV reduced the need for intubation, and reduced mortality among the COPD subgroup of patients 2 months after hospital discharge (Confalonieri et al. 1999). But it is not clear whether NPPV should be used for severe community-acquired pneumonia in non-COPD patients.

3.3 Adjunct to early liberation

Patients with COPD can be considered for a trial of early extubation to NPPV in centres with extensive experience in the use of NPPV (Keenan et al. 2011). Guidelines suggest that NPPV be used to facilitate early liberation from mechanical ventilation in patients who have COPD, but only in centres that have expertise in this therapy (Grade 2B recommendation) (Keenan et al. 2011). Recent randomized controlled trials (RCTs) suggested benefit from NPPV after extubation in patients who had high risk of deterioration (Ferrer et al. 2006; Ferrer et al. 2009; Nava et al. 2005; Luo, Cheng, & Zhou 2001). The results of the RCTs of

Indications
• Increased dyspnea-moderate to severe • Tachypnea (>25 breaths per minute) • Signs of increased work of breathing, accessory muscle use, pursed lips breathing and abdominal paradox • Acute or chronic ventilatory failure (best indication), PaC02 >45 mmHg, pH <7.35 • Hypoxaemia (use caution), Pa02/Fi02 ratio < 200
Contraindications
Absolute • Cardiac or respiratory arrest • Severe encephalopathy • Unable to fit mask Relative • Severe haemodynamic instability with or without cardiac ischemia or arrhythmia • Severe gastrointestinal bleeding • Agitated, uncooperative state • Upper airway obstruction • Inability to protect the airway and/or high risk of aspiration • Inability to clear secretions • Multiple organ failure • Recent facial, upper airway or upper gastrointestinal surgery

[NPPV= non-invasive positive pressure ventilation; PaC02: arterial partial pressure of carbon dioxide; Pa02: arterial partial pressure of oxygen; Fi02: fraction of inspired oxygen]

Table 1. Indications and contraindications for NPPV in ARF

early extubation in COPD patients with NPPV are controversial, some showing significant benefit and the other showing no important benefit, but no attributable harm in either (Girault et al. 1999; Ferrer et al. 2003). Intubated COPD patients are appropriate candidates for early extubation by NPPV, but clinicians are advised to be cautious when selecting patients. The inability to sustain 5–10 min of unassisted breathing, a prior difficult intubation, multiple co-morbidities, copious secretions, a weakened cough, or the need for high levels of pressure support prior to extubation (>20 cm H2O) should exclude patients from consideration for early extubation (Hill 2004).

3.4 After planned extubation

Extubation failure occurs after 5-20% of planned (Epstein, Ciubotaru, and Wong 1997) and 40-50% of unplanned extubation (Chevron et al. 1998) NPPV may prevent the need for reintubation if applied immediately after planned extubation. NPPV is recommended to be used after planned extubation in patients who are considered to be at high risk of recurrent respiratory failure, but only in centres that have expertise in this type of therapy (Grade 2B recommendation) (Keenan et al. 2011). We should be careful to avoid delays in intubation in the face of deterioration and to select the patients for extubation.

3.5 Postoperative patients

It has been shown that NPPV in post-lung-resection patients with acute respiratory failure results in significantly less need for intubation, shorter ICU stay, and lower mortality rate than conventionally treated controls (Auriant et al. 2001) . The use of NPPV in selected postoperative patients (especially COPD patients) could maintain improved gas exchange and avoid reintubation and its complications.

3.6 Do-not-intubate patients

In the studies of patients in whom endotracheal intubation was contraindicated or postponed, COPD subgroup were supported with NPPV and weaned more successfully than the pneumonia or cancer subgroup of patients (Benhamou et al. 1992; Meduri et al. 1994). Thus, NPPV is indicated in do-not-intubate patients with acutely reversible processes that are known to respond well, including COPD exacerbations. However, if NPPV is to be used in a do-not-intubate patient, the patient and/or the family should be informed that NPPV is being used as a form of life support that may be uncomfortable and can be removed at any time (Hill 2004).

3.7 Overlap syndrome

The term ''overlap syndrome'' was introduced by Flenly to describe the association of obstructive sleep apnea syndrome (OSAS) and COPD (Flenley 1985). Even by chance alone, a patient with one of the disorders has a greater than 10% probability of also having the other disorder. Thus, when seeing a patient with either OSAS or COPD, it is reasonable to screen for the lower and longer nocturnal oxyhemoglobin desaturations, which produces more severe pulmonary hemodynamic complications (Chaouat et al. 1995; Bednarek et al. 2005). Concomitant COPD in patients with severe OSAS so called critical care syndrome is frequently associated with diurnal hypercapnia and acute ventilatory failure (Fletcher et al. 1991). There is an increase in the morbidity and mortality and risk of developing pulmonary hypertension and hypercapnic respiratory failure in patients with overlap syndrome than patients with OSAS alone and patients with usual COPD (Chaouat et al. 1995; Chaouat et al. 1999). NPPV with or without supplemental oxygen is now the treatment of choice for the patients with overlap syndrome (Mayos et al. 2001).

Improvement in daytime hypercapnia and gas exchange has been reported in overlap syndrome with continuous positive airway pressure (CPAP) treatment (Owens & Malhotra. 2010). Mild bronchodilatory effect due to amelioration of chronic irritation and responsiveness of the upper airway and reduction of the chronic airway has also been suggested as the possible mechanisms for the benefits of CPAP. Bilevel positive airway pressure (BPAP) may be preferred if the patient experiences difficulty in exhaling against a fixed pressure or has persistent intermittent hypoxemia despite adequate airflow (Kushida et al. 2006). Supplemental oxygen can be added to NPPV to eliminate persistent intermittent nocturnal hypoxemia (Kakkar & Berry 2007). In a cohort of overlap syndrome patients, CPAP added to long term oxygen treatment as compared to long term oxygen treatment resulted in a survival benefit with 5 years-survival rates of 71% and 26%, respectively (Machado et al. 2010). In another study including COPD and overlap syndrome patients, CPAP therapy eliminated the additional risk of mortality due to OSA in overlap syndrome

patients as compared to COPD- only patients (Marin et al. 2010) . One RCT and another study using a historical cohort showed reduction of mortality in overlap syndrome with NPPV (McEvoy et al. 2009; Windisch et al. 2009). In the study by Windisch et al., intensive pressure settings (average inspiratory pressure 28 cm H2O, average expiratory pressure 5 cm H2O and a high respiratory rate of about 21 breaths/min) were used with inhospital acclimatization and improvement in spirometry and arterial blood gas were reported (Windisch et al. 2009) . Finally, BPAP may be more comfortable and effective than CPAP in lowering CO2 and increasing tidal volume for patients with overlap syndrome, COPD component of which is much more related to moderate to severe hypercapnia and more prominent than the OSAS component.

3.8 Severe stable COPD/Chronic respiratory failure in patients with COPD

Despite the reported benefits of NPPV application in COPD patients with ARF, the role of NPPV in chronic respiratory failure (CRF) remains controversial. COPD patients with both increased hypercapnia and sleep-disordered breathing may be the ones, who are most likely to benefit from NPPV (Hill 2004). However the evidence to support the use of NPPV in CRF in the setting of severe stable COPD has been less consistent. COPD treatment guidelines does not recommend NPPV treatment routinely in end stage stable hypercapnic COPD in addition to conventional treatment (Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2010).

Once hypercapnia develops, 2-year mortality is approximately 30-40% (Foucher et al. 1998). The reported studies show some physiological benefits for the use of NPPV in stable COPD, but clear survival benefit has not yet been demonstrated (Leger et al. 1994; Jones et al. 1998; Tuggey, Plant, & Elliott 2003). All of these and most other studies used a moderately aggressive ventilation to treat stable hypercapnic COPD patients and so an impressive reduction in hypercapnia was not achieved. In contrast, more aggressive form of ventilation with mean IPAP of up to 30 cmH20 or even higher was used in recent studies by Windish et al. and a remarkable reduction of PC02 was achieved (Windisch et al. 2002; Windisch et al. 2005; Windisch et al. 2006). Another RCT also has shown an improvement in survival with the application of nocturnal NPPV in end stage chronic hypercapnic COPD. The authors reported that the use of higher IPAP levels sufficient to be cardioprotective (but not to awake central respiratory drive) may result in greater treatment benefits (McEvoy et al. 2009). High intensity NPPV therefore offers a new and promising therapeutic option in the treatment of patients with CRF. High intensity NPPV is better tolerated in patients with severe chronic hypecapnic COPD and has been shown to be superior to the conventional and widely used form of low intensity NPPV in controlling nocturnal hypoventilation (Dreher et al. 2010). Nevertheless, higher leak volume, side effects and impairments in sleep quality are the main disadvantages of this modality.

NPPV might rest the chronically fatigued muscles and increase the muscle strength during daytime, could improve sleep time and efficiency, and sleep disordered breathing with episodes of hypoventilation. NPPV use in a select proportion of patients with severe stable COPD can improve gas exchange, exercise tolerance, dyspnea, work of breathing, frequency of hospitalisation, health-related quality of life and functional status (Kolodziej et al. 2007). Inconsistency in the effectiveness of all assessed outcomes may be due to the variability in degree of lung hyperinflation and NPPV levels and duration of use. As yet, no study has

provided convincing evidence that survival in COPD is prolonged by NPPV. Further work is also required to evaluate the effect of NPPV on reducing frequency and severity of COPD exacerbation. The general consensus, however, is that there is insufficient evidence to recommend NPPV for routine use in stable hypercapnic COPD (Kolodziej et al. 2007; Wijkstra et al. 2003). Despite the insufficient evidence, the ACCP consensus group opined that a trial of NPPV was justified with a symptomatic but stable and optimally treated patient who has daytime PaCO2 > 55 mm Hg, if OSA had been excluded. For PaCO2 between 50 and 54 mm Hg, , the ACCP consensus group suggested that there should be evidence of worsening hypoventilation during sleep, as suggested by a sustained (> 5 min) desaturation during use of the usual oxygen supplementation. In addition, the need for repeated hospitalizations was deemed a justification for a trial of NPPV (ACCP consensus conference 1999).

The other limitation of NPPV use in patients with stable hypercapnic COPD is poor compliance to NPPV in this group of patients. Criner et al., found that only 50% of COPD patients were still using NPPV after 6 months, compared to 80% for neuromuscular patients (Criner et al. 1999). Reasons for poor adherence are unclear, but probably include the advanced age of COPD patients, frequent occurrence of co morbidities and cognitive defects, lack of motivation and appropriate/inefficient setting of NPPV. Close follow-up is probably helpful to optimize compliance rates.

3.9 Sleep related hypoventilation/Hypoxemia due to COPD

The latest edition of The International Classification of Sleep Disorders: Diagnostic and Coding Manual (ICSD-2) subsumes a broad range of disorders under the heading ''Sleep Related Hypoventilation/hypoxemic Syndromes.'' (American Academy of Sleep Medicine. 2005). Some are quite common, such as COPD with worsening gas exchange during sleep; while some are exceedingly rare, such as congenital central hypoventilation syndrome. The ICSD-2 manual recommended the use of NPPV in addition to optimal treatment of the underlying disorder in selected subgroups of the patients (Casey, Cantillo, & Brown 2007).

In normal subjects, minute ventilation changes little, whereas minute ventilation in COPD patients falls approximately 16% from wakefulness to non REM sleep and almost 32% during REM sleep, compared to wakefulness, largely as a result of decreased tidal volumes. The greater drop in minute ventilation in subjects with COPD may reflect increased dependence on accessory muscles that become hypotonic during sleep, particularly in REM sleep leading to Sleep Related Hypoventilation/hypoxemic Syndrome due to COPD.

NPPV devices are used during sleep to treat patients with Sleep Related Hypoventilation/ hypoxemic syndromes. Compelling evidence exists to support the use of NPPV during sleep in the management of selected Sleep Related Hypoventilation/ hypoxemic syndromes. NPPV has been used in Sleep Related Hypoventilation/ hypoxemic due to central respiratory control disturbances, restrictive thoracic cage disorders, neuromuscular diseases and the obesity hypoventilation syndrome. A select subgroup of COPD patients also appears to have improved sleep after treatment with NPPV but specific characteristics that describe this subgroup well remain to be elucidated. It is unclear whether exclusively nocturnal hypoxemia in these patients will be deleterious and therefore whether isolated sleep-related hypoxemia should be treated. COPD patients with clear evidence of hypoventilation while awake as evidenced by daytime hypercapnia are a reasonable starting target group. Those COPD

patients who also show continued sleep disruption or worsening hypercapnia and nocturnal hypoventilation despite oxygen therapy should be further investigated probably with polysomnography to rule out other sleep related breathing disorders. Finally we need to define optimal NPPV and interface design and settings in hopes of improving compliance of long-term therapy for all types of appropriate patients, who are likely to benefit from NPPV.

3.10 Adjunct to exercise training in pulmonary rehabilitation programs

Another potential application of NPPV in patients with severe stable COPD is to enhance exercise training during rehabilitation. It has been shown that when delivered during cycle ergometry, CPAP, pressure-support ventilation, and proportional-assist ventilation all reduce inspiratory effort and dyspnea in hypercapnic COPD patients (Petrof, Calderini, & Gottfried 1990; Bianchi et al. 1998). Recent studies in patients with severe COPD in a 6-week exercise training program has reported that, NPPV alone was more effective than supplemental oxygen alone as adjunct to physical exercise in improving submaximal exercise tolerance and health related quality of life (HRQOL) (Borghi-Silva et al. 2010). These studies demonstrated that NPPV can be used to increase or prolong the intensity of exercise training sessions in patients with severe COPD.

4. Where to administer NPPV?

Any patient on NPPV is classified as receiving Critical Care Level 2 care, defined as ''Patients requiring more detailed observation or intervention including support for a single failed organ system''. This suggest NPPV should be administered in an intensive care unit (ICU) or high dependency unit (HDU) setting, but it has been widely recognised that NPPV can be successfully used outside the ICU and HDU with dedicated NPPV team able to provide 24/7 care. This is however only feasible in large units with many trained staff (Manuel, Russell, & Jones. 2010). NPPV is more frequently used outside the ICU, in HDU, respiratory wards and emergency departments (EDs) (Brochard, Mancebo, & Elliott 2002; Hill 2004). It has been suggested that each hospital should have a specific designed area with experienced staff, where patients requiring NPPV can be transferred with the minimum delay (British Thoracic Society Standards of Care Committee 2002).

5. Selection of optimal ventilator and mode of NPPV

NPPV is broadly classified into volume preset and pressure preset devices, early studies of long-term domiciliary NPPV mainly concern patients on volume preset ventilators, whereas in the last 5-10 years pressure preset machines, particularly bilevel pressure support equipment has become more prominent.

Volume preset machines gives the adjusted tidal volume regardless of mechanics of respiratory system (i.e. compliance, resistance and active inspiration) and if there is a leak from mask or mouth, patient cannot deliver the adjusted tidal volume.

On the contrary **pressure preset** machines gives the adjusted pressure according to respiratory system mechanics by changing the flow and compensates the mask leaks. However pressure preset machines may not to be sufficient in patients who need high inspiratory pressure. Pressure support ventilators on a first line basis, especially with pressure support mode, is easier to adjust and to synchronise with the patient. CPAP and BPAP are the pressure support

ventilators. CPAP as the name implies, requires the airway pressure not to change between inspiration and expiration. However BPAP therapy was originally conceived with the idea of varying the administered pressure between the inspiratory and expiratory cycles. BPAP is the commonly used pressure preset method. BPAP devices deliver separately adjustable inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP). The IPAP and EPAP levels are adjusted to maintain upper airway patency, and the pressure support (PS=IPAP-EPAP), which augments ventilation.

Three modes of NPPV were also defined according to principles of cycling of inspiration. NPPV devices can be used in the 1) **spontaneous mode** (the patient cycles the device from EPAP to IPAP), 2) the **spontaneous timed (ST)**/assisted-controlled (AC) mode (a backup rate is available to deliver IPAP for the set inspiratory time if the patient does not trigger an IPAP/EPAP cycle within a set time window otherwise patient the device from EPAP to IPAP), 3) the **timed (T)** /pressure controlled (PC) mode (patient cannot trigger and cycle the inspiration- inspiratory time and respiratory rate are fixed).

Volume assured pressure support / volume target BPAP (VT-BPAP) which is a hybrid mode of volume preset and pressure support ventilation was available by the end of the 1990s. Release of dual portable ventilators providing either pressure support ventilation or volume preset ventilation opened the way for new potent turbine pressure support ventilators able to deliver real volume ventilation with the average volume assured pressure support ventilation mode which represents a flexible way for managing the most difficult patients (Storre et al. 2006). Patient delivers the target tidal volume by the support of adjusted pressure support range. VT-BPAP has been developed in which the IPAP-EPAP difference is automatically adjusted to deliver a target tidal volume (Storre et al. 2006; Ambrogio et al. 2009; Janssens, Metzger, & Sforza 2009; Jaye et al. 2009)

Proportional Assist Ventilation is another mode still under investigation. It provides a level of ventilatory assistance which is proportional to the patient's respiratory effort throughout the respiratory cycle. Some studies reported better comfort and tolerance with proportional assist ventilation but found no differences in rates of mortality or intubation (Fernandez-Vivas et al. 2003; Gay, Hess, & Hill 2001). Guidelines make no recommendation about the use of proportional assist ventilation versus pressure support ventilation in patients who are receiving NPPV for ARF, due to lack of sufficient evidence.

6. Selection of interface

Interfaces connect the patient's airway to the NPPV tubing. The main six interfaces for NPPV are nasal mask, full face or oronasal mask, total face mask, helmet mask, nasal pillow or plugs and mouthpieces. Usually made of silicone, masks need to be carefully fitted to the individual to obtain optimum results. Variations include the bubble-type mask, and gel masks. Mask fit can be enhanced using mask cushions and seal/support rings which are supplied with the mask.

Nasal mask: Nasal mask covers nose and does not cover mouth so allows speaking, drinking and cough also reduces the risk of vomiting and asphyxia. Disadvantages of nasal masks are air leaks if mouth opens, possible nasal skin damage and the need for patent nasal passages.

Oronasal /Full face mask: Oronasal mask cover the nose and mouth and can prove valuable in patients with nasal airway blockage or acute confusional state. Oronasal mask is

recommended rather than nasal mask in patients who have ARF. Although there was no difference in endotracheal intubation or mortality rates, the oronasal mask was better tolerated (Keenan et al. 2011). The use of an oronasal mask seem a logical solution to maximize the NPPV efficacy, presumably due to lower leakage with oronasal mask compared to nasal mask in dyspneic patients who are mostly mouth-breathers (Carrey, Gottfried, & Levy 1990). However during long-term use the face mask can be poorly tolerated, thus causing a premature NPPV interruption (Carlucci et al. 2001).

Total face mask: Total face mask covers mouth, nose and eyes. Advantages of this type of masks are minor air leaks, little cooperation required and easy fitting application. Risks of asphyxia, claustrophobia, speaking difficulty are the main disadvantages.

Helmet: Helmet mask covers whole head and all or part of the neck without a contact with face. Advantages of this type of masks are minor air leaks, little cooperation required and absence of nasal or facial skin damage. The risk of vomiting, worsening of C02 clearance due to rebreathing, asynchrony with pressure support ventilation and discomfort of axillae are the disadvantages of the helmet.

Nasal pillow or plugs: These masks are inserted into the nostrils. This type of the mask may be suitable for claustrophobic patients with chronic stable COPD who do not need high pressures. Nasal irritation is the main disadvantage.

Mouthpieces: They are placed between lips and held in place by lip seal. Mouthpieces can be applied with other interfaces. The risk of vomiting and salivation, possible air leaks, gastric distension and speaking difficulty are the disadvantages of the mouthpieces. Mouthpiece ventilation is mainly used in patients with neuromuscular disease.

7. Application, setting and adjustments of NPPV

The first hours of NPPV are associated with an increased workload for health care personnel that requires a specific management protocol, including monitoring mask ventilation and monitoring the patient (Nava and Hill 2009). Recommended application, setting and adjustments of NPPV in the ICU, HDU, respiratory wards and emergency departments (EDs) are summarised as in the following:

1. Explain technique to patient (if competent).
2. Choose correct interfaces and size.
3. Set pressure starting from low levels (minimum starting IPAP and EPAP should be 8 cm H_20 and 4 cm H_20, respectively).
4. Place mask gently over face, holding it in place and start ventilation.
5. When patient is tolerant, tighten straps just enough to avoid major leaks, but not keep it too tight.
6. Set Fi02 on ventilator or add low-flow oxygen into the circuit, aiming for S02>90%.
7. Set alarms-low pressure alarm should be above PEEP level.
8. Be mindful of and try to optimise patient's comfort.
9. Reset pressures (pressure support increased to obtain inspired tidal volume 6mL/kg or higher, achieving a respiratory rate <25 breaths/min, PaC02 <45 mmHg and also raise EPAP to obtain S02 of 90% or higher). The recommended maximum IPAP should be 30 cm H_20 for patients ≥ 12 years. The recommended minimum and maximum levels of PS

are 4 cm H_20 and 20 cm H_20, respectively. PS should be increased in order to optimize CO2 removal and control of auto-positive end expiratory pressure (PEEP), according to the patient's tolerance. A backup rate (ST mode) should be used in all patients with low respiratory rate, in patients who unreliably trigger IPAP/EPAP cycle due to muscle weakness and in patients who do not achieve adequate ventilation or respiratory muscle rest with the maximum tolerated PS in the spontaneous mode. The inspiratory duration should be as short as possible.

10. Protect site of skin pressure from the interface.
11. Consider use of mild sedation if the patient is agitated.
12. Monitor comfort, respiratory rate, oxygen saturation and dyspnea every 30 minute for 6-12 hours and then hourly.
13. Measure arterial blood gases at baseline and within 1 hour from the start.
14. Humidification is advised for longer application.

