

Evaluation of Methods for Treating Obstructive Lung Disease

Minireview Based on a Doctoral Thesis

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Abbreviations: COPD, Chronic obstructive pulmonary disease; CPAP, Continuous positive airway pressure; EIA, Exercise-induced asthma; FEF_{25} , Forced expiratory flow at 25% of FVC; FEF_{75} , Forced expiratory flow at 75% of FVC; FEV_1 , Forced expiratory volume in one second; HR_{max} , Maximal heart rate; LTOT, Long-term oxygen therapy; MRC, Medical Research Council working party; NOTT, Nocturnal oxygen therapy trial; $PaCO_2$, Arterial carbon dioxide tension; PaO_2 , Arterial oxygen tension; PEF, Peak expiratory flow; PEP, Positive expiratory pressure; PLB, Pursed lips breathing; $PtcCO_2$, Transcutaneous carbon dioxide tension; $PtcO_2$, Transcutaneous oxygen tension; RI, Respiratory insufficiency; SaO_2 , Arterial oxygen saturation; SpO_2 , Oxygen saturation by pulse oximeter; SIP, Sickness impact profile; VO_{2max} , Maximum oxygen uptake; V_T , Tidal volume.

INTRODUCTION

The health situation of patients with obstructive lung disease has been greatly improved by modern pharmacological innovations. A vast amount of research has been carried out in this field. In general the results have rested firmly on a scientific basis, and the absolute magnitude of the improvement and effects has been verified.

Pharmacological treatment is not, however, the only therapy these patients receive. Conventional respiratory treatment modalities, for example, are widely used. These modalities are often applied in clinical settings, but there has been little systematic research to evaluate their effects. The therapeutic methods are often based on intuition, experience and clinical praxis. For various theoretical reasons, the patients are treated on the trial-and-error principle, and can receive a variety of treatments for exactly the same condition. Moreover, the facts that the procedures are not effective in all patients and that many treated patients will either improve very little or not at all, or even become worse, are sometimes forgotten.

In order not merely to switch from one procedure to another and hope to hit upon a successful one, evaluation and verification of their effects are of great importance. The evaluation must be based on scientific research, where both short-term and long-term effects are considered.

It is difficult, however, to evaluate physiotherapeutic methods. Scientific research in this area is limited by a lack of tradition of such investigations. Double-blind studies are usually not possible. There is also the problem of finding patient groups that are sufficiently large and have

homogeneous background characteristics. In the treatment and evaluation of severely ill patients randomization and the use of control groups are not always possible. The drop-outs from these patient groups are often considerable.

A lack of suitable methods of evaluation is also a problem that is often encountered in attempts to compare physiotherapeutic techniques. New methods of evaluation need to be added to the "old" ones. Forms of assessment in which both objective and subjective gains and limitations are considered, are of importance. For example non-invasive assessment, with continuous transcutaneous measurements, in addition to measurements of arterial blood gases, gives more information than occasional arterial puncture alone. Subjective evaluation, such as evaluation of the quality of life, using study-specific questionnaires and visual analogue scales, adds a great deal of information to objective parameters. The above methods, among others, have been used in this investigation to evaluate the effects of a selection of therapies used by patients with obstructive lung disease.

BRONCHIAL ASTHMA

"Asthma is a chronic inflammatory disorder of the airways in which many cells play a role, including mast cells and eosinophils. In susceptible individuals this inflammation causes symptoms which are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment, and causes an associated increase in airway responsiveness to a variety of stimuli" (92).

Airway responsiveness is the tendency of the airways to narrow acutely in response to non-sensitizing physical or chemical stimuli, and it probably plays a normal physiological role (46). The responsiveness of the airways is usually measured by inhalation of a pharmacological bronchoconstrictor, e.g. histamine or methacholine, which directly stimulates airway smooth muscle to produce airflow obstruction (132). Airway hyperresponsiveness in asthmatic individuals is greater than in normal subjects (46). In general, the more severe the asthma the greater the degree of hyperresponsiveness (132).

Airway hyperresponsiveness can be demonstrated by means of stimuli such as exercise, hyperventilation, cold air and chemical agents (132). This enhanced airway responsiveness is called non-specific, since almost all asthmatic persons will show bronchoconstriction as a reaction to these stimuli (18). These stimuli cause acute airway constriction (92) and probably act either through mediator release or through neural pathways (132). The strength of the stimulus and the degree of airway responsiveness determine the severity of the bronchoconstrictor response (96).

Airway inflammation is a critical feature in the pathogenesis of asthma. Experimental studies have demonstrated that there is a close association between the degree of inflammation in the airway wall and the degree of airway hyperresponsiveness (18). Asthma stimuli, such as allergens, occupational sensitizing agents and probably viral infections of the upper respiratory tract are considered to cause this hyperresponsiveness (46).

These stimuli are specific, since they produce bronchoconstriction only in asthmatic patients sensitive to these agents (18).

Acute asthma

A severe asthmatic attack can occur spontaneously or as a result of some triggering factors. It can develop quickly, as in exposure to an allergen (135), or gradually, as in a respiratory tract infection (11). Dyspnoea is the most common symptom for which patients with asthma seek and receive acute medical care. Dyspnoea has been defined as "an uncomfortable awareness of breathing or an increased respiratory effort that is unpleasant and regarded as inappropriate by the patient" (142). "A sensation of breathlessness becomes a symptom either when it occurs in abnormal circumstances or when it is abnormal in quality" (89). The precise cause of dyspnoea in acute asthma is unknown. It has been suggested, however, that dyspnoea in asthma is more closely related to the secondary overinflation of the lungs and thorax than to increased airflow resistance (89). When arriving in the emergency room, the patients often have a severe airflow obstruction, as quantified by measurement of peak expiratory flow (PEF) or forced expiratory volume in one second (FEV₁) (126). They are commonly also found to have tachycardia (60) and hypoxia (144). The patients experience a varying degree of wheezy breathing. When admitted to hospital, the treatment of asthma is often focused on improving objective variables, such as PEF and FEV₁, rather than on relieving the patient's dyspnoea.

Short-acting β_2 agonists are the first-line treatment in acute asthma. Studies have shown that inhaled bronchodilator agents are as effective as those given by parenteral routes (106). Inhalation treatment has also been found to have fewer side-effects (26). Therefore, the initial bronchodilator drug of choice is nebulized salbutamol or terbutaline (96). An addition of nebulized ipratropium bromide to a β_2 agonist further enhances the effect of the treatment (138). The nebulization should be carried out with oxygen, as many patients with acute asthma are hypoxaemic. Intravenous theophylline may also be required, although its value has been questioned (94). High-dose systemic corticosteroids are also used in treatment of severe, acute asthmatic exacerbations (92).

Exercise-induced asthma

One of the non-specific factors that trigger asthma is exercise (132). Brief exercise for 1 to 2 minutes is known to cause bronchodilation, but continuation of exercise for 5 to 10 minutes is usually followed by bronchospasm. Practically all persons with asthma have these characteristic changes in the ventilatory capacity during and after physical exertion (63). When a large increase in airway resistance occurs after exercise, the reaction is described as exercise-induced asthma (EIA) (36). EIA is a common phenomenon that occurs in almost 80% of asthmatic individuals (55). It is even postulated that EIA occurs in all individuals suffering from asthma if the work load is sufficiently high (50). It is very common in young patients, in whom it may be a very troublesome symptom. Classically, in EIA, there is an initial bronchodilation during exercise (152), followed by airway narrowing which reaches its peak about 5 to 10 minutes after

termination of the activity (63). It usually wears off gradually within one hour (146) and has not been reported to result in "status asthmaticus" (36).

Inman and colleagues (91) demonstrated that there is a potent mechanism that protects asthmatic subjects against bronchoconstriction during exercise. The nature of this mechanism is not known. Inhibitory mediator release (prostaglandins) during exercise may be partly responsible for the protective effect (69). On the other hand, release of constrictor mediators during exercise does not appear to result in bronchoconstriction, presumably because of the protection afforded by exercise. This protection, however, is transient and bronchoconstriction occurs within 5 minutes after the exercise is completed (91). The normal physiological effect of exercise is bronchodilation (132), which is thought to be related to release of catecholamines into the circulation (7). The increase in tidal volume (V_T) that occurs during exercise may also cause this dilatation (91). Further, deep inhalation has also been found to reduce airway resistance in normal human subjects (124).

An ideal exercise challenge test for EIA would consist in having the patient undertake whatever task has caused the problem (8). In a standardized setting, the test can be performed, for example, with treadmill exercise, bicycle ergometry or running (57). The sensitivity of the test may be enhanced by lowering the ambient temperature and increasing the humidity, i.e. by running outdoors (146). The treadmill is generally believed to be the best form of exercise for assessing EIA (52). The exercise challenge can be undertaken either with fixed-level exercise or with use of progressively increasing work loads (6).

An immediate reaction, i.e. a decrease in pulmonary function (PEF or FEV_1) by more than 10 to 20%, is usually required to confirm the EIA (146). However, Kattan et al (98) considered a decrease of 10 % to be too low and found that 15% was more acceptable, as this would avoid the possibility of confusing the effect of variability of the spirometric technique with a true reduction in pulmonary function. This is in agreement with other reports (62, 149).

In some patients a late EIA reaction appears within 4 to 12 hours after the initial exercise challenge. This often disappears spontaneously without medication within 24 hours. Late EIA reactions are more likely to occur in subjects who have marked airway hyperresponsiveness (24) and are probably of an inflammatory nature. Observations have suggested that the immediate response to exercise takes place predominantly in the large airways, and the late response in the small airways (74). Unlike dual responses to allergens, where the late reaction is often more severe than the immediate one, the late reaction to exercise appears to be less severe than the immediate reaction (24). The late exercise reaction has not been demonstrated by all authors (63, 97).

