Induction of metabolic acidosis in chronic hypercapnic COPD patients

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Induction of metabolic acidosis in chronic hypercapnic COPD patients

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Abbreviations

ATP	Adenosine Triphosphate
BE	Base Excess
BMI	Body Mass Index
BODE	Survival Grading System
CA	Carbonic Anhydrase
CO_2	Carbon Dioxide
COPD	Chronic Obstructive Pulmonary Disease
FEV_1	Forced Expiratory Volume in-one-second
FRC	Functional Residual Capacity
H^+	Hydrogen ion
HCO_3^-	Bicarbonate
HCVR	Hypercapnic Ventilatory Response
HR	Hazard Ratio
HVR	Hypoxic Ventilatory Response
LTOT	Long Term Oxygen Therapy
NH_4Cl	Ammonium Chloride
6MWD	Six-Minute Walking Distance
$PaCO_2$	Arterial Carbon Dioxide Tension
PaO_2	Arterial Oxygen Tension
$P_e$max	Maximal Expiratory Mouth Pressure
$P_i$max	Maximal Inspiratory Mouth Pressure
R_{aw}	Airway Resistance
RV	Residual Volume
sG_{aw}	Specific Airway Conductance
TLC	Total Lung Capacity
VC	Vital Capacity
VO_2	Oxygen Consumption
VQ	Ventilation/Perfusion

Chapter 1

Hypotheses and aims of the thesis

1.1 Metabolic acidosis and hypercapnia in COPD patients

Arterial carbon dioxide (CO_2) retention, know as *hypercapnia*, in patients with severe chronic obstructive pulmonary disease (COPD) has been related to a poor survival of these patients.[1-3] Hypercapnia is an expression of alveolar hypoventilation resulting from an imbalance between load on the ventilatory pump versus its capacity.[4] The load on the ventilatory pump is determined by airway resistance and the degree of hyperinflation.[4-6] The capacity of the pump depends, among others, on chemoreceptor drive[7,8], the strength and endurance of its respiratory muscles[5,6], and on the acid-base status of the muscles.

In the regulation of the ventilation there is a close interaction between the lungs, the kidneys and the acid-base equilibrium, as indicated by the Henderson-Hasselbalch equation[9]:

$$pH = pK + \log [HCO_3^-]/(0.03 \cdot PCO_2)$$

Hypercapnia causes a respiratory acidosis, but when CO_2 retention becomes chronic, the kidneys retain bicarbonate [HCO_3^-] and pH tends to normalize. Acidosis, however, stimulates both central and peripheral chemoreceptors, increasing the ventilation and lowering the arterial carbon dioxide tension ($PaCO_2$).[7,8] Induction of an acute metabolic acidosis, causing a further drop in arterial pH, could, therefore, in chronic hypercapnic COPD patients increase the ventilatory drive and could diminish hypercapnia.

However, it is still controversial whether chronic hypercapnia should be treated at all. Due to an efficient renal compensatory mechanism, hypercapnia seems to be quite well tolerated.[10,11] Hypercapnia may even be considered “permissive” in COPD patients that require mechanical ventilation during an acute exacerbation of their disease. In these patients controlled mechanical alveolar hypoventilation is given priority over an increase in hyperinflation.[12] If hypercapnia is short-term (< 24 hours) and within limits (< 79.0 mmHg) the benefits of the limited hyperinflation (i.e. improved VQ mismatch) seem to be greater than the relatively negative effects of hypercapnia.[12] Some authors even suggest that chronic hypercapnia in severe COPD patients may be a physiological adaptation that may lead to better survival rates. By

allowing *P*aCO_2 to rise, work of breathing can be decreased.[13,14] On the other hand, the increased CO_2 level may not be so harmless. Chronic hypercapnia affects, among others, cellular tissue[12], the cardiovascular system (impaired contractility of cardiac and vascular smooth muscle[15], decrease in systemic vascular resistance[16]), and the central nervous system (cerebral vasodilatation, increased intra-cranial pressure).[12] Especially when hypercapnia is accompanied by hypoxemia these effects seem to be more outspoken.[12] Treating hypercapnic COPD patients with long-term oxygen therapy (LTOT) may improve their survival, but does not decrease CO_2 retention.[17,18] Therefore, other systemic effects may still be present.

1.2 Aims of the thesis

The survival of chronic hypercapnic COPD patients is less than in normocapnic ones. The aim in **chapter three** was to determine the parameters that predict survival of COPD patients with chronic hypercapnia. It was studied whether the variables that are known to be associated with a poor prognosis in *normocapnic* COPD patients (e.g. severity of airway obstruction, body mass index, smoking status, and the presence of co-morbidity), also predict survival of COPD patients once they have become *chronically hypercapnic*. It was also hypothesized that a lowered respiratory muscle strength and a diminished ventilatory response to CO_2 could possibly predict survival of chronic hypercapnic COPD patients, since these factors could be responsible for maintaining hypercapnia.

It was theorized that by inducing a metabolic acidosis, and subsequently a ventilatory response, hypercapnia could be diminished and that eventually survival of these patients could possibly improve. However, some previous studies have indicated that metabolic acidosis might decrease respiratory and peripheral muscle strength[19-21], which could cause a further increase in CO_2 retention. In **chapter four** the effects of acute metabolic acidosis, induced by ammonium chloride (NH_4Cl), in a large population of respectively healthy subjects, stable asthma patients and stable normocapnic COPD patients are reported. The effects of acute metabolic acidosis on respiratory and peripheral muscle function, airway resistance and on blood gas values were studied. In **chapter five** the acute, chronic and acute-on-chronic effects of metabolic acidosis, induced by NH_4Cl, in chronic hypercapnic COPD patients were

described, because as mentioned before, theoretically the alveolar ventilation of these patients could benefit from a metabolic acidosis. Respiratory and peripheral muscle function, airway resistance, blood gas values, ventilatory responses to CO_2 (HCVR) and O_2 (HVR), and exercise tolerance by the 6-minute walking distance (6MWD) were measured.

The purpose of the study in **chapter six** was to evaluate the long-term effects of metabolic acidosis, induced by acetazolamide, in chronic hypercapnic COPD patients. To be able to improve survival of these patients, $PaCO_2$ should be permanently reduced. This implicates that metabolic acidosis should be induced during longer periods of time. However, previous studies of acetazolamide have only evaluated short-term effects.[22,23] Therefore, it was interesting to investigate 1) the long-term effects of acetazolamide on the acid-base equilibrium (does the body compensate the chronic metabolic acidosis?) and 2) the effects of chronic metabolic acidosis on respiratory and peripheral muscle function, airway resistance, blood gas values, ventilatory responses to CO_2 (HCVR) and O_2 (HVR), and exercise tolerance measured by the 6-minute walking distance (6MWD).

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Chapter 2

General introduction

2.1 Survival in COPD

Chronic obstructive pulmonary disease (COPD) is defined as *a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.*[1] The reserve capacity of the normal lung at rest is enormous (in sedentary subjects, the lungs can sustain on oxygen consumption (VO_2) that is increased 10-fold during exercise). Therefore, in early stages of COPD there is usually a lack of symptoms. In advanced stages, however, the mismatch between ventilation and perfusion (VQ mismatch), the limited alveolar to end-capillary diffusion for oxygen and intrapulmonary shunting-like phenomena[2-6] result in a low arterial oxygen tension (hypoxemia). Alveolar hypoventilation causes CO_2 retention (hypercapnia). Extreme VQ mismatch can worsen the hypercapnia. This latter stage of COPD is classified as severe (stage IV).[1]

Unlike other major chronic diseases, COPD has not shown declines in mortality over the past twenty years. Estimates indicate that by the year 2020, COPD might become the fifth cause of combined morbidity and mortality worldwide.[7-10] The increasing prevalence of COPD, the chronic progressive character of the disease, and the fact that advanced stages of COPD are often complicated by co-morbid diseases, make COPD a major health problem.[7]

As in all chronic diseases, the prevalence of COPD is strongly associated with age.[8,11] Survival of COPD patients is usually related to their forced expiratory volume in-one-second (FEV_1).[11,12,13] An important risk factor for developing COPD is cigarette smoking.[11] The influence of smoking on survival of COPD patients, however, occurs mainly in late stages of the disease, since mortality in COPD patients with post bronchodilator FEV_1 > 50% predicted is only slightly greater than in healthy smokers.[11] A review of the literature demonstrated that smoking cessation slows the rate of decline of FEV_1 and improves survival, even at advanced stages of COPD.[11,14]

COPD is a disease with a multidimensional character. This is also reflected in all parameters that have been associated with an impaired survival of COPD patients. Gender[8], a lower body mass index (BMI)[15-18], $alpha_1$-antitrypsine deficiency[2], airway hyper responsiveness[2], the presence of co-morbidities[19,20], and a lower socioeconomic status[2], but also röntgenologic parameters like a diminished CT density of the lung[21] are all related to an increased mortality risk. Celli et al.[18] were

able to predict survival of COPD patients by means of a grading system (BODE), based on the subject's BMI, degree of airflow Obstruction, severity of Dyspnoea, and Exercise-capacity measured by the six-minute walking distance (6MWD).

In severe COPD, the presence of hypoxemia[22-28] and hypercapnia[29-31] are also associated with an increased mortality. Although, some controversy still exists concerning the latter.[32-34] Use of long-term oxygen therapy (LTOT) has been shown to improve survival, especially in severe hypoxemic COPD patients.[22] In severe hypoxemic COPD patients with the presence of hypercapnia and cor pulmonale, administration of LTOT still improves survival, although carbon dioxide retention was not diminished.[23,34] Costello et al.[31] studied a cohort of 85 COPD patients that had been consecutively admitted to the hospital for an acute exacerbation of the disease. The cohort was followed during 5 years after having been divided into three groups, respectively normocapnic (age 69.1 ± 8.0 years; FEV_1 36.4 ± 16.2% predicted), reversible hypercapnic (age 69.1 ± 8.4 years; FEV_1 32.7 ± 13.3%), and chronic hypercapnic (age 68.4 ± 3.9 years; FEV_1 26.6 ± 7.0%) COPD patients. Five-year survival was significantly lower in chronic hypercapnic COPD patients (11%), whereas survival between normocapnic (33%) and reversible hypercapnic (28%) patients did not differ significantly.[31] Saryal et al.[32] did not find a difference in survival between chronic hypercapnic, respectively normocapnic and reversible hypercapnic COPD patients after 10 years of follow-up.

2.2 Hypercapnia and the control of breathing in COPD

2.2.1 Hypercapnic respiratory failure in COPD

Hypercapnic respiratory failure in COPD is the result of alveolar hypoventilation, due to an imbalance between the load on the ventilatory pump, versus its capacity. The processes that affect ventilation in COPD lead to an increase in ventilatory demand, whereas the ventilatory capacity is limited. Progressive airway obstruction causes an increase in airway resistance and hyperinflation, which leads to a higher load on the ventilatory pump.[4,35,36] Reduction of the ventilatory capacity in COPD is caused by a lower chemoreceptor drive[37,38], impaired respiratory muscle function[35,36], and the acid-base status of the respiratory muscles. Consequently, oxygen uptake is low and CO_2 washout is diminished.

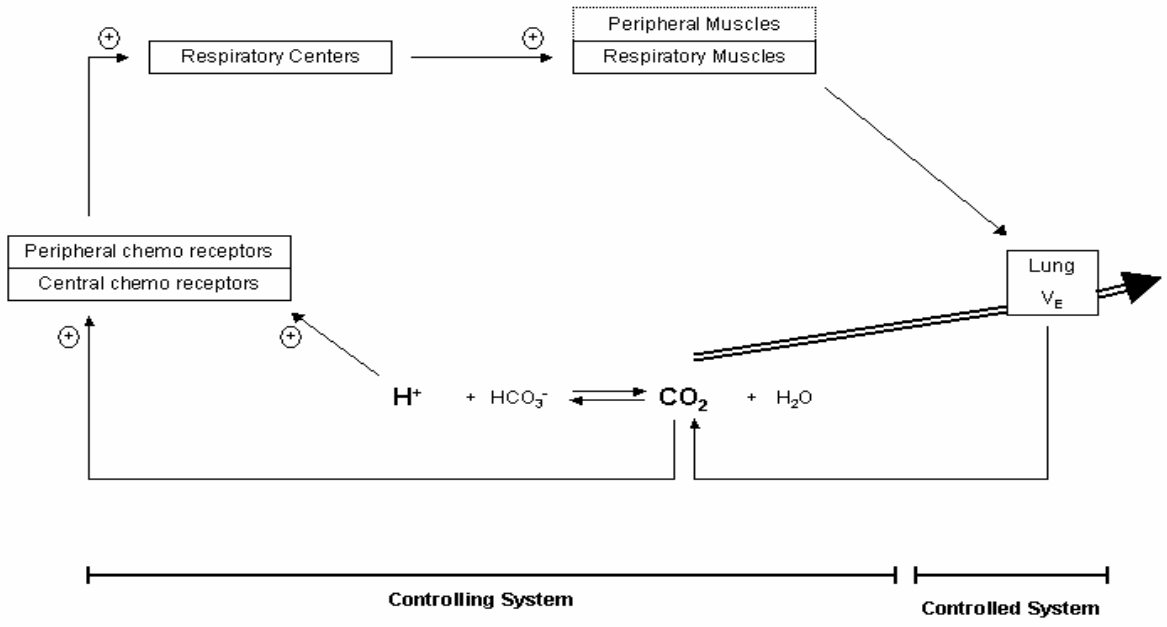
2.2.2 Hypercapnia and the control of breathing

The respiratory system is an important instrument in the homeostasis of the acid-base equilibrium of the body, as described by the Henderson-Hasselbalch equation.[39] Under normal conditions, the 'control of breathing' guarantees a constant arterial carbon dioxide tension ($PaCO_2$) and a constant pH.[40] CO_2 retention shifts the equilibrium of bicarbonate [HCO_3^-] and increases the hydrogen ion [H^+] concentration, causing a respiratory acidosis.

The respiratory control system can be divided into a controlled system and a controlling system. In a "closed-loop" situation, the output of one sub-system is related to the input of the other sub-system.[40] The controlling system has an input of arterial blood gas values (i.e. pH, $PaCO_2$, PaO_2) and an output of ventilatory parameters (e.g. minute ventilation). The controlled system has ventilation as input and arterial blood gas values as output parameters.[40] (Figure 1)

An increase in $PaCO_2$, and the subsequent decrease in pH, influence the respiratory control system by stimulating the peripheral and central chemoreceptors.[40] Stimulation of these receptors increases the respiratory drive, causing an increase in minute ventilation and eventually leading to an increased CO_2 washout. (Figure 1)

Figure 1. *The relationship between ventilation and the acid-base equilibrium.*



2.2.3 Ventilatory responses to hypercapnia and hypoxemia.

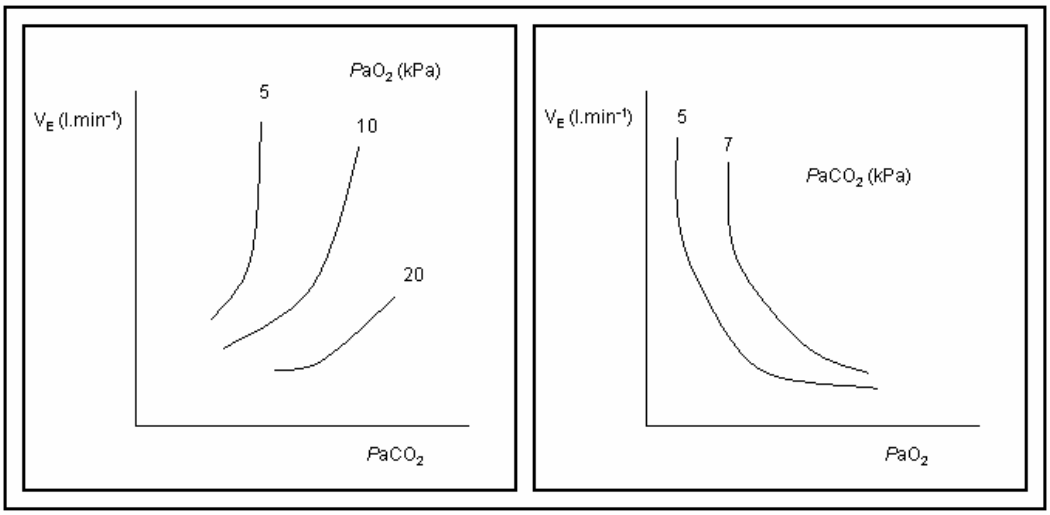
The ventilatory response curves to hypercapnia or hypoxemia quantify the relationship between input and output of the controlling system.