Predictors of NPPV failure are no improvement or a fall in pH and PC02, no change or a rise in breathing frequency after 1-2 hours and lack of cooperation. Delays in intubation of these patients run the risk of unanticipated respiratory or cardiac arrest with attended morbidity and mortality. NPPV failure occurs more frequently in the first hours of ventilation, and was reported to be predicted by the following clinical factors: severe acidosis, high severity score, severe impairment of consciousness, presence of co-morbidities and lack of improvement of arterial blood gases after 1-2 hours of initial ventilation (Ambrosino et al. 1995; Elliott 2002; Nava & Ceriana 2004)

8. Complications of NPPV

Complications of NPPV therapy are minor and preventable. Major complications of NPPV such as pneumothorax and pneumocephalus are so rare (Grunstein 2005). The most common complications effecting almost half of the patients who are administered NPPV are due to mask leak and/or mask pressure injury (Pepin et al. 1999; Hoffstein et al. 1992; Abisheganaden et al. 1998; Lojander, Brander, & Ammala 1999; Sanders, Gruendl, & Rogers 1986). The main complications of NPPV therapy are listed in Table 2.

Due to Mask	**Due to Device**
Facial and nasal pressure injury/ ulcerations / pain	Rhinitis, Rhinorrhea
Mask allergy	Sinusitis
Conjunctivitis	Tinnitus
Dermatitis	Otitis /ear pain
Claustrophobia	Epistaxis
General	Gastric distension
Anxiety	Dry mucous membranes and thick secretions
Insomnia	Aspiration of gastric contents
Chest pain	Barotrauma (pneumothorax, pneumocephalus)
Headache	Central Sleep Apnea
Periodic Legs Movement Syndrome	Hypotension related to positive intrathoracic pressure

Table 2. Complications of NPPV Therapy

9. Conclusion

For COPD exacerbations NPPV should now be considered as a standard of care in properly selected patients, used in preference to invasive mechanical ventilation. Available evidence and experience have indicated that NPPV has an important role in managing COPD exacerbations, markedly by reducing the need for intubation and improving outcomes, including lowering complication and mortality rates, as well as shortening the hospital stay. NPPV can also be used in certain other situations in COPD patients: in respiratory failure precipitated by a superimposed pneumonia, in postoperative respiratory failure, in intubated patients to facilitate extubation with the aim of reducing the complications of prolonged intubation, in patients with postextubation failure to avoid reintubation, and in do-not-intubate patients; although the evidence to support these applications is not as strong as for NPPV in typical COPD exacerbations. For patients with severe stable COPD, currently available evidence suggests that NPPV can improve daytime and nocturnal gas exchange, prolong sleep duration, improve quality-of-life scores, and possibly reduce the need for hospitalization. However, the findings among studies have not been consistent on these benefits, partly related to numerous methodological shortcomings in most studies performed to date. Despite the weakness of the evidence base, however, some of the consensus and guidelines agree that COPD patients with substantial daytime carbon dioxide retention and evidence of superimposed nocturnal hypoventilation are the ones most likely to benefit (ACCP consensus conference 1999). Achieving desired NPPV adherence by COPD patients will remain still a challenge. Identification of eligible patients, establishment of the appropriate settings and close monitoring of the patients with trained staff are the key points of success of NPPV therapy. Technological improvement of NPPV devices and masks besides new guidelines on the selection of patient, ventilation mode and interface may achieve better NPPV adherence in patients with COPD in the future.

10. References

Abisheganaden, J., Chan C. C., Chee C. B., Yap J. C., Poh S. C., Wang Y. T., & Cheong T. H. (1998). The obstructive sleep apnoea syndrome--experience of a referral centre. Singapore Med J 39 (8):341-6.

Ambrogio, C., Lowman X., Kuo M., Malo J., Prasad A. R., & S. Parthasarathy. (2009). Sleep and non-invasive ventilation in patients with chronic respiratory insufficiency. Intensive Care Med 35 (2):306-13.

Ambrosino, N., Foglio K., Rubini F., Clini E., Nava S., & Vitacca M. (1995). Non-invasive mechanical ventilation in acute respiratory failure due to chronic obstructive pulmonary disease: correlates for success. Thorax 50 (7):755-7.

American Academy of Sleep Medicine. International classification of sleep disorders. Diagnostic and coding manual (ICSD-2), 2nd ed. American Academy of Sleep Medicine: Westchester, IL, 2005.

American College of Chest Physician Consensus Conference. Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, & nocturnal hypoventilation--a consensus conference report. (1999). Chest 116 (2):521-34.

Auriant I., Jallot A., Hervé P., Cerrina J., Le Roy Ladurie F., Fournier J.L., Lescot B., & Parquin F. (2001). Noninvasive ventilation reduces mortality in acute respiratory failure following lung resection. Am J Respir Crit Care Med 164 (7):1231-5.

Bardi G., Pierotello R., Desideri M., Valdisserri L., Bottai M., & Palla A. (2000). Nasal ventilation in COPD exacerbations: early and late results of a prospective, controlled study. Eur Respir J 15 (1):98-104.

Bednarek, M., Plywaczewski R., Jonczak L., & Zielinski J. (2005). There is no relationship between chronic obstructive pulmonary disease and obstructive sleep apnea syndrome: a population study. Respiration 72 (2):142-9.

Benhamou, D., Girault C., Faure C., Portier F., & Muir J. F. (1992). Nasal mask ventilation in acute respiratory failure. Experience in elderly patients. Chest 102 (3):912-7.

Bianchi, L., Foglio K., Pagani M., Vitacca M., Rossi A., & Ambrosino N. (1998). Effects of proportional assist ventilation on exercise tolerance in COPD patients with chronic hypercapnia. Eur Respir J 11 (2):422-7.

Borghi-Silva, A., Mendes R. G., Toledo A. C., Malosa Sampaio L. M., da Silva T. P., Kunikushita L. N., Dutra de Souza H. C., Salvini T. F., & Costa D. Adjuncts to physical training of patients with severe COPD: oxygen or noninvasive ventilation? (2010). Respir Care 55 (7):885-94.

British Thoracic Society Standards of Care Committee. BTS Guideline: Non-invasive ventilation in acute respiratory failure. (2002). Thorax 57 (3):192-211.

Brochard L., Isabey D., Piquet J., Amaro P., Mancebo J., Messadi A.A., Brun-Buisson C., Rauss A., Lemaire F., & Harf A. (1990). Reversal of acute exacerbations of chronic obstructive lung disease by inspiratory assistance with a face mask. N Engl J Med 323 (22):1523-30.

Brochard L., Mancebo J., Elliott M.W. (2002). Noninvasive ventilation for acute respiratory failure. Eur Respir J 19 (4):712-21.

Brochard L., Mancebo J., Wysocki M., Lofaso F., Conti G., Rauss A., Simonneau G., Benito S., Gasparetto A., Lemaire F., Isabey D., & Harf A. (1995. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med 333 (13):817-22.

Carlucci A., Richard J.C., Wysocki M., Lepage E., & Brochard L; SRLF Collaborative Group on Mechanical Ventilation. (2001). Noninvasive versus conventional mechanical ventilation. An epidemiologic survey. Am J Respir Crit Care Med 163 (4):874-80.

Carrey, Z., Gottfried S. B., & Levy R. D. (1990). Ventilatory muscle support in respiratory failure with nasal positive pressure ventilation. Chest 97 (1):150-8.

Casey, K. R., Cantillo K. O., & Brown L. K. (2007). Sleep-related hypoventilation/hypoxemic syndromes. Chest 131 (6):1936-48.

Celikel, T., Sungur M., Ceyhan B., & Karakurt S. (1998). Comparison of noninvasive positive pressure ventilation with standard medical therapy in hypercapnic acute respiratory failure. Chest 114 (6):1636-42.

Chaouat, A., Weitzenblum E., Krieger J., Ifoundza T., Oswald M., & Kessler R. (1995). Association of chronic obstructive pulmonary disease and sleep apnea syndrome. Am J Respir Crit Care Med 151 (1):82-6.

Chaouat, A., Weitzenblum E., Krieger J., Sforza E., Hammad H., Oswald M., & Kessler R. (1999). Prognostic value of lung function and pulmonary haemodynamics in OSA patients treated with CPAP. Eur Respir J 13 (5):1091-6.

Chevron, V., Menard J. F., Richard J. C., Girault C., Leroy J., & Bonmarchand G. (1998). Unplanned extubation: risk factors of development and predictive criteria for reintubation. Crit Care Med 26 (6):1049-53.

Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoventilation--a consensus conference report. Chest. 1999 Aug;116(2):521-34.

Confalonieri, M., Potena A., Carbone G., Porta R. D., Tolley E. A., & Umberto Meduri G. (1999). Acute respiratory failure in patients with severe community-acquired pneumonia. A prospective randomized evaluation of noninvasive ventilation. Am J Respir Crit Care Med 160 (5 Pt 1):1585-91.

Conti, G., Antonelli M., Navalesi P., Rocco M., Bufi M., Spadetta G., & Meduri G. U. (2002). Noninvasive vs. conventional mechanical ventilation in patients with chronic obstructive pulmonary disease after failure of medical treatment in the ward: a randomized trial. Intensive Care Med 28 (12):1701-7.

Criner, G. J., Brennan K., Travaline J. M., & Kreimer D. (1999). Efficacy and compliance with noninvasive positive pressure ventilation in patients with chronic respiratory failure. Chest 116 (3):667-75.

de Miguel, J., Cabello J., Sanchez-Alarcos J. M., Alvarez-Sala R., Espinos D., & Alvarez-Sala J. L. (2002). Long-term effects of treatment with nasal continuous positive airway pressure on lung function in patients with overlap syndrome. Sleep Breath 6 (1):3-10.

Dreher, M., Storre J. H., Schmoor C., & Windisch W. High-intensity versus low-intensity non-invasive ventilation in patients with stable hypercapnic COPD: a randomised crossover trial. (2010). Thorax 65 (4):303-8.

Elliott, M. W. (2002). Non-invasive ventilation in acute exacerbations of chronic obstructive pulmonary disease: a new gold standard? Intensive Care Med 28 (12):1691-4.

Epstein, S. K., Ciubotaru R. L., & Wong J. B. (1997). Effect of failed extubation on the outcome of mechanical ventilation. Chest 112 (1):186-92.

Fernandez-Vivas, M., Caturla-Such J., Gonzalez de la Rosa J., Acosta-Escribano J., Alvarez-Sanchez B., & Canovas-Robles J. (2003). Noninvasive pressure support versus proportional assist ventilation in acute respiratory failure. Intensive Care Med 29 (7):1126-33.

Ferrer, M., Esquinas A., Leon M., Gonzalez G., Alarcon A., & Torres A. (2003). Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. Am J Respir Crit Care Med 168 (12):1438-44.

Ferrer, M., Valencia M., Nicolas J. M., Bernadich O., Badia J. R., & Torres A. (2006). Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. Am J Respir Crit Care Med 173 (2):164-70.

Ferrer, M., Sellares J., Valencia M., Carrillo A., Gonzalez G., Badia J. R., Nicolas J. M., & Torres A. (2009). Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomised controlled trial. Lancet 374 (9695):1082-8.

Flenley, D. C. (1985). Sleep in chronic obstructive lung disease. Clin Chest Med 6 (4):651-61.

Fletcher, E. C., Shah A., Qian W., & Miller C. C., 3rd. (1991). "Near miss" death in obstructive sleep apnea: a critical care syndrome. Crit Care Med 19 (9):1158-64.

Foucher, P., Baudouin N., Merati M., Pitard A., Bonniaud P., Reybet-Degat O., & Jeannin L. (1998). Relative survival analysis of 252 patients with COPD receiving long-term oxygen therapy. Chest 113 (6):1580-7.

Gay, P. C., Hess D. R., & Hill N. S. (200)1. Noninvasive proportional assist ventilation for acute respiratory insufficiency. Comparison with pressure support ventilation. Am J Respir Crit Care Med 164 (9):1606-11.

Girault, C., Daudenthun I., Chevron V., Tamion F., Leroy J., & Bonmarchand G. (1999). Noninvasive ventilation as a systematic extubation and weaning technique in acute-on-chronic respiratory failure: a prospective, randomized controlled study. Am J Respir Crit Care Med 160 (1):86-92.

[GOLD] Global Initiative for Chronic Obstructive Lung Disease (updated 2010). [online]. URL: www.goldcopd.com

Grunstein, R. (2005). Continuous positive airway pressure treatment for obstructive sleep apnea-hypopnea syndrome. In Principles and practice of sleep medicine, edited by M. H. Kryger, Roth, T., Dement, W.C. Philadelphia: Elsevier Saunders.

Hill, N. S. (2004). Noninvasive ventilation for chronic obstructive pulmonary disease. Respir Care 49 (1):72-87; discussion 87-9.

Hoffstein, V., Viner S., Mateika S., & Conway J. (1992). Treatment of obstructive sleep apnea with nasal continuous positive airway pressure. Patient compliance, perception of benefits, & side effects. Am Rev Respir Dis 145 (4 Pt 1):841-5.

Janssens, J. P., Metzger M., & Sforza E. (2009). Impact of volume targeting on efficacy of bi-level non-invasive ventilation and sleep in obesity-hypoventilation. Respir Med 103 (2):165-72.

Jaye, J., Chatwin M., Dayer M., Morrell M. J., & Simonds A. K. (2009). Autotitrating versus standard noninvasive ventilation: a randomised crossover trial. Eur Respir J 33 (3):566-71.

Jones, S. E., Packham S., Hebden M., & Smith A. P. (1998). Domiciliary nocturnal intermittent positive pressure ventilation in patients with respiratory failure due to severe COPD: long-term follow up and effect on survival. Thorax 53 (6):495-8.

Kakkar, R. K., & Berry R. B. (2007). Positive airway pressure treatment for obstructive sleep apnea. Chest 132 (3):1057-72.

Keenan, S. P., Sinuff T., Cook D. J., & Hill N. S. (2003). Which patients with acute exacerbation of chronic obstructive pulmonary disease benefit from noninvasive positive-pressure ventilation? A systematic review of the literature. Ann Intern Med 138 (11):861-70.

Keenan, S. P., Powers C. E., & McCormack D. G. (2005). Noninvasive positive-pressure ventilation in patients with milder chronic obstructive pulmonary disease exacerbations: a randomized controlled trial. Respir Care 50 (5):610-6.

Keenan, S.P., Sinuff T., Burns K.E., Muscedere J., Kutsogiannis J., Mehta S., Cook D.J., Ayas N., Adhikari N.K., Hand L., Scales D.C., Pagnotta R., Lazosky L., Rocker G., Dial S., Laupland K., Sanders K., & Dodek P.; Canadian Critical Care Trials Group/Canadian Critical Care Society Noninvasive Ventilation Guidelines Group. (2011). Clinical practice guidelines for the use of noninvasive positive-pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting. CMAJ 183 (3):E195-214.

Kolodziej, M. A., Jensen L., Rowe B., & Sin D. (2007). Systematic review of noninvasive positive pressure ventilation in severe stable COPD. Eur Respir J 30 (2):293-306.

Kramer, N., Meyer T. J., Meharg J., Cece R. D., & Hill N. S. (1995). Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med 151 (6):1799-806.

Kushida, C.A., Littner M.R., Hirshkowitz M., Morgenthaler T.I., Alessi C.A., Bailey D., Boehlecke B., Brown T.M., Coleman J. Jr, Friedman L., Kapen S., Kapur V.K., Kramer M., Lee-Chiong T., Owens J., Pancer J.P., Swick T.J., & Wise M.S.; American Academy of Sleep Medicine. (2006). Practice parameters for the use of continuous and bilevel positive airway pressure devices to treat adult patients with sleep-related breathing disorders. Sleep 29 (3):375-80.

Leger, P., Bedicam J. M., Cornette A., Reybet-Degat O., Langevin B., Polu J. M., Jeannin L., & Robert D. (1994). Nasal intermittent positive pressure ventilation. Long-term follow-up in patients with severe chronic respiratory insufficiency. Chest 105 (1):100-5.

Lightowler, J. V., Wedzicha J. A., Elliott M. W., & Ram F. S. (2003). Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. BMJ 326 (7382):185.

Lojander, J., Brander P. E., & Ammala K. (1999). Nasopharyngeal symptoms and nasal continuous positive airway pressure therapy in obstructive sleep apnoea syndrome. Acta Otolaryngol 119 (4):497-502.

Luo, H., Cheng P., & Zhou R. (2001). [Sequential BiPAP following invasive mechanical ventilation in COPD patients with hypercapnic respiratory failure]. Hunan Yi Ke Da Xue Xue Bao 26 (6):563-5.

Machado, M. C., Vollmer W. M., Togeiro S. M., Bilderback A. L., Oliveira M. V., Leitao F. S., Queiroga F. Jr., Lorenzi-Filho G., & Krishnan J. A. (2010). CPAP and survival in moderate-to-severe obstructive sleep apnoea syndrome and hypoxaemic COPD. (2010). Eur Respir J 35 (1):132-7.

Mansfield, D., & Naughton M. T. (1999). Effects of continuous positive airway pressure on lung function in patients with chronic obstructive pulmonary disease and sleep disordered breathing. Respirology 4 (4):365-70.

Manuel, A., Russell R. E., & Jones Q. (2010). Noninvasive ventilation: has Pandora's box been opened? Int J Chron Obstruct Pulmon Dis 5:55-6.

Marin, J. M., Soriano J. B., Carrizo S. J., Boldova A., & Celli B. R. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. (2010). Am J Respir Crit Care Med 182 (3):325-31.

Martin, T. J., Hovis J. D., Costantino J. P., Bierman M. I., Donahoe M. P., Rogers R. M., Kreit J. W., Sciurba F. C., Stiller R. A., & Sanders M. H. (2000). A randomized, prospective evaluation of noninvasive ventilation for acute respiratory failure. Am J Respir Crit Care Med 161 (3 Pt 1):807-13.

Mayos, M., Hernandez Plaza L., Farre A., Mota S., & Sanchis J. (2001). [The effect of nocturnal oxygen therapy in patients with sleep apnea syndrome and chronic airflow limitation]. Arch Bronconeumol 37 (2):65-8.

McEvoy, R. D., Pierce R. J., Hillman D., Esterman A., Ellis E. E., Catcheside P. G., O'Donoghue F. J., Barnes D. J., & Grunstein R. R. Australian trial of non-invasive Ventilation in Chronic Airflow Limitation (AVCAL) Study Group. (2009).

Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial. Thorax 64 (7):561-6.

Meduri, G. U., Fox R. C., Abou-Shala N., Leeper K. V., & Wunderink R. G. (1994). Noninvasive mechanical ventilation via face mask in patients with acute respiratory failure who refused endotracheal intubation. Crit Care Med 22 (10):1584-90.

Mehta, S., & Hill N. S. (2001). Noninvasive ventilation. Am J Respir Crit Care Med 163 (2):540-77.

Nava, S., & Ceriana P. (2004). Causes of failure of noninvasive mechanical ventilation. Respir Care 49 (3):295-303.

Nava, S., Gregoretti C., Fanfulla F., Squadrone E., Grassi M., Carlucci A., Beltrame F., & Navalesi P. (2005). Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. Crit Care Med 33 (11):2465-70.

Nava, S., Navalesi P., & Conti G. (2006). Time of non-invasive ventilation. Intensive Care Med 32 (3):361-70.

Nava, S., & Hill N. (2009). Non-invasive ventilation in acute respiratory failure. Lancet 374 (9685):250-9.

Owens, R. L., & Malhotra A. (2010). Sleep-disordered breathing and COPD: the overlap syndrome. Respir Care 55 (10):1333-44; discussion 1344-6.

Pepin, J. L., Krieger J., Rodenstein D., Cornette A., Sforza E., Delguste P., Deschaux C., Grillier V., & Levy P. (1999). Effective compliance during the first 3 months of continuous positive airway pressure. A European prospective study of 121 patients. Am J Respir Crit Care Med 160 (4):1124-9.

Petrof, B. J., Calderini E., & Gottfried S. B. (1990). Effect of CPAP on respiratory effort and dyspnea during exercise in severe COPD. J Appl Physiol 69 (1):179-88.

Rochester, D. F., Braun N. M., & Arora N. S. (1979). Respiratory muscle strength in chronic obstructive pulmonary disease. Am Rev Respir Dis 119 (2 Pt 2):151-4.

Sanders, M. H., Gruendl C. A., & Rogers R. M. (1986). Patient compliance with nasal CPAP therapy for sleep apnea. Chest 90 (3):330-3.

Soo Hoo, G. W., Santiago S., & Williams A. J. (1994). Nasal mechanical ventilation for hypercapnic respiratory failure in chronic obstructive pulmonary disease: determinants of success and failure. Crit Care Med 22 (8):1253-61.

Squadrone, E., Frigerio P., Fogliati C., Gregoretti C., Conti G., Antonelli M., Costa R., Baiardi P., & Navalesi P. (2004). Noninvasive vs invasive ventilation in COPD patients with severe acute respiratory failure deemed to require ventilatory assistance. Intensive Care Med 30 (7):1303-10.

Storre, J. H., Seuthe B., Fiechter R., Milioglou S., Dreher M., Sorichter S., & Windisch W. (2006). Average volume-assured pressure support in obesity hypoventilation: A randomized crossover trial. Chest 130 (3):815-21.

Tuggey, J. M., Plant P. K., & Elliott M. W. (2003). Domiciliary non-invasive ventilation for recurrent acidotic exacerbations of COPD: an economic analysis. Thorax 58 (10):867-71.

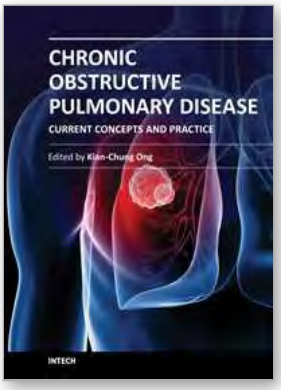
Wijkstra, P. J., Lacasse Y., Guyatt G. H., Casanova C., Gay P. C., Meecham Jones J., & Goldstein R. S. (2003). A meta-analysis of nocturnal noninvasive positive pressure ventilation in patients with stable COPD. Chest 124 (1):337-43.

Windisch, W., Vogel M., Sorichter S., Hennings E., Bremer H., Hamm H., Matthys H., & Virchow J. C., Jr. (2002). Normocapnia during nIPPV in chronic hypercapnic COPD reduces subsequent spontaneous PaCO2. Respir Med 96 (8):572-9.