There appears to be a refractory period after an exercise challenge, i.e. a decrease in the bronchoconstrictive response to further exercise repeated within one hour of the initial exercise (74). The degree of bronchoconstriction is then often significantly lower (146). Refractoriness to exercise is known to decline with an increasing interval between two periods of exercise (139),

and normally lasts for four hours (169). The refractory period is believed to be a consequence of prostaglandin release (91). In previous studies, approximately 50% of subjects with EIA have been shown to develop refractoriness (139). With repeated exercise some subjects may temporarily lose their EIA completely (169). There has been some debate as to whether EIA needs to occur to induce a refractory period. Ben-Dov and his colleagues (22) found in their study, however, that the majority of their asthmatic patients were refractory to a subsequent exercise test even when the initial test did not itself cause EIA. Weiler-Ravell et al (169) have also observed a diminished response to antigen challenge in the refractory period induced by exercise.

Mechanisms of exercise-induced asthma

The mechanisms responsible for EIA are still not fully understood despite considerable research. For a long time, many clinicians believed that it was the exercise itself that triggered EIA (74) and it has also been suggested that the level of hyperventilation is the major determinant of EIA (35). Bar-Yishay and co-workers (14) have shown, however, that hyperventilation-induced asthma is not the same as exercise-induced asthma in most subjects.

Most current theories on the mechanisms of EIA focus on heat and water loss from the airway mucosa. Studies have demonstrated that water loss will initiate bronchospasm. It is thought that airway water loss leads to an increase in airway osmolarity, causing constriction in the smooth muscles (148). Deal and co-workers (51) have shown that the magnitude of exercise-induced bronchoconstriction is significantly correlated with the calculated total respiratory heat loss. However, there is some evidence that neither water loss nor heat loss alone induces EIA (22). One theory is that EIA results from loss of both heat and water from the lung during exercise (42). This loss is due to hyperventilation of air, which is cool and dry (8). The water and heat loss may not entirely explain the magnitude of exercise-induced bronchoconstriction. However, more recently it has been found that the inspired air conditions during the recovery period after exercise challenge can also influence the degree of EIA. Boulet and Turcotte (31) observed that EIA worsened when recovery took place in humid air.

It is almost 300 years since it was first recognized that physical exertion could induce an attack of asthma (172, 63). Some types of exercise are considered to be more asthmogenic than others. Free running and stair climbing have been found to be stronger and more reproducible stimuli for EIA than cycling, walking or swimming.

More recent studies have provided some evidence that if in laboratory settings the level of ventilation and the inspired air conditions - temperature and humidity - are identical, the EIA will also be the same (165). The nature of the exercise and the environment in which it is performed have been shown to be of importance, however, and to influence the severity of EIA (122). Swimming does seem to offer the asthmatic individual some advantage, because of the warmer temperature and higher humidity around the swimming pools (61). The severity of EIA is also dependent upon the intensity and duration of the exercise. Silverman and Anderson (149)

observed that the severity of EIA increased with increasing work loads and with increasing duration of exercise up to certain plateau values. They noted that patients who developed severe EIA after 6 to 8 minutes got less asthma after more prolonged exercise. Noviski and co-workers (129) also claim that the severity of EIA is determined by the intensity of the exercise and that the airway temperature or humidity acts as a modifying factor.

Ability to exercise

Adults need regular exercise to maintain their general level of health, to improve their cardiac output and aerobic capacity (40), to reduce body fat (121), and to reduce stress (147). Among other benefits, it lowers the risk of stroke (168) and osteoporosis (105) and increases muscle mass (121). Patients with asthma have the same overall need for exercise as all other individuals (153).

In normal subjects both fitness and physical stamina are diminished by prolonged inactivity and increased by training (44). This is also true in asthmatics. Indeed, recent studies have shown that patients with asthma, both adults (43) and children (131), have diminished physical fitness compared with healthy normals.

Increasing public awareness of the long-term health benefit of regular exercise has encouraged healthy people to take part in various physical activities (13). Despite the fact that the cardiovascular fitness can be improved in asthmatic subjects also (45), and that patients with asthma can participate in most physical activities (36), patients are seldom seen to exercise (67). Asthmatics often perceive the disease as a barrier to exercise and imagine that the restrictions are imposed by their illness (67). But it has been proven that patients with asthma have sufficient ventilatory reserve to allow tolerance of training routines (44). The exercise capacity is not restricted by the patients' baseline obstruction (176). There is no relationship between the degree of obstruction at rest and the severity of EIA (6). In fact the functional limitation is probably due to deconditioning (147). Past episodes of dyspnoea and lack of confidence to attempt physical exertion could be one of the reasons why asthmatics do not exercise (2). They are not always able to distinguish between the sensation associated with external loads and that of bronchoconstriction, or to discriminate the dyspnoea of asthma from the normal breathlessness caused by exercise (89). The extent of physical achievement in most individuals with asthma appears to be the same as in those without asthma; it is based primarily on the athletic capabilities and in the interest in (153) and motivation for maximal work (43), and has little or nothing to do with the asthma itself (153).

Benefits from a physical training programme

The benefits provided regular exercise are similar in individuals with and without asthma (44). Asthmatic patients who are least fit at the outset of the training gain most in terms of a training effect, as has been reported in healthy subjects (170). The cardiorespiratory performance (45) and cardiovascular function (100) have been reported to increase after a training programme. After training both the heart rate and ventilation at a given work load are decreased (2). Some studies have also shown an improvement in lung function after a training programme (158). It has been

claimed that EIA can be treated successfully by physical exercise (10, 82), but this contrasts to other findings (41, 107). An improved efficiency of movement and better neuromuscular control (167), as well as an improved sense of well-being and a decreased sense of breathlessness (87), are reported benefits from a physical training programme. Some authors have also obtained evidence that a regular exercise programme will result in a reduction in the overall need for medication to control asthma (93). The number of asthma attacks has decreased (133), as well as visits to emergency rooms and admissions to hospital (90). Physical fitness programmes probably also produce a variety of psychological (114), emotional and social benefits (153).

Guidelines for a physical training programme

One of the goals of physical training is to increase cardiovascular fitness, i.e. to increase the capacity of the central circulation. A training programme should therefore provide hard, repetitive, large-muscle mass dynamic exercise, which is aerobic in nature, to produce a heavy load on the circulation (21, 100).

The effects of training are dependent upon the intensity and frequency of the training and the duration of each training session. The mode of activity and the initial fitness of the individual also affect the magnitude of the training effect (170).

Training intensity and duration of training are interrelated, the total amount of work accomplished being an important factor in the improvement in fitness (170). The use of a person's individual heart rate in per cent of the predicted maximum heart rate (HR_{max}) as an estimate of the intensity of training is a common standard and has the virtue of being easy to measure (40). However, the training intensity corresponding to a given heart rate varies widely among subjects (100). Maximum oxygen uptake (maximum aerobic power), VO_{2max} , is considered to be the best measure of intensity and the best variable for assessing the cardiovascular effects of training (170). Measurement of VO_{2max} is much more complicated, however, than measurement of HR_{max} .

The greatest effect, i.e. the greatest increase in VO_{2max} , is found with exercise intensities of 90 to 100% of VO_{2max} (above 90% of HR_{max}) (170). The minimum intensity for a cardiovascular effect is 50% of VO_{2max} (65% of HR_{max}) (4). On the whole, it appears that the greater the intensity the better the effect, up to a certain limit. Training intensities which exceed VO_{2max} (>100%) are less effective, because of muscle fatigue (170). It is commonly recommended that the exercise rate during training should be approximately 75-85 of HR_{max} (177).

As the intensity and duration of the training session increase, the VO_{2max} level also improves. The maximum effect of training occurs already in 15 to 25 minutes, when the training has an intensity giving 90-100% of VO_{2max} . If the training results in 70 to 90% of VO_{2max} , its duration must be at least 35 to 45 minutes for it to have the same effect as that of higher intensity (170). This suggests that the improvement will be similar with activities performed at a lower intensity and for a longer

ration compared with higher intensity and a shorter duration, if the total energy costs of the activities are equal (4).

For cardiovascular fitness to be developed and maintained, the training has to be repeated several times a week. The best improvement in fitness is obtained by training at high intensity four times a week. However, maintenance of physical fitness can be achieved with a frequency of two sessions per week (170).

The importance of the training intensity is further accentuated when considered in relation to the length of the training. When the intensity is 90-100% of $\dot{V}O_{2max}$, 10 to 11 weeks seems to give the maximum effect (170). In general the exercise programme must be sustained at least five weeks, as the effect on the working capacity begins to occur approximately four weeks from the beginning of training (82).

The structural and physiological changes that accompany training regress almost as fast as they are achieved (40). There is a significant reduction in working capacity after only two weeks without participation in regular exercise (153). A return to the pre-training status occurs after 10 weeks to 8 months of detraining. Therefore, once established, exercise programmes must be sustained (40). All programmes should include activities suited to the participants' personality and resources to assure that they will be sustainable and lifelong (153).

The same training principles concern both asthmatic individuals and healthy subjects regarding improvement of cardiovascular fitness. There are some important additional factors to be considered, however, when planning a training programme for asthmatics.

In order to prepare the airways for exercise, pre-treatment with a β_2 agonist in aerosol before all training is of great importance. β_2 agonists abate EIA in more than 90% of the subjects (7). The protection afforded by β_2 stimulation lasts for several hours (55). A training session for asthmatic persons should start with a warming-up period, in order to build up a refractoriness to the intended exercise (153). Warming-up is described as a brief period of submaximal exercise before undergoing the intended exercise. It might possibly deplete the mast cell mediators (152). A warming-up period should last from 5 to 10 minutes (153), as a shorter period is not sufficient to attenuate EIA (122). The exercise then continues with an interval training principle. Interval training, as the name implies, is a series of repeated bouts of intensive exercise alternated with periods of recovery (71). The recovery period usually consists of light exercise, also with the aim of inducing a refractory period without EIA (153). Furthermore, there is no doubt that interval training is less exhausting, since continuous training leads to an accumulation of blood lactate (100). As a high minute ventilation can only be tolerated for a short time (44), the intensive intervals should not be longer than 2 minutes. Periods of 2 minutes usually do not provoke EIA but are long enough to give high pulse rates and good training effects (6). McFadden and co-workers (115) have demonstrated that EIA can be ameliorated by the use of a cooling-down period

at the end of the exercise, and all training programmes should therefore finish with a slow, low-intensity period.