The peripheral chemoreceptors include the aortic and the carotid bodies. These receptors respond to changes in arterial oxygen tension (PaO_2) and also act on differences in pH and $PaCO_2$.[41] Ventilatory responses to hypoxia (HVR) can be measured by delivering a hypoxic gas mixture to the patient via a rebreathing apparatus, while $PaCO_2$ levels are kept constant.[42] The induced progressive hypoxemia stimulates the peripheral chemoreceptors, resulting in an increase of the respiratory drive.

The central chemoreceptors are located on the ventral surface of the medulla and are mainly responsible for maintaining the acid-base equilibrium in the brain.[43] Changes in $PaCO_2$ stimulate these chemoreceptors in about 90 seconds, since CO_2 passes the blood-brain membrane rapidly. This causes an instant shift in the local acid-base equilibrium. On the other hand, responses of the central chemoreceptors to metabolic acid-base shifts are much slower.[44] The ventilatory response to hypercapnia (HCVR) is for 70-80% effectuated by activation of central chemoreceptors. This response can be assessed by three different techniques. The most frequently used techniques are the rebreathing method by Read et al.[45] and the so-called steady-state technique.[40] In the latter, $PaCO_2$ is brought to a higher steady-state level during 7-10 minutes, e.g. by breathing via a closed system apparatus.[40] The third is the dynamic end-tidal forcing technique which is a complex technique to assess HCVR that can distinguish central and peripheral chemoreceptor components in the ventilatory response to hypercapnia.[40]

Moreover, it has been demonstrated that there is an interaction of between HCVR and HVR when hypoxemia and hypercapnia are both present, as demonstrated in figure 2.[46]

Figure 2. *The interaction between hypoxemia and hypercapnia on ventilation.*



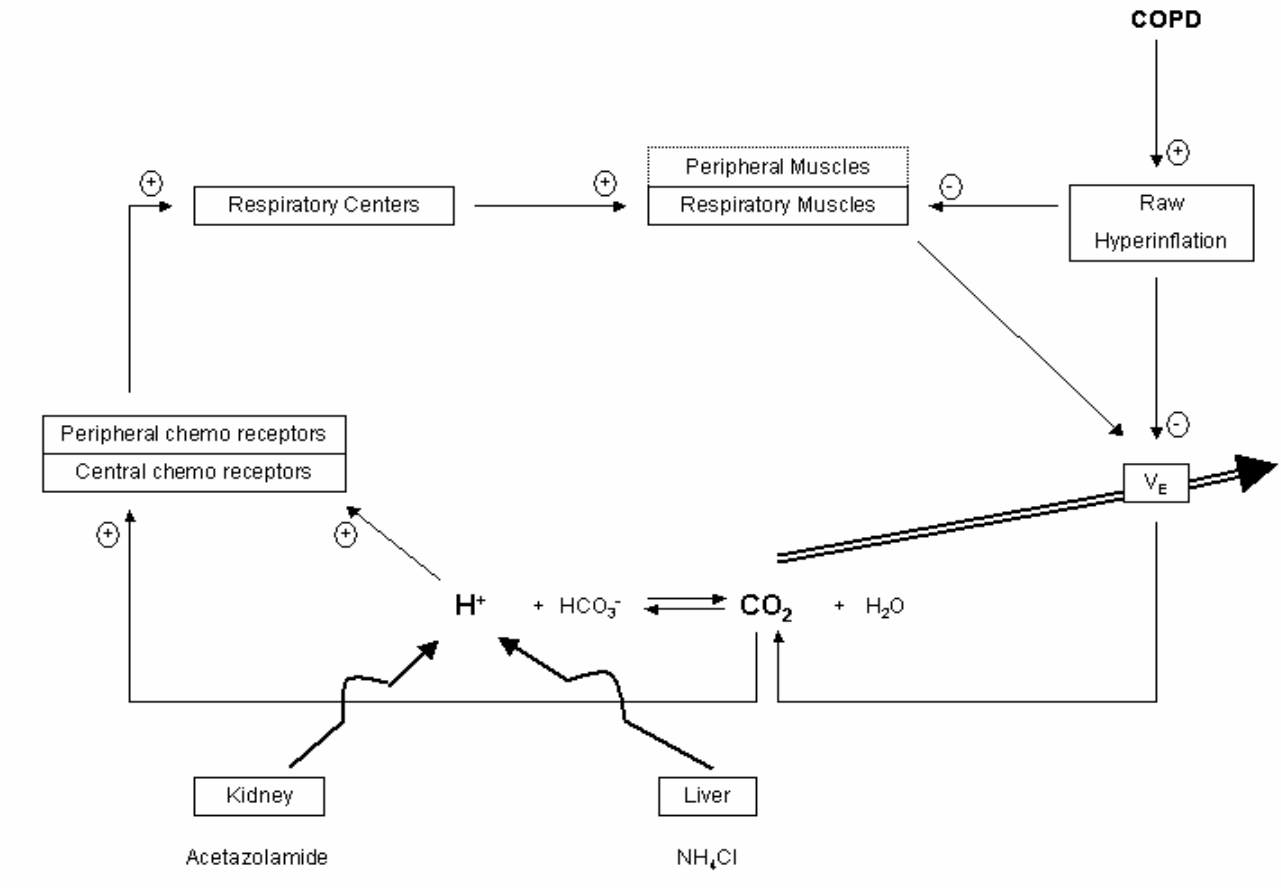
2.3 Respiratory stimulation

When respiratory acidosis becomes chronic, due to chronic hypercapnia, the kidney retains [HCO_3^-], leading to higher serum levels and higher cerebrospinal [HCO_3^-] concentration. This decreases [H^+] concentration, more or less normalizes pH, and lowers the central respiratory drive.[47] Moreover, in COPD patients with a chronic CO_2 retention, the ventilatory response to hypercapnia is often diminished.[37,38,48] Chronic hypercapnia has also been associated with a decreased cerebrovascular CO_2 responsiveness.[49,50] Van de Ven et al.[50] demonstrated that in chronic hypercapnic COPD patients the ventilatory as well as the cerebrovascular response to CO_2 was diminished as compared to normocapnic COPD patients.

The pattern of breathing in hypercapnic COPD patients is characterized by a low tidal volume and a high breathing frequency.[51-53] This leads to an increased dead space ventilation, a diminished alveolar ventilation and, subsequently to further CO_2 retention.[51,54] Some hypoxemic COPD patients become hypercapnic when oxygen is administrated.[55,56] In these patients the HCVR, as well as the HVR are both blunted.[57]

Hypercapnia and hypoxemia in severe COPD patients may be reduced by administrating drugs that induce a metabolic acidosis. By causing a fall in the numerator of the Henderson-Hasselbalch equation, a further fall in pH occurs, augmenting the drive to breathe in these patients. (Figure 3) However, side effects and an additional metabolic acidosis have kept these drugs from officially being recommended in daily practice. Furthermore, one may question whether the ventilation of the hypercapnic COPD patient does adequately respond to extra H^+ ions, considering the fact that these patients have decreased ventilatory responses and impaired effector organs (i.e. impaired respiratory muscle function).

Figure 3. *The effect of acetazolamide and NH_4Cl on ventilation.*



2.3.1. Acetazolamide

Acetazolamide is a reversible inhibitor of the enzyme carbonic anhydrase (CA) and an effective respiratory stimulant.[58-61] Its use as a respiratory stimulant has been successful in respiratory failure in COPD[60,62], and in sleep-related breathing problems.[63]

The enzyme is present widespread throughout the body, including the kidney[64,65], red cells[65,66], capillary vascular endothelium, brain[64], and the central and peripheral chemoreceptors.[64] A low dose of acetazolamide is sufficient to (partially) block the enzyme in these tissues. Due to complex interactions between these tissues, the actual respiratory response is not always easy to predict.[60,67] The main increase in respiratory drive by acetazolamide, however, is thought to be caused by induction of a metabolic acidosis, due to inhibition of renal tubular [H^+] excretion with increased urinary [HCO_3^-] excretion.[59,64,67-70] (Figure 3)

The ensuing increase in ventilation generally reduces the arterial carbon dioxide tension by 5.3-6.0 mmHg.[60,64] A significant improvement of PaO_2 was also found.[71] In a study in healthy subjects, the slope of the HCVR was not altered by acetazolamide, but a parallel shift of the CO_2 response curves to the left was noted.[72] Short-term administration of acetazolamide in COPD patients with hypercapnic ventilatory failure, reduced $PaCO_2$ by 5.3 mmHg and increased PaO_2 by 7.5 mmHg.[62]

However, due to the complexity of the enzyme, acetazolamide may have side effects, e.g. headache, depression, paresthesiae, hypokalemia, and gastrointestinal disturbances. Therefore, it is not yet clear whether the physiological improvements are associated with clinical benefit.[73]

2.3.2 Ammonium Chloride

Ammonium chloride (NH_4Cl) also acts as a respiratory stimulant by inducing a metabolic acidosis.[74-77] (Figure 3) In healthy subjects the minute ventilation increases, due to a rise in breathing frequency.[76] Moreover, NH_4Cl increases the HVR in healthy subjects, suggesting that NH_4Cl acts mainly on peripheral chemoreceptors.[76] Induction of metabolic acidosis by NH_4Cl did not have a stimulating effect on the cerebrovascular response in healthy subjects.[78,79]

2.3.3 Other respiratory stimulants

2.3.3.1 PROGESTERONE

The synthetic hormone medroxyprogesterone acetate increases the ventilatory drive[68,80], leading to a fall in $PaCO_2$ of about 5.0 mmHg in healthy males.[68] Progesterone has been proven an effective respiratory stimulant in COPD patients.[62,81,82] In a group of stable hypercapnic COPD patients, medroxyprogesterone acetate significantly decreased daytime $PaCO_2$.[62] However, no changes were found in daytime PaO_2, or in nocturnal oxygen saturation.[62]

2.3.3.2 ALMITRINE BISMESYLATE

Almitrine bismesylate stimulates the peripheral chemoreceptors, but has no effect on central chemoreceptors.[67] It can almost double the peripheral ventilatory sensitivity to CO_2 during hyperoxia, as well as during mild hypoxia.[83] In a study among 89 hypoxic COPD patients, almitrine treatment significantly increased PaO_2 from 56.3 to 61.5 mmHg, and significantly decreased $PaCO_2$ from 45.8 to 43.5 mmHg.[84] In comparison to oxygen suppletion, however, almitrine bismesylate did not have any effect on survival.[84]

2.3.3.3 DOXAPRAM

Doxapram stimulates peripheral chemoreceptors.[67] Used as a respiratory stimulant in COPD patients with a respiratory insufficiency, it is only slightly superior to placebo in preventing blood gas deterioration.[85]

2.4 Acidosis and muscle dysfunction in COPD

2.4.1 Muscle dysfunction in COPD

Muscle function can be expressed in terms of strength[86-88] and endurance.[89-91] COPD is a disease that has been associated with general impaired muscle function[37,92-97], although this is still under debate.[98]

2.4.1.1 RESPIRATORY MUSCLE DYSFUNCTION IN COPD

The altered respiratory muscle function in COPD patients is mainly secondary to the mechanical disadvantages caused by hyperinflation. The force generating capacity of (respiratory) muscles is determined by muscle length. The optimal length for

generating pressure depends, among others, on the intrinsic length-tension relationship of the muscle. Hyperinflation shortens mainly the diaphragm, displacing it on a less advantageous position on the length-tension curve, and making it more vulnerable for exhaustion during exercise.[93,99-106] The continuous increased workload on respiratory muscles in COPD has been associated with changes in respiratory muscle fibre structure[100] and muscle metabolism.[107-110] Changes in respiratory muscle structure include a shift from fast-twitch (glycolytic) type IIb fibres into slow-twitch (oxidative) type I fibres. With increasing workload energy demand of the muscles also rises. When oxygen demand overcomes the oxygen supply, local metabolic changes occur.[107,110]

2.4.1.2 PERIPHERAL MUSCLE DYSFUNCTION IN COPD

The dyspnoea due to increasing airway obstruction leads to a decrease in daily activities of COPD patients. The impairment of skeletal muscle strength in COPD could be due to this deconditioning.[111,112] In COPD patients the maximal strength of the quadriceps muscle can be reduced by 20-30%, compared to age-matched healthy subjects.[111] Changes in peripheral muscle structure in COPD include muscle atrophy, and a shift from type I fibres towards type IIb fibres.[113,114] As in respiratory muscles, the metabolic capacity of the peripheral muscles is also altered: i.e. a low intracellular pH, a reduced adenosine triphosphate (ATP), lower oxidative enzymes, a lower phosphocreatinine as well as a higher lactate concentration.[114-117]

2.4.2 Acidosis and muscle dysfunction

A decrease the pH diminishes the influx of calcium into the myocyte, reduces the affinity of troponine for calcium and increases the calcium binding to the sarcoplasmatic reticulum.[118,119] Therefore, it has been suggested that acidosis negatively affects contractility of striated muscles by decreasing the regeneration of ATP via the glycolytic pathway.[118,119] Reduction of the ATP resynthesis makes the muscle more prone for fatigue during exercise. Although a relationship between pH, muscle contractility and fatigue has been recognized earlier, the underlying mechanism is not yet completely understood.[120,121] Results of previous investigations involving acidosis and muscle function are conflicting.