Windisch, W., S. Kostic, M. Dreher, J. C. Virchow, Jr., & S. Sorichter. (2005). Outcome of patients with stable COPD receiving controlled noninvasive positive pressure ventilation aimed at a maximal reduction of Pa(CO2). Chest 128 (2):657-62.

Windisch, W., Dreher M., Storre J. H., & Sorichter S. (2006). Nocturnal non-invasive positive pressure ventilation: physiological effects on spontaneous breathing. Respir Physiol Neurobiol 150 (2-3):251-60.

Windisch, W., Haenel M., Storre J. H., & Dreher M. (2009). High-intensity non-invasive positive pressure ventilation for stable hypercapnic COPD. Int J Med Sci 6 (2):72-6.



Chronic Obstructive Pulmonary Disease - Current Concepts and Practice

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A decade or so ago, many clinicians were described as having an unnecessarily 'nihilistic' view of COPD. This has certainly changed over the years... This open access book on COPD provides a platform for scientists and clinicians from around the world to present their knowledge of the disease and up-to-date scientific findings, and avails the reader to a multitude of topics: from recent discoveries in the basic sciences to state-of-the-art interventions on COPD. Management of patients with COPD challenges the whole gamut of Respiratory Medicine - necessarily pushing frontiers in pulmonary function (and exercise) testing, radiologic imaging, pharmaceuticals, chest physiotherapy, intensive care with respiratory therapy, bronchology and thoracic surgery. In addition, multi-disciplinary inputs from other specialty fields such as cardiology, neuro-psychiatry, geriatric medicine and palliative care are often necessary for the comprehensive management of COPD. The recent progress and a multi-disciplinary approach in dealing with COPD certainly bode well for the future. Nonetheless, the final goal and ultimate outcome is in improving the health status and survival of patients with COPD.

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18

Types of Physical Exercise Training for COPD Patients

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1. Introduction

Pulmonary diseases are increasingly important causes of morbidity and mortality in the modern world (Ries et al., 2007). Chronic obstructive pulmonary disease (COPD) is the most common chronic lung disease, and a major cause of lung-related death and disability (Fishman, 2008). COPD is characterized by chronic airflow limitation, progressive and largely irreversible, associated with an abnormal inflammatory reaction (Ancochea Bermúdez et al., 2009). COPD is very disabling and features extra-pulmonary manifestations, but it can be prevented and treated.

The disease is diagnosed by a clinical history based on the combination of history, physical examination and confirmation of the presence of airflow obstruction with the use of spirometry (Figure 1 Spirometry). Spirometric assessment is performed according to the guidelines of the American Thoracic Society (ATS) (Laszlo, 2006). The technician asks the subjects three exhaling exercises and the best is used for the analysis (Miller et al., 2005). If the Tiffenau rate (value of FEV_1/FVC) is less than seventy percent, COPD exists (Global initiative for chronic obstructive lung disease *[GOLD]*, 2010). Smoking is the major risk factor for the disease (Hilberink et al. 2011).

Fig. 1. Spirometry

The most common symptoms of COPD are breathlessness, chronic cough, wheezing, sputum production, recurrent respiratory infection may be associated with some of the following systematic effects such as undernourishment, weight loss, exercise limitation and muscle weakness (*GOLD,* 2010). Knowledge regarding the disturbance of muscle function that occurs in patients with COPD is continuously increasing. Initially muscular dysfunction was considered to be a self-limiting disease resulting from inactivity and lack of exercise. However, recent studies have shown that in addition to this factor, peripheral muscles such as the quadriceps seem to have some type of myopathy (Couillard & Prefaut, 2005). Although the presence of myopathy is still being debated, there is some evidence pointing to myopathy associated with oxidative stress (Rabinovich et al., 2001). Recent studies in COPD have highlighted the role of the ubiquitine proteasome system in the breakdown of skeletal muscle protein in COPD patients. Malfunction of the mitochondria has also recently been identified in these patients (Rabinovich & Vilaro, 2010).

COPD is a major cause of disability and mortality worldwide and the prevalence increases with age. COPD will increase by more than thirty percent in the next ten years, if the population does not cut down smoking (Ancochea Bermúdez et al., 2009). Actually, due to high prevalence, associated to high morbilidity, economic and social cost COPD is a major health problem (Ramsey & Sullivan, 2003; Sullivan, Ramsey, & Lee, 2000). COPD is not curable, but treatments can help to control symptoms and improve quality of life of patients. It is necessary to reduce risk factors such as smoking and physical inactivity *(GOLD,* 2010).

Many people suffer from COPD for years and die prematurely of it or its complications. The goals of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (Rabe et al., 2007) are to improve prevention and management of COPD through a concerted worldwide effort of people involved in all facets of health care and health care policy, and to encourage an expanded level of research interest in this highly prevalent disease. The GOLD report separates COPD patients into the four different stages (figure 2) *(GOLD,* 2010).

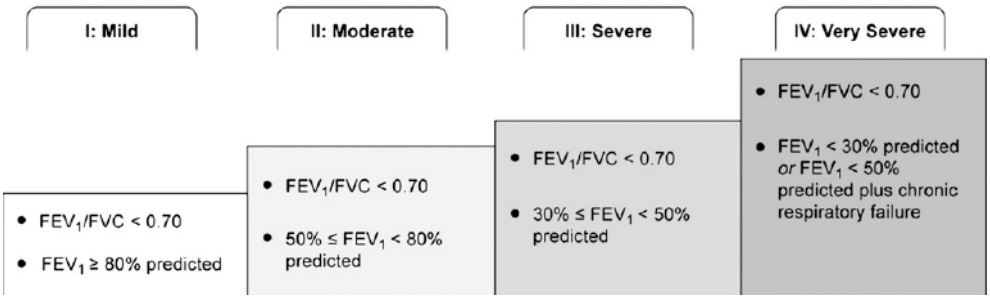


Fig. 2. Stages for Chronic Obstructive Pulmonary Disease

Pulmonary rehabilitation has emerged as a recommended standard of care for patients with chronic lung disease based on a growing body of scientific evidence. The American Thoracic Society and European Respiratory Society (ATS /ERS) published a document in 2006 defining respiratory rehabilitation as "a multidisciplinary and comprehensive intervention has proved effective from the perspective of evidence-based medicine for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities. Integrated into individualized treatment of the patient, pulmonary rehabilitation is designed to reduce

symptoms, optimize functional status, increase participation, and reduce health-care costs by stabilizing or reversing systemic manifestations of the disease" (Nici et al., 2006). This definition focuses on three aspects of successful rehabilitation: a multidisciplinary approach; an individualized program; tailored to the patient´s needs; and attention to physical psychological and social functioning (Ries, 2008). Not forgetting a primary goal of rehabilitation interventions for people with COPD is to optimize function (Nici et al., 2006).

The components of multidisciplinary respiratory rehabilitation programs include education of patients and their families, chest physiotherapy, muscle training, the emotional support, nutritional support, occupational therapy (Ries et al., 2007). Physiotherapy consists of various phases of treatment (exercise training, peripheral and respiratory muscle training, and breathing exercises) that are considered cornerstones of the physiotherapeutic intervention (Langer et al., 2009). Also consider patients that are incorporated into a respiratory rehabilitation program must have an optimal pharmacological treatment, although not analyzed in this chapter.

There is no consensus of opinion regarding the optimal duration of the pulmonary rehabilitation intervention (Ries et al., 2007). The duration depends on changes in the patient´s lifestyle. A number of external factors also influence program duration including health-care systems and reimbursement policies, access to programs, level of functional disability, health-care provider referral patterns, and the ability of individual patients to make progress toward treatment goals.

Few clinical trials have focused on the impact of program duration on rehabilitation outcomes, but existing data suggest that gains in exercise tolerance may be greater following longer programs (Berry et al., 2003; Foy, Rejeski, Berry, Zaccaro, & Woodard, 2001; Green, Singh, Williams, & Morgan, 2001; Troosters, Gosselink, & Decramer, 2000). Besides Verrill et al. (2005) demonstrated that patients achieved significant gains in exercise tolerance in the six minute walk distance, after twelve weeks of pulmonary rehabilitation. However, in an older trial Wijkstra et al. (1995) showed that there was no difference noted between groups in the magnitude of gains in the six minute walk distance for patients who underwent 18 months and three months of home-based rehabilitation.

Moreover, although some studies suggest that the duration of the pulmonary rehabilitation program has an impact on exercise tolerance improvement, it is not clear that other outcomes such as health status or dyspnea are similarly affected by program duration (Ries et al., 2007). Thus, given the variations found in types of rehabilitation programs and content as on duration (Clini et al., 2001). Besides the differences found in clinical study design, patient populations, health systems in different countries, program location, and program content.

The purpose of this literature review is to compare the effectiveness of various exercises training programmes in the rehabilitation of COPD patients. This study analyzes the different types of aerobic exercises that are carried out with different intensities, doses and frequencies.

2. Exploratory testing

The chronic symptoms of COPD (cough, expectoration, wheezing, dyspnea and exercise tolerance) are the major factors responsible for altering the relationship between health and

quality of life. Studies of health-related quality of life (HRQoL) in patients with COPD with varying degrees of severity have consistently shown that patients have significant decrements in HRQoL (Okubadejo, Jones, & Wedzicha, 1996; Schrier, Dekker, Kaptein, & Dijkman, 1990). Therefore, HRQoL is an important clinical outcome in COPD. The Chronic Respiratory Disease Questionnaire (CRQ) (Guyatt, Berman, Townsend, Pugsley, & Chambers, 1987) and St George´s Respirtory Questionnaire (SGRQ) (Jones, Quirk, Baveystock, & Littlejohns, 1992; Jones, 2001) are the main questionnaires used to measure the quality of life in COPD patients.

The evidence-based clinical practice guidelines document concluded that there was a strong level of type A evidence, that Pulmonary Rehabilitation Programmes (PRP) improve the symptom of dyspnea in patients with COPD with a strong level of type A evidence (Jones, 2002). Dyspnea is a sensation of respiratory discomfort and the evaluation of the degree of dyspnea provides an independent dimension that is not provided by pulmonary function tests or by measuring dyspnea in an exercise laboratory. So, dyspnea is a main symptom associated with exercise performance and, therefore, quality of life. One of the major goals of COPD treatment is a reduction in dyspnea. The severity of the disease can be determined by the intensity of dyspnea (Camargo & Pereira, 2010). The severity of COPD is habitually classified by forced expiratory volume in the first second (FEV_1) after bronchodilator use (Rabe et al., 2007). Various instruments are available to measure the degree of dyspnea during exercise; the modified Medical Research Council (mMRC) dyspnea scale is the most used (Barbera et al., 2001). The mMRC has five levels that increase with the level of activity in which dyspnea appears. It assesses common tasks the patient can develop without displaying dyspnea. Levels of Dyspnea are graded as follows. Grade 0: "I only get breathless with strenuous exercise"; grade 1: "I get short of breath when hurrying or walking up a slight hill"; grade 2: "I walk slower than people of the same age because of breathlessness or have to stop for breath when walking at my own pace"; grade 3: "I stop for breath after walking 100 yards or after a few minutes"; grade 4: "I am too breathless to leave the house".

The mMRC was unidimensional, to overcome this limitation; Mahler (Mahler, Mejia-Alfaro, Ward, & Baird, 2001) designed the index known as the Baseline Dyspnea Index (BDT), which was later supplemented with the Transitional Dyspnea Index (TDI). BDT analyzes dyspnea from a triple perspective; the difficulty of the task, magnitude of effort and functional impairment, each of the sections will be assessed from 0 (severe) to 4 (none), so total amount can range between 0 and 12 (Mahler, 2006). TDI assessed changes over time compared to baseline (BDI), the changes in each of the three sections are measured between -3 and +3. Therefore, the total score can be between +9 and -9. A score of 0 indicates no changes have occurred, while -9 is very negative result (Sobradillo et al., 1999). Both multidimensional scales, BDT and TDI, are clinical instruments that can be used during cardiopulmonary exercise testing for clinical and research purposes. Besides, Borg et al., (Borg, Borg, Larsson, Letzter, & Sundblad, 2010) described the matching of the increase in dyspnea related to ventilation and oxygen consumption in exercise.

In a review of application of dyspnea and quality of life scales in COPD, it was concluded that a unidimensional scale can be used if applied in conjunction with specific quality of life scales. Alternatively, a multidimensional scale, which correlates better with quality of life, can be used (Bausewein, Farquhar, Booth, Gysels, & Higginson, 2007). Consequently, multidimensional clinical instruments were developed in order to provide a more

comprehensive assessment of the severity of dyspnea, combined with the Chronic Respiratory Disease Questionnaire (CRQ) incorporates five physical activities that are specific for individual patients (Guyatt et al., 1987). These instruments have been shown to be valid, reliable, and responsive (Reda, Kotz, Kocks, Wesseling, & van Schayck, 2010).

In 2004, Celli et al. created a mortality prediction index, known as the BODE index. It encompassed the body mass index (B), the degree of airflow obstruction as expressed by the FEV_1 (O), dyspnea with the modified medical research council (D), and exercise (E) measured with six-minute walk distance (Table 1 Variables and point value used for the computation of BODE index) data adaptated from Celli et al. (2004). The cut-off values for the assignment of points are shown for each variable. *The FEV_1 categories were identified by the American Thoracic Society (1995).† Scored on the modified Medical Research Council (mMRC) dyspnea scale can range from 0 to 4, with a score of 4 indicating that the patient is too breathless to leave the house or becomes breathless when dressing or undressing.

BODE index				
Variables	Points on BODE index			
	0	1	2	3
FEV_1% of predicted *	≥ 65	50–64	36–49	≤ 35
Six-minute walk distance (m)	≥ 350	250–349	150–249	≤ 149
MRC dyspnea score †	0–1	2	3	4
Body mass index (kg/m^2)	>21	≤ 21		

Table 1. Variables and point value used for the computation of BODE index, adapted from Celli et al. (2004)

The BODE index is a multidimensional classification system that systemically determines the degree of mortality in individuals with COPD, that provides useful prognostic information in patients with COPD and might be able to measure health status. However, it is unknown whether the BODE index is a sensitive tool for predicting the impact of quality of life in such patients. Araujo (Araujo & Holanda, 2010) found correlations between the BODE index scores and all of the CRQ domains in COPD patients. Moreover, there are studies where patients who moved from moderate to high physical activity improved their SGRQ scores by 18.4 and their CRQ scores by 14.8 (Esteban et al., 2010).

Over recent decades, several organizations have championed pulmonary rehabilitation and developed comprehensive statements, practice guidelines, and evidence-based guidelines (Ries, 2008), however there are differences about how assessment of severity of disease. The 2010 NICE Guidelines defended that multidimensional assessment tool (BODE index) is a better predictor of mortality and exacerbation rate than FEV_1 alone (Gruffydd-Jones & Loveridge, 2011).

Exercise testing is frequently used in the clinical evaluation of patients with COPD to evaluate the functional impact of a treatment (American Thoracic Society & American College of Chest Physicians, 2003). Exercise testing is a useful evaluative tool, allowing standardized measurement of exertional dispnea and exercise tolerance *(GOLD,* 2010). There is, however, no consensus regarding which exercise testing protocol should be used for this application (Pepin, Saey, Whittom, LeBlanc, & Maltais, 2005). A research indicated that walking, as performed in the endurance shuttle walk, is sensitive to detect changes in exercise performance after bronchodilation (Pepin et al., 2005). Besides Pepin et al. (2007)

indicate that the response of the 6MWT test is not sensitive to change and may not be appropriate for an assessment tool. Another research also suggests that the endurance shuttle walk is more responsive to the effects of pulmonary rehabilitation than the 6MWT for detecting changes in exercise performance following broncholdilations (Eaton, Young, Nicol, & Kolbe, 2006). Together, these findings provide growing support for the use of the endurance shuttle walk as an evaluative tool to monitor response to treatment to COPD.

The six minute walk test (6MWT) is used in order to determine the six-minute walk distance (6MWD), which correlates with the performance of activities of daily living in patients with COPD (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002; Brooks, Solway, & Gibbons, 2003). The 6MWT measures the global and integrated responses of all organ systems involved during exercise, has been shown to be an important parameter related to morbility and mortality in COPD (Casanova et al., 2007), and is also part of the BODE index (Celli et al., 2004). Although rehabilitation improves both exercise tolerance and quality of life in COPD, it is not known whether these improvements are related to each other. Several trials show the weak correlation between quality of life and the six minute walking distance in patients with COPD suggests that these parameters measure different aspects of health (Wijkstra et al., 1995).

Recently, the use of accelerometer has been incorporated as an objective measure to assess physical activity level of the patient performs daily (Troosters et al., 2010). It is necessary to analyze physical activity in daily life in patients across different disease stages according to GOLD. Other studies have shown that grip strength in the wrist is a strong independent predictor of mortality in COPD (Cortopassi, Divo, Pinto-Plata, & Celli, 2011). A significant relationship was found between hand grip strength and peripheral muscle strength (flexion of elbow and knee) and strong relationship ($r = - 0.75$, $p < 0.0001$) with the force respiratory muscles (maximum inspiratory muscles, inspiratory capacity, forced vital capacity and maximum volume ventilation).

There is no clinical trial review that has found a connection between rehabilitation respiratory programs and an increase in exercise tolerance. It is necessary to clarify the change in quality of life was related with a change in exercise tolerance in COPD patients. The difference between current studies and previous controlled studies (Sinclair, 1980; Vale, Reardon, & ZuWallack, 1993) are the use of the 12 minute walking distance which is probably more sensitive to change than the six minute walking distance (Wijkstra et al., 1995).

COPD is often associated with exacerbation of symptoms. An exacerbation of COPD is defined as "an event in the natural course for the disease characterized by a change in the patient´s baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD" (Burge & Wedzicha, 2003). The most common causes of an exacerbation are infection of the tracheobronchial tree and air pollution (White, Gompertz, & Stockley, 2003). Studies investigating effects on pulmonary function and oxigenation did not show benefits in either acute exacerbations of COPD (Newton & Bevans, 1978) or in chronic COPD (May & Munt, 1979). Assessment of the severity of an exacerbation is based on the patient´s medical history before the exacerbation, pre-existing comorbidities, symptoms, physical examination, arterial blood gas measurements, and other laboratory

test. Physicians should obtain the results of previous evaluations, where possible, to compare with the current clinical data. Specific information is required on the frequency and severity of attacks of breathlessness and cough, sputum volume and color, and limitation of daily activities (Vilaró et al., 2007).

Other targets of rehabilitation are anxiety control, dyspnea reduction and improvement of the health-related quality of life (Lacasse et al., 2006). The illness evolution can be associated with extra-pulmonary components, such as muscle loss is related with reduction of physical activity. After exacerbation, symptoms of depression have been identified as an independent factor of mortality risk (Yohannes, Baldwin, & Connolly, 2005), as well as risk a factor for rehabilitation program drop-outs (Garrod, Marshall, Barley, & Jones, 2006). The skeletal muscle dysfunction and depressive symptoms are potencially amenable to rehabilitation with exercise training (Rodrigues, 2010). We have made the following figure 3 in order to collect intra-pulmonary components (airways obstruction and dyspnea) with extra-pulmonary factors (muscle wasting, reduce mobility, exercise limitation, depression and sedentary lifestyle).

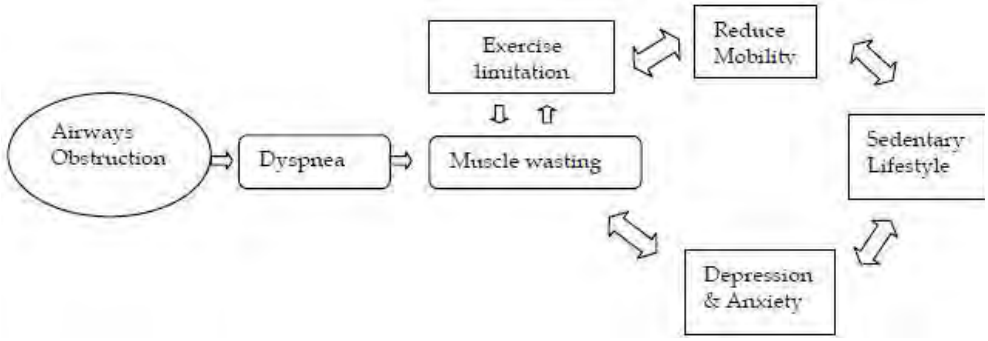


Fig. 3. Relation between intra-pulmonary components with extra-pulmonary factors.

3. Types of exercises

Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure beyond resting energy expenditure (Thompson et al., 2003). Information on the importance of physical activity in COPD has grown, especially in the last few years, although major questions remain to be answered. The present chapter aims to provide an update on the most important studies of physical activity in COPD (Esteban, 2009).

Findings from meta-analysis of pulmonary rehabilitation strongly supports that exercise training as part of treatment of patients with COPD should last at least four weeks (Lacasse, Goldstein, Lasserson, & Martin, 2006). Exercise training should be available to people with COPD, because it improves breathlessness, quality of life, exercise tolerance and functional ability (Lacasse et al., 2006). Physical therapists are crucial to the delivery of rehabilitation because of their training in exercise and movement therapies (Garrod & Lasserson, 2007).

The primary goal of the rehabilitation programs is to restore the patient to the highest possible level of independent function (Ries et al., 2007). This goal is accomplished by

helping patients become more physically active, and to learn more about their disease, treatment options, and how to cope. Within the program of rehabilitation, the physiotherapeutic intervention is responsible for various treatment phases (specifically physical exercise training, peripheral and respiratory muscle training, and breathing exercises) (Langer et al., 2009).

Aerobic exercise is the main non-pharmacological treatment better tolerated by patients with COPD (Martín-Valero, Cuesta-Vargas, & Labajos-Manzanares, 2010). Exercise training is one of the key components of pulmonary rehabilitation. The exercise prescription for the training program is guided by the following three parameters: intensity; frequency; and duration.