In summary, in order to gain maximum cardiovascular fitness without negative asthmatic reactions, the training programme should be carried out as follows. The programme starts with a warming-up period, lasting for at least 5 minutes. It then continues with interval training. Each intensive interval should not be longer than 2 minutes and should consist of large-muscle dynamic exercise. The interval training continues for at least 15 minutes, with an intensity corresponding preferably to 90-100% but at least to 70-90% of VO_{2max} . A cooling-down period completes the training programme. The total duration of an appropriate fitness programme is 35 to 45 minutes. The programme should preferably be continued four times a week, but twice a week is considered enough for maintenance of training effects. Swimming and physical exercise in an indoor pool are a good choice, because of the warm and humid surroundings. The training should be carried out for at least 10 weeks, although for asthmatic persons exercise training should be lifelong. However, high motivation is required, as variations in the disease may interrupt the exercise programme. Many patients require active intervention and repeated follow-ups should be included in all exercise programmes. Fitness programmes should preferably be organized and supervised in order to provide benefit (45).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) is a condition with irreversible airflow obstruction caused by chronic bronchitis and emphysema in various combinations. The major factors generating this airflow limitation are reduced elastic recoil and airway narrowing induced by an inflammatory process. The loss of elastic recoil and additionally the loss of alveolar walls occur progressively, as does the inflammation in both small and large airways. Dyspnoea, a recognizable symptom especially on exertion, is caused by increased work of breathing due to hyperinflation and airway obstruction. Cough and mucus hypersecretion occur in COPD patients in varying degrees. The inflammation can also give rise to bronchial hyperreactivity, at least in the early stages of the disease. COPD, usually a result of years of inhalation of tobacco smoke, is the most common cause respiratory insufficiency (134).

Respiratory insufficiency

"The function of the respiratory system is to secure gas exchange between the blood and ambient air so that the arterial blood gas pressures are kept in certain limits. Respiratory insufficiency may therefore be defined as impairment of this function of such degree that the arterial blood gas pressures depart from these limits" (38).

Respiratory insufficiency (RI) is present when the arterial blood tension of oxygen (PaO_2) is below 8.0 kPa (hypoxia) or the tension of carbon dioxide ($PaCO_2$) is above 6.5 kPa (hypercapnea), or both (38).

Since oxygen diffuses more slowly than carbon dioxide, PaO_2 falls before PaCO_2 rises during the development of respiratory insufficiency, particularly in COPD. Two types of RI can be recognized. Firstly, the type in which PaO_2 falls but PaCO_2 remains normal. In the literature these COPD patients are called "pink puffers". The patients have a tendency to hyperventilate and their respiratory centre has a normal sensitivity to carbon dioxide. In the second type the patients are called "blue bloaters". These patients show a concomitant rise in PaCO_2 . Their respiratory centre has adapted to a higher PCO_2 value. The respiratory centre does not react when the carbon dioxide increases. Secondary polycythaemia, pulmonary hypertension and cor pulmonale are seen in these patients (162).

Causes of chronic hypoxia and hypercapnea

Several physiological mechanisms can account for chronic hypoxia. Ventilation-perfusion mismatch is the major cause of arterial hypoxia in lung disease (64). The ideal amounts of gas and blood are not in apposition, because of destroyed airways and lung capillaries (88). In some patients alveolar hypoventilation, in which the alveoli do not receive an adequate volume of air for gas exchange, contributes to hypoxia.

Impaired diffusion, due to thickening of the alveolar membrane, and shunt hypoxia, may reduce PaO_2 and arterial oxygen saturation (SaO_2), but is uncommon in COPD (64).

One major cause of hypercapnea in COPD, as of hypoxia, is the alveolar hypoventilation (64). Ventilation-perfusion imbalance (88), reduced respiratory drive (68) and inspiratory muscle weakness (20) have also been suggested as responsible factors for chronic hypercapnea.

Consequences of chronic hypoxia and hypercapnea

Hypoxia is often complicated by pulmonary hypertension, initially caused by vasoconstriction in the pulmonary circulation. CO_2 retention accentuates pulmonary arterial hypertension (77). Exercise and exacerbations of COPD also temporarily increase the arterial pressure (99). Pulmonary hypertension is responsible for cor pulmonale, with dilatation and hypertrophy of the right ventricle (140). Oedema is caused by an effect of hypoxia and hypercapnea on the kidneys (141). Chronic hypoxia also leads to an increase in blood volume and haematocrit as well as in red cell mass (77). The polycythaemia caused by hypoxia may increase pulmonary vascular resistance (3) and apparently is associated with a reduction of cerebral blood flow (175). Neurological complications can result from both hypoxia and hypercapnea (76, 171). A carbon dioxide narcosis with mental and behavioral changes, headache, somnolence and unconsciousness is described in the literature (171). Patients with COPD have been found to have a subclinical autonomic neuropathy which correlates with the severity of hypoxia (151). Chronic hypoxia and hypercapnea are also known to decrease the overall survival (120), and premature death is often caused by hypoxic cor pulmonale and respiratory failure.

Oxygen therapy

Oxygen has been used in medicine for nearly 200 years (136). The use of oxygen therapy in pulmonary medicine began in 1922, with Alvan Barach, who applied it in patients with lobar pneumonia and later in many other clinical situations. He stated that "oxygen therapy in suitable cases relieves difficult breathing, restores strength and helps reduce the swelling in the patient's legs and back" (15). His special interest was the use of oxygen for relief of dyspnoea during activity (134). Barach and Cotes and Gilson (16) were the first to develop portable oxygen devices, in the mid-1950s.

One of the first studies to evaluate the effectiveness of long-term oxygen therapy (LTOT) was undertaken in Denver in 1965 (109). It was designed to study hypoxaemic COPD patients with reversible pulmonary hypertension and polycythaemia. The patients displayed a remarkable improvement in exercise tolerance and general sense of well-being after only one month of oxygen treatment. One year later Abraham and co-workers (1) reported effects of oxygen similar to those observed by the Denver group. These two investigations set the stage for broader oxygen treatment and further studies in home oxygen therapy.

An important advance was made when electrically powered oxygen concentrators became available. Oxygen concentrators separate O_2 from NO_2 in the ambient air either by a molecular sieve or by a semi-permeable membrane. This system is quite convenient from the standpoint of a continuous oxygen supply. Liquid oxygen technology has also advanced considerably. One of the greatest advantages of the liquid system is its portability (134).

Two randomized controlled trials published in the early 1980s demonstrated the benefit of long-term oxygen therapy in hypoxic chronic COPD, namely the NOTT study (127) and the MRC study (119). In the NOTT study continuous oxygen therapy for 18 hours per day was found to improve survival as compared with nocturnal oxygen therapy for 12 hours. The MRC study showed that oxygen therapy for a minimum of 15 hours per day improved survival compared with no oxygen therapy. Some oxygen appeared to be better than none, but more appeared to be even better. These two studies established that LTOT improves the chances of survival of COPD patients with cor pulmonale. A Swedish study in unselected COPD patients receiving LTOT also showed improved survival, although the survival rates were markedly lower than those in the NOTT and MRC study patients (156). The two-year actuarial survival in patients with COPD was 54%. The study showed that the WHO performance status was the best predictor of survival. However, when the selection criteria of the NOTT and MRC studies were applied to the Swedish patients, the survival was similar. In Sweden, with a population of 8.4 million, approximately 1 400 patients are currently receiving LTOT (1.1.1993 Kerstin Ström, personal communication).

Current guidelines for the use of LTOT in COPD patients have been issued by the Swedish Society of Chest Medicine (154), among other authorities. The indication for LTOT is hypoxia when breathing air and PaO_2 less than 7.0-7.5 kPa in a steady state (according to NOTT and MRC), or signs of cor pulmonale or a haematocrit >50% and room air PaO_2 around 7.5 kPa.

LTOT is given for most of the 24-hour day, although the daily requirement of oxygen has been stated to be at least 15 hours. The treatment is potentially for the rest of the patient's life, although Levi-Valensi et al (108) found that a substantial number of patients (45 %) using O₂ did not require further oxygen therapy when tested again one to three months after initiation of this treatment.

Effects of long-term oxygen therapy

As stated earlier, LTOT has been proved to add substantially to the length of life of hypoxic patients with COPD (NOTT and MRC trials). Moreover, if oxygen therapy is prolonged over several years, it has been shown to reverse the progression of pulmonary hypertension (47), although the magnitude of the effect is moderate. LTOT reverses the process of secondary polycythaemia (NOTT and MRC) and reduces the total red cell mass and haematocrit (125) and the tendency towards oedema (112). Supplemental oxygen has been shown to improve exercise tolerance in hypoxic COPD patients (174). A possible mechanism of this response is that O₂ decreases the ventilatory drive and the sense of dyspnoea (53). Swinburn and colleagues (159) have demonstrated that supplemental oxygen reduces breathlessness at rest in hypoxaemic patients with COPD. Oxygen also improves ventilatory muscle function (37). Walter O'Donahue (130) has observed that O₂ improves gas exchange in some COPD patients. The improved oxygenation was observed when after several months of treatment the patients were breathing ambient air, an observation in accordance with that of Levi-Valensi (108). This beneficial effect is probably due to improved ventilation-perfusion matching (130).