Metabolic acidosis has shown to decrease muscle contractile properties of myocardial[122], and peripheral muscles.[123] In dogs, metabolic acidosis decreased

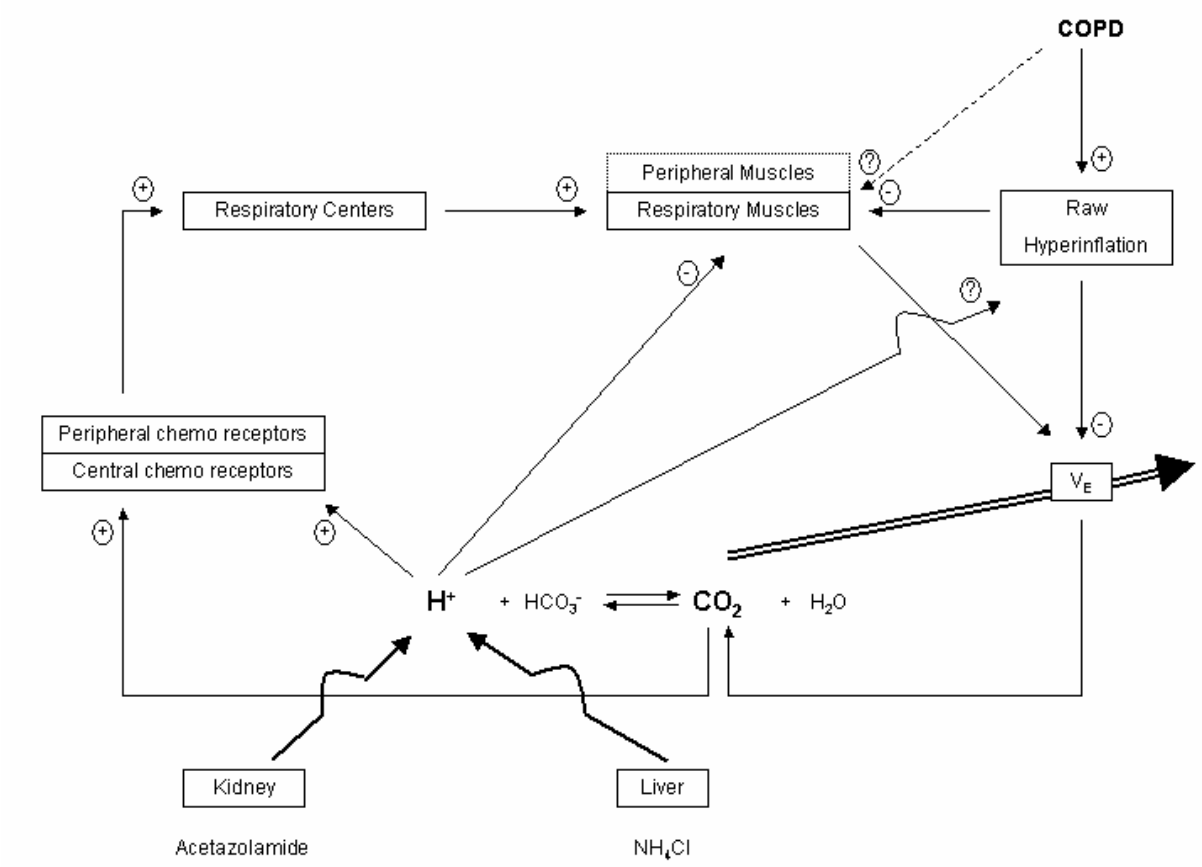
diaphragm contractility in one study[124], whereas in another study neither diaphragm contractility, nor skeletal muscle function was altered.[125] This was also found in the study by Brijker et al.[126] among healthy subjects. After induction of acute metabolic acidosis, no changes were found in muscle strength of either respiratory muscles or peripheral muscles.[126] The effect of metabolic acidosis on muscle endurance has not been investigated yet.

Controversy has also been found in studies investigating the effect of *respiratory* acidosis on muscle contractility. In some studies respiratory acidosis reduced contractility of the diaphragm[118,125,127,128], whereas in others it did not.[129,130] Juan et al.[127] studied four healthy men and found that acute respiratory acidosis, equivalent to a $PaCO_2$ of 54.0 mmHg, decreased not only diaphragm contractility at rest, but also diaphragm endurance time. Ameredes et al.[129] studied seven healthy subjects during normocapnia ($PaCO_2$ 41.3 mmHg), hypercapnia ($PaCO_2$ 52.5 mmHg), and hypocapnia $PaCO_2$ 26.3 mmHg). Maximum mouth pressure at rest, as well as the sustainable force output at the end of an endurance trial were not affected by changes in carbon dioxide tension.[129]

A shift in the acid-base equilibrium may not only influence muscle contractility of striated muscles, but also has an effect on bronchial smooth muscles. In normal[130] and asthmatic subjects respiratory acidosis has been associated with bronchodilatation and a subsequent decrease in airway resistance[131] Respiratory alkalosis caused bronchoconstriction in these subjects.[131] A significant increase in airway resistance was also found in metabolic alkalosis.[126] Metabolic acidosis showed a small, yet not statistically significant decrease in airway resistance.[126]

Severe COPD is often accompanied by respiratory acidosis, due to hypercapnic respiratory failure.[132] Whether there is an interaction between the impaired muscle function in COPD patients and this respiratory acidosis, has not yet been investigated. A model of the effect of metabolic acidosis on hypercapnia and muscle function is shown in figure 4.

Figure 4. *The effect of metabolic acidosis on hypercapnia in COPD patients.*



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Chapter 3

Survival of chronic hypercapnic COPD patients is predicted by smoking habits, co-morbidity, and hypoxemia

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3.1 Abstract

Chronic hypercapnia in patients with chronic obstructive pulmonary disease (COPD) has been associated with a poor prognosis. We hypothesized that, within this group of chronic hypercapnic COPD patients, factors that could mediate this hypercapnia, such as decreased maximum inspiratory mouth pressure ($P_i$max), decreased maximum expiratory mouth pressure ($P_e$max), and low hypercapnic ventilatory responses (HCVR), could be related to survival. Other parameters, such as arterial blood gas values, airway obstruction (FEV_1), body mass index (BMI), current smoking status, and the presence of co-morbidity were studied as well.

A cohort of 47 chronic hypercapnic COPD patients who had been recruited for short-term trials (1-3 weeks) in our institute was followed for 3.8 years on average. Survival was analyzed using Cox's proportional hazards model. The risk factors considered were analyzed, optimally adjusted for age and gender.

At the time of analysis 18 patients (10 male) were deceased. After adjusting for age and gender, $P_i$max, $P_e$max, and HCVR were not correlated with survival within this hypercapnic group. Current smoking (Hazard Ratio 7.0; 95%-CI [1.4 – 35.3]) and the presence of co-morbidity (HR 5.5; [1.7 – 18.7]) were associated with increased mortality. A higher arterial oxygen tension (PaO_2) affected survival positively (HR 0.6 per 5 mmHg; [0.4 –1.0]). Arterial carbon dioxide tension ($PaCO_2$) tended to be lower in survivors, but this did not reach statistical significance (HR 2.0 per 5 mmHg; [0.9 – 4.3]). FEV_1 and BMI were not significantly related with survival in hypercapnic COPD patients.

In chronic hypercapnic COPD patients only smoking status, the presence of co-morbidity, and PaO_2 level are significantly associated with survival. Airway obstruction, age, and BMI are known to be predictors of survival in COPD patients in general. However, these parameters do not seem to significantly affect survival once patients have become chronic hypercapnic.

Key Words: *Pulmonary diseases, chronic obstructive; Survival; Hypercapnia; Respiratory muscle function; Control of breathing*

3.2 Introduction

Chronic obstructive pulmonary disease (COPD) is an important cause of death and leads to a substantial disability.[1,2] By the year 2020, COPD might become the fifth-leading cause of combined mortality and disability worldwide.[3] Therefore, determining factors that might influence the course and prognosis of this disease is essential for making treatment decisions.

Several studies have been performed to establish parameters associated with an increased risk of death in COPD patients.[1,4-10] A low forced expiratory volume in-one-second (FEV_1)[6,11-13] and cigarette smoking are the most important factors related to mortality.[1,11,12,14-18] A number of other variables, such as hypercapnia, hypoxemia[19,20], body mass index (BMI)[5-7,9,11-13], environmental exposures, bronchial responsiveness, alpha-1-antitrypsin deficiency, lower social economic status[1,4], and the presence of co-morbidities[6,21] are also considered to be related to poor prognosis. Regarding treatment options, long-term oxygen therapy (LTOT) improves outcome in severely hypoxemic COPD patients.[22-24] Nevertheless, the course and prognosis of COPD are still partially unclear and some factors associated with death remain controversial.

Previous studies determining predictors of survival in COPD patients have mostly been conducted in normocapnic patients[1,4,5,7,9] or in severe hypoxemic patients requiring LTOT.[6,8,10] Survival studies among hypercapnic COPD patients have focused on hypercapnia acquired during an acute exacerbation of the disease.[19,25,26] Costello et al.[19], as well as Saryal et al.[25], included COPD patients during an acute exacerbation, and divided them into three groups: normocapnic, reversible hypercapnic, and chronic hypercapnic COPD patients. Costello et al. found a higher mortality rate in chronic hypercapnic COPD patients after 5 years of follow-up.[19] Saryal et al. were not able to demonstrate a difference in survival between groups after 10 years of follow-up.[25]

Hypercapnia is an expression of alveolar hypoventilation resulting from an imbalance between load on the ventilatory pump versus its capacity. The load on the ventilatory pump is determined by airway resistance or the degree of hyperinflation. The capacity of the pump depends on chemoreceptor drive, the strength and endurance of its respiratory muscles, and on the acid-base status of the muscles. A rise in arterial carbon dioxide tension ($PaCO_2$) causes a disturbance in the acid-base equilibrium, manifested in plasma pH changes in the acute phase before renal compensation has

occurred. These pH changes are sensed by central as well as peripheral chemoreceptors and initiate a respiratory response. A stimulation of ventilation follows, resulting in a higher arterial oxygen tension (PaO_2) and an increased carbon dioxide (CO_2) washout. In COPD patients with a chronic CO_2 retention this ventilatory response is often diminished.[27,28]

We hypothesized that respiratory muscle failure and a diminished ventilatory response to CO_2 might be predictors of survival of chronic hypercapnic COPD patients, because these factors may sustain or augment hypercapnia. Beside these parameters, already known factors related to a poor prognosis in normocapnic COPD patients, such as the severity of hypoxemia, the severity of airway obstruction, BMI, smoking status, and co-morbidity were analyzed as well.

3.3 Methods

3.3.1 Study Population

A cohort of 47 chronic hypercapnic COPD patients (28 male; mean age 66.3 ± 6.7 years) recruited for other trials, of 1 to 3 weeks in duration, in our institute between January 1996 and February 2000 was prospectively followed, yielding 178.8 person-years in total.[29-31] Follow-up time ranged from 3.1 to 7.1 years among survivors.

COPD was defined according to the standards of the American Thoracic Society.[17] Chronic hypercapnia was defined as $PaCO_2$ > 45.0 mmHg recorded twice with an interval of at least 6 weeks. At time of entry all patients were clinically stable (i.e. no changes in medication dosage or frequency and no exacerbations of disease or hospital admissions in the preceding 6 weeks). Patients with sleep-related breathing disorders, chronic renal or liver failure were excluded. During follow-up, patients received their usual medical care, adjustments were made if necessary, according to GOLD-standards. [32] Subjects were included after having given their written informed consent. The study has been evaluated and approved by the local Medical Ethics Committee.

3.3.2 Data Collection

The following data were collected: anthropometric parameters (including age, gender, and BMI), smoking status (described as smoking ≥ 1 cigarette per day at entry-time),

the presence of significant co-morbidity (which was defined as the existence of malignancies, cardiovascular disease, diabetes mellitus, rheumatologic diseases, or immunosuppression), use of medication (maintenance of oral steroids > 5mg/day, inhaled steroids, theophylline, diuretics, and LTOT), pulmonary function parameters, arterial blood gas values, respiratory muscle strength ($P_i$max, $P_e$max), and ventilatory response data.[33-35]

3.3.3 Statistical Analysis

Analyses were performed using statistical software (SPSS for Windows, Version 10.0; SPSS; Chicago, IL; and Egret, Version 2.0.3; CYTEL Software; Cambridge, MA). Descriptive data are presented as mean ± standard deviation (SD) or as number (percentage). Survival was analyzed using Cox's proportional hazards model. Due to a small number of deaths, risk factors were analyzed one by one. Co-morbidity and use of diuretics were the only parameters that were analyzed simultaneously, because we reasoned that the presence of cardiovascular disease would be related with the use of diuretics. All survival analyses were optimally adjusted for age and gender simultaneously, by taking age as staggered entry-time variable while stratifying by gender. Estimated hazard ratios (HR) and 95% confidence intervals (95%-CI) were calculated. A p-value < 0.05 was considered significant.

3.4 Results

At the time of analysis 18 deaths had occurred (10 males) out of 47 chronic hypercapnic subjects, contributing in total 178.8 person-years of follow-up. Thus, the overall survival rate after 3.8 years was 61.7%. Ten subjects (55.6%) died of acute-on-chronic respiratory failure, which was triggered by an acute exacerbation of COPD (n=9) or pneumonia (n=1). Two subjects (11.1%) died of the consequences of late-stage lung cancer. The others died of unknown causes.

Our group of subjects consisted of 14 current smokers (30.6 ± 18.3 packyears), 30 ex-smokers (35.1 ± 22.6 packyears), and 3 never-smokers. The number of packyears was not significantly different between current smokers and ex-smokers (p=0.5).

Co-morbidity was present at study entry-time in 38.3% of our study population. The most common co-morbidities found in our group of hypercapnic COPD patients were

cardiovascular diseases (17%), followed by diabetes mellitus (14.9%), respectively hypertension (8.5%). Patients' characteristics are further presented in Table 1.

Table 1. *General characteristics of all subjects.*

Characteristics	Entire cohort (n = 47)	Characteristics	Entire cohort (n = 47)
Age, years	66.3 ± 6.7	Diuretics (y)	20 (42.6)
Gender, male	28 (59.6)	LTOT (y)	7 (14.9)
Height, cm	168.5 ± 10.7	FEV_1, L	0.8 ± 0.33
Weight, kg	72.5 ± 14.6	FEV_1, % predicted	32.4 ± 14.11
BMI, kg m^{-2}	25.6 ± 5.5	FEV_1/VC	34.0 ± 11.0
Current smoker (y)	14 (29.8)	FRC, % predicted	118.1 ± 41.8
Co-morbidity (y)	18 (38.3)	TLC, % predicted	100.5 ± 17.4
Cardiovascular	8 (17.0)	RV, % predicted	154.2 ± 45.5
Diabetes Mellitus	7 (14.9)	$PaCO_2$, mmHg	48.8 ± 4.5
Hypertension	4 (8.5)	PaO_2, mmHg	61.5 ± 8.3
Other co-morbidity	4 (8.5)	BE, mmol L^{-1}	3.6 ± 2.2
Oral steroid (y)	11 (23.4)	$P_i$max, % predicted	76.1 ± 33.5
Theophylline (y)	22 (46.8)	$P_e$max, % predicted	75.8 ± 30.0
Inhaled steroid (y)	31 (66.0)	HCVR, $L.min^{-1}.mmHg^{-1}$	0.7 ± 0.5

Data are presented as mean ± SD (standard deviation) or number (%). Y (yes): parameter is present in subject.

Hazard ratios for death were calculated for each of the collected variables. Results are shown in Table 2a.

After optimal adjustment for age and gender, analysis demonstrated an increased mortality risk in current smokers (Hazard Ratio (HR) 7.0; (95%-CI) [1.4 – 35.3]) and in patients with the presence of co-morbidity (HR 5.5; [1.7 – 18.7]). Use of diuretics seemed to be predictive as well (HR 4.4; [1.3 – 14.7]). However, after correction for co-morbidity no independent risk of death was found for use of diuretics (HR 2.0; [0.5 – 8.5]) (Table 2b).

Table 2a. *Hazard ratios for death after optimal simultaneous correction for age and gender.*

Parameters	HR	[95%-CI]
Height, cm	1.0	[0.9-1.1]
Weight, kg	1.0	[0.96-1.0]
BMI, kg m^{-2}	1.0	[0.9-1.1]
Current smoker (y)	7.0*	[1.4-35.3]
Co-morbidity (y)	5.5*	[1.7-18.7]
Oral steroid (y)	2.9	[0.7-11.4]
Theophylline (y)	1.1	[0.4-3.1]
Inhaled steroid (y)	1.1	[0.3-3.9]
Diuretics (y)	4.4*	[1.3-14.7]
LTOT (y)	0.3	[0.03-2.4]
FEV_1, L	0.4	[0.1-2.2]

Parameters	HR	[95%-CI]
FEV_1, % predicted	1.0	[0.9-1.0]
FEV_1/VC	1.0	[0.9-1.0]
FRC, % predicted	1.0	[0.97-1.01]
TLC, % predicted	1.0	[0.95-1.01]
RV, % predicted	1.0	[0.98-1.01]
$PaCO_2$, mmHg	2.0	[0.9-4.3]
PaO_2, mmHg	0.6*	[0.4-1.0]
BE, mmol L^{-1}	1.0	[0.8-1.3]
$P_i$max, % predicted	1.0	[0.98-1.01]
$P_e$max, % predicted	1.0	[1.0 -1.04]
HCVR, $L.min^{-1}.mmHg^{-1}$	1.1	[0.9 –1.5]

*HR: Hazard Ratio. 95%-CI: 95% confidence interval. Y (yes): parameter is present in subject. * significant ($p < 0.05$). HR for $PaCO_2$, PaO_2, and HCVR were calculated in units of 5 mmHg.*

Table 2b. *Effect of co-morbidity and diuretics simultaneously.*

Parameters	HR	[95%-CI]
Co-morbidity (y)	3.8	[0.9-15.8]
Diuretics (y)	2.0	[0.5-8.5]

*HR: Hazard Ratio. 95%-CI: 95% confidence interval. Y (yes): parameter is present in subject. * significant ($p < 0.05$).*

A higher PaO_2 positively affected the survival rate (HR 0.6 per 5 mmHg; [0.4 – 1.0]). A higher $PaCO_2$ showed a tendency towards increasing the death rate (HR 2.0 per 5 mmHg), but this did not reach statistical significance (95%-CI [0.9-4.3]).