The standarized criterions on intervention period, dose, intensity of physical exercises in COPD patients is needed. Seven (Coppoolse et al., 1999; Kurabayashi et al., 2000; O'Shea, Taylor, & Paratz, 2004; Puente-Maestu, Sanz, Sanz, Cubillo et al., 2000; Puente-Maestu, Sanz, Sanz, Ruiz de Ona et al., 2000; Wadell, Sundelin, Henriksson-Larsen, & Lundgren, 2004; Wijkstra et al., 1995) agreed with the criteria of the American College of Sports Medicine (ACSM) (Garber et al., 2011) for the intervention period and number of sessions varied from eight weeks in the majority on trials to twelve weeks in two trials and from two to four sessions a weeks. Therefore, the number sessions a week were at least between two or four sessions a week. Only one trial (Wijkstra et al., 1995) took into account, that patients had to practise twice a day for an individualised protocol, for 0 to 5 hours the first three months and then once a day only for 0-5. The time of sessions is variable in these seven articles with a minimum of 20 minutes up to 60 minutes because two articles do not talk about the time of sessions.

According to the recommendations of the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR), *high-intensity training targets* have been operationally defined to be at least 60 to 80% of the peak work rate achieved in an incremental maximum exercise test. The intensity of the training sessions in five articles (Coppoolse et al., 1999; Puente-Maestu, Sanz, Sanz, Cubillo et al., 2000; Puente-Maestu, Sanz, Sanz, Ruiz de Ona et al., 2000; Wadell, Sundelin, Henriksson-Larsen, & Lundgren, 2004; Wijkstra et al., 1995) showed that the goal is 60-90% of heart rate maximum (HR_{max}) set by the ACSM for improving aerobic fitness ("American college of sports medicine position stand. exercise and physical activity for older adults,"1998a; "American college of sports medicine position stand. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults,"1998b)

Exercise training intervention can be adapted to the individual exercise limitations of the patient (Troosters, Gosselink, Langer, & Decramer, 2007). Troosters et al. review focused on different training types (endurance, interval and resistance training) (Troosters et al., 2007). In this chapter regarding types of exercise training intervention, it has been divided into aerobic and resistance training types. Aerobic exercise training for older people should have a target intensity of 50-85% of the oxygen uptake reserve – a range that includes both moderate exercise (minimum of 30 minute five days a week) or vigorous exercise (20 minutes three days each week)(Garber et al., 2011).

Resistance training is an ideal intervention for patients with peripheral muscle weakness and pronounced symptoms of dyspnea during exercise (O´Shea, Taylor, & Paratz, 2004).

There is not consensus on the optimal method of resistance training (callisthenics, resistance weight training, isometrics or isokinetic-type training) in patients with COPD. Each type produces strength gains highly specific to the type of training. There are no studies that compared different intensities of resistance training in patients with COPD. It is recommended to use (lower limb) resistance training according to ACSM (two or three times a week) ("ACSM", 1998a; "ACSM", 1998b; Garber et al., 2011). Exercises should be performed at 60-80% of the first repetition maximum (RM), resistance exercises should train 8-10 exercises involving the major muscle groups in bouts of 8-15 repetitions at least 30 minutes a day of moderate-intensity activity on two or three non-consecutive days each week (Nelson et al., 2007). Multiple sets of repetitions (2-5 sets) provide greater benefit (Langer et al., 2009). Resistance activities include a progressive-weight training program, done with therabands (wrist or ankle weights) or progressive weight.

Given that muscle weakness is a common problem in this population, progressive resistance exercise represents a beneficial treatment for improvements in muscle strength (O´Shea, Taylor, & Paratz, 2009). Moreover, improvements in muscle strength can be obtained when progressive resistance exercise is conducted alone or in combination with aerobic training, indicating that it can be successfully performed in conjunction with other training types during pulmonary rehabilitation (O´Shea, Taylor, & Paratz, 2009).

Careful consideration is also required when prescribing progressive resistance exercise programs for people with COPD who have comorbid health conditions (O´Shea, Taylor, & Paratz, 2004). Therefore, progresive resitance exercise may not be appropriate for all people with COPD attending pulmonary rehabilitation, and it is recommended that prescription be targeted to the individual (Storer, 2001).

It is essential to educate the patient about the importance of the training program begining with an initial phase: warming up and stretching (Table 2 Session outline). The central part consists in aerobic training (endurance or interval exercise), resistance training and breathing retraining. Finally, the sessions finish with stretching and relaxation exercises.

Initial phase	Central phase	Final phase
*Stretching *Warming up	*Aerobic training (Endurance or Interval) *Resistance training *Breathing retraining	*Stretching *Relaxation exercises

Table 2. Session outline

It is recommended to apply training strategies that enable patients to resume participation in a rehabilitation programme after an acute exacerbation as soon as possible (Puhan, Scharplatz, Troosters, Walters, & Steurer, 2009). Resistance training and interval training are best suited for early reactivation of patients. Moreover, arm exercises in patients with COPD were shown to increase arm muscle force (Epstein et al., 1997) and reduce symptoms of dyspnea and fatigue during arm activities (Bauldoff, Hoffman, Sciurba, & Zullo, 1996).

Patient education is included as an important recommendation in current clinical practice guidelines for COPD *(GOLD,* 2010; Celli, MacNee, & ATS/ERS Task Force, 2004) Education should be an integral component of pulmonary rehabilitation (Ries et al., 2007). Moreover,

education should include information on collaborative self-management and prevention and treatment of exacerbation. So, patient education interventions are necessary to ensure long-term maintenance of treatment effects. Studies with successful results in chronically ill adults both used physical activity self-monitoring (pedometers or diaries) and applied behavioural strategies to increase patient´s self efficacy and self-regulatory skills (Conn, Hafdahl, Brown, & Brown, 2008). It is necessary to initiate and maintain physical activity behaviour change during and after supervised physical exercise training programs. Rose et al., (Baraniak & Sheffield, 2011; Rose et al., 2002) evaluated psychosocial interventions to treat anxiety and panic in patients with COPD; however the data indicated that there were no changes in cognitive function. Overall, the educational intervention may have facilitated aspects of program adherence.

3.1 Continuous or incremental aerobic exercise

In this section different types of physical exercise training that can be applied to improve exercise performance in patients with COPD are presented. The authors have compared programmes with constant load training and incremental load training in COPD patients. There is high level evidence that aerobic training is effective for aerobic capacity and there is moderate evidence that interval training is effective for strength, endurance, functionality and psychosocial parameters (Normandin et al., 2002).

Endurance or continuous training

Supervised continuous training is recommended for patients in all stages of the disease who are able to perform continuous training of at least moderate intensity. Training frequency should be three times weekly in the first weeks of the exercise programme (Langer et al., 2009). Patients with severe symptoms of dyspnea during exercise are frequently not capable of performing high-intensity (70 to 80% of the peak work rate) continuous type training (Casaburi et al., 1997; Maltais et al., 1997). It seems that moderate intensity continuous training (50 to 60% of the peak work rate or 5-6 out of 10 according to the modified Borg Scale) is minimally required to achieve changes in physical fitness. Improvements in health-related quality of life after training at moderate intensities were comparable with those observed after high intensity training (Puente-Maestu, Sanz, Sanz, Cubillo et al., 2000).

Lower extremity exercise training at higher exercise intensity produces greater physiologic benefits than lower intensity training in patients with COPD. Moreover, both low-intensity and high-intensity exercise training produce clinical benefits for patients with COPD (Ries, 2008).

Two categories of tasks can be found during everyday activities, endurance and strength tasks. Endurance tasks require repetitive actions over an extended period of time (walking, cycling and swimming) as shown in figure 4. While strength tasks require explosive performance over short time periods (jumping, lifting weights, sprinting)(Ries et al., 2007). The addition of a strength-training component to a program of pulmonary rehabilitation increases muscle strength and muscle mass (Ries, 2008).

Interval training

Interval training is recommended as an alternative to continuous training in patients with severe symptoms of dyspnea due to the fact that they are unable to sustain continuous

Fig. 4. Endurance tasks taken from "Manual de Rehabilitación Respiratoria para personas con EPOC".

training at the recommended intensities. Short high intensity (at least 70-80% of peak work rate) exercise bouts of 30-180 seconds are necessary during interval training. Recommended frequency of training is the same as with continuous training (Langer et al., 2009).

Only one article (Puente-Maestu, Sanz, Sanz, Cubillo et al., 2000) showed that patients responded to supervised training with incremented loads also changed their ventilatory pattern to deeper, slower breathing. Therefore, improved ventilation this type of incremental training also tended to be more efficient with an average decrease in dead space. Perhaps, the quality of life questionnaires are not sensitive tools to detect changes in the functional variables of disease progression. The changes produced by aerobic physical training in COPD do not have clinical relevance, but they are a success because it slows down disease progression.

Most patients with severe COPD are not able to sustain a continuous exercise protocol. For these patients, interval exercise represents an alternative because it offers the same benefit as high-intensity exercise. Besides, incremental exercise is better tolerated, as expressed by fewer breaks during the rehabilitation program and better adherence to exercise protocols (Puhan MA et al., 2006). Therapeutic intervention can be done in or out of water; the next section explains the therapeutic aquatic exercise intervention.

3.2 Therapeutic aquatic exercise intervention

This intervention is known for its power of prevention and treatment in different conditions, although not considered part of standard pulmonary rehabilitation. Therapeutic aquatic exercise intervention is a discipline that includes hydrotherapy, spa therapy, balneotherapy and physiotherapy, and is used for the prevention and treatment of diseases through water (Geytenbeek, 2008). Hydrotherapy is defined as a complementary therapy that uses the temperature and pressure of water as a therapeutic agent at a given temperature (Geytenbeek, 2002).

There is controversy in the scientific literature regarding the beneficial and harmful effects of water exercise for the respiratory system in people with respiratory problems. Different types of exercises can be carried out: walking, cycling, lifting weights in a swimming pool (figure 5), and so on. Previous studies show that hydrostatic pressure exerts on inspiratory muscle strength and limited chest expansion; this effect is enhanced as the temperature of the pool water decreases (Frontera, Herring, Micheli, & Silver, 2008). In addition, the diaphragm moves during diving due to compression by the abdomen, thus decreasing respiratory vital capacity (Greenleaf, 1984). Patients with chronic obstructive pulmonary disease benefit from the hydrostatic pressure exerted during immersion, which facilitates expiration and reduces the residual volume, decreasing the air trapped in this pathology (Asanuma, 1999; Dahlback, 1975; Schoenhofer, Koehler, & Polkey, 2004). Previous studies show that water exerts hydrostatic pressure on inspiratory muscle strength and limited chest expansion, this effect is enhanced with decreasing the temperature of the pool water (Agostoni, Gurtner, Torri, & Rahn, 1966). Therapeutic aquatic exercise intervention is known for its ability to prevent and treat different conditions. This intervention is a specialized field of physical training and therapy, used to achieve certain physical and functional goals using the properties of water (Geytenbeek, 2008).

The reviewed articles covered incremental therapeutic aquatic exercise with an intensity ranging from 50% to 90% of maximal oxygen consumption (VO_{2max}) with sessions of 30 to 50 minutes 2 to 5 days a week, for a total of 8 to 24 weeks at a temperature of 29 ºC to 38 ºC (Kurabayashi et al., 2000; Wadell, Sundelin, Henriksson-Larsen, Lundgren, 2004). COPD patients walked in water to the level of their shoulders, and they breathed out slowly through their mouth into water after sinking their nose 3-5 cm below the water level. The patients` eyes were not under the water. After exercise, patients dressed and rested on a chair in a comfortable room (25ºC) for 30 minutes. Two studies showed clinical changes in the questionnaire of quality of life for respiratory patients. People who performed incremental exercise in the water showed functional changes in the distance walked in the walking test, in forced vital capacity and forced expiratory volume (Kurabayashi et al., 2000; Wadell, Sundelin, Henriksson-Larsen, & Lundgren, 2004). The aquatic intervention group that performed incremental exercise had improved health-related quality of life, compared to a control group without intervention (Wadell, Sundelin, Henriksson-Larsen, & Lundgren, 2004).

Fig. 5. Cycling and lifting weights

Physical therapy for COPD requires a certain duration and frequency in order to improve clinical parameters. Wadell et al. (2005a) indicated that training once a week (high intensity/low frequency) was not sufficient to sustain the improvements in physical capacity and quality of life achieved after a period of 3 months of high frequency aquatic exercise training with three sessions of 45 minutes each a week (high intensity/high frequency). However, high intensity physical training once a week for 6 months seemed to be enough to avoid deterioration compared to baseline. According to Kurabayashi's study, 6 consecutive days of exercise a week would be preferable to 3 alternative days of exercise a week, even if the cumulative exercise period was the same (Kurabayashi et al., 1998). The studies reviewed showed much heterogeneity with respect to the duration of treatment, ranging from 6 to 24 weeks. However, the typical duration of treatment was 8 to 12 weeks. Further studies should direct more attention to the specific duration, frequency and accuracy of aerobic intensity thresholds. Other authors found that exercise in water tends to provide even greater benefits than similar exercise training on land (Wadell, Sundelin, Henriksson-Larsen, & Lundgren, 2004).

Breathing exercises during immersion in water at 38 ^{o}C could be recommended as physical therapy after diagnosis of COPD. Elevation of the sub-peritoneal diaphragmatic pressure by the hydraulic pressure could help raise the diaphragm and assist in the evacuation of air during exhalation, resulting in a decrease in dead space. In addition, hydraulic pressure was reported to increase cardiac output, resulting in an improvement in blood gas exchange in lung capillaries. Besides these effects, inhalation of gas containing thermal hydrogen sulfate lowers the viscosity of sputum (Asanuma, Fujita, Ide, & Agishi, 1971). Only three studies (Kurabayashi et al., 2000; Kurabayashi et al., 1998; Perk, Perk, & Bodén, 1996) included breathing exercises during therapeutic aquatic exercise intervention.

3.3 Respiratory muscle training

In general, patients with COPD have weak inspiratory muscles (Polkey et al., 1996). This weakness may contribute to dyspnea and exercise limitation in patients with significant COPD. When evaluating the strength of respiratory muscles we should be aware that we are focusing primarily on the ability of these muscles to generate tension during a forced inspiratory or expiratory maneuver. The result of the maneuver can be measured with the mouth (Figure 6 Equipment to maneuver), and it is measured in centimeters H_2O. This primarily reflects a set of variables such as muscle mass (ability to generate force) and length-tension relationship.

The role of inspiratory muscle training (IMT) for individuals with stable COPD is unclear (Geddes, O'Brien, Reid, Brooks, & Crowe, 2008). The first systematic review on IMT found little evidence to support the use of IMT (Shoemaker, Donker, & Lapoe, 2009). The Amercian Thoracic Society/European Respiratory Society standards (Celli, MacNee et al., 2004) nor the Canadian Thoracic Society Recommendations for the Management of COPD (O'Donnell et al., 2008) recommend the incorporation of IMT into management plan. The Global Initiative for Chronic Obstructive Lung Disease *(GOLD,* 2010) states that "respiratory muscle training is beneficial, especially when combined with general exercise training" based on non-randomized trials and observational studies.

Fig. 6. Equipment to maneuver

In an attempt to reduce the severity of breathlessness and to improve exercise tolerance, IMT has been applied in many COPD patients (Weiner, Magadle, Beckerman, Weiner, & Berar-Yanay, 2003). Several different respiratory muscle training devices are available, ranging from sophisticated computerized systems to simple hand-held resistive devices. In addition, the relative benefits of strength versus endurance training, inspiratory versus expiratory training and effect in patients of differing severity are unknown (Garrod & Lasserson, 2007)

Types of intervention: Sham, low- and high-intensity IMT

There are studies comparing the effect of different types of intervention (Geddes, Reid, Crowe, O'Brien, & Brooks, 2005). In order to standardize studies that showed sham IMT and low intensity IMT at similar percentages of maximum inspiratory pression (PImax). Bégin et al., (Begin & Grassino, 1991) measured these loads using the tidal inspiratory pressure (PI) of individuals with COPD. Sham IMT was defined as that using the same type of device as the intervention group at an intensity less than or equal to the mean plus one standard deviation (SD). Since PI is directly proportional to the partial pressure of carbon dioxide in the arterial blood (PCO_2) of patients with COPD (Begin & Grassino, 1991), sham IMT for normocapneic individuals was defined as intensity p8.3 cm H_2O (mean PI +1 SD) and for individuals with moderate hypercapnia, as intensity p11.5 cm H_2O (Geddes et al., 2005).

Using IMT in combination with other interventions and using flow-dependent resistive training is important in the pulmonary rehabilitation program (Geddes et al., 2008). However, there are no established thresholds for what constitutes a clinically meaningful change in inspiratory muscle strength or endurance, other methods must be utilized to infer clinical benefit (Shoemaker et al., 2009). Geddes et al. (2005) recommended using IMT at least a total of 30 minutes daily but can be spread over more than one session a day. Training should occur at least 5 days a week. While gains may be measurable after as short

as 5 weeks, IMT should become part of the individual´s exercise program. The minimal training intensity necessary could start as low as 22% PImax and be progressed to as high as 60% PImax using a targeted inspiratory resistive or threshold trainer (Geddes et al., 2005). Therefore, IMT significantly increased inspiratory muscle strength and inspiratory muscle endurance (Lotters, van Tol, Kwakkel, & Gosselink, 2002). In addition, research review found a clinically significant decrease in dyspnea sensation at rest and during exercise is observed after IMT (Lotters et al., 2002).

In conclusion, IMT improves inspiratory muscle strength and endurance, functional exercise capacity, dyspnea and quality of life. Inspiratory muscle endurance training was shown to be less effective than respiratory muscle strength training. In patients with inspiratory muscle weakness, the addition of IMT to a general exercise training program improved PImax and tended to improve exercise performance (Gosselink et al., 2011).

Furthermore, maximal inspiratory pressure is a volitional test and therefore open to criticism (Polkey & Moxham, 2004). Futher research is needed to explore the impact that different training protocols (frequency, intensity and duration of IMT, supervision) may have on outcomes and to determine the extent to which changes in outcomes associated with IMT translate into clinically important improvement for adults with COPD (Geddes et al., 2008).

4. Implications

In the research reviewed, there are strong arguments that pulmonary rehabilitation is beneficial for improving the quality of life related to health at the beginning of the program. Furthermore pulmonary rehabilitation reduces symptoms and increases participation in everyday activities. However, it is necessary to do more randomized controlled trials to clarify which components of the lung rehabilitation are essential. Future studies to discover the ideal length of treatment, the necessary degree of supervision, training intensity and how long the treatment effect persists.

Without no doubt, it is necessary to individualize programs for this population taking into account their different levels of severity. The prescription should begin at low intensity and short duration, for both parameters gradually increasing to the threshold of fatigue.

In summary, incremental aerobic resistance physical exercises are better than constant load physical exercises at an intensity range from 90% to 50 % of $VO_{2\,max}$, with a frequency of two or four days a week, the session is from 30 to 60 minutes during a period of treatment from eight to twelve weeks. Exercise training induces several symptomatic and functional adaptations resulting in an increased aerobic capacity, although clinical relevance is not collected in the study population. Maybe, for further studies we should take intrinsic patient factor (severity of COPD) into account over a longer period of time and how extrinsic factors of the exercises affect disease progression. Moreover, it is important to determine whether these physiological benefits of COPD patients who have performed an incremental aerobic resistance physical exercises program supervised justify the increased costs. Therefore, a cost/effectiveness analysis is necessary to determining whether the type of intervention program is supervised or not.

It is essential to investigate physical activity in daily life in patients with COPD in accordance to the GOLD stages. Pulmonary rehabilitation programs should incorporate the

use of an accelerometer, the values of respiratory muscle strength and peripheral muscle strength (hand grip, knee- extension); also more sensitive tools for detecting changes in exercise tolerance should be included.

5. References

Agostoni, E., Gurtner, G., Torri, G., & Rahn, H. (1966). Respiratory mechanics during submersion and negative-pressure breathing. *Journal of Applied Physiology, 21*(1), 251-258.

American college of sports medicine position stand exercise and physical activity for older adults. (1998a). *Medicine and Science in Sports and Exercise, 30*(6), 992-1008.

American college of sports medicine position stand. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults.(1998b). *Medicine and Science in Sports and Exercise, 30*(6), 975-991.

American Thoracic Society, & American College of Chest Physicians. (2003). ATS/ACCP statement on cardiopulmonary exercise testing. *American Journal of Respiratory and Critical Care Medicine, 167*(2), 211-277. doi:10.1164/rccm.167.2.211

Ancochea Bermúdez J, et al. (2009). *Estrategia en EPOC del sistema nacional de salud* Retrieved 2011, from http://www.msc.es/organizacion/sns/planCalidadSNS/docs/EstrategiaEPOCSNS.pdf

Araujo, Z. T., & Holanda, G. (2010). Does the BODE index correlate with quality of life in patients with COPD*? Jornal Brasileiro De Pneumologia: Publicacao Oficial Da Sociedade Brasileira De Pneumologia e Tisilogia, 3*6(4), 447-452.

Asanuma Y, Fujita S, Ide H, & Agishi Y. (1971). Improvement of respiratory resistane by hot water immersing exercise in adult asthmatic patient. *Clinical Rehabilitation,* 1, 211-217.

Asanuma Y. (1999). Influence of water immersion on lung volumes and pulmonary diffusing capacity. A comparison of healthy subjects and patients with chronic obstructive pulmonary disease. *Japanese Journal of Clinical Physiology, 2*9(3), 187-192.

ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. (2002). ATS statement: Guidelines for the six-minute walk test. *American Journal of Respiratory and Critical Care Medicine, 166*(1), 111-117.

Baraniak, A., & Sheffield, D. (2011). The efficacy of psychologically based interventions to improve anxiety, depression and quality of life in COPD: A systematic review and meta-analysis. *Patient Education and Counseling, 8*3(1), 29-36. doi:10.1016/j.pec.2010.04.010

Barbera, J. A., Peces-Barba, G., Agustí, A. G., Izquierdo, J. L., Monsó, E., Montemayor, T., et al. (2001). Guía clínica para el diagnóstico y el tratamiento de la enfermedad pulmonar obstructiva crónica. *Archivos Bronconeumología, 37*(6), 297-316.