Risks of oxygen therapy

Once a patient develops chronic hypercapnea, the regulation of ventilation tends to become defective and the PCO₂ tends to become unstable. The therapeutic use of oxygen entails the risk of adverse reactions in patients with high PCO₂, i.e. "blue bloaters". When the PaO₂ is raised by oxygen therapy, part of the drive to breathe may be lost, resulting in further hypoventilation and a further rise in the carbon dioxide level (66).

There is a good correlation between respiratory response to CO₂ and resting PaCO₂, when breathing air. The lower the CO₂ sensitivity the higher the resting PaCO₂ (145). Lopez-Majano et al (111) have also found that the rise in PaCO₂ after oxygen therapy correlates with the initial degree of hypoxia and hypercapnea. The higher the PaCO₂ level when breathing air, the greater the rise in PaCO₂ after oxygen administration. It has also been established in several studies that significant CO₂ retention is more likely to occur in COPD patients with very low PaO₂ values (27, 111). CO₂ retention is also a much more pronounced response to O₂ administration in patients with acute exacerbation than in the same patients when stable (27, 145).

The risks of oxygen therapy in chronic hypoxic and hypercapnic COPD are low, and CO₂ narcosis is seldom seen in these patients. Nevertheless, even when oxygen is given under controlled conditions with low flow, hypercapnea often complicates the treatment. In some

patients mechanical ventilation may be needed, not for hypoxia but for hypercapnea and poorly compensated respiratory acidosis.

Non-invasive methods for treating hypercapnea

A concomitant rise in PaCO_2 sometimes prevents the administration of oxygen in amounts sufficient to maintain an adequate level of oxygenation. It is therefore desirable to prevent an increase in CO_2 tension by not allowing the CO_2 elimination to decrease as a result of oxygen treatment. This could be done by increasing the alveolar ventilation, e.g. by increasing V_T or increasing the sensitivity of the respiratory centre.

Kolaczowski et al (101) observed increased oxygenation with use of a "respiration assistance technique". The goal was to assist complete expiration by compressing the chest wall and abdomen. An increase in oxygen saturation was seen up to 45 minutes after cessation of the treatment. However, the CO_2 elimination was not measured.

Pursed lips breathing (PLB), performed as expiration against pursed lips, is a strategy employed by many COPD patients. Previously reported responses to PLB are a decrease in arterial CO_2 (123, 161), an increase in arterial oxygenation and a change in the breathing pattern (33). The data suggest that PLB improves arterial blood gases by increasing V_T and decreasing the respiratory rate (123). The effects of PLB are, however, maintained for only a short time.

PLB is a predecessor to many modern techniques for applying positive expiratory pressure to the airways. Positive expiratory pressure (PEP), which is mainly used for re-expanding atelectasis and for clearing the lungs from secretion (163), has also been found to improve the oxygenation (59). Continuous positive airway pressure (CPAP) was described for the treatment of COPD by Barach (15). Several studies have focused on blood gases with the use of this therapeutic method. CPAP has been found to result in a decrease in CO_2 (16, 19, 160), an increase in oxygenation (49) and improvement of inspiratory muscle efficiency (75). However, in a study of Barat (17) it resulted in a small increase in PaCO_2 . A decreased ventilatory drive and a decrease in the inspiratory work of breathing has also been observed (150). The effects of PEP and CPAP are, like those of PLB, only of short duration.

The physiological mechanisms in PLB, PEP and CPAP are somewhat similar. They are believed to increase the end-expiratory transpulmonary pressure and to improve the distribution of ventilation by re-expanding collapsed lung tissue. This presumably by collateral reinflation (5).

Patients can also lower their PaCO_2 to normal or below by voluntarily hyperventilating (73) or by physical exercise (65). Robin and O'Neill (143) noted that many hypercapnic COPD patients are able to normalize their PaCO_2 if the ventilation is voluntarily increased.

Quality of life in chronic obstructive pulmonary disease

As the disease progressively worsens, the signs and symptoms will become more pronounced, and the patient's quality of life becomes severely impaired (117, 118). Prigatano et al (137) conclude from their study that the severity of the disease correlates with the reduced quality of life, measured with the Sickness Impact Profile (SIP). Dudley and co-workers (56) claim that patients with COPD are often apathetic and withdrawn, because of their inability to express emotion. These patients are also found to have significant mood dysfunction (117, 137), and depression has been described by several authors (110, 137). Studies in hypoxaemic COPD patients have shown that these patients have impaired neuropsychological function such as loss of memory as well as loss of cognitive function. COPD is also known to restrict the daily activities of life and the levels of exercise (137). A further deterioration of the quality of life is seen in association with hypoxia (118). In the NOTT study small improvements in the quality of life were observed after one year of LTOT (102). A study conducted in Finland showed improvement in coping skills after 6 months of this therapy (104).

MATERIAL AND METHODS

Subjects and study design

Fifty-eight asthmatic subjects (35 men and 23 women) arriving at the emergency room for treatment of an acute asthmatic attack were investigated (95). Their mean age was 61 years (range 22 to 84). All the patients had a previous diagnosis of asthma, i.e. a previous history of variable dyspnoea, wheezing and response to β_2 agonists. All of them also had a recorded airway reversibility of at least 20%, as measured previously from the change in PEF or FEV₁ after β_2 agonist treatment. Patients with very severe acute asthma, 4 and 5 on Hedstrand's asthma severity scale, were excluded. The patients were randomized to receive either treatment with a combination of inhaled terbutaline and ipratropium (n=37) or subcutaneously injected terbutaline and intravenous aminophylline (n=21). On arrival the severity of the asthmatic attack was ranked according to Hedstrand's asthma severity scale. The patients estimated their sense of dyspnoea according to Borg's 10-graded scale. Measurements were made of the airflow (PEF and FEV₁), blood pressure, pulse rate and respiratory frequency. Changes in PEF and FEV₁ were expressed as absolute values, in per cent of the patient's predicted value (78, 80) and in per cent of the baseline value. The measurements were repeated 30, 60 and 150 minutes after the start of the emergency asthma treatment.

Studies (58, 85) comprised 26 patients (6 men and 20 women) with chronic, well controlled mild to moderate bronchial asthma. All patients had a recorded airway reversibility of at least 20% as measured by a change in PEF after β_2 agonist treatment. FEV₁ was 63% of the predicted value, when the patients were not receiving bronchodilator therapy. Their ages varied between 23 and 58 years (mean 41 years). Out of the 26 subjects, 17 showed a fall in PEF by more than 15% after the pre-programme exercise test. The initial PEF value was compared with the value after cycling. These patients were considered to have EIA. All 26 patients participated in a 10-week

rehabilitation programme. They carried out physical training five times weekly during the first two weeks of the programme and then continued exercising twice a week.

Each 45-minute training session, which took place in an indoor swimming pool consisted of a warming-up period, interval training and a cooling-down period. The target heart rate during the training was 80-90% of the predicted maximum heart rate. The patients were tested at the start and after 2, 6 and 10 weeks according to a specific schedule.

A subsample of seven patients out of the 26 were chosen to serve as their own controls, which meant that they were also studied 10 weeks prior to the rehabilitation programme.

Fifteen patients (8 men and 7 women) with RI were studied (83). Ten of them had COPD, three had post-tuberculous thoracic abnormalities and two had bronchiectasis as the underlying disease. All the patients had hypoxia and hypercapnea and were treated with oxygen therapy. Their mean age was 66 years (range 50 to 83 years). The treatments compared were thoracic compressions (combined with PLB) and PEP, which were applied on two consecutive days in cross-over order. The effects on respiration were evaluated using transcutaneous measurements of O₂ and CO₂. The study was a short-term study, in which a single treatment of thoracic compressions and PEP were compared.

Nine patients (4 men and 5 women) with stable COPD and chronic hypoxia and hypercapnea were studied (84). At the start the mean PaO₂ was 8.6 kPa and mean PaCO₂ the same, 8.6 kPa. Blood gases were measured in samples taken when the patients were breathing oxygen. All were on LTOT. FEV₁ was less than 32% of the predicted in all the patients. Their ages ranged from 60 to 81 years (mean 69 years). PEP and nasal CPAP were each given for three days in random order once every hour during the day and three times overnight. The effects of the treatments were compared with those in a 3-day period in which the patients had no specific treatment for CO₂ elimination. The long-term effects were evaluated on the basis of the arterial blood gases on the third day of treatment. The blood gases were measured at 11 p.m. and 07 a.m. The short-term effects of a single PEP, CPAP and hyperventilation manoeuvre were assessed by transcutaneous measurements of O₂, CO₂ and SO₂.

Additional data concerning a group of 14 normal, healthy subjects are presented in the results below. Six male and eight female subjects aged 19 to 58 years, were chosen from the medical staff. They underwent transcutaneous monitoring during the same PEP and hyperventilation manoeuvres as the COPD patients.

Forty-one patients (16 men and 25 women), aged 49 to 85 years (mean 69 yrs) were studied (155). All of them were being treated with LTOT according to the Swedish guidelines for patient selection for oxygen therapy. All the patients were enrolled in the Swedish Oxygen Register. Eighteen patients were using high-pressure gas cylinders and 23 oxygen concentrators. The quality of life was measured using a Sickness Impact Profile (SIP) questionnaire. A questionnaire

(66 questions) concerning the ability to handle the oxygen equipment, their sense of well-being and their social habits were also administered.