Analysis revealed that BMI, FEV_1, FEV_1/VC, FRC, TLC, RV, oral steroid use, inhaled steroid use, theophylline use, and LTOT were not significantly predictive in these chronic hypercapnic COPD patients. The same holds true for $P_i$max, $P_e$max, and HCVR.

To ensure that our results would not be biased by a possible difference in the blood gas profile of patients receiving LTOT, we also analyzed our data with the exception of these patients. LTOT patients did not significantly differ ($p > 0.05$) from patients without LTOT in terms of age (66.2 ± 6.4 versus 63.5 ± 6.7 years), FEV_1 (32.9 ± 13.0 versus 24.0 ± 10.6 % predicted), $PaCO_2$ (48.8 ± 3.8 versus 49.5 ± 4.5 mmHg), nor PaO_2 (61.5 ± 9.0 versus 58.5 ± 6.8 mmHg). Hazard Ratios for death of the patients without LTOT were comparable to HR for death of the total cohort, and did not alter our conclusions.

3.5 Discussion

Respiratory muscle strength and HCVR were not related to the prognosis of chronic hypercapnic COPD patients. Current smoking, the presence of co-morbidity, and the level of hypoxemia, on the other hand, did predict survival in these patients.

Respiratory muscle weakness in COPD patients causes hypoventilation with subsequent hypercapnia and hypoxemia. Hypercapnia is regarded a poor prognostic indicator in COPD patients in general.[19,26] We hypothesized that within the subgroup of hypercapnic COPD patients, the severity of CO_2 retention would further influence survival. Moreover, knowing that respiratory muscle weakness and hypercapnic ventilatory response are mediators of hypercapnia, we reasoned that it would be possible to predict survival by the level of respiratory muscle function and HCVR. We were not able to confirm this hypothesis. Survival analysis in our group of patients demonstrated no difference in respiratory muscle strength, nor in HCVR in survivors compared to non-survivors. We did find a tendency towards a lower $PaCO_2$ level in survivors. The narrow range in $PaCO_2$ (48.8 ± 4.5 mmHg) in our group of hypercapnic COPD patients makes it difficult to detect differences between survivors and non-survivors. In our opinion however, a tendency of lower $PaCO_2$ in survivors, probably underlines the prognostic value of hypercapnia in hypercapnic COPD patients. The absence of effect of chronic ventilatory support on survival by noninvasive ventilation, as described by Clini et al.[36] and Cuvelier et al.[37], support the notion that the degree of hypercapnia does not further affect survival, once the COPD patient has become hypercapnic. By some authors it has even been suggested that “permissive hypercapnia” may be a physiological adaptation that may lead to better survival rates.

By allowing $PaCO_2$ to rise, work of breathing can be decreased.[38,39] However, Zimmerman et al. studied 50 patients with chronic airflow obstruction for four years and found that hypercapnia was related to survival.[20] As one would expect, also a relationship between HCVR and hypercapnia was found. However, these authors did not observe a relationship between chemoreceptor sensitivity to hypercapnia and ventilatory response on one hand, and survival on the other hand. Their suggestion was that other, not yet identified factors might affect the relationship between HCVR and survival.

Many studies demonstrated that smoking is the most dominant etiological factor causing COPD.[1,11,12,14-18] Smoking cessation in older adults was shown to slow the rate of decline in pulmonary function.[18] In our study we demonstrated a significant higher mortality among current smokers, although the number of packyears smoked did not significantly differ from ex-smokers. In previous studies, this high mortality was found as well and has been associated with the development and progression of several major chronic conditions, loss of mobility, and poorer physical function in patients who continue smoking.[18]

The presence of co-morbidities lowered the survival rates in our group of hypercapnic COPD patients. Crockett et al. studied 505 patients with chronic airflow limitation (249 male) to whom LTOT was prescribed. Multivariate analysis of their data showed that the number of co-morbidities was a prognostic indicator for death in females.[6] Antonelli Incalzi et al. demonstrated that survival was predicted by the presence of chronic renal failure, myocardial infarction, or ischemia in 270 COPD patients (age 67.0 ± 9.0 years), consecutively discharged after hospital admission for an acute exacerbation. The most common comorbid diseases in their study population were hypertension (28%), diabetes mellitus (14%), and ischemic heart disease (10%).[21] In our own group of chronic hypercapnic COPD patients cardiovascular diseases were the most common co-morbidity, followed by diabetes mellitus, respectively hypertension (table 1). We also found that use of diuretics could predict survival of chronic hypercapnic COPD patients. (Table 2) Ischemic heart diseases and hypertension are co-morbidities that are often treated with diuretics. Therefore, we were interested whether the use of diuretics was *directly* related to survival or *indirectly* via the presence of co-morbidities. By analyzing the two parameters simultaneously, we corrected the use of diuretics for the presence of co-morbidities. We did not find an independent risk for diuretics.

Severe COPD is often accompanied by failure in gas exchange, expressed as hypoxemia and hypercapnia. Chronic hypoxemia eventually leads to hypertension and right heart failure (cor pulmonale). Costello et al. followed a cohort of COPD patients (age 68.3 ± 7.1 years; FEV_1 32.1 ± 13.4 % predicted) that had been admitted to an emergency hospital because of an acute exacerbation. The authors conducted a survival analysis after dividing the group into 19 chronic hypercapnic (age 68.4 ± 3.9 years; FEV_1 26.6 ± 7.0 %), 22 reversible hypercapnic (age 69.1 ± 8.4 years; FEV_1 32.7 ± 13.3 %), and 27 normocapnic COPD patients (age 69.1 ± 8.0 years; FEV_1 36.4 ± 16.2 %). Hypercapnia was defined as $PaCO_2$ > 50 mmHg. Five-year survival in chronic hypercapnic COPD patients was significantly lower (11%); in patients with reversible hypercapnia and normocapnia survival rates were 28% and 33%, respectively.[19]

LTOT improves survival in selected patients with severe hypoxic COPD, especially in patients with few co-morbidities. In patients with mild or moderate hypoxemia this effect is less obvious.[22-24] A study by the Medical Research Working Party demonstrated that in hypoxemic COPD patients (PaO_2 40.0-60.0 mmHg; FEV_1 < 1.2 liters) survival was improved after three years of oxygen administration, 2 $L.min^{-1}$ for 15 hours per day.[23] Statistical analysis of our hypercapnic patients did not show better survival rates among those receiving LTOT. However, only 7 out of 47 patients used LTOT. Therefore, this number was too small to draw any definite conclusion.

Results of previous studies among COPD patients demonstrate that the degree of airway obstruction predicts long-term outcome in these patients.[6,11-13] Hypercapnia was not a selection criterium in these studies. Surprisingly, in our study we did not find evidence for an association between severity of airway obstruction and mortality risk. This was also described in a study by Oswald-Mammosser et al. among eighty-four COPD patients receiving LTOT.[40] Survival analysis of their study revealed that not FEV_1, but the level of pulmonary artery pressure predicted survival. These authors suggested that this might have been due to a small cohort, as may also be the case in our study. Nevertheless, Cooper et al. who included 72 patients were able to detect an association between a low FEV_1 and lower survival rates.[41] Oswald-Mammosser et al. concluded that their relatively homogeneous study population explained their lack of effect of FEV_1 on survival (FEV_1 0.85 ± 0.34 liters). The narrower the range of the included parameters, the smaller the prognostic value will be. Our own study also shows this relative homogeneity (FEV_1 0.83 ± 0.33 liters).

Several studies have demonstrated a relationship between low BMI and survival in COPD patients.[5-7,9,11-13] Landbo et al. studied 2,132 COPD patients (FEV_1 64.7 ± 18 % predicted for men, respectively 66.1 ± 16.6 % for women). The relative risk ratios for all-cause mortality in these COPD patients were 1.6 [1.2-2.2] for men, and 1.4 [1.1-1.9] for women with a BMI lower than 20 $kg.m^{-2}$. However, in patients with a BMI of 25-29.9 $kg.m^{-2}$ no increased risk for death was found (RR 1.0 [0.9-1.2] for men, respectively 0.9 [0.6-1.1] for women). Our group of hypercapnic COPD patients had a mean BMI of 25.6 ± 5.5 $kg.m^{-2}$. Similar to Landbo et al., we were not able to demonstrate a relationship with survival.[9]

The survival rate in this study of 61.7% is higher than the rates found in other studies.[10,22] Foucher et al. analyzed survival in 252 hypoxemic COPD patients (age 69.7 ± 9.9 years; FEV_1 0.77 ± 0.28 liters) with a mean PaO_2 level of 49.7 ± 7.0 mmHg and a mean $PaCO_2$ level of 45.6 ± 7.1 mmHg. After correction for follow-up time the survival rate in that study was 41.4% after 3.8 years of follow-up.[10] Connors et al. studied a prospective cohort of 1,016 hypercapnic COPD patients (523 male; age 70 ± 7 years; mean FEV_1 0.80 liters) hospitalized for an acute exacerbation of their disease. Their mean $PaCO_2$ was 56.3 mmHg. A 2-year survival of 51% was found.[26] Survival after 3.8 years in the study by Costello et al. was respectively 43% for normocapnic and reversible hypercapnic COPD patients, and 22% for chronic hypercapnic COPD patients.[19] In comparison to the studies by Foucher, Costello, and Connors our group of hypercapnic COPD patients was clinically stable at the time of measurement. The COPD patients included in the studies by Foucher were severely hypoxemic and those included in the studies by Costello and Connors were analyzed during an acute exacerbation. This could explain the differences in survival rates.

Studying a small cohort of hypercapnic COPD patients, in which even a smaller number of deaths has occurred, causes two difficulties in the analysis of the results. The first difficulty is that the asymptotically normal behavior of the estimates is not yet reached. Therefore, we analyzed only one variable at a time. Secondly, a small cohort of severe COPD patients with hypercapnia decreases the possibility to detect relationships between explanatory variables and mortality, i.e. the so-called type-2 error problem. This was probably the case in our analysis of FEV_1, $PaCO_2$, and HCVR.

The purpose of our study was to define predictors of a decreased survival of clinically stable hypercapnic COPD patients. Identification of these factors is crucial for a better understanding of not only the course and prognosis of the disease, but also of its

possibilities for treatment and rehabilitation. We hypothesized that a low survival in hypercapnic COPD patients could be associated with a low respiratory muscle strength, a decreased HCVR and a lower FEV1. However, we were not able to confirm this hypothesis. On the other hand, we did find a low survival rate in hypercapnic COPD patients who were currently smoking. Also the presence of co-morbidity was associated with a poorer outcome. This stresses the need for interventions reducing mortality in this subgroup of COPD patients, such as smoking cessation programs and the treatment of co-morbidities. Moreover, future studies should focus on therapeutic interventions that will improve arterial blood gas values, e.g. the use of respiratory stimulants, or respiratory muscle training. Unlike other trials studying survival parameters in COPD patients in general, we did not find airway obstruction, age, or BMI to be predictors of survival in hypercapnic COPD patients, suggesting that once COPD patients have become hypercapnic, these factors no longer affect survival.

3.6 Acknowledgement

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3.7 References

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Chapter 4

Respiratory muscle strength and muscle endurance are not affected by acute metabolic acidemia

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4.1 Abstract

Respiratory muscle fatigue in asthma or chronic obstructive lung disease (COPD) contributes to respiratory failure with hypercapnia, and subsequent *respiratory* acidosis. Therapeutic induction of acute *metabolic* acidosis further increases the respiratory drive and, therefore, may diminish ventilatory failure and hypercapnia. On the other hand, it is known that acute metabolic acidosis can also negatively affect (respiratory) muscle function and, therefore, could lead to a deterioration of respiratory failure. Moreover, we reasoned that the impact of metabolic acidosis on respiratory muscle strength and muscle endurance could be more pronounced in COPD patients as compared to asthma patients and healthy subjects, due to already impaired respiratory muscle function. In this study, the effect of metabolic acidosis was studied on peripheral muscle strength, peripheral muscle endurance, airway resistance, and on arterial carbon dioxide tension ($PaCO_2$).

Acute metabolic acidosis was induced by administration of ammonium chloride (NH_4Cl). The effect of metabolic acidosis was studied on inspiratory and expiratory muscle strength and on respiratory muscle endurance. Effects were studied in a randomized, placebo-controlled cross-over design in 15 healthy subjects (4 male; age 33.2 ± 11.5 years; FEV_1 108.3 ± 16.2 % predicted), 14 asthma patients (5 male; age 48.1 ± 16.1 years; FEV_1 101.6 ± 15.3% predicted), and 15 moderate to severe COPD patients (9 male; age 62.8 ± 6.8 years; FEV_1 50.0 ± 11.8% predicted).

An acute metabolic acidemia of ΔBE –3.1 $mmol.L^{-1}$ was induced. Acute metabolic acidemia did not significantly affect strength or endurance of respiratory and peripheral muscles, respectively. In all subjects airway resistance was significantly decreased after induction of metabolic acidemia (mean difference –0.1 $kPa.sec.L^{-1}$ [95%-CI: -0.1 - -0.02]). In COPD patients $PaCO_2$ was significantly lowered during metabolic acidemia (mean difference –1.73 mmHg [-3.0 - -0.08]). In healthy subjects and in asthma patients no such effect was found.

Acute metabolic acidemia did not significantly decrease respiratory or peripheral muscle strength, respectively muscle endurance in normal subjects, asthma, or COPD patients. Metabolic acidemia significantly decreased airway resistance in asthma and COPD patients, as well as in healthy subjects. Moreover, acute metabolic acidemia slightly improved blood gas values in COPD patients. The results suggest that

stimulation of ventilation in respiratory failure, by induction of a metabolic academia, will not lead to deterioration of the respiratory failure.

Keywords: *Pulmonary Diseases, Chronic Obstructive; Asthma; Respiratory Muscles; Hyperinflation; Ammonium Chloride; Metabolic Acidosis; Control of breathing*

4.2 Introduction

An exacerbation of obstructive lung diseases, i.e. asthma and chronic obstructive pulmonary disease (COPD), is often accompanied by a disturbance in the acid-base equilibrium.[1] In COPD, progressive airway obstruction and dynamic increase in end-expiratory volume increase the workload on the ventilatory pump.[2-4] The hyperinflation leads to respiratory muscle shortening, deteriorating the force generating capacity of inspiratory muscles.[2-5] Eventually, this may lead to respiratory failure with hypoxemia and carbon dioxide retention.[2,6,7] The subsequent respiratory acidosis is sensed by peripheral and central chemoreceptors. This increases the respiratory drive and may improve arterial oxygen tension (PaO_2) and arterial carbon dioxide tension ($PaCO_2$).[8,9] Respiratory stimulants such as acetazolamide are often used in clinical practice for treatment of respiratory failure by increasing chemoreceptor stimulation.[10] Induction of an acute metabolic acidosis, in patients with respiratory acidosis, causes a further drop in arterial pH and, therefore, will increase the respiratory drive.