Bauldoff, G. S., Hoffman, L. A., Sciurba, F., & Zullo, T. G. (1996). Home-based, upper-arm exercise training for patients with chronic obstructive pulmonary disease. *Heart & Lung : The Journal of Critical Care,* 25(4), 288-294.

Bausewein, C., Farquhar, M., Booth, S., Gysels, M., & Higginson, I. J. (2007). Measurement of breathlessness in advanced disease: A systematic review. *Respiratory Medicine, 10*1(3), 399-410. doi:10.1016/j.rmed.2006.07.003

Begin, P., & Grassino, A. (1991). Inspiratory muscle dysfunction and chronic hypercapnia in chronic obstructive pulmonary disease. *The American Review of Respiratory Disease, 143*(5 Pt 1), 905-912.

Berry, M. J., Rejeski, W. J., Adair, N. E., Ettinger, W. H.,Jr, Zaccaro, D. J., & Sevick, M. A. (2003). A randomized, controlled trial comparing long-term and short-term exercise in patients with chronic obstructive pulmonary disease. *Journal of Cardiopulmonary Rehabilitation, 23*(1), 60-68.

Borg, E., Borg, G., Larsson, K., Letzter, M., & Sundblad, B. M. (2010). An index for breathlessness and leg fatigue. *Scandinavian Journal of Medicine & Science in Sports, 20*(4), 644-650. doi:10.1111/j.1600-0838.2009.00985.x

Brooks, D., Solway, S., & Gibbons, W. J. (2003). ATS statement on six-minute walk test. *American Journal of Respiratory and Critical Care Medicine, 167*(9), 1287.

Burge, S., & Wedzicha, J. A. (2003). COPD exacerbations: Definitions and classifications. *The European Respiratory Journal.Supplement, 41*, 46s-53s.

Camargo, L. A., & Pereira, C. A. (2010). Dyspnea in COPD: Beyond the modified medical research council scale. *Jornal Brasileiro De Pneumologia: Publicacao Oficial Da Sociedade Brasileira De Pneumologia e Tisilogia, 36*(5), 571-578.

Casaburi, R., Porszasz, J., Burns, M. R., Carithers, E. R., Chang, R. S., & Cooper, C. B. (1997). Physiologic benefits of exercise training in rehabilitation of patients with severe chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 155*(5), 1541-1551.

Casanova, C., Cote, C. G., Marin, J. M., de Torres, J. P., Aguirre-Jaime, A., Mendez, R., et al. (2007). The 6-min walking distance: Long-term follow up in patients with COPD. *The European Respiratory Journal: Official Journal of the European Society for Clinical Respiratory Physiology, 29*(3), 535-540. doi:10.1183/09031936.00071506

Celli, B. R., Cote, C. G., Marin, J. M., Casanova, C., Montes de Oca, M., Mendez, R. A., et al. (2004). the body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *The New England Journal of Medicine, 350*(10), 1005-1012. doi:10.1056/NEJMoa021322

Celli, B. R., MacNee, W., & ATS/ERS Task Force. (2004). Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper. *The European Respiratory Journal : Official Journal of the European Society for Clinical Respiratory Physiology, 23*(6), 932-946.

Clini, E., Foglio, K., Bianchi, L., Porta, R., Vitacca, M., & Ambrosino, N. (2001). In-hospital short-term training program for patients with chronic airway obstruction. *Chest, 120*(5), 1500-1505.

Conn, V. S., Hafdahl, A. R., Brown, S. A., & Brown, L. M. (2008). Meta-analysis of patient education interventions to increase physical activity among chronically ill adults. *Patient Education and Counseling, 70*(2), 157-172. doi:10.1016/j.pec.2007.10.004

Coppoolse, R., Schols, A. M., Baarends, E. M., Mostert, R., Akkermans, M. A., Janssen, P. P., et al. (1999). Interval versus continuous training in patients with severe COPD: A randomized clinical trial. *The European Respiratory Journal : Official Journal of the European Society for Clinical Respiratory Physiology, 14*(2), 258-263.

Cortopassi, F., Divo, M., Pinto-Plata, V., & Celli, B. (2011). Resting handgrip force and impaired cardiac function at rest and during exercise in COPD patients. *Respiratory Medicine, In Press, Corrected Proo*f doi:DOI: 10.1016/j.rmed.2010.12.011

Couillard A, & Prefaut C. (2005). From muscle disuse to myopathy in COPD: Potencial contribution of oxidative stress. *European Respiratory journal, 2*6(4), 703-719.

Dahlback, G. O. (1975). Influence of intrathoracic blood pooling on pulmonary air-trapping during immersion. *Undersea Biomedical Research,* 2(2), 133-140.

Eaton, T., Young, P., Nicol, K., & Kolbe, J. (2006). The endurance shuttle walking test: A responsive measure in pulmonary rehabilitation for COPD patients. *Chronic Respiratory Disease,* 3(1), 3-9.

Epstein, S. K., Celli, B. R., Martinez, F. J., Couser, J. I., Roa, J., Pollock, M., et al. (1997). Arm training reduces the VO2 and VE cost of unsupported arm exercise and elevation in chronic obstructive pulmonary disease. *Journal of Cardiopulmonary Rehabilitation, 17*(3), 171-177.

Esteban, C. (2009). Role of physical activity in chronic obstructive pulmonary disease. [Impacto de la actividad física en la EPOC] *Archivos de Bronconeumología, 45 Suppl* 5, 7-13. doi:10.1016/S0300-2896(09)72949-7

Esteban, C., Quintana, J. M., Aburto, M., Moraza, J., Egurrola, M., Perez-Izquierdo, J., et al. (2010). Impact of changes in physical activity on health-related quality of life among patients with COPD. *The European Respiratory Journal : Official Journal of the European Society for Clinical Respiratory Physiology, 3*6(2), 292-300. doi:10.1183/09031936.00021409

Fishman, A. P. (2008). *Pulmonary diseases and disorder*s (4th ed.). New York: McGraw-Hill.

Foy, C. G., Rejeski, W. J., Berry, M. J., Zaccaro, D., & Woodard, C. M. (2001). Gender moderates the effects of exercise therapy on health-related quality of life among COPD patients. *Chest, 119*(1), 70-76.

Frontera W.R., Herring S.A., Micheli L.J., & Silver J.K. (2008). *Medicina deportiva clínica: tratamiento médico y rehabilitació*n Elsevier.

Garber, C. E., Blissmer, B., Deschenes, M. R., Franklin, B. A., Lamonte, M. J., Lee, I. M., et al. (2011). Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: Guidance for prescribing exercise. *Medicine and Science in Sports and Exercise, 4*3(7), 1334-1359. doi:10.1249/MSS.0b013e318213fefb

Garrod, R., Marshall, J., Barley, E., & Jones, P. W. (2006). Predictors of success and failure in pulmonary rehabilitation. *The European Respiratory Journal : Official Journal of the European Society for Clinical Respiratory Physiology, 27*(4), 788-794. doi:10.1183/09031936.06.00130605

Garrod, R., & Lasserson, T. (2007). Role of physiotherapy in the management of chronic lung diseases: An overview of systematic reviews. *Respiratory Medicine, 10*1(12), 2429-2436. doi:10.1016/j.rmed.2007.06.007

Geddes, E. L., Reid, W. D., Crowe, J., O'Brien, K., & Brooks, D. (2005). Inspiratory muscle training in adults with chronic obstructive pulmonary disease: A systematic review. *Respiratory Medicine, 9*9(11), 1440-1458. doi:10.1016/j.rmed.2005.03.006

Geddes, E. L., O'Brien, K., Reid, W. D., Brooks, D., & Crowe, J. (2008). Inspiratory muscle training in adults with chronic obstructive pulmonary disease: An update of a systematic review. *Respiratory Medicine, 10*2(12), 1715-1729. doi:10.1016/j.rmed.2008.07.005

Geytenbeek, J. (2002). Evidence for effective hydrotherapy. *Physiotherapy, 8*8(9), 514-529. doi:DOI: 10.1016/S0031-9406(05)60134-4

Geytenbeek J. (2008). *Aquatic physiotherapy evidence-based practice guide*. Retrieved from http://www.npz-nrz.nl/downloads/files/Plenair%20Marijke%20HopmanRock2.pdf

Global iniciative for chronic obstructive lung disease (GOLD). (2010). Retrieved Marzo/23, 2011, from http://www.goldcopd.com

Gosselink, R., De Vos, J., van den Heuvel, S. P., Segers, J., Decramer, M., & Kwakkel, G. (2011). Impact of inspiratory muscle training in patients with COPD: What is the evidence? *The European Respiratory Journal : Official Journal of the European Society for Clinical Respiratory Physiology, 37*(2), 416-425. doi:10.1183/09031936.00031810

Green, R. H., Singh, S. J., Williams, J., & Morgan, M. D. (2001). A randomised controlled trial of four weeks versus seven weeks of pulmonary rehabilitation in chronic obstructive pulmonary disease. *Thorax, 56*(2), 143-145.

Greenleaf J E. (1984). Physiological responses to prolonged bed rest and fluid immersion in humans. *Journal of Applied Physiology, 57*(3), 619-633.

Gruffydd-Jones, K., & Loveridge, C. (2011). The 2010 NICE COPD guidelines: How do they compare with the GOLD guidelines? *Primary Care Respiratory Journal: Journal of the General Practice Airways Group, 20*(2), 199-204. doi:10.4104/pcrj.2011.00011

Guyatt, G. H., Berman, L. B., Townsend, M., Pugsley, S. O., & Chambers, L. W. (1987). A measure of quality of life for clinical trials in chronic lung disease. *Thorax, 42*(10), 773-778.

Hilberink, S. R., Jacobs, J. E., van Opstal, S., van der Weijden, T., Keegstra, J., Kempers, P. L., et al. (2011). Validation of smoking cessation self-reported by patients with chronic obstructive pulmonary disease. *International Journal of General Medicine, 4*, 85-90. doi:10.2147/IJGM.S15231

Jones, P. W., Quirk, F. H., Baveystock, C. M., & Littlejohns, P. (1992). A self-complete measure of health status for chronic airflow limitation. the st. george's respiratory questionnaire. *The American Review of Respiratory Disease, 145*(6), 1321-1327.

Jones, P. W. (2001). Health status measurement in chronic obstructive pulmonary disease. *Thorax, 56*(11), 880-887.

Jones PW. (2002). Interpreting thresholds for a clinically significant change in health status in asthma and COPD. *Eur Respir j., 19*, 398-404. doi:10.1183/09031936.02.00063702

Kurabayashi H, Machida I, Tamura K, Iwai F, Tamura J, & Kubota K. (2000). Breathing out into water during subtotal immersion: A therapy for chronic pulmonary emphysema. *American Journal of Physical Medicine & Rehabilitation, 79*, 150-153.

Kurabayashi, H., Machida, I., Hnda H., Akiba T., Kubota K., et al. (1998). Comparison of three protocols for breathing exercises during immersion in 38ºC water for chronic obstructive pulmonary disease. *American Journal of Physical Medicine & Rehabilitation, 77*(2), 145-147.

Lacasse, Y., Goldstein, R., Lasserson, T. J., & Martin, S. (2006). Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews (Online), (4)*(4), CD003793. doi:10.1002/14651858.CD003793.pub2

Langer, D., Hendriks, E., Burtin, C., Probst, V., van der Schans, C., Paterson, W., et al. (2009). A clinical practice guideline for physiotherapists treating patients with chronic obstructive pulmonary disease based on a systematic review of available evidence. *Clinical Rehabilitation, 23*(5), 445-462. doi:10.1177/0269215509103507

Laszlo, G. (2006). Standardisation of lung function testing: Helpful guidance from the ATS/ERS task force. *Thorax, 61*(9), 744-746. doi:10.1136/thx.2006.061648

Lotters, F., van Tol, B., Kwakkel, G., & Gosselink, R. (2002). Effects of controlled inspiratory muscle training in patients with COPD: A meta-analysis. *The European Respiratory Journal: Official Journal of the European Society for Clinical Respiratory Physiology, 20*(3), 570-576.

Mahler, D. A., Mejia-Alfaro, R., Ward, J., & Baird, J. C. (2001). Continuous measurement of breathlessness during exercise: Validity, reliability, and responsiveness. *Journal of Applied Physiology (Bethesda, Md.: 1985), 90*(6), 2188-2196.

Mahler, D. A. (2006). Mechanisms and measurement of dyspnea in chronic obstructive pulmonary disease. *Proceedings of the American Thoracic Society, 3*(3), 234-238. doi:10.1513/pats.200509-103SF

Manual para la rehabilitación respiratoria para personas con EPOC. Retrieved from Manual_de_Rehabilitacion_Respiratoria_para_personas_con_EPOC.pdf

Maltais, F., LeBlanc, P., Jobin, J., Berube, C., Bruneau, J., Carrier, L., et al. (1997). Intensity of training and physiologic adaptation in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 155*(2), 555-561.

Martín-Valero R, Cuesta-Vargas AI, & Labajos-Manzanares MT. (2010). Revisión de ensayos clínicos sobre rehabilitación respiratoria en enfermos pulmonares obstructivos crónicos. *Rehabilitación, 44*(2), 158-66.

May, D. B., & Munt, P. W. (1979). Physiologic effects of chest percussion and postural drainage in patients with stable chronic bronchitis. *Chest, 75*(1), 29-32.

National Clinical Guideline Centre. (2010) Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. London: National Clinical Guideline Centre. Available from: http://guidance.nice.org.uk/CG101/Guidance/pdf/English

Miller, M. R., Hankinson, J., Brusasco, V., Burgos, F., Casaburi, R., Coates, A., et al. (2005). Standardisation of spirometry. *The European Respiratory Journal: Official Journal of the European Society for Clinical Respiratory Physiology, 26*(2), 319-338. doi:10.1183/09031936.05.00034805

Nelson, M. E., Rejeski, W. J., Blair, S. N., Duncan, P. W., Judge, J. O., King, A. C., et al. (2007). Physical activity and public health in older adults: Recommendation from the american college of sports medicine and the american heart association. *Circulation, 116*(9), 1094-1105. doi:10.1161/CIRCULATIONAHA.107.185650

Newton, D. A., & Bevans, H. G. (1978). Physiotherapy and intermittent positive-pressure ventilation of chronic bronchitis. *British Medical Journal, 2*(6151), 1525-1528.

Nici, L., Donner, C., Wouters, E., Zuwallack, R., Ambrosino, N., Bourbeau, J., et al. (2006). American thoracic Society/European respiratory society statement on pulmonary rehabilitation. *American Journal of Respiratory and Critical Care Medicine, 173*(12), 1390-1413. doi:10.1164/rccm.200508-1211ST

Normandin, E. A., McCusker, C., Connors, M., Vale, F., Gerardi, D., & ZuWallack, R. L. (2002). An evaluation of two approaches to exercise conditioning in pulmonary rehabilitation. *Chest, 121*(4), 1085-1091.

O'Donnell, D. E., Hernandez, P., Kaplan, A., Aaron, S., Bourbeau, J., Marciniuk, D., et al. (2008). Canadian thoracic society recommendations for management of chronic obstructive pulmonary disease - 2008 update - highlights for primary care. *Canadian Respiratory Journal : Journal of the Canadian Thoracic Society, 15 Suppl A*, 1A-8A.

Okubadejo, A. A., Jones, P. W., & Wedzicha, J. A. (1996). Quality of life in patients with chronic obstructive pulmonary disease and severe hypoxaemia. *Thorax, 51*(1), 44-47.

O'Shea, S. D., Taylor, N. F., & Paratz, J. (2004). Peripheral muscle strength training in COPD: A systematic review. *Chest, 126*(3), 903-914. doi:10.1378/chest.126.3.903

O'Shea, S. D., Taylor, N. F., & Paratz, J. (2009). Progressive resistance exercise improves muscle strength and may improve elements of performance of daily activities for people with COPD: A systematic review. *Chest*, 136, 1269-1283. Doi 10.1378/chest.09-0029

Pepin, V., Saey, D., Whittom, F., LeBlanc, P., & Maltais, F. (2005). Walking versus cycling: Sensitivity to bronchodilation in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 172*(12), 1517-1522. doi:10.1164/rccm.200507-1037OC

Pepin, V., Brodeur, J., Lacasse, Y., Milot, J., Leblanc, P., Whittom, F., et al. (2007). Six-minute walking versus shuttle walking: Responsiveness to bronchodilation in chronic obstructive pulmonary disease. *Thorax, 62*(4), 291-298. doi:10.1136/thx.2006.065540

Perk J, Perk L, & Bodén C. (1996). Cardiorespiratory adaptation of COPD patients to physical training on land and in water. *European Respiratory Journal, 9*(2), 248-252.

Polkey, M. I., Kyroussis, D., Hamnegard, C. H., Mills, G. H., Green, M., & Moxham, J. (1996). Diaphragm strength in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 154*(5), 1310-1317.

Polkey, M. I., & Moxham, J. (2004). Improvement in volitional tests of muscle function alone may not be adequate evidence that inspiratory muscle training is effective. *The European Respiratory Journal : Official Journal of the European Society for Clinical Respiratory Physiology, 23*(1), 5-6.

Puente-Maestu, L., Sanz, M. L., Sanz, P., Cubillo, J. M., Mayol, J., & Casaburi, R. (2000). Comparison of effects of supervised versus self-monitored training programmes in patients with chronic obstructive pulmonary disease. *The European Respiratory Journal: Official Journal of the European Society for Clinical Respiratory Physiology, 15*(3), 517-525.

Puente-Maestu, L., Sanz, M. L., Sanz, P., Ruiz de Ona, J. M., Rodriguez-Hermosa, J. L., & Whipp, B. J. (2000). Effects of two types of training on pulmonary and cardiac responses to moderate exercise in patients with COPD. *The European Respiratory Journal: Official Journal of the European Society for Clinical Respiratory Physiology, 15*(6), 1026-1032.

Puhan MA, Büsching G, Chünemann HJ, vanOort E, Zaugg C, & Frey M. (2006). Interval versus continuous high-intensity exercise in chronic obstructive pulmonary disease. A randomized trial. *Annals of Internal Medicine, 145*, 816-825.

Puhan, M., Scharplatz, M., Troosters, T., Walters, E. H., & Steurer, J. (2009). Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews (Online), (1)*(1), CD005305. doi:10.1002/14651858.CD005305.pub2

Rabe, K. F., Hurd, S., Anzueto, A., Barnes, P. J., Buist, S. A., Calverley, P., et al. (2007). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *American Journal of Respiratory and Critical Care Medicine, 176*(6), 532-555. doi:10.1164/rccm.200703-456SO

Rabinovich, R. A., Ardite, E., Troosters, T., Carbo, N., Alonso, J., Gonzalez de Suso, J. M., et al. (2001). Reduced muscle redox capacity after endurance training in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 164*(7), 1114-1118.

Rabinovich, R. A., & Vilaro, J. (2010). Structural and functional changes of peripheral muscles in chronic obstructive pulmonary disease patients. *Current Opinion in Pulmonary Medicine, 16*(2), 123-133. doi:10.1097/MCP.0b013e328336438d

Ramsey, S. D., & Sullivan, S. D. (2003). The burden of illness and economic evaluation for COPD. *The European Respiratory Journal.Supplement, 41*, 29s-35s.

Reda, A. A., Kotz, D., Kocks, J. W., Wesseling, G., & van Schayck, C. P. (2010). Reliability and validity of the clinical COPD questionniare and chronic respiratory questionnaire. *Respiratory Medicine, 104*(11), 1675-1682. doi:10.1016/j.rmed.2010.04.023

Ries, A. L., Bauldoff, G. S., Carlin, B. W., Casaburi, R., Emery, C. F., Mahler, D. A., et al. (2007). Pulmonary rehabilitation: Joint ACCP/AACVPR evidence-based clinical practice guidelines. *Chest, 131*(5 Suppl), 4S-42S. doi:10.1378/chest.06-2418

Ries, A. L. (2008). Pulmonary rehabilitation: Summary of an evidence-based guideline. *Respiratory Care, 53*(9), 1203-1207.

Rodrigues, F. (2010). Role of extra-pulmonary factors - depression, muscle weakness, health-related quality of life - in COPD evolution. *Revista Portuguesa De Pneumologia, 16*(5), 709-715.

Rose, C., Wallace, L., Dickson, R., Ayres, J., Lehman, R., Searle, Y., et al. (2002). The most effective psychologically-based treatments to reduce anxiety and panic in patients with chronic obstructive pulmonary disease (COPD): A systematic review. *Patient Education and Counseling, 47*(4), 311-318.

Schoenhofer, B., Koehler, D., & Polkey, M. I. (2004). Influence of immersion in water on muscle function and breathing pattern in patients with severe diaphragm weakness. *Chest, 125*(6), 2069-2074.

Schrier, A. C., Dekker, F. W., Kaptein, A. A., & Dijkman, J. H. (1990). Quality of life in elderly patients with chronic nonspecific lung disease seen in family practice. *Chest, 98*(4), 894-899.

Shoemaker, M. J., Donker, S., & Lapoe, A. (2009). Inspiratory muscle training in patients with chronic obstructive pulmonary disease: The state of the evidence. *Cardiopulmonary Physical Therapy Journal, 20*(3), 5-15.

Sinclair DJM, I. C. (1980). Controlled trial of supervised exercise training in chronic bronchitis. *BMJ, 1*, 519-521.

Sobradillo, V., Miravitlles, M., Jiménez, C. A., Gabriel, R., Viejo, J. L., Masa, J. F., et al. (1999). Estudio IBERPOC en españa: Prevalencia de sintomas respiratorios habituales y de limitación crónica al flujo aéreo. *Archivos Bronconeumologia, 35*(4), 159-166.

Storer, T. W. (2001). Exercise in chronic pulmonary disease: Resistance exercise prescription. *Medicine and Science in Sports and Exercise, 33*(7 Suppl), S680-92.

Sullivan, S. D., Ramsey, S. D., & Lee, T. A. (2000). The economic burden of COPD. *Chest, 117*(2 Suppl), 5S-9S.