A population study of 112 women (mean age 57 years) conducted in 1980-1981 in Göteborg served as a reference group (12)

Lung function tests

Spirometry was performed with a body plethysmograph (Jaeger Masterlab body 175 050) for measurement of lung volumes and specific airway conductance (sGaw), a wedge spirometer (Ohio) for recording of flow-volume curves, and a pneumotachograph with a linearity in flow rate between 0-12 l/sec (Fleisch) connected to a CO (Catharometer) and He infrared light cell analyser for measurement of the diffusion capacity of CO (DLCO). From the flow-volume curve the forced expiratory volume (FVC), the maximal expiratory flow (MEF), flow at 75% of FVC (FEF₇₅) and flow at 25% of FVC (FEF₂₅) were determined. Reference values were obtained from Hedenström (78,79,80).

PEF was measured with a Mini-Wright peak flow meter (58, 85, 95). FEV₁ was recorded with a portable bellows spirometer (Vitalograph) (95) and Vitalograph-alpha spirometry (Buckingham, England) (58, 85).

Assessment of exertion and dyspnoea (58, 85, 95)

The subjects were asked to estimate the magnitude of their perceived exertion and breathlessness by means of a Borg category scale. We used a 10-graded Borg's scale, where zero (0) stands for nothing at all and 10 for maximal (29, 30).

Classification of asthma severity (95)

The severity of the asthma was classified by a consultant physician when the patients arrived at the hospital with an acute asthmatic attack. Hedstrand's asthma severity scale was used for ranking the attack. On this scale the attack is scored from 0 to 5 on the basis of the clinical signs of asthma (81).

Exercise tests (58,85)

Cycle ergometry testing with ECG was performed at the laboratory of clinical physiology. The test was a maximal exercise test using progressive load increments. An electromagnetically braked cycle was used (Rodby RE 900).

A simplified sub-maximal exercise test was performed on a cycle ergometer with a mechanical friction load (Cardionics weight-braked ergometer, type 992), using a constant pedalling rate (50 rounds/min). The work load was adjusted individually and was kept constant during the 6-minute cycling period.

The load was chosen so as to achieve a heart rate of 130-160 beats/minute after 6 minutes, and the chosen work load was maintained during the remaining tests (177).

A 12-minute walking test was carried out in a hospital corridor 100 m long, with the aim of measuring the distance the patients could walk during this 12 minutes. The patients were instructed to walk as far as they could (116).

Asthma questionnaire (58, 85)

A study-specific questionnaire with five items was constructed in order to measure the subjective severity of the asthma symptoms and the patients' attitude towards their asthma. A further purpose was to assess the ability to work and exercise. The subjects responded to each item on a 10 cm visual analogue scale (VAS) (54).

Twenty-nine asthmatic subjects from another hospital (Örebro Regional Hospital) completed the same questionnaire twice with one week in between in order to test the questionnaire for reliability. The reliability (r_{11}) was tested with the Spearman rank correlation test and was found to vary between 0.68 and 0.87.

Arterial blood gas analysis (84)

Arterial blood samples were taken while the patients were receiving continuous oxygen from nasal prongs or from a CPAP mask. PO_2 and PCO_2 were measured with a blood gas analyser ABL 300 (Radiometer, Copenhagen) and SO_2 with an OSM 3 analyser (Radiometer, Copenhagen). The body position was chosen individually, either sitting or supine, but was the same on all occasions.

Hyperventilation (84)

Hyperventilation was performed for 2 minutes, taking 20 maximal breaths per minute. A metronome was used and the manoeuvre was carried out on the third day of the first period.

Non-invasive methods for blood gas analysis (83, 84)

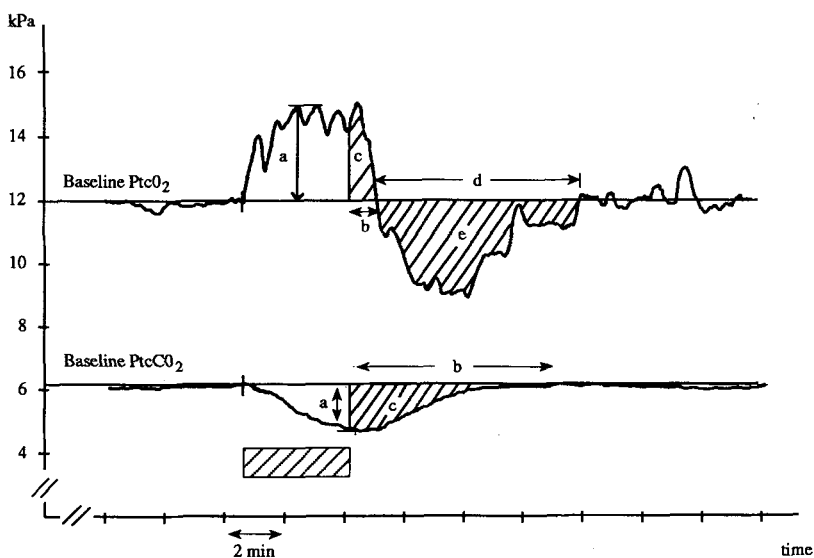
Transcutaneous partial pressure of CO_2 ($PtcCO_2$) was measured with a pH electrode (System E 5230/TCM 20) calibrated with 5% CO_2 . Transcutaneous partial pressure of O_2 ($PtcO_2$) was measured with the same electrode system (System E 5242/TCM 2) (Radiometer, Copenhagen). $PtcCO_2$ and $PtcO_2$ were recorded continuously on a paper recorder with a paper speed of 2 cm/min (TCM 200) (Radiometer, Copenhagen). Both electrodes were attached to the upper anterior part of the thorax, in the mid-subclavian region. The electrodes were heated to a temperature of +44 °C, and were switched to the other side of the thorax after four to five hours (83, 84).

transcutaneous O₂ saturation (SpO₂) was measured using a Biox 3700 (Ohmeda, Colorado) or a pulse oximeter (Radiometer, Copenhagen). According to the manufacturers, these pulse oximeters have identical algorithms. The probe was attached to the patient's finger. SpO₂ was recorded continuously on a paper recorder with a paper speed of 5 cm/min (84).

Analysis of transcutaneous tracings (83, 84)

The tracings of PtcCO₂ and PtcO₂ were analysed as shown in **Figure 1**, using an Apple digitizer. SpO₂ was evaluated likewise. The treatment period is shown in a shaded box.

Figure 1



Analysed (83, 84)

- a. Initial response (kPa)
- b. Duration of change (min)

Analysed (84)

- c. Remaining effect (mm²)
- d. Duration of late response (min)
- e. Area size of late response (mm²)

Quality of life and coping capacity (155)

The SIP questionnaire, adapted to Swedish conditions by Marianne Sullivan (157), was used for measurement of the quality of life. SIP is a standardized general health status questionnaire made up of 136 items designed to assess sickness-related behavioral dysfunction. The items are grouped into 12 categories, of which four cover a psychosocial dimension and three others a physical dimension. Summary scores are provided for both dimensions, for an overall behavioral dysfunction as well as for each of the 12 categories. The individual patient scores are expressed in per cent of the maximal possible scores of dysfunction. The higher the percentage, the more severe the indicated dysfunction (23).

A study-specific questionnaire was used to measure the coping capacity. Both questionnaires were answered during an interview conducted by a person who was not associated with the care of the patient in question.

Statistical methods

The methods used to test differences, relationships and correlations are described in detail in each paper.

Ethics

The protocols of all studies were approved by the Ethics Committee of the Medical Faculty of Uppsala University. All participants gave their informed consent.

RESULTS AND DISCUSSION

Dyspnoea in acute asthma: relationship with other clinical and physiological variables (95)

Results

There was a significant decrease in bronchial obstruction 150 minutes after the start of the treatment. On arrival at the hospital the mean FEV₁ and PEF were 35% and 43% of the predicted values, respectively. After 150 minutes FEV₁ and PEF had increased to 50% and 61% of the predicted. The scores for the estimated sense of dyspnoea decreased from 6 to 3 during this period. The mean heart rate decreased after the inhalation treatment by 8 beats/min, and increased after the injection treatment by 11 beats/min ($p<0.001$). The mean breathing rate decreased by 3 breaths/min with inhalation treatment, but remained unchanged after injection of terbutaline and theophylline ($p<0.01$). There was no significant difference between the two treatment groups before or after the treatment either in airflow obstruction or in dyspnoea. In this study the results were not separated according to treatment group.

On arrival, the dyspnoea correlated most closely with the Hedstrand asthma severity score ($r=0.51$ $p<0.001$). There was also a significant correlation with breathing rate ($r=0.38$ $p<0.01$) and PEF measured as per cent of the predicted value ($r=-0.28$ $p<0.05$). FEV₁, as well as the other variables measured, showed no significant correlation with dyspnoea. The change in dyspnoea score correlated most closely with FEV₁ when expressed as per cent of the baseline value ($r=-0.30$ after 30 min, $r=-0.42$ after 60 min and $r=-0.34$ after 150 min). An intraindividual correlation coefficient of more than 0.80 between the decrease in dyspnoea score and the increase in FEV₁ was found in 74% of the patients.

Patients with both a decrease in dyspnoea of ≥ 3 categories and an increase in FEV₁ of $>20\%$ from baseline were considered to have a high response. Thirty-one patients (53%) fulfilled these conditions. A high response in dyspnoea and a low response in FEV₁ were found in 11 patients

(19%), while nine of the patients (16%) had an increase in FEV₁ of >20% but a decrease in dyspnoea of < 3 categories. Seven patients (12%) had a low response in both variables.

Discussion

Dyspnoea constitutes the primary reason for the asthmatic patient to seek help from the emergency room. Effects of bronchodilating drugs on the airflow in acute asthma are routinely measured and are thought to indicate whether bronchodilator therapy is likely to be subjectively beneficial (9). However, the measurements of airflow obstruction do not necessarily predict this outcome (173).