However, acidosis itself deteriorates muscle contractility.[11-16] The underlying mechanism is not yet completely understood, but it has been hypothesized that a decrease in pH affects muscle contractility by lowering the rate of glycolysis and adenosine triphosphate (ATP) resynthesis.[11,17] Thus theoretically, a reduction in respiratory muscle function due to metabolic acidosis may add to a further deterioration of the clinical state in times of an exacerbation, and may counteract the increased respiratory drive.

Hypercapnia and respiratory acidosis reduce diaphragm contractility[11-14] and even endurance time[12], although some controversy exists.[18,19] Previous studies have demonstrated that metabolic acidosis decreases the strength of myocardial[15] and peripheral muscles.[16] However, the effect of metabolic acidosis on respiratory muscles remains unclear.[14,20] Besides an effect on striated muscles, acidosis also seems to have an effect on bronchial smooth muscle.[21,22] Hypercapnia causes bronchodilatation[21], and in metabolic acidosis a tendency was found for decreasing airway resistance.[22]

Respiratory muscle strength and endurance of COPD patients is impaired in comparison to stable asthma patients and healthy subjects.[2,23,24] An increased workload at rest[6], catabolism[25], and hyperinflation[26], among others, lead to an impaired muscle oxidative capacity and an altered metabolic regulation.[27]

The hypotheses of this study were that: 1) metabolic acidosis deteriorates respiratory, as well as peripheral muscle function, in terms of a decrease in muscle strength and endurance; 2) metabolic acidosis affects muscle endurance to a greater extent than muscle strength, since repetitive contractions depend more on ATP resynthesis; 3) metabolic acidosis will decrease airway resistance; 4) the effect of metabolic acidosis on muscle strength and endurance would differ between healthy subjects, asthma patients, and COPD patients; 5) metabolic acidosis increases chemoreceptor stimulation and will improve ventilation and blood gas values.

We reasoned that the already impaired muscle function and altered muscle metabolism of COPD patients, e.g. low intracellular pH and reduced ATP resynthesis, would make their muscles more vulnerable for fatigue during metabolic acidosis, compared to healthy subjects and asthma patients. We expected the decrease in airway resistance to be more noticeable in subjects with an increased airway resistance, namely asthma and COPD patients. The net effect of metabolic acidosis on the gas exchange and on arterial blood gas values is the result of the above mentioned counteracting mechanisms, and, therefore, cannot easily be predicted.

4.3 Methods

4.3.1 Subjects

Fifteen healthy subjects (4 male; mean age 33.2 ± 11.5 years) were recruited from the general population. Fourteen asthma patients (5 male; 48.1 ± 16.1 years) and 15 COPD patients (9 male; 62.8 ± 6.8 years) were selected consecutively from the outpatient pulmonary department of the Rijnstate Hospital Arnhem (NL). Selection criteria for asthma patients were mild to moderate persistent asthma, according to NHLBI/WHO guidelines, and increased bronchial responsiveness (PC_{20} histamine < 4.0 $mg.ml^{-1}$).[28] COPD patients with stage II and III according to GOLD criteria were selected.[29]

All patients were clinically stable, i.e. no changes in medication and no exacerbations or hospital admissions in the preceding six weeks. Exclusion criteria were other pulmonary diseases, relevant co-morbidity, use of oral corticosteroids, theophyllines, drugs influencing acid-base equilibrium (e.g. carbonic anhydrase inhibitors, loop-diuretics), or drugs influencing muscle tone (e.g. benzodiazepines). Use of alcoholic or

caffeine containing beverages 6 hours prior to the tests was prohibited. Use of regular pulmonary medication was allowed.
All participants gave their written informed consent. The study was approved by the local Medical Ethics Committee.

4.3.2 Design and Intervention

Isolated metabolic acidosis was induced by drinking a solution containing ammonium chloride (NH_4Cl) (15 $mg.ml^{-1}$) and liquorice. The aim was to cause a decrease in base excess (BE) of 2 $mmol.L^{-1}$. The amount of fluid that needed to be ingested to reach this degree of acidification was calculated, assuming an extra cellular water compartment of one third of body weight.[30] After baseline measurements subjects received either NH_4Cl or a solution containing only liquorice, in a randomized double-blind cross-over design. Administration of the fluid was repeated after 60 minutes in order to keep plasma levels constant.[30] Measurements were repeated 90 minutes after ingestion of the first dose. Cross-over took place approximately one week later and another series of measurements was performed.

4.3.3 Capillary blood gas values

Arterialized capillary blood gas samples were taken to determine BE and carbon dioxide tension.

4.3.4 Pulmonary function testing

Baseline pulmonary function consisted of measuring forced expiratory volume in-one-second (FEV_1), forced expiratory ratio (FEV_1/IVC), total lung capacity (TLC) and residual volume (RV), using standard techniques.[31] Airway resistance (R_{aw}) and specific airway conductance (sG_{aw}) were assessed using bodyplethysmography (Masterlab Pro, Jaeger Würzburg).

4.3.5 Respiratory muscle strength and endurance

Primary endpoints of the study were respiratory muscle strength ($P_i$max and $P_e$max) and respiratory muscle endurance. $P_i$max and $P_e$max, measured at RV and TLC respectively, were defined as the highest plateau-value out of three reproducible measurements with a maximum variability of 10%. Values are presented as percentage predicted.[32]

Respiratory muscle endurance was determined by incremental threshold loading.[33,34] The procedure was modified and described by Heijdra et al.[35] Respiratory muscle endurance was expressed as sustainable inspiratory pressure for ≥ 45 seconds (SIP) and total endurance time (TEND). The ratio between SIP and $P_i$max was also calculated.

4.3.6 Peripheral muscle strength and endurance

Peripheral muscle strength was determined by measuring maximal isometric handgrip strength (P_{grip}) with a hand-dynamometer (JAMAR 5030J1 Hydraulic hand dynamometer, Sammons Preston® Bolingbrook, IL 60440). The dynamometer was adjusted to individual hand size to provide optimal grip. The subject was asked to squeeze the handle of the dynamometer as hard as possible during a short period of time. The highest value for left and right hand of at least three reproducible attempts was retained as maximal isometric handgrip strength (kilograms force). Values were presented as percentage predicted.[36]

Peripheral muscle endurance was assessed by measuring repetitive maximal isometric contraction force during 180 seconds.[37] The subject was instructed to grip the dynamometer with maximal force during 1 second and then to release for 1 second, using the dominant hand. This sequence was repeated during 3 minutes. A metronome was set at 60 per minute to pace contractions and relaxations. Isometric contraction force (kilograms force) was noted every ten seconds.

4.3.7 Statistical analysis

Statistical analyses were performed using statistical software (SPSS for Windows; Version 11.0; SPSS: Chicago, IL; and SAS; Version 8.2; Institute Inc.; Cary, NC). Descriptive data are presented as mean ± standard deviation (SD) or as number (percentage). Differences between groups in means of descriptive variables were analyzed by one-way ANOVA. A p-value of 0.05 was considered to be significant.

Repeated measurements (mixed model ANOVA) was performed to evaluate the effect of metabolic acidosis on the outcome variables investigated. A linear model was specified in which the outcome variable at hand was explained by therapy, period and group. Therapy and period were within-subject factors, each with two levels, and group was a between-subjects factor with three levels (healthy subjects, asthma patients, and COPD patients). Also the group by therapy interaction was tested. If this

interaction turned out to be significant with a p-value below 0.10, then the therapy effects were to be presented per group. Otherwise, one common effect for all subjects and patients was to be presented. Before starting this study we made a priori the highly plausible assumption that a carry-over effect was impossible when crossing over from one therapy to the other, with a wash-out period of one week in between.
The handgrip endurance data were analyzed as an exponential decay function of time in which the coefficients (intercept and slope of the log force versus time curve) were assumed to be random between subjects. The within-subject structure of the residual correlation was assumed to depend on the time interval between repeated measurements. A mixed model ANOVA was used to estimate and test how intercept and slope, averaged across subjects, were modified by therapy, group and their interaction. If this interaction turned out to be significant ($p < 0.10$), then the therapy effect on average intercept and slope was to be presented per group. In the analysis also adjustment was made for the period effect.

4.4 Results

Fifteen healthy subjects (4 male), 14 asthma patients (5 male) and 15 COPD patients (9 male) completed the study. Further characteristics are described in Table 1.

Baseline parameters that differed significantly between groups were age, FEV_1, FEV_1/IVC, RV, R_{aw}, $P_i$max, $PaCO_2$, packyears, and current smoking (Table 1). $P_i$max and $P_e$max differed significantly between subjects, however, in all subjects values were above 100% predicted value.
The effects on the investigated variables, after ingestion of NH_4Cl, are presented in Table 2. If the effect was not different between groups, i.e. if no therapy by group interaction was found, an overall effect on all subjects was presented. In all subjects a significant metabolic academia was induced by NH_4Cl. The mean difference in pH was –0.04 (95%-confidence interval [-0.05 - -0.03]), the change in BE was –3.1 $mmol.L^{-1}$ [-3.6 - -2.6] respectively. (Table 2)

Table 1. *Patients' characteristics.*

Variables	Healthy subjects		Asthma		COPD		*p*-value
N	15		14		15		
Gender, male	4	(26.7)	5	(35.7)	9	(60.0)	
Age, years	33.2	± 11.5	48.1	± 16.1	62.8	± 6.8	<0.001
BMI, $kg.cm^{-2}$	26.2	± 5.1	25.4	± 3.0	27.3	± 4.4	0.47
FEV_1, L	3.8	± 0.8	3.0	± 0.6	1.4	± 0.5	<0.001
FEV_1, % predicted	108.3	± 16.2	101.6	± 15.3	50.0	± 11.8	<0.001
FEV_1/IVC, %	84.7	± 7.3	73.7	± 11.4	40.7	± 10.3	<0.001
TLC, % predicted	107.2	± 15.8	111.7	± 16.1	111.3	± 12.0	0.70
RV, % predicted	87.0	± 14.3	124.9	± 46.2	146.3	± 25.7	<0.001
R_{aw}, $kPa.sec.L^{-1}$	0.2	± 0.1	0.3	± 0.2	0.6	± 0.3	<0.001
$P_i$max , % pred	138.2	± 29.5	116.5	± 29.5	109.5	± 39.7	0.02
$P_e$max, % pred	120.2	± 23.4	102.8	± 24.4	103.8	± 35.0	0.03
P_{grip} right, % pred	95.1	± 11.3	91.3	± 14.6	101.6	± 18.3	0.12
$PaCO_2$, mmHg	37.5	± 3.8	36.8	± 3.0	41.3	± 3.8	0.01
Packyears	2.3	± 5.8	10.9	± 10.6	30.1	± 27.3	<0.001
Current smoking	1	(6.7)	4	(28.6)	6	(40.0)	<0.001

Data are presented as mean ± SD or number (percentage). BMI: body mass index. FEV_1: forced expiratory volume in-one-second. FEV_1/IVC: forced expiratory ratio. TLC: total lung capacity. RV: residual volume. R_{aw}: airway resistance. $P_i$max: maximum inspiratory pressure. $P_e$max: maximum expiratory pressure. $PaCO_2$: carbon dioxide tension. P-value < 0.05: significant difference in means between groups.

When analyzing the effects of metabolic academia on $PaCO_2$, a significant therapy by group interaction was found (p = 0.09). After analyzing the effect of metabolic academia on $PaCO_2$ per group individually, only a significant effect was found in COPD patients (mean difference –1.73 mmHg [-3.0 - -0.08]) (Table 2). Metabolic academia did not alter $PaCO_2$ in healthy subjects (p = 0.5). In asthma patients the mean difference in $PaCO_2$ after ingestion of NH_4Cl was almost the same as in COPD patients (-1.65 mmHg), however, not statistically significant (p = 0.06). Results are also shown in Figure 1.

Table 2. *Effects after induction of metabolic acidosis.*

	Group	Placebo	NH_4Cl	NH_4Cl-Placebo	95%-CI		*p*-value
					Lower	Upper	
PH		7.39	7.35	-0.04	-0.05	-0.03	< 0.001
BE		-0.3	-3.3	-3.1	-3.6	-2.6	< 0.001
*P*aCO_2, mmHg	Healthy	37.5	37.5	0.53	-0.8	+2.3	0.5
	Asthma	39.0	37.5	-1.7	-3.0	+0.08	0.06
	COPD	41.3	39.8	-1.7	-3.0	-0.08	0.04
R_{aw}, kPa.sec.L^{-1}		0.4	0.3	-0.1	-0.1	-0.02	0.003
sG_{aw}, 1/(kPa.sec)		1.2	1.3	0.1	-0.02	+0.3	0.1
$P_i$max , % pred		124.2	121.1	-3.1	-7.6	+1.5	0.2
$P_e$max, % pred		111.4	112.5	1.1	-6.7	+9.0	0.8
SIP, mmHg		39.8	38.3	-2.3	-4.5	+0.8	0.2
SIP/$P_i$max, %		51.6	51.9	-0.4	-5.0	+4.3	0.9
TEND, sec		508.8	519.4	2.2	-44.2	+48.6	0.9
P_{grip} right, % pred		94.3	95.0	0.7	-2.2	+3.5	0.6
P_{grip} left, % pred		103.4	103.5	0.2	-5.2	+5.5	0.95

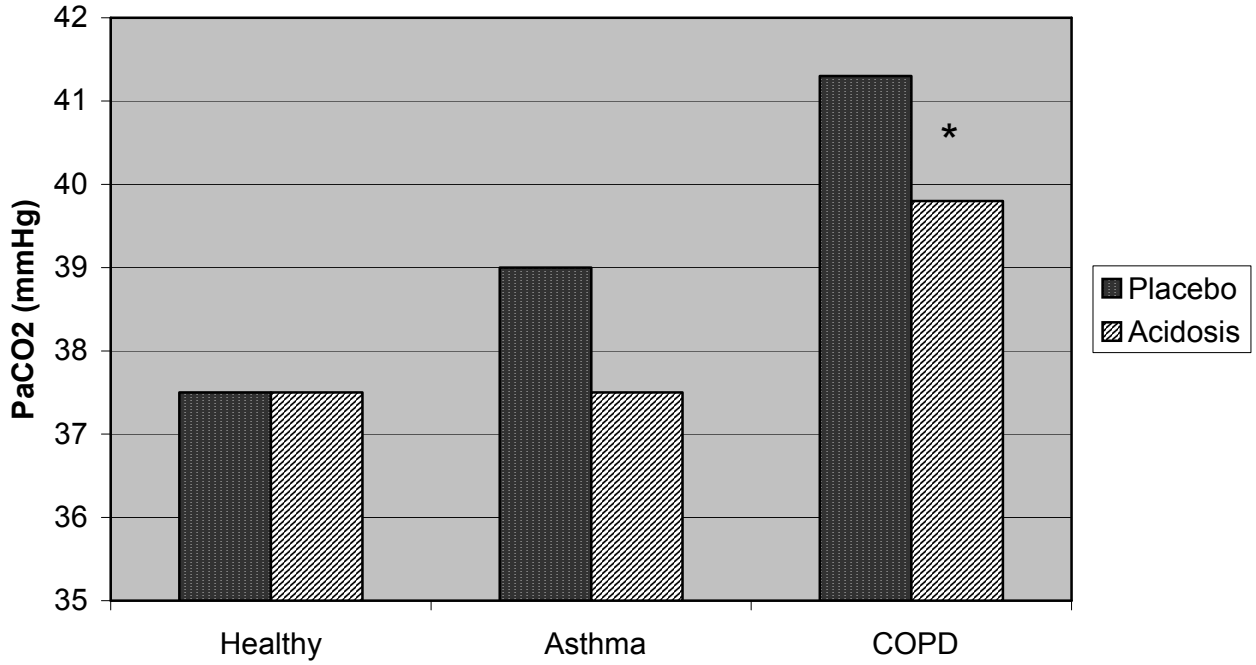
For all investigated variables the average value after placebo, respectively after NH_4Cl, the mean difference between NH_4Cl and placebo and the 95%-confidence interval of this difference are shown. Presentation of the effect of NH_4Cl, respectively placebo for all groups individually, implicates that a significant therapy by group interaction was found ($p < 0.10$).