Thompson, P. D., Buchner, D., Pina, I. L., Balady, G. J., Williams, M. A., Marcus, B. H., et al. (2003). Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: A statement from the council on clinical

cardiology (subcommittee on exercise, rehabilitation, and prevention) and the council on nutrition, physical activity, and metabolism (subcommittee on physical activity). *Circulation, 107*(24), 3109-3116. doi:10.1161/01.CIR.0000075572.40158.77

Troosters, T., Gosselink, R., & Decramer, M. (2000). Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: A randomized trial. *The American Journal of Medicine, 109*(3), 207-212.

Troosters, T., Gosselink, R., Langer, D., & Decramer, M. (2007). Pulmonary rehabilitation in chronic obstructive pulmonary disease. *Respiratory Medicine: COPD Update, 3*(2), 57-64. doi:DOI: 10.1016/j.rmedu.2007.02.003

Troosters, T., Sciurba, F., Battaglia, S., Langer, D., Valluri, S. R., Martino, L., et al. (2010). Physical inactivity in patients with COPD, a controlled multi-center pilot-study. *Respiratory Medicine, 104*(7), 1005-1011. doi:DOI: 10.1016/j.rmed.2010.01.012

Vale F, Reardon JZ, ZuWallack RL. (1993). The long-term benefits of outpatient pulmonary rehabilitation on exercise tolerance and quality of life. *Chest, 103*, 42-45.

Verrill, D., Barton, C., Beasley, W., & Lippard, W. M. (2005). The effects of short-term and long-term pulmonary rehabilitation on functional capacity, perceived dyspnea, and quality of life. *Chest, 128*(2), 673-683. doi:10.1378/chest.128.2.673

Vilaró, J., Gimeno, E., Sánchez Férez, N., Hernando, C., Díaz, I., Ferrer, M., et al. (2007). Actividades de la vida diaria en pacientes con enfermedad pulmonar obstructiva crónica: Validación d. *Medicina Clínica, 129*(9), 326-332. Retrieved from http://external.doyma.es/pdf/2/2v129n09a13109543pdf001.pdf

Vu, K., & Mitsunobu, F. (2005a). Five year observation of the effects of spa therapy for patients with pulmonary emphysema, evaluated by %low attenuation area (%LAA) of the lungs on high-resolution CT, %Dlco and %residual volume (RV). *Alternative and Complementary Therapies, 11*(2), 89-93.

Vu, K., & Mitsunobu, F. (2005b). Spa therapy for chronic obstructive pulmonary disease. Studies at the Misasa medical center. *Alternative & Complementary Therapies,* (April), 89-93.

Wadell, K., Sundelin, G., Henriksson-Larsen, K., & Rune Lundgren. (2004). High intensity physical group training in water – an effective training modality for patients with COPD. *Respiratory Medicine, 98*, 428-438.

Wadell, K., Henriksson-Larsen, K., Lundgren, R., & Sundelin, G. (2005a). Group training in patients with COPD – long- term effects after decreased training frequency. *Disability and Rehabilitation, 27*(10), 571-581. doi:10.1080/09638280400018627

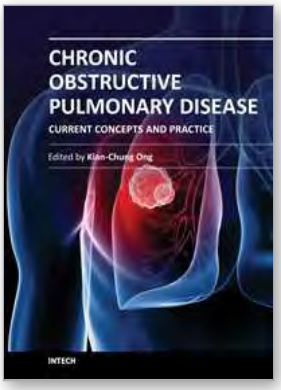
Wadell, K., Sundelin, F., Lundgren, R., Henriksson-Larsén, K., & Lindström, B. (2005b). Muscle performance in patients with chronic obstructive pulmonary disease – effects of a physical training programme. *Advances in Physiotherapy, 7*, 51-59.

Weiner P, Magadle R, Beckerman M, Weiner M, & Berar-Yanay N. (2003). Specific expiratory muscle training in COPD. *Chest, 12*4(2), 468-473.

White, A. J., Gompertz, S., & Stockley, R. A. (2003). Chronic obstructive pulmonary disease . 6: The aetiology of exacerbations of chronic obstructive pulmonary disease. *Thorax, 5*8(1), 73-80.

Wijkstra, P. J., Ten Vergert, E. M., van Altena, R., Otten, V., Kraan, J., Postma, D. S., et al. (1995). Long term benefits of rehabilitation at home on quality of life and exercise tolerance in patients with chronic obstructive pulmonary disease. *Thorax, 5*0(8), 824-828.

Yohannes, A. M., Baldwin, R. C., & Connolly, M. J. (2005). Predictors of 1-year mortality in patients discharged from hospital following acute exacerbation of chronic obstructive pulmonary disease. *Age and Ageing, 34*(5), 491-496. doi:10.1093/ageing/afi163



Chronic Obstructive Pulmonary Disease - Current Concepts and Practice

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A decade or so ago, many clinicians were described as having an unnecessarily 'nihilistic' view of COPD. This has certainly changed over the years... This open access book on COPD provides a platform for scientists and clinicians from around the world to present their knowledge of the disease and up-to-date scientific findings, and avails the reader to a multitude of topics: from recent discoveries in the basic sciences to state-of-the-art interventions on COPD. Management of patients with COPD challenges the whole gamut of Respiratory Medicine - necessarily pushing frontiers in pulmonary function (and exercise) testing, radiologic imaging, pharmaceuticals, chest physiotherapy, intensive care with respiratory therapy, bronchology and thoracic surgery. In addition, multi-disciplinary inputs from other specialty fields such as cardiology, neuro-psychiatry, geriatric medicine and palliative care are often necessary for the comprehensive management of COPD. The recent progress and a multi-disciplinary approach in dealing with COPD certainly bode well for the future. Nonetheless, the final goal and ultimate outcome is in improving the health status and survival of patients with COPD.

12

Chronic Obstructive Pulmonary Disease and Diabetes *Mellitus*

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1. Introduction

The progressive increase in the average age of the population leads to chronic diseases that are increasingly important. Chronic conditions are large in number, the prevalence of each one is high and so does the annual cost of their care. Moreover, clinicians alert about the impact of one disease on the development and severity of others. Among chronic morbidities the most prevalent are cardiovascular disease (CV), cancer, diabetes *mellitus* (DM) and chronic obstructive pulmonary disease (COPD) (Chillón et al., 2009). Noticeably, a 25% of patients older than 65 years have two chronic conditions and this figure rises to 40% in population over 75 years old (Chatila et al., 2008).

The following text focuses on two of these pathologies: COPD and DM. Our group provided data on COPD pathophysiology, particularly about hypoxia and related oxidative stress, the effect of nutritional status, physical exercise and sleep disorders (Álvarez-Sala R, 2010; García-Río et al., 2009, 2011; Braghiroli & Álvarez-Sala, 2010; Alcolea et al., 2007). In addition, the sleep apnea hypopnea syndrome (SAHS), its association with metabolic syndrome (MS) constituents and the sum of SAHS plus COPD in the so called "overlap syndrome" were studied (Santiago-Recuerda et al., 2007; De Miguel et al., 2002). We made a search in PubMed including articles published during the last ten years about COPD and DM, in order to review how one disease influences the onset, evolution, treatment and prognosis of the other one.

2. Chronic obstructive pulmonar disease and diabetes *mellitus* definitions, epidemiology and comorbidities

COPD is defined as a preventable and treatable entity caused by toxic gases, mainly tobacco. Its main feature is poorly reversible obstruction of airflow that is progressive and is associated with a systemic inflammatory response (Álvarez-Sala, 2010). This proinflammatory state may lead to extrapulmonary manifestations (Global initiative for obstructive lung disease [GOLD], 2008) in the majority of patients have a negative effect on the overall prognosis of the disease (Peces Barba et al., 2008). Its prevalence sharply

increases with age and tobacco consumption, and is estimated at around 4-10% globally (Mathers, 2008). Nowadays this disease is considered the fourth leading cause of death and the WHO assessed that in 2020 ranked third in terms of mortality and the fourth in prevalence. In Spain there have been two major studies on the prevalence of COPD. On the one hand we have the IBERPOC study that estimated a 9.1% in patients aged between 40 and 70 years. Most recently EPI-SCAN obtained a 10.2% in subjects between 40 and 80 years (Álvarez-Sala, 2010). In recent years, COPD is considered a disease that goes beyond the lungs involvement. The high morbidity associated with this condition makes some authors (Álvarez- Sala,2010; Sevenoaks et al., 2006; Oudijk et al., 2003) think that pulmonary disease is just an expression of a multisystemic inflamatory disease. The main comorbidities associated with COPD are diabetes, hypertension, ischemic heart disease and heart failure. In addition, other illnesses converge such as malnutrition, osteoporosis, anemia, endocrine disorders, depression or anxiety (Moussas et al., 2008). Most of the comorbidities influence prognosis and length of hospital stay for these patients. One example is low weight, defined as a body mass index (BMI) below 18.5 kg/m^2, and considered a predictor of poor prognosis in patients with COPD. In particular, loss of muscle compartment is the most affected in the body and its measurement is a better predictor of mortality than total body weight. Another important aspect is osteoporosis, which is present in up to 68% of patients with severe COPD, with a consequent increase in fracture risk. There are several risk factors that may influence the development of osteoporosis in these patients: age, malnutrition, weight loss, smoking, hypogonadism, sedentary lifestyle or the use of glucocorticoids.

In addition, patients with more severe lung disease, have endocrine alterations, the most frequent is exogenous hypercorticism that associated with hyperglycemia, infections and cardiovascular complications (Chillón et al., 2009).

With reference to DM, it is a frequent consequence of corticosteroid therapy in individuals with advanced COPD and those receiving high and continued doses. However, coincidence with primary diabetes predominates in COPD patients, even if we assume there is no linkage between both diseases. There are two types of primary diabetes, type 1 is characterized by absolute insulin deficiency secondary to an autoimmune cause in 90% of cases or idiopathic destruction of pancreatic beta cells. These patients require insulin to survive. Type 2 DM is far more frequent in COPD. The natural history of type 2 begins with insulin resistance with a compensatory hyperinsulinemia that maintains normal glucose tolerance at the outset. Persistent insulin resistance facilitates the final expression of a latent β cell dysfunction thus resulting in hyperglycemia and frank diabetes. Diabetes has become one of the most prevalent health problems in recent years, according to some authors, affect over 366 million people worldwide in 2030 (Wild et al., 2004).

3. Links between chronic obstructive pulmonary disease and diabetes *mellitus*

At this point, the question arises about the relationship between both disorders. To answer this question, we will refer to the so called cardiovascular risk of COPD. COPD and DM are associated with an enhanced cardiovascular risk profile. COPD patients have a two to three-fold cardiovascular related mortality when compared to the general population rates. Cardiovascular disease is the second cause of death among COPD patients and the first one

among patients with DM. COPD predisposes to pulmonary hypertension, right ventricular dysfunction and arrhythmias. DM is often accompanied by systemic hypertension, left ventricular dysfunction and congestive heart failure. Carotid and peripheral atherosclerosis are also macrovascular complications of DM. Finally, both COPD and DM converge in a higher occurrence of coronary events and sudden death (Falk et al., 2008).

Probably all these comorbidities are influenced by the inflammatory and oxidative stress in these patients after exposure to tobacco (Lavi S et al., 2007). One hundred million people will be affected by tobacco during the XXI century. The tobacco is currently responsible for five million and six hundred thousand deaths each year worldwide. It acts synergistically with other risk factors and may increase cardiovascular mortality by 20, but after leaving tobacco for two or three years, the risk is superimposed to non-smokers.

The prognostic significance of hyperglycemia in these patients has been evaluated in several studies, especially during exacerbations. It seems that the poor glycemic control increases hospital stay, the isolation of gram-negative bacteria in sputum, increased pulmonary artery pressure and the risk of death (Archer & Baker, 2009; Gudmundsson et al., 2006; Makarevich et al., 2007; Sicras et al., 2007; Parappil et al., 2010). Moreover, it seems that sustained hyperglycemia may have other effects that worsen the prognosis. The vascular damage should be highlighted in the first place. Microvascular diabetic disease may affect the alveolus-capillary barrier. Pulmonary microvascular involvement may worsen respiratory function in patients with COPD and DM. Pulmonary diffusing capacity in patients with type 1 or type 2 DM is decreased and this decrease may be more pronounced in those with other microvascular complications.

It is known that early diagnosis and treatment of COPD and its comorbidities, including DM, have prognostic implications. However, the association and interactions between COPD and DM are not completely understood. Under the current evidence, coincidence is more plausible than a causative connection. Whether causality exists or not, the high rate of simultaneity in general population will give ground for concern. We consider that DM affects 1.6 to 16% among subjects with COPD. DM prevalence increases in relation with pulmonary impairment, older age and BMI of 30 kg/m2 (Lavi et al, 2007).

Pathogenic links between COPD and DM have been hypothesized in the setting of population-based and clinical observational studies. The Atherosclerosis Risk Assessment in Communities (ARIC) and the Fremantle Diabetes Study (FDS) found a lung vital capacity declining in persons with type 2 diabetes (Yeh et al., 2008; Davis et al., 2004). Lung dysfunction was predominantly restrictive, while COPD is an obstructive disorder. Excessive weight could be an explanation as mean BMI of diabetic patients (30.9 ± 5.7 kg/m^2) significantly exceeded BMI of the non diabetic group (27.2 ± 4.8 kg/m^2) in the ARIC study. DM patients who subsequently developed COPD also had a higher BMI in data by Ehrlich et al. (Ehrlich et al., 2010). A theoretical risk for COPD in a diabetic environment is based on several mechanisms: glycation of proteins of lung parenchyma and bronchial tree, thickening of basal lamina, increased susceptibility to infections and a modified sarcolema with subsequent skeletal muscle weakness (Weynand et al., 1999; Dalquen, 1999). Nevertheless, hyperglycemia has mostly been associated with a modest restrictive defect due to diabetic microangiopathy that thickens the epithelial and capillary basement membrane. The result is an increased extracellular matrix and connective tissue and an altered alveolar diffusion capacity of the lungs (Popov & Simioescu, 1997).

Conversely, development of DM once COPD has been diagnosed was also shown by Mannino et al. (Ford & Mannino, 2004; Mannino et al., 2008). Again, more than 60% of patients with COPD and DM were overweight or obese. Stronger evidence of the COPD-DM association comes from the Nurses Health Study (NHS) that involved 97,245 30-55 year old female nurses, 1,342 of whom reported COPD (Rana et al., 2004). The risk of DM among COPD patients was statistically significant (RR 1.8, 95%CI 1.1-2.8) despite the scarce number of incident diabetes cases (n = 19) and after exhaustive adjustment for covariates. It has to be said that a detection bias can not be ruled out in NHS and other cited studies. Besides, among other limitations, data from NHS could only be generalized to median-age Caucasian women. Nevertheless, this study provides the best evidence available due to the homogeneous anthropometry and lifestyle habits of the nurses enrolled including smoking, dietary and exercise, and because of the long-term prospective follow-up.

Beyond diabetes itself, glycemic exposure seems to be relevant. Severity of hyperglycemia was a negative predictor of a reduced lung volume in the FDS. With reference to COPD, a complementary analyses by Ehrlich et al. (Ehrlich et al., 2010) showed the disease was more prevalent among poorly controlled diabetic patients, with an hazard ratio of 1.03 (95%CI 1.01-1.04) per each unit increase in baseline glycated hemoglobin (A1C). To the date, diabetes has not been proven to be a determinant factor for COPD exacerbations, but poor glycemic control is a risk factor of pneumonia related hospitalization in type 1 and type 2 diabetes *mellitus* (Kornum., 2008). Consistent with this findings, in vitro studies under hyperglycemic conditions have shown an abnormal neutrophil function such impaired chemotaxis, phagocytes and bacterial killing (Pozzilli, 1994, as cited in Ehrlich et al., 2010).

We can assume there is a high proportion of undiagnosed glucose intolerance, obstructive and restrictive lung disorders. Thus, one possibility is that untreated diabetes contributes to pulmonary dysfunction and that non diagnosed decreased lung function favors diabetes development in predisposed patients (Davis et al., 2004). Once diabetes is evident, a vital capacity loss was found in the ARIC study. An 8% different FVC in diabetic compared to nondiabetic subjects was found in the Copenhagen City Heart Study (Heindl et al., 2001). The baseline difference was similar in ARIC, but further declining linked to diabetes was not found after 15 years of follow-up. In contrast, more rapid declines of FVC and FEV1 were observed in patients with higher baseline A1C in FDS. Tobacco may contribute to explain these differences. A secondary analysis of diabetic individuals in the Framingham Cohort Study found that the decrease in pulmonary function, with a restrictive pattern, was greater in smokers than in never smokers, inferring that diabetes may increase susceptibility to the adverse pulmonary effects of smoking. A similar interaction was proposed in the NHS (Rana et al., 2004; Walter et al., 2003).

To add complexity, sleep apnea hypopnea syndrome is often added in many of diabetic patients. SAHS is mainly secondary to obesity and is also associated with an increased insulin resistance. There have been several studies linking SAHS and DM. This relationship could be based on a common point such as obesity. In this sense, members of the Wisconsin Sleep Cohort were followed for four years. It was demonstrated that patients with an AHI ≥ 15 had an increased risk of developing diabetes type 2 (odds ratio 2.3 [1.28 to 4 11], adjusted for age, gender and body habitus) (Watz et al., 2009). In the same line, longitudinal follow-up of the cohort of Affairs Connecticut Healthcare System Veteran concluded an independent association between SAHS and incidence of new cases of diabetes type 2

(hazard ratio: 1.43 [1.10 to 1.86], adjusted for age, gender, race, fasting glucose, BMI and weight change) (Reichmuth et al., 2005).

A further step would be the association of COPD and SAHS in the same individual or "overlap syndrome". The prevalence of overlap varies depending on SAHS clinical or subclinical definition. The latter identifies individuals with at least 5 hypopneas or apneas per hour during a polysomnography or polygraphy whom diurnal sleepiness does not necessarily occur. The prevalence of SAHS is estimated to be 1-4% in general population. The percentage of overlap is 3-11% among subjects with SAHS and 16-20% among COPD patients (Owens & Malhotra, 2010; Zamarrón et al., 2008). COPD clinics is characterized by cough, sputum production and dyspnea. Most common symptoms of SAHS include loud snoring, excessive daytime sleepiness, personality changes and deterioration of quality of life. Overlap syndrome is characterized by older, more hypoxemic and hypercapnic patients with higher mean pulmonary pressure and similar or less BMI as compared with single SAHS. Thus, the overlap syndrome is a singular entity that may allow a deeper knowledge of the interactions between COPD, SAHS and glycemic-metabolic related disruptions.

4. Chronic obstructive pulmonary disease and diabetes *mellitus* related pathogenesis

COPD and DM share relevant features in their genesis and course. Hypoxia, insulin resistance, oxidative stress and inflammation are the basis of a common pathogenesis. Concomitant factors such as tobacco, obesity and sleep disorders merge in endothelial dysfunction and atherosclerosis leading to a high cardiovascular risk of both conditions (Figure 1).

Inflammation is a well recognized phenomenon in COPD and DM pathogenesis. In COPD, inflammation and oxidative stress require an energy expenditure that exacerbate the pre-existing hypoxia. In a parallel way, inflammatory cytokines exacerbate insulin resistance through diverse mechanisms. Impaired function of the type 1 insulin receptor substrate (IRS-1) is a key, direct mechanism. Thus, there is a chronic, subclinical inflammation at the background of COPD and DM. The question about its significance in patients with simultaneous COPD and DM is then arised. Being not fully clarified, we propose the following sequence of events: common COPD and DM related pathogenesis would start by hypoxia and insulin resistance followed by systemic inflammation, oxidative stress and a final coexistence of endothelial dysfunction and subsequent cardiovascular events.

4.1 Hypoxia

Hypoxemia and also hypercapnia, though in a less extent, are a stimulus for the hyperactivation of the sympathetic nervous system. In this setting, the activity of the sympathetic system is sustained in a non-resting anomalous way (Ashley et al., 2010; Heindl et al., 2001; Raupauch et al., 2008). Sustained hypoxia in COPD is an important central sympathetic system drive. A higher and long-lasting muscle sympathetic nerve activity (MSNA) is seen in COPD patients. Its direct consequence is a permanent vasoconstriction of the muscle vessels. Ashley et al. did not only show a sympathetic burst of multiple neurones, but they also graded the intensity of the response. The method used was the measurement of the firing probability and mean firing rates of single muscle vasoconstrictor

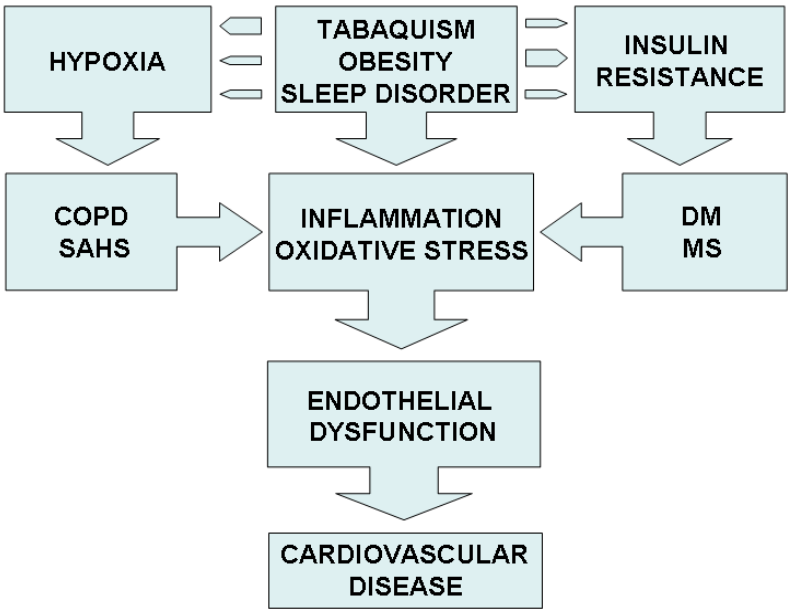


Fig. 1. Convergent pahogenesis of chronic obstructive pulmonary disorders, diabetes *mellitus* and metabolic syndrome. COPD: Chronic obstructive pulmonary disease; SAHS: Sleep apnea-hypopnea syndrome; DM: Diabetes *mellitus*; MS: Metabolic syndrome.

neurons. These authors observed a general and markedly higher sympathoexcitation in COPD patients when compared to SAHS, bronchiectasis or healthy subjects. The individual neurone firing probability and mean firing rate were comparable to those recorded in SAHS, but higher than those observed in the healthy group. This finding suggests that muscle vasoconstrictor response is sustained long-after intermittent hypoxia, as it would occur in SAHS patients. Permanent vasoconstriction causes further resistance to the airway flow in any chronic obstructive disorder that is not completely reversed by normoxia. With respect to DM, the noradrenalin liberation of spontaneously active neurons has also been observed in the isolated disease.