Three variables correlated significantly with dyspnoea on admission to the emergency room: the asthma severity score measured with Hedstrand's scale, the breathing rate, and PEF in per cent of the predicted. FEV₁ did not correlate significantly with dyspnoea. In this study the breathing rate was more closely correlated to dyspnoea than were PEF and FEV₁. This indicates that estimations of the clinical severity of the asthma and the breathing rate might be useful as a complement to airflow measurements in the clinical management of acute asthma. The improvement in dyspnoea during the treatment correlated most closely with the improvement in FEV₁ expressed as per cent of the baseline value. The correlation between change in dyspnoea and airflow obstruction was low, though statistically significant, regardless of how the change was expressed. There was a close intraindividual correlation between change in dyspnoea and change airflow obstruction, while the interindividual variation was quite large.

The poor correlation between PEF and FEV₁ as measured by routine spirometry and dyspnoea as assessed by a Borg scale could be due to several causes. PEF and FEV₁ are used in evaluating changes in asthma severity and in the response to bronchodilating drugs. They are considered to measure airflow obstruction in the large airways. Dyspnoea, being subjective, is difficult to describe and quantify. It is uncertain whether dyspnoea is a single basic sensation or a combination of several different sensations depending upon the cause. The airway resistance due to obstruction could be one cause of the sense of dyspnoea. Another is secondary hyperinflation of the lungs (89). However, it is more likely that the obstruction in the small airways giving a ventilation-perfusion mismatch and a reduced compliance causes the sense of dyspnoea, rather than airflow obstruction in the large airways (103). The poor correlation between the spirometric values (PEF and FEV₁) and the dyspnoea could be due to the fact that they were measuring measure different factors.

Another possible reason for the poor relationship between the increase in PEF and FEV₁ and the decrease in the dyspnoea score is that in asthmatic patients the respiratory sensory mechanism becomes adapted and that the level of adaptation varies between different patients (28). Our patients had a rather low perception of the severity of their asthma. The patients with a low response in FEV₁ without being aware of dyspnoeic symptoms might be in particular danger. The impaired perception may lead to underestimation of the severity of asthma, resulting in undertreatment.

High-intensity physical training in adult asthmatic persons - a rehabilitation programme (58)
Improvement of asthma and exercise-induced bronchoconstriction in adults undergoing ten weeks of high-intensity training (85)

Results

The 26 patients attended all the training sessions during the first two weeks. After this time 22 patients continued with the regular fitness training. The heart rate during the initial two weeks was at least 80% of HR_{max} in all subjects during the 16-minute interval training. In spite of a low initial fitness level and unfamiliarity with physical training, the patients appreciated the exercise and none of them were injured. They were also able to maintain a very high intensity during the training session without experiencing asthma symptoms.

There were significant bronchodilation during the 45-minute training session. The PEF increase after the warming-up period was 5% , with a further increase of 2% during the interval period ($p < 0.001$). The PEF values during the exercise were compared with the initial PEF value. The patients with EIA (fall in PEF $> 15\%$) showed the same PEF increase as those without EIA. The bronchodilation that occurred during the training session lasted more than one hour post-exercise. Two hours after termination of the exercise there was a slight decrease in PEF, which persisted for a further 3 hours. The PEF values were compared with the initial PEF value. The reduction was at most 6%, and this was noted 5 hours after cessation of training.

There was significant improvements in the mean baseline values of FEV_1 (0.3 L), FEF_{25} (0.1 L) and FEF_{75} (0.8 L) after the 10-week training period as compared with the pre-training values.

The mean walking distance increased significantly from 1,350 m before the rehabilitation to 1,486 m after six weeks and to 1,461 m after 10 weeks. The initial walking distance had no or only a weak correlation with the spirometric values, the strongest being with FEV_1 ($r = 0.45$, $p < 0.05$) after β_2 agonist treatment. After 10 weeks the correlation between FEV_1 and walking distance was $r = 0.48$ ($p < 0.05$)

Compared with the start of the 10-week programme, the mean heart rate at the end of the six-minute cycle test at a constant work load was significantly decreased by 9 beats/minute after 6 weeks of training and by 12 beats/min after 10 weeks. The score for perceived exertion also decreased from 8 at the start to 6 after 6 and 10 weeks. Moreover, the mean heart rate measured at 5, 10 and 15 minutes after the cycle test was significantly lower after the rehabilitation programme.

During the cycle test there was an increase in PEF, i.e. bronchodilation had occurred. When the cycling was stopped, bronchoconstriction took over and the maximal decrease in PEF was recorded 10-15 minutes after the cessation of cycling. The fall in PEF was 18% before the training programme and 12% after the 10 weeks of exercise. Of the 17 subjects with EIA before the training programme, only three had EIA after 10 weeks of training.

Some differences were found between the PEF values obtained after the training session in the pool at 2 weeks and those obtained after the 6-minute cycling test at 2 weeks. After completion of the training session in the pool, there was an increase in PEF, which was 10% after an interval of 30 minutes ($p<0.01$). After cycling there was a fall in PEF, which amounted to 7% after 30 minutes ($p<0.05$).

The difference between the decrease in PEF 30 minutes after the cycle ergometry test and the increase 30 minutes after the training session was significant ($p<0.01$).

The study-specific questionnaire showed that from being afraid of exerting themselves in the beginning, the patients felt no restriction to maximal exercise (VAS from 3 to 1 cm, $p<0.05$) or fear of experiencing breathlessness (VAS 3 to 1 cm, $p<0.05$) after 2 weeks of training. The improvements in these two items remained constant during the rest of the programme. The patients also estimated that their asthma symptoms had decreased significantly throughout the study (VAS 5 cm at the start, 4 cm after 2 weeks, 3 cm after 6 and 10 weeks, $p<0.05$).

Ten weeks after termination of the training programme there had been only three occasions among the 26 subjects when acute medical care for asthma was required, compared with nine occasions during the 10 weeks before the training period.

Discussion

The initial physical fitness was lower in 15 of our subjects than in a Swedish population of the same age (128). In order to increase not only the patients' well-being but also their physical fitness, the training programme was planned to comprise a certain work load. Since it was intended that the physical training should affect cardiovascular function, the intensity of the training was essential. Our target heart rate was 80-90% of predicted HR_{max} , although the greatest training effect is seen at HR_{max} of above 90% (170). The heart rate was measured at the training each day during the initial two weeks. During these two weeks all patients had a heart rate of at least 80% of HR_{max} during the interval training. Although we had a target heart rate, during the first two weeks the patients were encouraged to exercise to tolerance limit in the high-intensity intervals, in order to give them the experience of being able to exercise maximally. A mean of 93% of HR_{max} was found during one interval training session (day seven). After experiencing confidence and safeness when exercising at an almost maximal intensity level, the patients rather chose a higher intensity level during the interval training in the remaining 8 weeks of the rehabilitation programme. After the initial two weeks, the heart rate was not checked during the rehabilitation programme. The intensity level was measured only from the patients' estimation of their perceived exertion. They were encouraged to exercise to scores of at least 7 to 8 on the Borg scale, as the mean heart rate of 93% of HR_{max} corresponded to 8 on the scale. During the remaining training sessions the exertion was 7 to 10 on the 10-grade Borg scale. As the heart rate of 50% of HR_{max} roughly corresponds to a level at which the person is slightly out of breath (177), 80-90% of HR_{max} was associated with considerable dyspnoea.

Asthmatic patients often have difficulty in distinguishing between the normal dyspnoea due to exercise and that of bronchoconstriction (89). The maximal training level thus also served the purpose of teaching the patients the difference.

Bronchodilation occurred during the 45-minute training session, and lasted more than one hour after the session had ended. Furthermore, no EIA or late reaction was observed, as the PEF decrease 5 hours after the end of the session was at the most only 6% (97). The PEF values were compared with the initial PEF value. Only one patient needed supplementary medication after the session. She received this on two occasions, 3 and 4 hours after the training had ended.

These asthmatic patients were thus capable of exercising at a high intensity and there were no asthma symptoms during or after the physical exercise. In fact, the exercise caused long- standing bronchodilation. The difference between the dilation after the training session and the constriction after the cycle test could be due to progressively increasing refractoriness after the training session (146). After completion of the training session in the pool, there was an increase in PEF, which amounted to 10% 30 minutes after the end of the session ($p < 0.01$). The design of the exercise programme, with a long, slow warming-up period (139), interval training (71) and a cooling-down period could (115) cause this refractoriness. Premedication with a β_2 agonist is also of importance.

The circulatory parameters, measured at the cycle test and the 12-minute walking test, showed improvements after only six weeks of training, with no further increase after 10 weeks. Lung function, expressed as FEV₁, FEF₂₅ and FEF₇₅, was improved after the 10-week training period, indicating an attenuation of airflow obstruction. Although significant regarding lung function, the improvements were small and probably of no clinical relevance. Of the 17 EIA patients only three had EIA after 10 weeks, and thus the airway reactivity and the propensity to develop EIA were obviously reduced, although in two of the patients without EIA initially EIA occurred after 10 weeks. To judge from the fact that the severity of the asthma was decreased and the patients needed less acute asthma care after the rehabilitation programme, the training also had a positive effect on the underlying asthma disease.

Chest Physiotherapy: Evaluation by Transcutaneous Blood Gas Monitoring (83)

Effects of Positive Expiratory Pressure (PEP), Continuous Positive Airway Pressure (CPAP) and Hyperventilation in COPD Patients with Chronic Hypercapnea (84)

Results

Thoracic compressions and PEP gave the same mean decrease in PtcCO₂ (0.6 ± 0.4 kPa) and mean increase in PtcO₂ (0.7 ± 0.7). The individual variation in both PtcCO₂ and PtcO₂ was large. Three patterns of treatment effect could be recognized: 1) no response to treatment, 2) a small initial response with a long duration (>20 min), and 3) a large initial response but of a short duration (Figure 1).