BE: base excess. $PaCO_2$: carbon dioxide tension. R_{aw}: airway resistance. sG_{aw}: specific airway conductance. $P_i$max: maximum inspiratory pressure. $P_e$max: maximum expiratory pressure. SIP: sustainable inspiratory pressure. TEND: total endurance time. P_{grip}: maximum isometric contraction force.

Metabolic academia significantly decreased R_{aw} in all groups (mean difference –0.1 kPa.sec.L^{-1} [-0.1 - -0.02] (Table 2) Specific airway conductance (sG_{aw}) was not altered by metabolic acidosis.

No differences were found in respiratory muscle strength, respiratory muscle endurance, peripheral muscle strength, and respectively handgrip endurance after induction of metabolic acidosis in either group (Tables 2 and 3).

Figure 1. *The effect of metabolic acidosis on carbon dioxide tension.*



*Vertical axis represents carbon dioxide tension ($PaCO_2$) in mmHg. Horizontal axis represents effect of acidosis versus placebo in respectively healthy subjects, asthma patients and COPD patients. * p=0.04*

Table 3. *Effects of metabolic acidosis on handgrip endurance.*

	Placebo	NH_4Cl	NH_4Cl-Placebo	95%-CI		*p*-value
				Lower	Upper	
Intercept, geometric mean	32.4	32.3	1.0	0.9	1.1	0.95
Slope, % per minute	-21.8	-20.5	1.0	0.97	1.1	0.3

For intercept and slope of the log force versus time curve, the average value after placebo, respectively after NH_4Cl, the mean difference between NH_4Cl and placebo and the 95%-confidence interval of this difference are shown.

4.5 Discussion

Acute isolated metabolic academia did not affect respiratory muscle strength or respiratory muscle endurance in healthy subjects, stable asthma patients, and stable COPD patients. Peripheral muscle strength and peripheral muscle endurance were also not altered by metabolic acidemia. In all subjects airway resistance decreased during metabolic acidemia. $PaCO_2$ decreased only in COPD patients.

Our first hypothesis was that acute metabolic acidosis would decrease strength and endurance of respiratory and peripheral muscles. Moreover, we reasoned that metabolic acidosis would affect muscle endurance to a greater extent than muscle strength. It has been recognized that pH, muscle contractility, and fatigue are related, although the precise interaction between those factors is not yet completely understood.[38,39] Intracellular acidosis could cause a decrease in cellular influx of calcium, a reduction of troponine affinity for calcium, and an increase in calcium binding to the sarcoplasmatic reticulum, and therefore, may reduce the rate of glycolysis and ATP resynthesis.[12,17] Thus, an acidifying shift in the acid-base equilibrium could make the muscle more prone for fatigue during exercise. Previous studies have demonstrated that hypercapnic *respiratory* acidosis reduces diaphragm contractility.[11-16] Jonville et al.[13] studied 14 healthy subjects performing moderate exercise and demonstrated that during voluntarily hypercapnic hypoventilation ($PaCO_2$ 51.0 mmHg), twitch mouth pressure decreased significantly compared to spontaneous breathing (17.1 versus 19.1 cmH_2O). Juan et al.[12] studied four healthy men and found that acute respiratory acidosis equivalent to a $PaCO_2$ of 54.0 mmHg decreased not only diaphragmatic contractility at rest, but also diaphragmatic endurance time. Metabolic acidosis has also been found to decrease contractility of myocardial muscles[15] and of peripheral muscles.[16]

However, there have also been studies that could not demonstrate an effect of acidosis on muscle contractility.[14,18,19,22] Ameredes et al.[18] studied seven healthy subjects breathing a CO_2-O_2 mixture while performing maximal inspiratory manoeuvres from FRC. Measurements were repeated during normocapnia ($PaCO_2$ 41.3 mmHg), hypercapnia (52.5 mmHg), and hypocapnia (26.3 mmHg). Maximum mouth pressure at rest, as well as sustainable force output at the end of an endurance trial were not affected by changes in end-tidal $PaCO_2$.[18] In a study in dogs[14], transdiaphragmatic pressure did significantly decrease (57.8 ± 12.8 mmHg versus

70.5 ± 11.3 mmHg at baseline) during *respiratory* acidosis, whereas *metabolic* acidosis did not alter transdiaphragmatic pressure (72.8 ± 12.0 mmHg versus 70.5 ± 11.3 mmHg) in these dogs. pH in these dogs was 7.39 ± 0.01 at baseline, whereas pH was 7.07 ± 0.01 during respiratory acidosis, and 7.10 ± 0.03 during metabolic acidosis respectively.[14] The effect of metabolic acidosis on muscle strength has also been studied by Brijker et al.[22] After induction of metabolic acidosis in a group of healthy subjects (24-56 years old) no changes were found in respiratory muscle strength ($P_i$max 75.8 (40.5-109.5) mmHg versus baseline 63.8 (41.3-113.3) mmHg, nor in peripheral muscle strength (P_{grip} 36 (29-68) kgf versus baseline 36 (29-77) kgf). In accordance with them, we were also not able to demonstrate an effect of acute metabolic academia on respiratory and peripheral muscle strength. Moreover, in our study respiratory and peripheral muscle endurance were not altered either by metabolic acidemia. An in vitro study, Coast et al.[40] showed that rat diaphragm strips exposed to lactic acidosis, were also not more fatigueable.

Impaired lung function and subsequent shortness of breath leads to a decrease in daily life activities in COPD patients. This deconditioning mainly affects the quadriceps muscle strength, which can be reduced by 20-30% in COPD patients.[41] We reasoned that peripheral muscle atrophy, the shift from slow-twitch type I fibers towards fast-twitch type IIb fibers[42], and the altered metabolic capacity[43], such as a low intracellular pH and reduced ATP concentration, in COPD patients, could make the muscle more vulnerable to fatigue. We did not find any differences after induction of metabolic acidosis in muscle strength nor endurance between healthy subjects, asthma patients, and COPD patients. However, predicted values of respiratory and peripheral muscle strength in our group of COPD patients were within normal values. Heijdra et al. studied 32 COPD patients (FEV_1 38 ± 11% predicted) with a normal fat free mass index and also found that respiratory muscle strength was not impaired in this group of COPD patients.[44] This is consistent with our findings of no difference in the effect of metabolic acidosis on muscle strength between the three groups.

In comparison to quadriceps muscle strength, upper limb muscle strength seems to be relatively preserved in COPD patients.[41] This is probably due to normal use in daily living and the possible accessory activity as inspiratory muscles.[45] The fact that we only measured strength and endurance of hand grip could be another explanation why we did not find a difference in peripheral muscle function between COPD patients and healthy subjects, or asthma patients.

Our third hypothesis was that metabolic acidosis could decrease R_{aw} and consequently might decrease hyperinflation. We were able to demonstrate a reduction in R_{aw} after metabolic acidosis. SG_{aw}, the inverse of airway resistance with correction for thoracic gas volume, did not change during metabolic acidosis. Brijker et al.[22] found a similar effect in their study. They found that during *metabolic alkalosis* R_{aw} increased from 0.16 (0.13 – 0.26) to 0.17 (0.13-0.27) kPa.sec.L^{-1}, but sG_{aw} remained unchanged. The fact that sG_{aw} did not change in our study after induction of metabolic acidosis, further implicates that the decrease in R_{aw} was probably due to an increase in dynamic end-expiratory volume as a result of a higher ventilatory drive. The force generating capacity of the diaphragm is determined by muscle length. The optimal length for generating pressure depends on the intrinsic length-tension relationship of the muscle. Hyperinflation causes a shortening of the respiratory muscles, displacing them to a less advantage position on the length-tension curve.[2-5] Therefore, a decrease in R_{aw} based on an increase in end-expiratory volume could negatively affect the diaphragm's position on the curve and possibly decrease muscle strength. However, in our study the decrease in R_{aw} was not accompanied by a decrease in muscle function. The difference in R_{aw} and in expiratory lug volume was probably too small to affect respiratory muscle strength. The decrease in R_{aw} was found in obstructive and hyperinflated COPD patients, as well as in healthy subjects and stable asthma patients. Therefore, the effect of metabolic acidosis on R_{aw} did probably not depend on baseline R_{aw} values, and was not specific for obstructive lung disease.

Regarding the net effect of acute metabolic acidosis on blood gas values only a decrease in $PaCO_2$ was found in COPD patients. It has been demonstrated previously that metabolic acidosis induced by NH_4Cl stimulates the respiratory drive and increases minute ventilation.[46] The secondary hyperventilation lead to a fall in $PaCO_2$. We did not find a decrease in $PaCO_2$ in healthy subjects. Van de Ven et al.[30] found a similar result. After induction of metabolic acidosis by NH_4Cl (ΔBE –4.9 ± 2.2 mmol.L^{-1}) in eight healthy subjects (age 37.0 ± 16.0 years), $PaCO_2$ did not significantly change.[30] In our group of asthma patients the decrease was not statistically significant. A possible explanation for the difference between COPD and the other groups could be that asthma patients and healthy subjects are more on the horizontal part of the ventilatory response curve to CO_2, since baseline $PaCO_2$ was relatively lower in asthma patients and healthy subjects, compared to COPD patients (table 1).

We conducted this study to bring light on the short-term physiological consequences of isolated metabolic acidosis on muscle strength and endurance in healthy subjects, asthma patients and COPD patients in order to evaluate possible negative effects of treatment of respiratory failure with induced metabolic acidosis. We concluded that isolated acute metabolic academia does not decrease muscle strength nor muscle endurance. Moreover, there seems to be a positive effect on airway resistance and an improvement of carbon dioxide tension by increasing the respiratory drive. In conclusion, we suggest that induction of a metabolic acidosis in times of acute exacerbation does not seem to deteriorate the patients' clinical situation by decreasing respiratory muscle function and subsequently maintaining the respiratory insufficiency. It even seems that this metabolic acidosis may positively affect the clinical state of COPD patients by improving blood gas values. This finding confirms the feasibility of the use of respiratory stimulants, such as carbonic anhydrase inhibitors, that stimulate ventilation by inducing metabolic acidosis, in respiratory failure.

4.6 Acknowledgement

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Chapter 5

Induced acute metabolic acidosis improves alveolar ventilation in chronic hypercapnic COPD patients

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5.1 Abstract

Induction of acute metabolic acidosis in chronic hypercapnic COPD patients causes a further drop in arterial pH, stimulating the ventilatory drive. We hypothesized that induction of acute metabolic acidosis by orally administrated ammonium chloride (NH_4Cl) would increase the ventilatory drive of chronic hypercapnic COPD patients and improve their arterial blood gas values. Secondarily we hypothesized that acute metabolic acidosis would decrease airway resistance (R_{aw}), affect respiratory and peripheral muscle function and increase exercise capacity. Moreover, we investigated effects of chronic and acute-on-chronic ingestion of NH_4Cl on the acid-base equilibrium and respiratory parameters.

Metabolic acidosis was induced by administration of NH_4Cl. Acute (day 1), chronic (day 7) and acute-on-chronic (day 7 after a second dose) effects of metabolic acidosis were studied on arterial carbon dioxide tension ($PaCO_2$), arterial oxygen tension (PaO_2), hypercapnic ventilatory responses (HCVR) and hypoxic ventilatory responses (HVR). Effects were studied in a randomized, placebo-controlled cross-over design in 9 chronic hypercapnic COPD patients (7 male; mean age 65.3 ± 8.5 years; $PaCO_2$ 48.0 ± 3.0 mmHg). Secondarily effects were studied on R_{aw}, $P_i$max and $P_e$max, handgrip strength, six minute walking distance (6MWD) and dynamic hyperinflation.

Ingestion of NH_4Cl caused an acute metabolic acidosis (base excess (BE) 1.5 ± 2.0 $mmol.L^{-1}$ in NH_4Cl, versus 4.3 ± 0.8 in placebo). A significant effect on BE was also seen in acute-on-chronic ingestion of NH_4Cl ($p=0.01$). Chronic ingestion of NH_4Cl did not cause changes in the acid-base equilibrium. Only in acute metabolic acidosis a statistically significant decrease (1.5 mmHg) was seen in $PaCO_2$ ($p=0.02$). HCVR and HVR did not increase in metabolic acidosis in chronic hypercapnic COPD patients. No effects were found on R_{aw}, $P_i$max and $P_e$max, handgrip strength, 6MWD or dynamic hyperinflation.

Only acute metabolic acidosis induced by oral NH_4Cl decreases $PaCO_2$. Therefore, we conclude that oral NH_4Cl cannot be used as a clinically relevant respiratory stimulant in chronic hypercapnic COPD patients.

Key Words: *Pulmonary diseases, chronic obstructive; Metabolic Acidosis; Hypercapnia; Respiratory muscle function; Control of breathing*

5.2 Introduction

Respiratory failure in severe chronic obstructive pulmonary disease (COPD) is caused by an imbalance between the load on the ventilatory pump and the ventilatory capacity. The subsequent alveolar hypoventilation leads to low arterial oxygen tensions (PaO_2) and high arterial carbon dioxide tensions ($PaCO_2$). Acute carbon dioxide (CO_2) retention (hypercapnia) in COPD causes a *respiratory* acidosis. The increase in hydrogen ion [H^+] concentration stimulates both central and peripheral chemoreceptors. This increase in ventilatory drive can raise minute ventilation and, consequently, improve gas exchange.[1,2]

A subgroup of severe COPD patients becomes *chronic* hypercapnic. After 3-5 days renal compensation occurs[3], by retention of bicarbonate [HCO_3^-] in the kidney. However, the normalization of the pH limits the stimulus to respiration, aggravating hypoxemia and hypercapnia.[4]

Induction of an acute *metabolic* acidosis, in chronic hypercapnic COPD patients, causes a further drop in arterial pH, causing a new stimulus for the ventilatory drive. Theoretically, induction of acute metabolic acidosis could be beneficial for these chronic hypercapnic COPD patients.

Metabolic acidosis also has an effect on striated as well as on smooth muscles. Decreases have been found in contractility of peripheral[5], myocardial muscles[6] as well as respiratory muscles.[7] Moreover, metabolic acidosis has been shown to cause a small, yet not statistically significant decrease in airway resistance in healthy subjects.[8]

Ammonium chloride (NH_4Cl) induces a metabolic acidosis by decreasing plasma bicarbonate [HCO_3^-] concentration.[9] In a study in healthy male subjects, ammonium chloride increased inspiratory minute ventilation and ventilatory response slopes to hypercapnia as well as hypoxemia.[10]

Therefore, the hypotheses were 1) that induction of isolated metabolic acidosis by NH_4Cl in chronic hypercapnic COPD patients a) increases the ventilatory drive, b) decreases airway resistance, c) decreases dynamic hyperinflation, d) improves exercise tolerance and e) lowers respiratory and peripheral muscle function and 2) that there would be different effects on the outcome variables after induction of *acute* metabolic acidosis, *chronic* metabolic acidosis, respectively *acute-on-chronic* metabolic acidosis. We reasoned that chronic administration of NH_4Cl could possibly

generate a mechanism to compensate this chronic acidosis. Acute-on-chronic metabolic acidosis, on the other hand, might still have a beneficial effect on the parameters of chronic hypercapnic COPD patients.

5.3 Methods

5.3.1 Study Population

Nine chronic hypercapnic COPD patients (7 male; mean age 65.3 ± 8.5) years were selected consecutively from the outpatient pulmonary department of the Rijnstate Hospital Arnhem (NL). COPD was determined according to GOLD criteria.[11] Chronic hypercapnia was defined as $PaCO_2$ > 45.0 mmHg recorded twice with an interval of at least 6 weeks. All patients were clinically stable (i.e. no changes in medication dosage or frequency and no exacerbations of disease or hospital admissions in the preceding 6 weeks). Patients with other pulmonary diseases, sleep-related breathing disorders, chronic renal or liver failure, long term oxygen therapy (LTOT) or use of drugs influencing the control of breathing (e.g. carbonic anhydrase inhibitors, barbiturates, CNS depressants) were excluded. Use of alcoholic or caffeinated beverages 6 hours prior to the tests was prohibited. Use of regular pulmonary medication was allowed. All patients gave their written informed consent. The study was approved by the local Medical Ethics Committee.