Obesity also increases the MSNA burst incidence, but at lower levels than those seen in COPD or SAHS. Multiple firing of single-unit neurones has not been shown in obese subjects. Advanced age neither seems to be an explanation for the MSNA hyperactivity linked to COPD.

4.2 Inflammation

Systemic inflammation is a common bound between COPD and DM. Both conditions are a proinflammatory state characterized by transcription and expression of hypoxia-induced factor 1 (HIF-1) and increased levels of serum inflammatory cytokines such as C-reactive protein (CRP), interleukin (IL) 1, IL-6 and tumor necrosis factor α (TNF-α) (Archer & Baker 2009). C-reactive protein (CRP) and the nuclear factor NF-κβ pathway are important mediators of the inflammatory response in this context (McNicholas, 2009).

CRP is a type I phase protein with the ability to bind the bacteria surface facilitating the fixation of complement that mediates bacterial killing and/or phagocytosis. CRP stimulates further cytokine production mainly through macrophages activation. TNF-α, IL-1 and IL-6 stimulate CRP synthesis by inducing its hepatic gene expression. NF-κβ is the master regulator of TNF-α, IL-8 and other cytokines transcription and synthesis. TNF-α and other cytokines are produced by monocytes and leukocytes and are enhanced by hypoxia in vitro studies (Takabatake et al., 2000 in Sevenoaks & Stockley, 2006).

TNF-α pathway is related with the deterioration of accessory muscles involved in ventilation. TNF-α induces loss of fat-free mass in COPD patients with subsequent loss of skeletal muscle function. Muscle wasting is also directly mediated by nuclear factor-κβ (NF-κβ) that inhibits the MyoD gene expression. MyoD regulates myofibril synthesis and repairs. Secondly, TNF-α interaction with its receptor can activate muscle and other cellular apoptosis. Reduced IGF-1 and testosterone levels are also adjuvant factors leading to muscle wasting (Sevenoaks & Stockley, 2006).

CRP is a marker of COPD exacerbations and elevated pulmonary pressure in the stable disease (Zamarrón et al., 2008). If we look at the intermittent side of the obstructive disease, CRP is not identified as a prognostic marker of SAHS after adjustment for BMI. TNF-α pathway is related with muscle wasting and pulmonary hypertension commonly developed in COPD disease. NF-κβ and HIF-1 pathways are closely related and may have a differential role in chronic and intermittent hypoxia. Indeed, HIF-1 seems to have a predominant role in COPD, while NF-κβ pathways may predominate in the intermittent hypoxia of SAHS. TNF-α levels can be predicted by the oxygen desaturation index in SAHS. Its levels are increased with independence of obesity (McNicholas, 2009). The prognostic value of these markers in overlap syndrome is unknown.

4.3 Oxidative stress

Now considering the cellular immune response, the leucocitary drive in COPD is a fountain of reactive oxygen species (ROS). The oxidative response advocates a protein, lipid and DNA damage within the cell. Oxidative stress influences NF-κβ cascade through mitogenesis activating protein kinases (MAP-k) perpetuating inflammation this way.

On the inverse loop, TNF-α stimulates ROS production. Indeed, an additional ROS-related mechanism seems to exacerbate TNF-α and NF- κβ effects on muscle wasting (Oudijk, 2003). TNF-α and ROS act in multiple ways. They have a common source in circulating leukocytes. Activation and dysfunction of leukocytes is shared by COPD, SAHS and DM. The activated leukocyte enhances the expression of adhesion molecules such as CD11b and CD18. This effect predominates in lung tissue if we look at COPD, while systemic endothelium is the main target in SAHS. In addition, exacerbations of COPD may deteriorate the antioxidant response, while ROS are particularly enhanced in SAHS when hypoxia is intermittent in a similar way to injury reperfusion syndrome (McNicholas, 2009). Because ROS production is also a direct effect of hyperglycemia, oxidative stress can be posed as a link between SAHS, DM, overlap syndrome and metabolic syndrome. MS is not so clearly identified in the particular case of COPD. A specific oxidative response in SAHS/ overlap may well account for this difference.

Another effect of neutrophil dysfunction is the inactivation of antiproteases leading to airspace ephitelial damage and mucus hypersecretion. As we see, TNF-α / neutrophil axis is

a key in maintenance of the lung COPD phenotype. Finally, advanced COPD stages are characterized by cachectic patients who have an impaired metabolism of proteins, lipids and carbohydrates that is thought to be the maximum expression of systemic inflammation and oxidative stress.

The different pathways involved are complex and the available knowledge on their confluence is still limited. We need to clarify if the mentioned markers of hypoxia, inflammation and oxidative stress have a predictive value of the highest morbidity and mortality in patients with COPD and DM. Moreover, COPD and DM cannot be fully understood if we do not consider classical risk factors, mainly tabaquism in COPD genesis, and obesity in DM. The influence of sleep architecture is an emerging aspect related to DM and hardly studied in COPD with the exception of the overlap syndrome (Zizi et al., 2010). The effect of age and physical activity should also be considered in the COPD and DM interaction. Among these factors, lately research has focused on obesity, sleep disorders and their consequences on respiratory and metabolic environments.

4.4 Insulin resistance and obesity

The inflamed adipose tissue is a well recognized trigger of insulin resistance. A theoretical link between COPD related inflammation and DM could be the switch to a protein depleted and more adipose skeletal muscle. This change of composition inside the sarcolema induces peripheral insulin resistance in the human organism. Such impairment is not necessarily reflected in a visceral fat excess or in obesity (Festa et al., 2002). If present, both conditions aggravate the risk for diabetes.

Then, obesity could be the cause of insulin resistance in patients with lung obstructive disorders. However, obesity does not seem to be the only mediator of insulin resistance. We need to consider a reduction of glucose uptake mediated by hypoxia. Under hypoxemic conditions, insulin resistance has been proved in both obese and lean mice (Polotsky et al., 2007). An explanation could be the hypoxia mediated sympathetic hyperactivity. But sympathetic hyperactivity does not seem to be the unique source of insulin resistance either. Indeed, pharmacologic blockage of autonomic nervous activity did not reverse the insulin resistance under intermittent hypoxia in animal models (Tasali et al., 2008). As we previously mentioned, oxidative stress is a plausible link between the cyclic hypoxia-reoxygenation phenomenon in SAHS and insulin resistance. A first argument is that oxidative stress entails glucose and lipid peroxidation. Secondly, it enhances the inflammatory status through activation of NF-κβ and reduction of nitric oxide bioavailability. Oxidative stress helps to understand why a link between hypoxia and DM seems to be stronger in SAHS than in COPD despite a more sustained and profound hypoxia in the latter. Nevertheless, experimental data about hypoxia and glucose metabolism under mimic SAHS and COPD conditions are still very limited.

The role of obesity in COPD is not established. However, and despite not being the only pathway, obesity is a clear line of causality between SAHS and type 2 DM. Indeed, obesity is the main risk factor for SAHS and type 2 DM. In data from the American National Sleep Foundation, high risk for SAHS is present in one out of four adults and in 57% of obese individuals. The proportion of mild or mild to moderate SAHS attributable to excess weight is 58% (Tasali et al., 2008). Some controversial results have been obtained regarding obesity.

Two epidemiological studies have suggested that obesity is the unique or main cause of insulin resistance in SAHS patients (Reichmuth et al, 2005; Stoohs et al., 1996). However, there is growing evidence about alternative links between SAHS and type 2 DM (Tasali et al., 2008). In terms of SAHS severity, only one study had a prospective design and assessed SAHS by polysomnography. An independent relationship between SAHS severity and glucose intolerance was not found after adjustment for body habitus, although the duration of follow up was only four years (Reichmuth et al., 2005).

SAHS itself aggravates obesity through several mechanisms that also enhances insulin resistance: neuroendocrine dysregulation and physical inactivity. Neuroendocrine dysregulation includes an enhanced ghrelin and leptin secretion. Hyperleptinemia has been proposed as a previous step to insulin resistance even in the absence of weight gain. Indeed, leptin was the only upregulated gene affecting glucose uptake in both obese and lean mice exposed to intermittent hypoxia (Polotsky et al., 2007). Hyperleptinemia may also be a marker of SAHS severity (Pillar & Shehadeh, 2008). Physical exercise increases after CPAP treatment of SAHS. However, the reversal of the insulin resistance by CPAP is controversial (Pillar & Shehadeh, 2008).

Ten out of thirteen clinical based studies suggested a body habitus non-related association between SAHS and insulin resistance or glucose intolerance (Tasali et al., 2008). Three studies considered waist-to-hip ratio because central fat distribution seems to be a more relevant mediator of insulin resistance than BMI (Sharma et al., 2007; McArdle et al., 2007; Tassone et al., 2003). There was a positive association in two out of three. In a similar fashion, three studies found higher HOMA-IR and fasting glucose after adjustment for visceral fat measurements (Kono et al., 2007; Makino S et al., 2006; Vgontzas et al., 2000).

Deposit of neck and abdominal fat alter the regular mechanics of ventilation. The most relevant accumulation of neck fat is located inside upper-airway muscles of the pharynx, this way changing the lumen to an oval shape. Also, abdominal fat exerts a mass effect that reduces the distension of the chest walls resulting in a decreased thoracic and tracheal traction during inspiration (Pillar & Shehadeh, 2008).

To conclude with, the impact of obesity on COPD disease is not as clear as the impact on SAHS. An overall role for obesity in SAHS is a common finding despite the diversity of ethnic and geographical origins of the studied subjects. We also have reasons to think that obesity, with its mechanical and metabolic effects, may impair COPD course, particularly in initial GOLD stages and/or overlap syndrome.

4.5 Sleep disorders

As an additional mechanism, obesity favors insulin resistance and SAHS development through sleep disturbance. Sleep curtailment, sleep fragmentation and a subsequent disrupted signalling lead to unbalanced energy expenditure and far too much appetite. Recent research proposes impaired sleep as a source of metabolic disturbances in SAHS and overlap syndrome patients.

Sleep disturbances are an invariable feature of COPD and SAHS patients. Both chronic and intermittent hypoxemia get worse during sleep. Sleep influences ventilation even in normal subjects due to: a reduced response to the hypoxic drive, a reduced ventilatory efficacy of

hyperrelaxed accesory muscles and upper-airway dilators and, finally, because lung residual capacity is reduced during sleep and so the pharyngeal traction is. Then, normally decreased nocturnal oxygen saturation becomes a challenge in COPD and SAHS patients. A more blunted chemical response to hypoxic drive is seen in both diseases. A diminished ventilation/perfusion quotient results from an hyperinflated lung, less activity of intercostal muscles and a dissociated diaphragmatic and intercostal activity in COPD patients. A collapsible pharynx is the main cause of hypoxia and sleep disturbance in SAHS. Associated symptoms, comorbid diseases, drugs and sedentary lifestyle also reduce sleep efficacy.

Evidence from extent population-based prospective and experimental studies links short and/or poor sleep and type 2 diabetes (Tasali et al., 2008). The sleep-related diabetes is not necessarily explained by apneas (Ayas et al., 2003; Mallon et al., 2005). Two laboratory studies performed in healthy young lean adults obtained an enhanced insulin resistance and a diminished insulin secretion related to sleep deprivation (Knutsonet al., 2007; Spiegel et al., 1999). Measurements of insulin-glucose homeostasis were based on intravenous glucose overload and minimal model technique respectively. Minimal model (Bergman, 2005) resulted in a glucose disposition index (DI) 40% lower than after sleep recovery. A low DI reflects an insulin secretion that is insufficient to compensate for insulin resistance. A low DI indicates a high risk for type 2 DM. Subjects underwent a relative short sleep restriction (4 h for 6 or 2 nights) however inducing a pre-diabetic state similar to the habitual in older adults. Reduction of slow-wave sleep and sleep fragmentation were assessed in another laboratory set-up (Tasali et al., 2008), resulting a similar marked decrease in insulin sensitivity without a balanced insulin secretion. The decrease in insulin sensitivity was correlated with a rise in heart rate variability as a measure of the daily sympathetic activity. In addition, insulin resistance was more related to sleep slow wave suppression than to sleep fragmentation. These experimental procedures have not been reproduced in specific SAHS and COPD settings.

We conclude that, in addition to hypoxia, sleep curtailment enhances sympathetic activation. Noradrenalin is a counter-regulatory hormone that reduces insulin release and function. There is also a decreased glucose uptake by muscle cells favored by high evening cortisol levels and extended duration of elevated growth hormone (GH) levels at night. Another relevant effect of short sleep is upregulation of appetite. A hormonal deregulation of appetite has been observed in the mentioned laboratory studies (Knutson et al., 2007). Ghrelin and leptin are hormones that exert respective hunger and satiety effects. Leptin inhibits appetite, modulates fat distribution and increases energy expenditure. Sleep debt shortens the adequate time that leptin levels require to balance the previous onset of a ghrelin peak. The ghrelin peak occurs during the first half of the night. An attenuated function of leptin due to leptin-CRP boundage has also been hypothesized (Chen et al., 2006). It is plausible in an inflammatory scene such sleep debt.

In diabetic patients, sleep duration and quality was associated with a poorer glycemic control in data from a cross-sectional study on African-American adults with type 2 DM (Knutson et al., 2006). Sleep characteristics were self-reported. Interestingly, sleep quality was associated with poorer glycemic control only in patients with chronic complications of diabetes. A theoretical explanation would be an impaired autonomic response at the background of those diabetic subjects. They would be more susceptible to a less-quality sleep. The cited results were adjusted for age, gender, insulin treatment and BMI. Central

obesity and respiratory conditions were not initially considered. Regarding these items, the authors found an association between A1C levels and sleep duration and quality that remained stable after excluding patients at high SAHS risk. Of note, the highest mean A1C was observed in those with higher versus lower risk for SAHS (9.7% vs. 7.9%, $p < 0.01$).

In an inverse direction, poor glycemic control and obesity are associated with a less quality of sleep. Intervention studies are needed to precise the sense of causality. To take into account, as a final insight sleep dept is a novel habit that could influence the exponential increase of diabetes, obesity and SAHS in our worldwide societies.

5. Metabolic syndrome

We can consider three group of factors in COPD patients: respiratory exacerbations and lung function, nutritional and muscle disorders and finally metabolic syndrome. There are several definitions of MS, but a common element is that all the components are related to the existence of insulin resistance, which will lead to glucose intolerance, abdominal obesity, elevated triglycerides, decreased HDL cholesterol and hypertension. It is estimated that 40-50% of individuals over 60 years have MS in industrialized countries. In Europe there is a prevalence of 15% (Hu et al., 2004; Botros et al., 2009). In a study of 170 patients with COPD and 30 with chronic bronchitis, Sicras et al. (Sicras et al., 2007) observed that the frequency of MS was 53%, 50%, 53% 37% and 44% in patients with chronic bronchitis, COPD I, II, III and IV respectively. They explained the lower incidence in the latter stages of the disease would be related to weight loss.

As previously mentioned, insulin resistance and the development of type 2 diabetes is the key point of MS. In this sense, we have discussed that hypoxia, obesity and sleep disturbances reduce the insulin sensitivity. We could say that the association between SAHS and DM resembles the clustering of metabolic diseases found in MS. The components of MS keep bidirectional links, such insulin resistance and obesity, that are plausible between SAHS and DM. Similarly, the sum of SAHS and DM may result in multiplied cardiovascular effects.

We discussed that the association between COPD and MS is far less clear than the parallel course of SAHS and MS. Due to hypoxia, a change towards multiple firing of vasoconstrictor neurons will increase noradrenalin levels, so we could expect at least arterial hypertension in COPD. Surprisingly, patients were not hypertensive in data by Ashley et al. (Ashley et al., 2010), and the authors posed tempering vascular factors that might balance the hypertensive drive. The links between COPD, metabolic syndrome and cardiovascular disease are largely unknown. Most of the data available deals with the association between SAHS, endothelial dysfunction and subsequent cardiovascular morbidity (Zamarron et al., 2008). There is also recent evidence of an increased mortality in overlap patients without CPAP therapy as compared to COPD (42.2 vs. 24.2%, $p < 0.001$) (Marin et al., 2010). Death was most commonly due to cardiovascular disease. A poorer quality of life was also demonstrated, even in patients without diurnal sleepiness.

The COPD, SAHS and DM shared inflammatory state perpetuates these chronic conditions and have a cardiovascular impact. Hypoxia induced factor (HIF-1) triggers inflammation and angiogenesis inside the atherosclerotic plaque this way facilitating the entry of phagocytes, red blood cells and lipoproteins. CRP is also directly related to atherosclerosis.

CRP interaction with Fcgamma receptor (Fcγ R) possibly increases the monocyte chemokine MCP-1 production, leading to monocyte adherence on to the arterial wall (Sevenoaks & Stockley, 2006). CRP also facilitates the production of foam cells that give shape to the atherosclerotic plaque. The "Third National Health and Nutrition Examination Survey" (NHANES III) denoted an association between CRP and myocardial ischemia. CRP levels higher than 3 mg/dl are significantly related to future cardiovascular events (Pai et al., 2004). This level is commonly surpassed in COPD patients. NF-κβ and TNF-α pathways leading to cardiovascular disease deserve a thorough research in COPD, SAHS and overlap syndrome. TNF- α induces the expression of CRP in the liver, being at the core of the process. TNF- α also has an active effect on macrophages migration, adhesion and differentiation within the atheroma plaque (Sevenoaks & Stockley, 2006). During COPD acute exacerbations, a further rise in CRP levels is also followed by a rise in fibrinogen as the expression of a thrombosis risk. Of note, cardiovascular mortality is particularly enhanced within and following hospital admission for an acute exacerbation (Sevenoaks & Stockley, 2006; Smeeth et al., 2004).

Briefly, the common consequence of COPD, SAHS, MS and DM is an inflammatory status that culminates in endothelial dysfunction leading to cardiovascular events. A novel explanation for the convergent endothelial dysfunction is a depletion or low response of bone marrow stem-cells. This phenomenon determines a reduction of circulating endothelial progenitor cells (EPC). Hyperglycemia, obesity, hypertension and dyslipidemia have been associated with a reduction of circulating EPC. Moreover, a synergistic reduction of EPC has been associated to the clustering of metabolic disruptions (Fadini et al., 2007; Werner et al., 2005, as cited in Tiengo et al., 2008).

6. Interactions of chronic obstructive pulmonary disease, sleep apnea hypopnea syndrome and diabetes *mellitus* treatment modalities

The treatment that has shown to increase survival in COPD is smoking cessation. This is the only measure that slows the accelerated decline in lung function in these patients. COPD therapeutic approach is based on: inhaled bronchodilators, inhaled and systemic corticosteroids, pulmonary and muscular rehabilitation, anti-inflammatory drugs, oxygen and palliative symptomatic treatment in the latter stages of the disease. In a greater or lesser extent, these treatments can influence the glycemic control of DM.

To begin with, systemic corticosteroids clearly alter the metabolism of carbohydrates. Corticosteroid treatment increases upperway resistance due to fluid retention in addition to myopathy and metabolic alkalosis. In addition, corticosteroids may predispose to SAHS by promoting central obesity. Among the most widely used, methylprednisolona is the one that worsens glycemic control the most, followed by hydrocortisone. Deflazacort has less effect on diabetic control.

We can not ignore the possible effect of inhaled corticosteroids on glycemic control. Many DM patients follow an inhaled drugs schedule for their coexistent COPD. Although considered a safe treatment, some systemic effects have been described. Cataracts and suppression of the hypothalamic-pituitary-adrenal are possible effects when maximum dose are given (Faul et al., 2009). In addition, some studies have shown (Faul et al., 1998) a significant increase (1.0%) in glycated hemoglobin and the persistence of glycosuria in

patients with DM 2 who used high-dose inhaled fluticasone (2 mg / day). Other study (Slatore et al., 2009), shows that high dose of inhaled corticosteroids are associated with small changes in glycemic control that are detectable but not clinically relevant as they would not be a criteria to stop or change the treatment.

One shared mainstay of COPD and DM treatment is physical exercise. Physical activity improves lung function and provides a better tolerance of the obstructive disease. It also reduces the risk of type 2 DM (13) and improves glycemic control with a lower dose of antidiabetic agents.

Weight loss can clearly be of benefit for patients with SAHS, obesity and/or DM. Probably, a benefit can be obtained in not advanced COPD stages with excessive weight. Weight loss improves SAHS but does not cure it. In a meta-analysis about bariatric surgery and SAHS, the baseline AHI was reduced from 54.7 to 15.8 events per hour, the latter indicating a moderate to severe SAHS still remaining (Greenburg et al., 2009). Patients should be alerted that they will probably need to continue SAHS treatment after surgery. Clinicians should also be aware that weight loss is associated with increased mortality in COPD. There is no evidence to recommend weight loss in overlap syndrome.

In an indirect way, the oxygen prescribed in advanced lung disease may also influence the management of diabetes. Unfortunately we lack solid studies to verify it. The hypothesis is that control of hypoxia may improve glucose tolerance and the associated MS. CPAP treatment of SAHS has not shown to improve metabolic syndrome in obese patients (Vgontzas et al., 2008), whereas it reduces visceral fat in non obese patients (Chin et al., 1999).

As we have described how hyperglycemia may worsen COPD outcome, we could pose if diabetes treatment can improve respiratory function. Being type 2 the most prevalent DM among COPD patients, insulin sensitizers could improve the lung function. This hypothesis was tested by Kim and colleagues (Kim et al., 2010) in a retrospective cohort study. After adjustment by weight, height and glycemic control, they found an improvement of FVC in subjects treated with insulin sensitizers compared to other DM treatments, with no significant changes in FEV1 or in FEV1/FVC.