Ten of the patients showed a decrease in $PtcCO_2$ of at least 0.5 kPa when treated with thoracic compressions and eight when treated with PEP. Some of the patients had no decreases in $PtcCO_2$ but an increase in $PtcO_2$, one treated with thoracic compressions and two with PEP. Some patients, two with each treatment, even showed a decrease in $PtcO_2$. There were considerable individual changes, and in two-thirds of the patients $PtcCO_2$ decreased both with thoracic compressions and PEP. In many cases, however, the decrease was of very short duration.

Even treatments with continuous positive airway pressure (CPAP) and hyperventilation were able to improve the blood gases (84). The mean initial response showed that PEP was as effective as hyperventilation in decreasing $PtcCO_2$, which was lowered to mean value of 0.5 and 0.7 kPa respectively. CPAP decreased $PtcCO_2$ significantly less ($p < 0.05$) than PEP and hyperventilation. The decrease was only 0.1 kPa.

The duration of change and the remaining effect (Figure 1) displayed the same pattern as the initial response. CPAP differed significantly ($p < 0.01$) from the other two methods. The duration of change was 3.8 min with PEP and 3.5 min with hyperventilation. The decrease in $PtcCO_2$ lasted only 1.0 min with CPAP treatment.

$PtcCO_2$ decreased in all nine studied patients with PEP and hyperventilation, but only in five patients with CPAP. In fact, the remaining four patients showed an increase in the $PtcCO_2$. However, the increase was only 0.4 kPa at the most and lasted for only a few minutes. There were no late responses in the COPD patients.

There was no significant difference between the three methods in the effects on $PtcO_2$ and SpO_2 . On the other hand, $PtcO_2$ and SpO_2 increased in more patients with PEP and CPAP than with hyperventilation.

The night-time treatments administered at 12 midnight, 3 a.m. and 6 a.m. gave the same pattern of $PtcCO_2$ as the treatments in the daytime. The mean initial response in $PtcCO_2$ was significantly ($p < 0.01$) greater (0.6 kPa) with PEP than with CPAP (0.3 kPa). The initial nocturnal response in SpO_2 showed a significant difference in favour of CPAP treatment.

The resting arterial blood gases, used as a basis for evaluation of the effects of the 3-day treatment periods, were measured at the beginning (11 p.m.) and at the end (7 a.m.) of each recording night. There was a significant ($p < 0.01$) increase in $PaCO_2$ (1.2 kPa) and a decrease in PaO_2 and SaO_2 during the night (from 11 p.m. to 7 a.m.) without treatment. $PaCO_2$ also increased with both therapies, by 1.3 kPa ($p < 0.01$) with PEP and 0.6 kPa with CPAP. There were no significant differences in the oxygenation variables between 11 p.m. and 7 a.m. except with CPAP, when SaO_2 was lower in the morning than in the evening.

In normal subjects, both PEP and hyperventilation led to an increase in the elimination of carbon dioxide. Hyperventilation was more effective than PEP, the mean initial response and the duration

of the change of $P_{t}CO_2$ being 2.2 kPa and 7.0 min with hyperventilation and 1.4 kPa and 5.2 min with PEP. $P_{t}CO_2$ and SpO_2 increased with both methods. With both forms of treatment there was a "late response", signified by a decrease in the oxygenation variables, in 13 of the 14 subjects. Both the duration and the "area size" of the late response were somewhat greater with hyperventilation than with PEP. With use of the hyperventilation manoeuvre, the late response was of significantly longer duration than the initial response.

Discussion

In these two studies, all the respiratory physiotherapeutic techniques employed (thoracic compression, PEP, CPAP and hyperventilation) resulted in an immediate and significant improvement in the blood gas variables $P_{t}CO_2$, $P_{a}CO_2$ and SpO_2 . Reduction of hypercapnea was the main purpose and it is concluded that the methods used decreased $P_{t}CO_2$ in the short term. This effect on PCO_2 should be brought about by effects of the treatments on hypoventilation and ventilation/perfusion mismatch, since these factors are main causes for hypercapnea in COPD. The treatment should increase the efficiency of ventilation.

PEP and CPAP are known to improve the efficacy of breathing by re-expanding collapsed lung tissue, presumably by collateral reinflation, and in this way they improve the distribution of gas and blood (5). PEP and CPAP also increase V_T and minute ventilation. It is suggested that PLB (used in treatment with thoracic compressions) may have an effect on respiration similar to those of PEP and CPAP (32). The decrease in transcutaneous CO_2 with use of PEP, CPAP and TC would then probably be due to an increase in intraluminal airway pressure and /or a change in the breathing pattern. As we did not measure either the airway pressure or the breathing pattern, it is difficult to decide the cause with certainty. Hyperventilation, where no resistance is added at the mouth, also decreased $P_{t}CO_2$ significantly. Thus an elevated intraluminal pressure is not necessary a prerequisite for a reduction of $P_{t}CO_2$. The effects of the respiratory methods used are probably therefore attributable to the changes in the breathing pattern (33). The methods result in a slower, deeper type of breathing, an increase in V_T , a decrease in the respiratory rate and more uniform emptying of different lung units.

The application of CPAP proved to be less effective in decreasing CO_2 than PEP and hyperventilation. There were also four patients in whom $P_{t}CO_2$ increased during the CPAP treatment. The additional load of the apparatus and the increased work of breathing could explain the increased CO_2 level with use of CPAP. The increased work of breathing probably expanded the lung volume and further diminished the alveolar hypoventilation.

Increased work of breathing also adds to patient discomfort and predisposes to respiratory muscle fatigue (86). In general, CPAP has been found to be effective in reducing the work of breathing and is associated with less work of breathing than PEP (32). However, complications of CPAP therapy have occurred when excessive loads have been used (32). Although the CPAP level in our study was only 7.5 cm H_2O , it resulted in further CO_2 retention in four patients. The decrease in $P_{t}CO_2$ in four patients treated with thoracic compressions or PEP (83) could also have been due to hyperinflation and inspiratory muscle fatigue produced by expiratory resistance (113).

PEP and CPAP increased oxygenation in the COPD patients (32). The slightly greater increase with CPAP treatment was probably due to the change from nasal prongs to a CPAP mask for oxygen administration. The SpO_2 increase would then be due to an increase in inspired oxygen (F_{IO_2}).

Although these two studies indicate that the gas exchange can be improved significantly for short periods, they do not point to any long-term effects. Thus we have failed to prove our hypothesis (84) that if these therapeutic methods decrease PCO_2 during a single manoeuvre, repeating their use will improve the ventilation and lead to greater CO_2 elimination during the 24 hours. Desaturation and an increase in carbon dioxide tension during the night were seen in these patients when not specifically treated for hypercapnea. The three-day treatment with PEP or CPAP did not alter this pattern. Nocturnal desaturations in COPD patients have also been observed in other studies, in spite of long-term oxygen therapy (39). Fluctuations in arterial blood gases have also been observed in normal subjects (25, 34). The rise in PCO_2 during the night is probably due to a change in the responsiveness of the respiratory centre and decreased ventilation. Our expectations of increasing the sensitivity of the respiratory centre, and by increasing the ventilation improving blood gases, were obviously not met by repeated PEP or CPAP treatment for three days.

"Late reactions", i.e. decreases in $PtcO_2$ and SpO_2 , after both PEP and hyperventilation were observed in normal subjects but not in the COPD patients. The effect in normal individuals is probably due to a reduction in respiratory drive as a result of the decrease in carbon dioxide tension. The mechanism is obviously not present in COPD patients, as these patients showed a constant increase in CO_2 tension.

Intermittent analyses of arterial blood gases only indicate the general respiratory condition. Continuous measurements of oxygen and carbon dioxide tensions using serial arterial punctures or an indwelling arterial cannula are difficult. Non-invasive measurements of $PtcO_2$, $PtcCO_2$ and SpO_2 demonstrate the changes in the arterial blood gases. The methods used in our study have been proven to have good accuracy and good correlation with blood gases (72, 164, 166). Furthermore, the absolute values were not used, but comparisons were made between treatment occasions and therapeutic methods. The error of the measurement, i.e. the accuracy and electrode delay, was the same on all occasions. We therefore consider that transcutaneous measurements reflect the effects of the different respiratory physiotherapeutic methods on blood gases.

Assessment of two oxygen treatment alternatives in the home (155)

Results

The patients on LTOT had higher dysfunction scores for the SIP categories as a whole than the reference group. The difference was significant for all categories except eating and emotional behaviour.

Figure 2

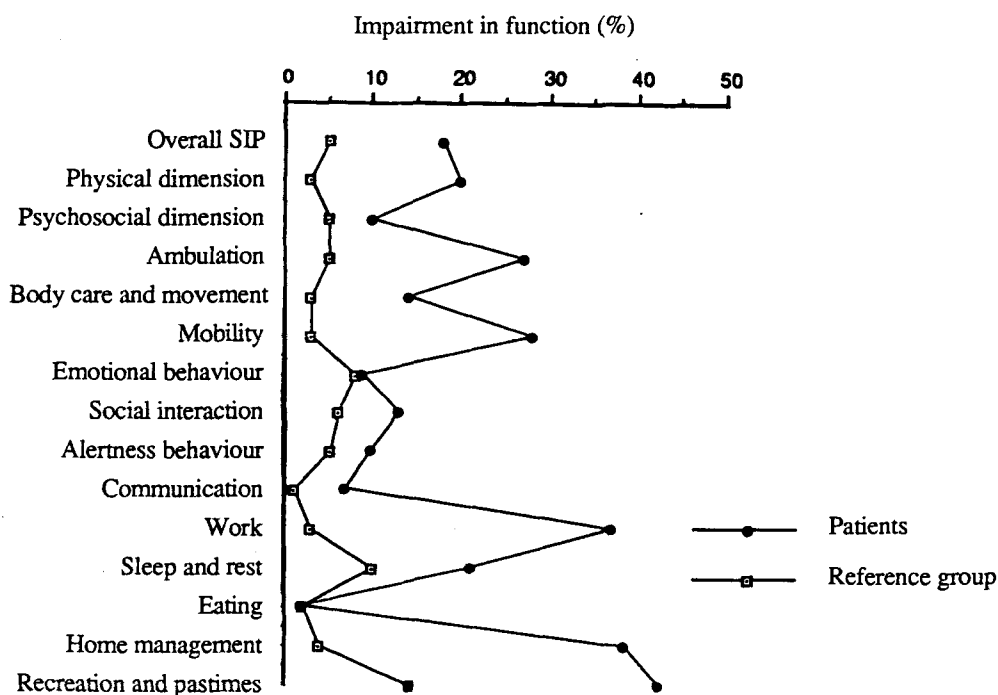


Figure 2 shows sickness-related behavioural dysfunction measured as SIP scores in patients receiving long-term oxygen therapy (n=41), compared with the reference group (Controls, n=112).