5.3.2 Design and intervention

Metabolic acidosis was induced by drinking a solution containing ammonium chloride (15 $mg.ml^{-1}$) and liqourice. The aim was to cause a decrease in base excess (BE) of 2 $mmol.L^{-1}$. The amount be ingested to reach this degree of acidification, was calculated by assuming an extra cellular water compartment of one third of body weight.[9] After baseline measurements, subjects received either NH_4Cl or a solution containing only liquorice, in a randomized and double-blind cross-over design. Administration of the fluid was repeated after 60 minutes in order to keep plasma levels constant. Measurements were repeated 90 minutes after ingestion of the first dose, to establish *acute* effects of metabolic acidosis. Thereafter, patients went home drinking the solution once a day during one week. After one week, assessments were repeated before and after ingestion of the fluid to measure *chronic*, respectively *acute-on-*

chronic effects of metabolic acidosis. After a washout-period of one week, cross-over took place and another series of measurements was performed.

5.3.3 Measurements

Baseline pulmonary function consisted of measuring forced expiratory volume in-one-second (FEV_1), forced expiratory ratio (FEV_1/FVC), total lung capacity (TLC), residual volume (RV) and inspiratory capacity (IC), using standard techniques.[12]

Primary variables included arterial blood gas values and ventilatory responses to hypercapnia (HCVR), respectively hypoxia (HVR). Secondary variables included airway resistance (R_{aw}), respectively airway conductance (sG_{aw}), respiratory and peripheral muscle function, exercise performance and dynamic hyperinflation.

Arterial blood gas values were obtained after at least 15 minutes of rest, to determine shifts in the acid-base equilibrium. HCVR was tested under normoxic conditions by the steady-state method.[13] Subjects were connected to a closed spirometry circuit, in which the CO_2 level could be increased by adjusting a 3-way valve, partially short-circuiting a CO_2 absorber in the inspiratory limb of the circuit. The end-tidal CO_2 tension ($P_{ET}CO_2$) was measured with a sampling capnograph (Multicap, Datex Instrumentarium Corp., Helsinki Finland). HCVR was expressed in terms of slope S ($\Delta VE/\Delta P_{ET}CO_2$) and intercept B of the ventilatory response curve ($VE=S(P_{ET}CO_2-B)$).

HVR was assessed by inducing progressive isocapnic hypoxia.[14] $P_{ET}CO_2$ was kept constant at baseline value. All subjects started the test at normoxia (SaO_2 > 95%). SaO_2 was measured by pulse oximetry (Criticare Systems Inc., 504-US). Inspiratory O2 was decreased by stopping the oxygen supplementation. The test was stopped when SaO_2 reached 80%. HVR was expressed as slope S ($\Delta VE/\Delta SaO_2$) and intercept B ($VE=S(SaO_2-B)$). During both HCVR and HVR, $P_{ET}CO_2$, breathing frequency (fr) and tidal volume (Vt) were recorded on an analogue chart recorder (Servogor 122 AC, Kipp & Zonen).

Airway resistance (R_{aw}) and specific airway conductance (sG_{aw}) were determined using body plethysmography (Masterlab Pro, Jaeger Würzburg).

Respiratory muscle strength was determined by $P_i$max and $P_e$max, measured at RV and TLC respectively. $P_i$max and $P_e$max were defined as the highest plateau-value out of three reproducible measurements with a maximum variability of 10%.[15] Peripheral muscle strength was assessed by maximal isometric hand grip strength (Pgrip) with a hand-dynamometer (JAMAR 5030J1 Hydraulic hand dynamometer, Sammons

Preston® Bolingbrook, IL 60440).[16] The highest value of the dominant hand of at least three reproducible attempts was noted as maximal isometric hand grip strength (kilograms force).

Exercise performance was determined by six-minute walking distance (6MWD) under standardized conditions.[17,18] Patients were encouraged every two minutes by the investigator. Heart rate and oxygen saturation (SaO_2) were measured by pulse oximetry during the test. Highest heart rate and lowest oxygen saturation were also noted. Dynamic hyperinflation was measured in terms of inspiratory capacity (IC) before and within three minutes after 6MWD.

5.3.4 Statistical Analysis

Statistical analyses were performed using statistical software (SPSS for Windows; Version 11.0; SPSS; Chicago, IL; and SAS; Version 8.2; Institute Inc.; Cary, NC). Descriptive data are presented as mean ± standard deviation (SD) or as number (percentage). A mixed model ANOVA was performed to evaluate the effect of metabolic acidosis on the outcome variables investigated. Adjustments were made for period (period 1 and 2) and time. Before starting this study we made a priori the highly plausible assumption that a carry-over effect was impossible when crossing over from one therapy to the other with a wash-out period of one week in between.

5.4 Results

Nine chronic hypercapnic COPD patients (7 male; mean age 65.3 ± 8.5 (SD) years) completed the study. Further characteristics are described in Table 1.

5.4.1 Induction of metabolic acidosis

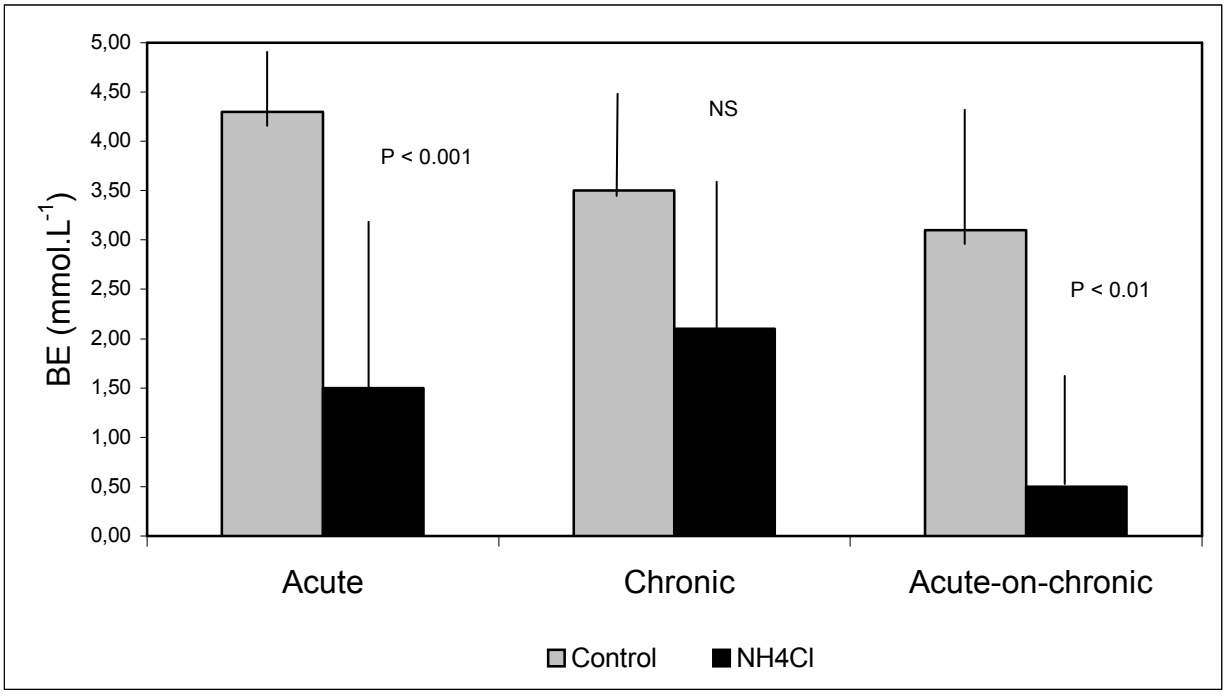
Ingestion of NH_4Cl significantly induced an acute metabolic acidosis. BE significantly decreased after NH_4Cl as compared to placebo (mean BE 1.5 ± 2.0 $mmol.L^{-1}$, respectively 4.3 ± 0.8 $mmol.L^{-1}$). (Figure 1)

Table 1. *Patients' characteristics*

Variables	Mean		Variables	Mean		
Number	9		RV, % predicted	178.8	±	55.1
Gender, male	7	(77.8)	R_{aw}, kPa.sec.L^{-1}	0.8	±	0.3
Age, years	65.3	± 8.5	sG_{aw}, 1/(kPa.sec)	0.3	±	0.1
BMI, kg.m^{-2}	26.9	± 4.2	$P_i$max, % predicted	106.5	±	27.7
Current smoking, yes	3	(33.3)	$P_e$max, % predicted	120.6	±	32.8
Packyears	27.8	± 18.4	$PaCO_2$, mmHg	48.0	±	3.0
FEV_1, % predicted	35.6	± 8.6	PaO_2, mmHg	64.5	±	6.8
FEV_1/VC, %	30.7	± 6.5	HCVR, L.min^{-1}.mmHg	0.6	±	0.3
IC, % predicted	88.7	± 14.0	HVR, L.min^{-1}.%	-0.2	±	0.5
TLC, % predicted	118.2	± 15.5	6MWD, meters	394.2	±	117.0

Data are presented as mean ± SD (standard deviation) or number (%). Y (yes): parameter is present in subject.

Figure 1. *Induction of metabolic acidosis*



Graph shows mean base excess (BE) values after ingestion of ammonium chloride (NH_4Cl) respectively placebo (control). Acute, chronic and acute-on-chronic effects are shown. P-value < 0.05 is considered significant. NS: not significant.

Likewise a significant drop was found in pH (p=0.04) and [HCO_3^-] (p<0.001). Chronic ingestion of NH_4Cl did not significantly lower pH, nor [HCO_3^-] (p= 0.5, respectively 0.2) BE also did not decrease after chronic NH_4Cl (2.1 ± 1.8, versus 3.5 ± 1.2 mmol.L^{-1} after placebo). (Figure 1) On the other hand, in the acute-on-chronic situation, BE dropped significantly in NH_4Cl (0.5 ± 1.4, versus 3.1 ± 1.6 in placebo). (figure 1) Similarly, a significant fall was found in pH (p=0.01) and [HCO_3^-] (p=0.01).

5.4.2 Effects of metabolic acidosis on ventilation.

Acute metabolic acidosis significantly lowered *P*aCO_2. (Table 2)

Table 2. *Effects of metabolic acidosis on ventilation.*

		***P*aCO_2** mmHg	***P*aO_2** mmHg	**Slope HCVR** L.min^{-1}.mmHg	**Slope HVR** L.min^{-1}.%
Acute	Control	48.8 ± 3.0	63.0 ± 6.8	0.7 ± 0.3	-0.1 ± 0.2
	Acidosis	47.3 ± 2.3	67.5 ± 7.5	0.6 ± 0.3	-0.4 ± 0.8
	p-value	***0.02***	*0.4*	*0.8*	*0.6*
Chronic	Control	48.0 ± 3.8	64.5 ± 7.5	0.8 ± 0.4	-0.4 ± 0.8
	Acidosis	46.5 ± 2.3	64.5 ± 4.5	0.6 ± 0.2	-0.01 ± 0.2
	p-value	*0.09*	*0.9*	***0.03***	*0.4*
Acute on chronic	Control	48.8 ± 3.8	63.0 ± 9.0	0.7 ± 0.2	-0.1 ± 0.2
	Acidosis	47.3 ± 3.8	66.8 ± 6.0	0.4 ± 0.2	-0.1 ± 0.1
	p-value	*0.3*	*0.5*	*0.06*	*0.6*

Effects are shown after acute, chronic, respectively acute-on-chronic metabolic acidosis. Data are presented as mean ± SD (standard deviation). P-value < 0.05 is considered significant. $PaCO_2$: arterial carbon dioxide tension (mmHg). PaO_2: arterial oxygen tension (mmHg). HCVR: hypercapnic ventilatory response (L.min^{-1}.mmHg). HVR: hypoxic ventilatory response (L.min^{-1}.%)

PaO_2 tended to be higher after induction of acute metabolic acidosis, however this was not statistically significant. (Table 2) Slopes of HCVR and HVR did not significantly change after induction of acute metabolic acidosis. (Table 2) The same was found for intercepts of HCVR, respectively HVR (p=0.7, respectively p=0.6) Chronic metabolic acidosis tended to lower *P*aCO_2, but without statistical significance. Chronic metabolic acidosis significantly lowered the slope of HCVR. However, neither

changes in breathing frequency nor in tidal volume reached statistical significance (p=0.4, respectively p=0.5). Intercept of HCVR after chronic induction of metabolic acidosis also did not significantly change (p=0.09) Other ventilatory parameters were not affected by either chronic or acute-on-chronic metabolic acidosis. (Table 2)

5.4.3 Effects of metabolic acidosis on other parameters

Table 3 shows that acute, chronic and acute-on chronic metabolic acidosis did not affect R_{aw}, $P_i$max, Pgrip and 6MWD. Maximum heart rate during 6MWD was significantly lower in chronic metabolic acidosis (116.3 ± 7.4 min^{-1}) as compared to placebo (119.5 ± 5.6 min^{-1}) (p=0.04). No statistically significant effects were found on sG_{aw}, $P_e$max, and dynamic hyperinflation (delta IC before and after 6MWD).

Table 3. *Effects of metabolic acidosis on airway resistance, muscle function and exercise tolerance.*

		R_{aw} kPa.sec. L^{-1}	$P_i$max % predicted	Pgrip % predicted	6MWD meters
Acute	Control	0.9 ± 0.3	102.3 ± 30.3	109.5 ± 19.3	389.4 ± 142.7
	Acidosis	0.8 ± 0.3	109.2 ± 29.6	103.9 ± 19.5	411.8 ± 107.8
	p-value	*0.4*	*0.3*	*0.06*	*0.3*
Chronic	Control	0.9 ± 0.3	103.3 ± 28.6	108.5 ± 19.0	382.0 ± 149.8
	Acidosis	0.9 ± 0.3	114.5 ± 27.9	104.5 ± 17.7	400.4 ± 97.4
	p-value	*0.6*	*0.1*	*0.2*	*0.6*
Acute on chronic	Control	0.8 ± 0.3	105.5 ± 27.1	108.9 ± 16.2	428.4 ± 97.3
	Acidosis	0.8 ± 0.2	104.6 ± 29.3	106.2 ± 22.4	357.2 ± 116.0
	p-value	*0.3*	*0.8*	*0.7*	*0.5*

Effects are shown after acute, chronic, respectively acute-on-chronic metabolic acidosis. Data are presented as mean ± SD (standard deviation). P-value < 0.05 is considered significant. R_{aw}: airway resistance (kPa.sec.L^{-1}). $P_i$max: maximum inspiratory pressure (% predicted). Pgrip: maximum isometric handgrip strength of the dominant hand (kgf). 6MWD: six minute walking distance (total distance walked in meters).

5.5 Discussion

Ingestion of NH_4Cl induced an acute metabolic acidosis. No change in the acid-base equilibrium was found after chronic ingestion of NH_4Cl, whereas acute-on-chronic ingestion of NH_4Cl again caused a metabolic acidosis in chronic hypercapnic COPD patients. $PaCO_2$ was lowered only in acute metabolic acidosis. Hypercapnic ventilatory response was lowered after chronic ingestion of NH_4Cl. No effects were found on hypercapnic and hypoxic ventilatory responses, airway resistance, respiratory and peripheral muscle function, or exercise tolerance of these chronic hypercapnic COPD patients.