We wonder if the new anti-inflammatory drugs (anti-phosphodiesterase 4) may have an effect on control of DM trying to improve the chronic inflammation of COPD. Modulators of the oxidative process such as methyl-bardoxolona are a possibility to be explored in both chronic conditions.

7. Conclusion

We think that we should estimate the risk of diabetes in a COPD patient and *vice versa,* given the frequent simultaneity of both conditions and the confluence of common related factors.

Definitely, prospective population-based and experimental evidence is needed to elucidate the crucial pathways between chronic hypoxemic status, insulin resistance and their contributing factors, mainly tabaquism, adiposity and disordered sleep. Of note, the architecture of sleep is of growing importance in DM. Understanding the clustering of these disorders and its cardiovascular prognosis may have an epidemiological impact on the tandem increase of COPD, DM and related conditions. Probably, lifestyle interventions on tobacco, diet and sleep habits are the key to keep the individual's health and long term well-being.

8. References

Ashley, C.; Burton, D.; Sverrisdottir, YB.; Sander, M.; McKenzie, DK.& Macefield, VG.(2010). Firing probability and mean firing rates of human muscle vasoconstrictor neurones are elevated during chronic asphyxia. *The Journal of Physiology*, Vol. 588, No. 4, pp. 701-711

Alcolea, S.; Villamar, J. & Alvarez-Sala R. (2007). Nutricional status in COPD. *Archivos de Bronconeumología*, Vol.43, No. 5, pp. 283-238

Álvarez- Sala, R. Chronic obstructive pulmonary disease: beyond the lungs. (2010). *Revista Clínica Española, V*ol. 210, No. 3, pp. 124-126

Archer, JR. & Baker, EH.(2009). Diabetes and metabolic dysfunction in COPD. COPD uptodate. *Respiratory Medicine,* Vol. 5, pp.67-74

Ayas, NT.; White, DP.; Al-Delaimy, WK., Manson, JE.; Stampfer, MJ.; Speizer, FE.; et al.(2003). A prospective study of self-reported sleep duration and incident diabetes in women. *Diabetes Care ,* Vol.26, No. 2, pp.380-384

Bergman RN. (2005). Minimal model: perspective from. *Hormone Research*, Vol. 64, pp.8-15

Botros, N., Concato, J.; Mohsenin, V.; Selim, B.; Doctor, K. & Yaggi, HK. (2009). Obstructive sleep apnea as a risk factor for type 2 diabetes. *The American Journal of Medicine*, Vol. 122, No. 12, pp. 1122-27

Braghiroli, A & Alvarez-Sala, R. (2002). Sleep disordered breathing and COPD. *Sleep Breath*, Vol.6, No.1, pp. 1-2

Chatila, WC.; Thomashow, BM.; Minai, OA.; Criner, GJ. & Make, BJ. (2008). Comorbidities in chronic obstructive pulmonary disease. *Proceedings of The American Thoracic Society*, Vol. 5, No. 4, pp. 549-555

Chen, K.; Li, F.; Li, J.; Cai, H.; Strom, S.; Bisello, A.; et al. (2006). Induction of leptine resistance through direct interaction of C-reactive protein with leptin. *Nature Medicine*, Vol.12, No. 4, pp.425-432

Chillón, MJ.; De Miguel, J.; Ferreira, A. & Sánchez, G. (2009). COPD and endocrine and metabolic alterations. *Archivos de Bronconeumología,* Vol. 45, No. 4 , pp. 42-46

Chin, K.; Shimizu, K.; Nakamura, T.; Narai, N.; Masuzaki, H.; Ogawa, Y. et al. (1999). Changes in intra-abdominal visceral fat and serum leptin levels in patients with intra-abdominal visceral fat and serum leptin levels in patients with obstructive sleep apnea syndrome following nasal continuous positive airway pressure therapy. *Circulation,* Vol.100, No. 7, pp. 706-712

Dalquen, P. The lung in diabetes *mellitus*. (1999). *Respiration,* Vol. 66, No.1 , pp. 12-13

Davis, WA.; Knuitman, M.; Kendall, P.; Grange, V. & Davis, TM. (2004). Glycemic exposure is associated with reduced pulmonary function in type 2 diabetes: the Fremantle Diabetes Study. *Diabetes Care*,Vol.27, No. 3,pp.752-757

De Miguel, J.; Cabello, J.; Sánchez-Alarcos, JM.; Alvarez-Sala, R.; Espinós, D. & Alvarez-Sala, JL. (2002). Long-term effects of treatment with nasal continuous positive airway pressure on lung function in patients with overlap syndrome. *Sleep Breath*, Vol. 6, No.1, pp.3-10

Ehrlich, SF.; Quesenberry, CP.; Van, SK.; Shan, J. & Ferrara, A. (2010). Patients diagnosed with diabetes are at increased risk for asthma, chronic obstructive pulmonary diseae, pulmonary fibrosis, and pneumonia but not lung cancer. *Diabetes Care* 2, Vol. 33, No.1, pp.55-60

Falk, JA.; Kadiev, S.; Criner, GJ.; Schof, SM.; Minai, OA. & Diaz P. (2008). Cardiac disease in chronic obstructive pulmonary disease. *Proceedings of The American Thoracic Society,* Vol. 5, No: 4 , pp. 543-548

Faul, JL.; Tormey, W.; Tormey, V. & Burke, C. (1998). High dose inhaled costicosteroid and dose dependent loss of diabetic control. *British Medical Journal* , Vol. 317, No. 7171, pp.1491

Faul, JL.; Wilson, S.; Chu, J.; Canfield, J. & Kuschner, W. (2009). The effect of an inhaled corticoid on glucose control in type 2 diabetes. *Clinical Medicine & Reserch,* Vol. 7, No.1-2 ,pp.14-20

Festa, A.; D'Agostino, RJ.; Tracy, RP. & Haffner, SM. (2002). Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes: the Insulin Resitance Atherosclerosis Study. *Diabetes,*Vol. 51, No. 4, pp. 1131-1137

Ford, ES. & Mannino, DM. (2004). Prospective association between lung function and the incidence of diabetes. Findings from the National Health and Nutrition Examination Survey Epidemiologic Follo-up Study. *Diabetes Care*, Vol.27, pp.2966-2970

Garcia-Rio, F.; Lores, V.; Mediano, O., Rojo, B.; Herranz, A.; López-Collazo, E. & Alvarez-Sala, R. (2009). Daily physical activity in patients with chronic obstructive pulmonary disease is mainly associated with dynamic hyperinflation. *American Journal of Respiratory and Critical Care Medicine*, Vol. 80, No.6, pp.506-512

García-Rio, F.; Romero, D.; Lores, V.; Casitas, R.; Herranz, A.; Galera, R.; et.al. (2011). Dynamic hyperinflation, arterial blood oxygen and airway oxidative stress in stable COPD patients. *Chest* (Epub ahead of print)

Greenburg, DL.; Lettieri, CJ. & Eliasson, AH. (2009). Effects of surgical weight loss on measures of obstructive sleep apnea: a meta-analysis. *The American Journal of Medicine,* Vol. 122, pp. 535-542

Gudmundsson, G.; Gislason, T.; Lindberg, E.; Hallin, R.; Suplí, C.; Brondum, E.; et al. (2006). Mortality in COPD patients ischarged from hospital: the role of treatment and co-morbidity. *Respiratory Research,* Vol. 7, pp. 109-117

Heindl, S.; Lehnert, M.; Criée, CP.; Hasenfuss, G. & Andreas S. (2001). Marked sympathetic activation in patients with chronic respiratory failure. *American Journal of Respiratory and Critical Care Medicine*, Vol.164, No. 4, pp.597-601

Hu, G.; Qjao, Q.; Toumilehto, J.; Balkau, B.; Borch-Johnsen, K. & Pyorala, K. (2004). DECODE study Group. Prevalence of the metabolic syndrome and its relation to all cause and cardiovascular mortality in non diabetic European men and women. *Archives of Internal Medicine*, Vol. 164, pp.1066-1076

Kim, HJ.; Lee, JY.; Jung, HS.; Kim, DK.; Lee, SM.; Yim, JJ.; et al.(2010). The impact of insulin sensitisers on lung function in patients with chronic obstructive pulmonary disease and diabetes. *The International Journal of Tuberculosis and Lung Disease* , Vol. 14, No.3, pp. 362-367

Knutson, KL.; Ryden, AM., Mander, BA.& Van Cauter, E. (2006). Role of sleep duration and quality in the risk and severity of type 2 diabetes *mellitus*. *Archives of Internal Medicine*, Vol.166, No. 16 , pp.1768-1774

Knutson, K., Spiegel, K.; Penev, P.& Van Cauter, E. (2007). The metabolic consequences of sleep deprivation. *Sleep Medicine Review* ,Vol.11, No.3, pp.163-178

Kono, M.; Tatsumi, K.; Saibara, T.; Nakamura, A.; Tanabe, N.; Takiguchi, Y.; et al. (2007). Obstructive sleep apnoea syndrome is associated with some components of metabolic syndrome. *Chest* , Vol. 131, pp.1387-1392

Kornum, JB.; Thomsen, RW.; Riis, A.; Lervang, HH.; Schonheyder, HC. & Sorensen, HT. (2008). Diabetes, glycemic control and risk of hospitalization with pneumonia: a population-based case-control study. *Diabetes Care*, Vol.31, No. 8, pp. 1541-1545

Lange, P.; Parner, J.; Schnohr, P. & Jensen, G. (2002). Copenhagen City Heart Study: longitudinal analysis of ventilatory capacity in diabetic and nondiabetic adults. *The European Respiratory Journal*, Vol.20, No. 6, pp.1406-1412

Lavi, S.; Prasad, A.; Yang, EH.; Mathew, V.; Simari, RD.; Rihal, CS.; et al. (2007). Smoking is associated with epicardial coronary endothelial dysfunction and elevated white blood cell count in patients with chest pain and early coronary artery disease. *Circulation,* Vol. 115, No. 20, pp. 2621-2627

Makarevich, AE.; Valevich, VE. & Pochtavtsev, AU. (2007). Evaluation of pulmonary hypertension in COPD patients wth diabetes. *Advances in Medical Sciences*, Vol.52, pp. 265-272

Makino, S.; Handa, H.; Suzukawa, K.; Fujiwata, M.; Nakamura, M.; Muraoka, S.; et al.(2006). Obstructive sleep apnoea syndrome, plasma adiponectin levels, and insulin resistance. *Clinical Endocrinology*, Vol.64, No. 1, pp.12-19

Mallon, L.; Broman, JE.& Hetta, J. (2005). High incidente of diabetes in men with sleep complaints or short sleep duration: a 12-year follow-up study of a middle-aged population. *Diabetes Care* ,Vol.28, No. 11, pp.2762-2767

Mannino, DM.; Thorn, D.; Swensen, A. & Holguin, F. (2008). Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *The European Respiratory Journal*, Vol.32, No.4, pp. 962-969

Marin, JM.; Soriano, JB.; Carrizo, SJ.; Boldova, A. & Celli, BR. (2010). Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. *The American Journal Respirtory Critical Care of Medicine,* Vol.182, No. 3, pp.325-331

Mathers, CD. (2008). The global burden of disease: 2004 uptodate. World Health Organization

McArdle, N.; Hillman, D.; Beilin, L.& Watts, G. (2007). Metabolic risk factors for vascular disease in obstructive sleep apnea: a matched controlled study. *The American Journal Critical Care of Medicine,* Vol.175, No. 2, pp.190-195

McNicholas, WT. (2009). Chronic obstructive pulmonary disease and obstructive sleep apnea. *The American Journal Critical Care of Medicine,* Vol.180, pp.692-700

Moussas, G.; Tselebis, A.; Karkanias, A.; Stamouli, D.; Ilias, I.; Bratis, D. & Vassila-Demi, K. (2008). A comparative study of anxiety and depression in patients with bronchial asthma, chronic obstructive pulmonary disease and tuberculosis in a general hospital of chest diseases. *Annals of General Psychiatry*, Vol. 7, pp. 1-4

Oudijk, EJ.; Lammers, JW. & Koenderman, L. (2003). Systemic inflammation in chronic obstructive pulmonary disease. European Respiriratory Journal, Vo. 46, pp.5-13

Owens, RL.; Malhotra, A. (2010). Sleep-disordered breathing and COPD: the overlap síndrome. *Respiratory Care*, Vol.55, No.10, pp.1333-1344

Pai, JK.; Pischon, T.; Ma, J.; Manson, JE.; Hankinson, SE.; Joshipura, K.; et al. (2004). Inflammatory markers and the risk of coronary heart disease in men and women. *The New England Journal of Medicine,* Vol.351, No.25, pp. 2599-2610

Parappil, A.; Depczynski, B.; Collett, P. & Marks, G.(2010). Effect of comorbid diabetes on length of stay and risk of death in patients admitted with acute exacerbations of COPD. *Respirology,*Vol.15, No. 6, pp. 918-922

Pauwels, RA.; Buist, AS.;Jenkins, CR. & Hurd, SS. GOLD Scientific Commitee. (2001). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *The American Journal Critical Care of Medicine,* Vol. 163, No. 5, pp. 1256-1276. Available from http:// www.goldcopd.org

Peces- Barba, G.; Barberá, JA.; Agustí, A.; Casanova, C..; Casas, A.; Izquierdo, JL.; et al. (2008). Diagnosis and management of chronic obstructive pulmonary disease: joint guidelines of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) and the Latin American Thoracic Society (ALAT). *Archivos de Bronconeumología*, Vol.5, pp. 271-281

Pillar, G. & Shehadeh, N. (2008). Abdominal fat and sleep apnea. The chicken or the egg?. *Diabetes Care*, Vol. 31, No. 2, pp. 303-309

Polotsky, VY.; Li, J.; Punjabi, NM.; Rubin, AE.; Smith, PL.; Schwartz, AR.; et al. (2007). Intermittent hypoxia increases insulin resistance in genetically obese mice. *The Journal of Physiology*, Vol.552, No. 1, pp.253-264

Popov, V. & Simionescu, M. (1997). Alterations of lung structure in experimental diabetes and diabetes associated with hyperlipidemia in hamsters. *The European Respiratory Journal*, Vol.10, No. 8 , pp.1850-1858

Rana, JS.; Mittleman, MA.; Sheikh, J.; Hu, FB.; Manson, JE.; Colditz, GA.; et al. (2004). Chronic obstructive pulmonary disease, asthma, and risk of type 2 diabetes in women. *Diabetes Care*, Vol.27, No. 10, pp.2478-2484

Raupach, T.; Bahr, F.; Herrmann, P.; Luethje, L.; Heusser, K.; Hasenfuss, G.; et al. (2008). Slow breathing reduces sympathoexcitation in COPD. *The European Respiratory Journal*, Vol. 32, No. 2, pp. 387-392

Reichmuth, KJ.; Austin, D.; Skatrud, JB. & Young, T. (2005). Association of sleep apnea and type II diabetes: a population-based study. *The American Journal Respiratory Critical Care of Medicine*, Vol. 172, No. 12, pp. 1590– 1595

Santiago-Recuerda, A.; Gómez-Terreros, FJ.; Caballero, P.; Martin-Duce, A.; Soleto, MJ.; Vesperinas, G.; et.al. (2007). Relationship between the upper airway and obstructive sleep apnea-hypopnea syndrome in morbidly obese women. *Obesity Surgery*, Vol.17, No.5, pp.689-97

Sevenoaks, M. & Stockley, RA. (2006). Chronic obstructive pulmonary disease, inflammation and co-morbidity – a common inflammatory phenotype?*Respiratory Research*, Vol.7, No.1, pp.70

Sharma, SK.; Kumpawat, S.; Goel, A.; Banga, A.; Ramakrishnan, L.& Chaturvedi, P. (2007). Obesity, and not obstructive sleep apnea, is responsible for metabolic abnormalities in a cohort with sleep-disordered breathing. *Sleep Med*, Vol.8, No. 1, pp.12-17

Sicras, A.; Navarro, R. & González, P. (2007). Influencia de la diabetes *mellitus* en los sujetos con enfermedad pulmonar obstructiva crónica en un ámbito ambulatorio. *Anales de Medicina Interna*, Vol. 24, No. 4, pp.201-203

Slatore, CG.; Bryson, CL. & Au, DH. (2009).The association of inhaled corticosteroid use with serum glucose concentration in a large cohort. *The American Journal of Medicine*, Vol.122, No. 5 , pp. 472-478

Smeeth, L.; Thomas, SL.; Hall, AJ.; Hubbard, R.; Farrington, P. & Vallance, P. (2004). Risk of myocardial infarction and stroke after acute infection or vaccination. *The New England Journal of Medicine*, Vol. 351, No. 25, pp.2611-2618

Spiegel, K.; Leproult, R. & Van Cauter, E. (1999). Impact of sleep debt on metabolic and endocrine function. *Lancet* , Vol.354, No. 9188, pp.1435-1439

Stoohs, R.; Facchini, F.& Guilleminault, C. (1996). Insulin resistance and sleep-disordered breathing in healthy humans. *The American Journal Critical Care of Medicine*, Vol.154, No. 1, pp.170-174

Tasali, E., Leproult, R.; Ehrmann, DA.& Van Cauter, E. (2008). Slow-wave sleep and the risk of type 2 diabetes in humans. *Procceedings of the National Academy of Sciences of the USA*, Vol. 105, No. 3, pp.1044-1049

Tasali, E.; Mokhlesi, B. & Cauter, EV. (2008). Obstructive sleep apnea and type 2 diabetes. Interacting epidemics. *Chest,* Vol. 133, No. 2, pp.496-506

Tassone, F.; Lanfranco, F.; Gianotti, L.; Pivetti, S.; Navone, F.; Rossetto, R.; et al.(2003). Obstructive sleep apnoea syndrome impairs insulin sensitivity independently of anthropometric variables. *Clinical Endocrinology*, Vol.59, No.3 ,pp.374-379

Tiengo, A.; Fadini, GP. & Avogaro, A. (2008). The metabolic syndrome, diabetes and lung dysfunction. *Diabetes & Metabolism* , Vol. 34, pp. 447-454

Vgontzas, AN., Papanicolaou, DA.; Bixler, EO.; Hopper, K.; Lotsikas, A.; Lin, HM.; et al. (2000). Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance and hypercytokinemia. *The Journal of Clinical Endocrinology and Metabolism*, Vol.85, No. 2, pp.1151-1158

Vgontzas, AN.; Zoumakis, E.; Bixler, EO.; Lin, HM.; Collins, B.; Basta, M.; et al. (2008). Selective effects of CPAP on sleep apnoea-associated manifestations. *European Journal of Clinical Investigation,* Vol.38, No. 8, pp.585-595

Walter, RE.; Beiser, A.; Givelber, RJ.; O'Connor, GT. & Gottlieb DJ. (2003). Association between glycemic state and lung function. The Framingham Heart Study. *American Journal of Respiratory and Critical Care Medicine*, Vol.167, No. 6, pp.911-916

Watz, H.; Waschki, B.; Kristen, A.; Muller, KC.; Kretschmar, G.; Meyer, T.; et al. (2009). The metabolic syndrome in patients with chronic bronchitis and COPD. *Chest* , Vol. 136, No .4 , pp. 1039-1046

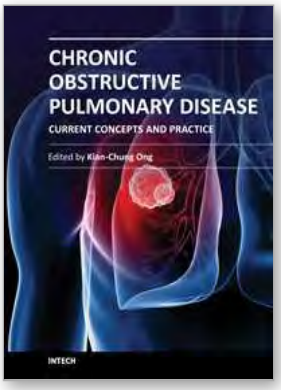
Weynand, B.; Jonckheere, A.; Frans, A. & Rahier, J. (1999). Diabetes *mellitus* induces a thickening of the pulmonary basal lamina. *Respiration* , Vol. 66, No. 1 ,p.14-19

Wild, S.; Roglic, G.; Green, A.; Sicree, R.& King, H. (2004). Global prevalence of diabetes. Estimates for the year 2000 and proyections for 2030. *Diabetes Care*, Vol.27, No. 5, pp.1047-1053

Yeh, HC.; Punjabi, NM.; Wang, NY.; Pankow, JS.; Duncan, BB.; Cox, CE.; et al. (2008). Cross-sectional and prospective study of lung function in adults with type 2 diabetes. The Atherosclerosis Risk in Communities (ARIC) Study. *Diabetes Care* , Vol. 31, No. 4, pp.741-746

Zamarrón, C.; García, V.; Morete, E. & Campo, F. (2008). Association of chronic obstructive pulmonary disease and obstructive sleep apnea. *International Journal of Chronic Obstructive Pulmonary Disease* , Vol.3, No. 4, pp. 671-682

Zizi, F.; Jean-Louis, G., Brown, CD.; Ogedegbe, G.; Boutin-Foster, C. & McFarlane, SI.(2010). Sleep duration and the risk of diabetes *mellitus*: epidemiologic evidence and pathophysiologic insights. *Current Diabetes Reports* , Vol. 10, No.1, pp. 43-47



Chronic Obstructive Pulmonary Disease - Current Concepts and Practice

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A decade or so ago, many clinicians were described as having an unnecessarily 'nihilistic' view of COPD. This has certainly changed over the years... This open access book on COPD provides a platform for scientists and clinicians from around the world to present their knowledge of the disease and up-to-date scientific findings, and avails the reader to a multitude of topics: from recent discoveries in the basic sciences to state-of-the-art interventions on COPD. Management of patients with COPD challenges the whole gamut of Respiratory Medicine - necessarily pushing frontiers in pulmonary function (and exercise) testing, radiologic imaging, pharmaceuticals, chest physiotherapy, intensive care with respiratory therapy, bronchology and thoracic surgery. In addition, multi-disciplinary inputs from other specialty fields such as cardiology, neuro-psychiatry, geriatric medicine and palliative care are often necessary for the comprehensive management of COPD. The recent progress and a multi-disciplinary approach in dealing with COPD certainly bode well for the future. Nonetheless, the final goal and ultimate outcome is in improving the health status and survival of patients with COPD.

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