The greatest disability was found in the physical dimension - ambulation and mobility. The independent categories needing physical activity, namely working capacity, home management, and recreation and pastimes, were also greatly impaired. There were no statistically significant differences in the mean SIP scores between the patients using gas cylinders and those using a concentrator.

The ability to cope with the daily care of the oxygen equipment differed between the two treatment modalities. Sixteen patients managed to take care of the concentrator, but only eight patients managed the gas cylinders. Handling the small gas cylinders was equally difficult in both groups. The patients felt that the greatest disadvantage of oxygen treatment was that they were tied up to their equipment. The mobility of the two treatment groups was equally restricted. With few exceptions (3 patients), the patients felt that the treatment was of benefit and improved their sense of well-being. Despite the severe disease and the disadvantages of the treatment, 14 patients using gas cylinders and 21 patients using a concentrator felt satisfied with their lives.

Discussion

The results of the comparison between our 41 patients having oxygen treatment and the reference group showed that in the patient group the physical dimension was more impaired than the psychosocial dimension. The NOTT study (118) showed a similar degree of impairment in the physical dimension but greater impairment in the psychosocial dimension, compared with our study. In fact the NOTT study patients were more impaired in their psychosocial function than in physical activity. Prigatano and co-workers (137) found a degree of psychosocial impairment in hypoxaemic COPD patients equal to that in the NOTT study. The psychosocial dimension was again more impaired than the physical dimension in the study by Prigatano et al. The reason why Swedish COPD patients seem to be more physically impaired and patients in the United States more psychosocially impaired, is not known.

In spite of the benefit in terms of an improved sense of well-being, no significant improvement in the quality of life was found in COPD patients using LTOT. The NOTT patients showed equal impairment after six months of LTOT. From a study in Finland it was concluded that LTOT improves the psychosocial function in patients with severe COPD, though to a limited extent (104). This indicates that the quality of life is probably poor not because of hypoxaemia and oxygen treatment, but because of the respiratory disease itself. In our study the quality of life was not measured before LTOT was introduced. At the time of the study the patients with gas cylinders had been treated, on average, for 42 months and patients with a concentrator for 24 months. Although our patients preferred oxygen concentrators to gas cylinders, the overall quality of life was just as impaired in the two groups.

CONCLUDING REMARKS

Most patients primarily seek emergency room care for acute asthma because of dyspnoea, not for treatment of a specific disease. From the patient's point of view the most important is whether the treatment relieves his subjective sense of breathlessness or not. The effects of different treatments are most often measured by estimates of airflow obstruction. The question is how well the objective measurements correlate with the patient's sense of dyspnoea and the change in breathlessness during the treatment.

On admission to the emergency room, the patients' sense of dyspnoea as measured by the Borg scale correlated most closely with the scoring of the asthma severity by the receiving doctor. The scoring was done with the Hedstrand scale. Dyspnoea also correlated significantly with breathing rate and PEF measured as per cent of the predicted. FEV₁, heart rate and blood pressure showed no correlation with dyspnoea. The correlation between decrease in dyspnoea and decrease in airflow obstruction was low, although statistically significant, irrespective of how the change was expressed. The closest correlation was found with FEV₁ expressed as per cent of the baseline value. The poor correlation of dyspnoea with PEF and FEV₁ could be due to the fact that these variables measure different factors. PEF and FEV₁ measure the airflow obstruction in the large airways. The sensation of dyspnoea is probably caused by several factors. Secondary

overinflation of the lungs and thorax could be partly responsible. However, it is more likely to be caused by the obstruction in the small airways, leading to a ventilation-perfusion mismatch and reduced compliance, than to airflow obstruction in the large airways. This study indicates that assessments of airflow obstruction in the clinical management of asthma are of importance but should not be the only factors considered. The estimated clinical severity and the breathing rate, as well as the patient's subjective experience of dyspnoea, should be taken into account.

There is good evidence that adult persons with asthma are less fit than healthy persons of the same age. The fact that physical training improves not only the individual sense of well-being but also health, is well known and accepted. Several investigations have indicated that physical training can give improvement also in asthmatic persons. In spite of the knowledge of the benefits of regular physical training, asthmatic people are seldom seen to take part in exercise programmes. This could be due to the attitudes and the beliefs held by the patients concerning themselves, their illness and its treatment. A contributory factor is the lack of availability of suitable training programmes for asthmatic persons.

The 10-week rehabilitation programme in the pool was designed to train the patient as a whole. All patients managed the training without any injuries and could sustain a high intensity of at least 80% of the maximum heart rate during the intensive period of the training session without experiencing asthma symptoms. There was significant bronchodilation during the 45-minute training session. The bronchodilation lasted more than one hour post-exercise. Furthermore, no EIA or late reaction was observed. There was significant improvements in the mean baseline values of FEV₁, FEF₂₅ and FEF₇₅ after the 10-week training period as compared with the pre-training values. The improvement in lung function was small and probably is not of clinical relevance, but it indicates an attenuation in airflow obstruction. The circulatory parameters measured with the cycle test and the 12-minute walking test, showed that the benefits of the training programme occurred during the first six weeks of training, with no further increase in the rest of the 10-week period. The cycle ergometry test also showed that airway reactivity and the propensity to develop EIA had decreased during the rehabilitation programme. As the asthma was less severe and less acute asthma care was needed after the training period, it appears that the training also had a positive effect on the underlying asthma disease. The benefits of this training programme were probably attributable to two major factors. Firstly, the design of the training programme, with slow warming-up, interval training and a cooling-down period. This training principle made high-intensity training possible by progressively increasing the refractoriness to exercise during the programme. Secondly, the high intensity of the exercises, especially during the intensive intervals. This high intensity, which is essential for such training programmes, was certainly responsible for the cardiovascular effects. Physical exercise is therefore an appropriate form of treatment for adult asthmatic individuals.

Chronic hypercapnea is a relatively common condition in patients with far-advanced but stable respiratory insufficiency. Whether this increased CO₂ tension is deleterious, is unknown. Thus attempts to eliminate carbon dioxide in these COPD patients are not unequivocally desirable. In

fact the decrease in CO₂ could be detrimental by causing an increase in dyspnoea due to increased ventilatory drive. In order to determine the effects of CO₂ elimination in patients with respiratory insufficiency, methods which decrease CO₂ in the long term have to be procured. This was one of the reasons for these studies. Another reason was that we wanted to improve the oxygenation in hypoxic and hypercapnic patients by adequate supplementation with oxygen without running the risk of a further increase in the carbon dioxide level.

Our physiotherapeutic methods, i.e. thoracic compressions, PEP, CPAP and hyperventilation, all had a significant short-term effect on the blood gases as measured by non-invasive methods. In a comparison of thoracic compressions and PEP, we found that these two methods were equally effective in decreasing CO₂. Regarding the effects of PEP, CPAP and hyperventilation, PEP and hyperventilation were equally good in decreasing carbon dioxide. The effect of CPAP treatment was somewhat less pronounced. In fact the application of CPAP caused an increase in PtcCO₂ in four patients. An increased work of breathing causing a further decrease in hypoventilation, could have caused this increase in CO₂.

Unfortunately, these methods did not have a long-lasting effect on carbon dioxide elimination. Their regular use for three days did not improve the ventilation and result in greater CO₂ elimination during the 24 hours. PaCO₂ measured in the morning (7 a.m.) showed an increase compared with the evening value (11 p.m.), despite the treatment with PEP or CPAP. Our data indicate that the effects were not of clinical significance and there is no justification for treating stable hypercapnic COPD patients with these methods.

Long-term oxygen therapy is an expensive and complicated way of treating hypoxia. It is widely used, however, in stable hypoxic COPD patients, mainly because it is known to increase the survival in these patients. LTOT also has other positive effects. It reverses the progression of pulmonary hypertension and secondary polycythaemia. From the patient's point of view it is proposed that the supplementary oxygen improves exercise tolerance and reduces breathlessness at rest. Patients with severe COPD have an impaired quality of life, which is further deteriorated in the presence of hypoxia. LTOT appears to give only minor improvements in the quality of life. In order to have the intended effects, LTOT should be given for most of the 24-hour day and should be life-long. However, this continuous attachment to the oxygen source might have a negative physical and psychosocial impact on the patient.

In our study the 41 patients had had LTOT for at least six months. Measurements of the quality of life by SIP showed that the patients had higher dysfunction scores than the reference group. The greatest disability was found in the physical dimension and in the independent variables requiring physical activity. The two modes of oxygen delivery, compressed gas cylinders and concentrators, did not differ in their effect on the quality of life, although concentrators were easier to handle by the patients. The mobility of the two treatment groups was equally restricted. With few exceptions, the patients felt that the treatment was of benefit and improved their sense of well-being. Despite the severe disease and the disadvantages of the treatment, most of the patients were satisfied with their lives. Without doubt LTOT should be instituted if it is expected to prolong life. Since the treatment does not improve quality of life, it should not be recommended otherwise.

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