We were able to induce an acute metabolic acidosis in chronic hypercapnic COPD patients by oral administration of NH_4Cl. Our hypothesis was that induction of a metabolic acidosis in these patients would stimulate ventilation and improve arterial blood gas values. We found that acute metabolic acidosis decreased $PaCO_2$ in these patients. However, the effect was very small and not accompanied by significant changes in breathing no frequency or tidal volume. Neither did we find any changes in ventilatory responses. A decrease in $PaCO_2$ has been found in other studies, investigating the effect of metabolic acidosis induced by oral NH_4Cl on ventilatory parameters.[9,10,19] Tojima et al.[10] studied a group of healthy male subjects and found that metabolic acidosis (delta $[HCO_3^-]$ 5.6 ± 1.8 $mmol.L^{-1}$) was followed by a decrease in $PaCO_2$, as well as an increase in inspiratory minute ventilation. Lerche et al.[19] induced a mean ΔBE of –6.0 $mmol.L^{-1}$ by oral NH_4Cl in their subjects and they also found a decrease in $PaCO_2$, as well as an increase in ventilation. In a study by van de Ven et al.[9] induction of acute metabolic acidosis in 15 healthy subjects (age 46-68 years) under normocapnic conditions (mean PCO_2 38.3 ± 3.0 mmHg) significantly decreased capillary arterialized PCO_2 by 1.5 ± 1.3 mmHg, whereas minute ventilation significantly increased from 7.6 ± 1.4 $L.min^{-1}$ to 10.0 ± 2.4 $L.min^{-1}$. [9] The decrease in BE in their study (–2.7 ± 1.3 $mmol.L^{-1}$) was comparable to our own results (delta BE –3.0 ± 0.8 $mmol.L^{-1}$) Neither van de Ven et al.[9], or Lerche et al.[19] found changes in the slopes of the ventilatory response curves after induction of metabolic acidosis. Tojima et al.[10], however, found that the HCVR slope significantly increased 0.6 ± 0.4 $L.min^{-1}$.mmHg in metabolic acidosis. Similarly, an increase was found in the slope of the hypoxic ventilatory response.[10]

Surprisingly, we found a decrease in the slope of the hypercapnic ventilatory response curve after induction of chronic metabolic acidosis. There could be several possible explanations for this. In patients with severe COPD, a trigger of the ventilation by metabolic acidosis could be limited by the severity of their disease.[20] Respiratory muscle fatigue could occur, increasing CO_2 retention and lowering HCVR.[20] However, we did not find lower respiratory muscle strength, or an increase in $PaCO_2$. Therefore, it is not likely that this was the case in our group of patients. Secondly, the result that we found could be a statistical coincidence, caused by the small number of patients. Considering the fact that "chronic metabolic acidosis" was never really accomplished, i.e. there was no statistical significant change in pH and BE, it is unlikely that any effect (positive or negative) would occur. If we compare the results of NH_4Cl on ventilation with another drug that induces a metabolic acidosis, namely acetazolamide, we might come to an interesting conclusion. Acetazolamide is a reversible inhibitor of the carbonic anhydrase enzyme and induces a metabolic acidosis by lowering the renal tubular [H^+] excretion and increasing the urinary [HCO_3^-] excretion.[21-23] However, the enzyme is widespread throughout the body, including the kidney, red cells, capillary vascular endothelium, brain, and central and peripheral chemoreceptors.[23, 24] Acetazolamide is a potent respiratory stimulant with effects on arterial blood gas values as well as on ventilatory responses. The increase in ventilation usually reduces $PaCO_2$ by 5.3-6.0 mmHg.[23] With NH_4Cl the effect on ventilation is not that strong. Therefore, the effect of acetazolamide on ventilation could more likely be due to this "carbon anhydrase effect" than to its "pH-effect". However, the effect of acetazolamide on pH seems to be larger than the effect of NH_4Cl.[14,25] In a study among chronic hypercapnic COPD patients, pH decreased from 7.39 ± 0.02 to 7.32 ± 0.02.[25] In our study pH decreased from 7.38 ± 0.02 to 7.35 ± 0.02 after ingestion of NH_4Cl.

We were not able to confirm our hypothesis that metabolic acidosis would affect airway resistance, muscle function, and eventually exercise tolerance and dynamic hyperinflation. A shift in the acid-base equilibrium is known to have an effect on bronchial smooth muscles. In normal[26] and asthmatic subjects respiratory acidosis has been associated with bronchodilatation and a decrease in airway resistance.[27] In a study in healthy subjects[8] induction of metabolic alkalosis significantly increased R_{aw} from 0.16 (0.13 – 0.26) to 0.17 (0.13-0.27) kPa.sec.L^{-1}, whereas sG_{aw} remained unchanged. Metabolic acidosis (a decrease in BE from -0.2 to 3.5 mmol.L^{-1}) showed a small decrease in R_{aw}, although this was not statistically significant.[8] Metabolic

acidosis has been associated with a decrease in muscle contractility of myocardial[5] and peripheral[6] muscles. A decrease in pH diminishes the influx of calcium into the myocyte, reduces the affinity of troponine for calcium and increases the calcium binding to the sarcoplasmatic reticulum.[28,29] Therefore, acidosis could negatively affect muscle function by decreasing the regeneration of adenosine triphosphate via the glycolytic pathway.[28,29] *Respiratory* acidosis ($PaCO_2$ of 54.0 mmHg) caused a significant decrease in diaphragmatic contractility in healthy men.[30] In a study in dogs, *metabolic* acidosis decreased diaphragmatic contractility.[7] However, Yanos et al.[31] did not find a decrease in diaphragm contractility, or in skeletal muscle function of dogs after induction of metabolic acidosis. Brijker et al.[8] studied the effect of metabolic acidosis on respiratory as well as peripheral muscle function in healthy subjects. As in our own study, neither respiratory muscle function was affected by acute metabolic acidosis ($P_i$max 60.8 (41.3-113.3) mmHg after placebo versus 75.8 (40.5-109.5 mmHg after NH_4Cl), nor was peripheral muscle function (Pgrip 36 (29-77) kgf respectively 36 (29-68) kgf).[8]

We also studied chronic and acute-on-chronic effects of NH_4Cl on the acid-base equilibrium. We reasoned that chronic induction of metabolic acidosis could be overruled by respiratory compensation by which possible effects could disappear. Our results show that chronic ingestion of NH_4Cl did not induce a metabolic acidosis. No changes in BE were found either after chronic ingestion of NH_4Cl. Therefore, the fact that the acid-base equilibrium remained unchanged after chronic ingestion was probably due to the short half-life of NH_4Cl. Since we did not induce a shift in the acid-base equilibrium after chronic ingestion of NH_4Cl, it is not surprisingly that we did not find any changes in ventilatory and other parameters. Acute-on-chronic ingestion of NH_4Cl did induce a metabolic acidosis. $PaCO_2$ decreased as well, although without statistical significance.

A possible limitation of this study could be the small number of subjects. In spite of that, we were able to find a statistical significant effect on acid-base changes. Therefore, it may be expected that the number of patients might have been sufficient to find a possible effect of metabolic acidosis on any of the other parameters as well, i.e. there would have been one.

We conducted this study to demonstrate that oral ammonium chloride could be a clinically relevant respiratory stimulant in chronic hypercapnic COPD patients. NH_4Cl only has an acute effect on ventilation in chronic hypercapnic COPD patients.

Nevertheless, with this study we were able to study the effects of pure isolated metabolic acidosis (without effects on CO_2 transport, as in acetazolamide) on several ventilatory and other clinical relevant parameters in chronic hypercapnic COPD patients. We did not find any negative effects of metabolic acidosis on respiratory muscle function. Therefore, this may also mean that a clinical situation in which metabolic acidosis may be present (e.g. ketoacidosis in diabetes mellitus, renal failure, sepsis) is not per se a potential hazard for severe COPD patients with respiratory failure. Moreover, it is assumable that the respiratory stimulatory effect of acetazolamide is reached by other pathways than through metabolic acidosis.

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Chapter 6

Long-term use of acetazolamide does not improve ventilation in chronic hypercapnic COPD patients

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6.1 Abstract

Chronic hypercapnic respiratory failure in COPD patients has been associated with lower survival rates. To improve survival of these patients by lowering hypercapnia, drugs that stimulate ventilation should be given for a longer period of time. Acetazolamide is a respiratory stimulant that acts by inducing a metabolic acidosis. However, metabolic acidosis has also been associated with lower respiratory muscle strength and, therefore, may counteract the respiratory response. The aim of this study was to investigate the effects of long-term use (6 months) of acetazolamide on arterial blood gas values ($PaCO_2$, PaO_2), ventilatory responses to hypercapnia (HCVR) and hypoxemia (HVR), airway resistance (R_{aw}) and respiratory muscle strength ($P_i$max and $P_e$max).

Fifteen chronic hypercapnic COPD patients (8 male; mean age 66.3 ± 9.6 years) participated in a randomized placebo-controlled study. 7 patients (3 male; mean age 67.8 ± 10.1 years) received acetazolamide 250mg b.i.d. during 6 months. $PaCO_2$, PaO_2, HCVR, HVR, R_{aw}, $P_i$max and $P_e$max were measured after three and six months. Acetazolamide induced a statistically significant metabolic acidosis after three months, as well as after six months (pH decreased from 7.38 ± 0.01 to 7.32 ± 0.02 after 3 months, respectively 7.33 ± 0.05 after 6 months). $PaCO_2$ tended to be reduced (49.5 ± 2.3 mmHg at baseline versus 48.0 ± 2.3 mmHg) after three months of acetazolamide, but did not reach statistical significance. (p=0.09) No effects were found on HCVR, HVR, R_{aw}, $P_i$max and $P_e$max.

In this study no clinical benefit of long-term administration of acetazolamide in stable chronic hypercapnic COPD patients was shown. We did not find any negative effects of acetazolamide. Therefore, we conclude that acetazolamide can be used safely in chronic hypercapnic COPD patients.

Key Words: *Pulmonary diseases, chronic obstructive; Carbonic Anhydrase Inhibitors; Acetazolamide; Hypercapnia; Respiratory muscle function; Control of breathing*

6.2 Introduction

A subgroup of COPD patients develops chronic hypercapnic respiratory failure. This is the result of alveolar hypoventilation, caused by an imbalance between the load on the ventilatory pump and the ventilatory capacity.[1] Acute hypercapnia causes a respiratory acidosis. This respiratory acidosis stimulates central and peripheral chemoreceptors, which leads to an increase in ventilation and, subsequently, to a reduction in arterial carbon dioxide tension.[2,3] However, when CO_2 retention becomes chronic, renal compensation occurs by retention of bicarbonate [HCO_3^-]. Normalization of pH limits the stimulus for ventilation and aggravates hypercapnia and hypoxemia. By inducing metabolic acidosis in chronic hypercapnic COPD patients, the drop in arterial pH causes a new stimulus for ventilation and could, therefore, decrease hypercapnia.

Chronic hypercapnia has been associated with a poor survival in COPD patients.[4-6] Moreover, the presence of hypercapnia has been related to several negative systemic effects on cellular tissue[7], the cardiovascular system (impaired contractility of cardiac and vascular smooth muscle[8], decrease in systemic vascular resistance[9]), and the central nervous system[7] (cerebral vasodilation, increased intra-cranial pressure). Therefore, a reduction in arterial carbon dioxide tension could, theoretically, be beneficial for chronic hypercapnic COPD patients.

To decrease hypercapnia, and subsequently improve survival in chronic hypercapnic COPD patients, drugs inducing metabolic acidosis might be of benefit when given for a longer period of time.

A drug that can induce metabolic acidosis is acetazolamide, a carbonic anhydrase (CA) inhibitor. Acetazolamide acts by lowering the proximal tubular [HCO_3^-] reabsorption and distal tubular hydrogen [H^+] secretion. Previous trials have concentrated on short term (up to 14 days) effects of acetazolamide treatment[10-14] or were carried out in animals.[15] The long term effect of acetazolamide on ventilation, particularly in patients with chronic hypercapnic COPD, is not well known.

Carbonic anhydrase is an enzyme, which is localized in many tissues, such as peripheral and central chemoreceptors, erythocytes, muscular tissue and in lung as well as cerebral capillary endothelium. This contributes to the complexity of the mechanism of control of breathing. It has been suggested that the efficacy of acetazolamide as a respiratory stimulant depends not only on the pH effect on central and peripheral chemoreceptors, caused by the generation of metabolic acidosis due to

renal CA inhibition, but also on local effects, i.e. inhibition of intracellular CA isoenzymes in red cells and tissues (e.g. brain, lung).[16]

The aim of our study was to investigate the long-term effect of acetazolamide on the acid-base equilibrium and on ventilation in stable chronic hypercapnic patients with COPD.

Metabolic acidosis has been shown to decrease respiratory muscle strength and endurance.[17] Moreover, it has been shown to affect smooth bronchial muscle as well. In a study in healthy subjects a small decrease in airway resistance was seen after induction of acute metabolic acidosis.[18] Therefore, we were also interested if long-term use of acetazolamide decreased respiratory muscle strength and airway resistance.

6.3 Methods

6.3.1 Study Population

Fifteen chronic hypercapnic COPD patients (8 male; mean age 66.3 ± 9.6 years) were selected consecutively from the outpatient pulmonary department of the Rijnstate Hospital Arnhem (NL). COPD was determined according to GOLD criteria.[19] Chronic hypercapnia was defined as $PaCO_2$ > 45.0 mmHg recorded twice with an interval of at least 6 weeks. All patients were clinically stable (i.e. no changes in medication, and no exacerbations of COPD or hospital admissions in the preceding 6 weeks). Patients with other pulmonary diseases, sleep-related breathing disorders, chronic renal or liver failure, known allergy for sulfates, use of drugs influencing the control of breathing (e.g. barbiturates, CNS depressants) or use of metformin were excluded. Use of alcoholic or caffeinated beverages 6 hours prior to the tests was prohibited. Use of regular pulmonary medication and use of long-term oxygen therapy was allowed. All patients gave their written informed consent. The study was approved by the local Medical Ethics Committee.

6.3.2 Design and intervention

After baseline measurements patients received either acetazolamide (Diamox ®), 250 mg b.i.d, or placebo in a randomized, placebo-controlled design during the period of six months.

6.3.3 Measurements

Baseline pulmonary function consisted of measuring forced expiratory volume in-one-second (FEV_1), forced expiratory ratio (FEV_1/FVC), total lung capacity (TLC), residual volume (RV) and inspiratory capacity (IC), using standard techniques.[20]

Primary variables included arterial blood gas values and ventilatory responses to hypercapnia (HCVR), respectively to hypoxia (HVR). Secondary variables included airway resistance (R_{aw}), respectively airway conductance (sG_{aw}), respiratory muscle function, and exercise performance.

The effect of acetazolamide versus placebo, on all variables was measured after six months. The effect on primary variables was investigated after three months as well.

Arterial blood gas values were obtained after at least 15 minutes of rest in sedentary position. HCVR was tested under normoxic conditions by the steady-state method.[21] Subjects were connected to a closed spirometry circuit, in which the CO_2 level could be increased by adjusting a 3-way valve, partially short-circuiting a CO_2 absorber in the inspiratory limb of the circuit. The end-tidal CO_2 tension ($P_{ET}CO_2$) was measured with a sampling capnograph (Multicap; Datex Instrumentarium Corp.; Helsinki Finland). HCVR was expressed in terms of slope S ($\Delta VE/\Delta P_{ET}CO_2$) and intercept B of the ventilatory response curve ($VE=S(P_{ET}CO_2-B)$).

HVR was assessed by inducing progressive isocapnic hypoxia.[22] $P_{ET}CO_2$ was kept constant at baseline value. All subjects started the test at normoxia (SaO_2 > 95%). SaO_2 was measured by pulse oximetry (Criticare Systems Inc.; 504-US). Inspiratory O_2 was decreased by stopping the oxygen supplementation. The test was stopped when SaO_2 reached 80%. HVR was expressed as slope S ($\Delta VE/\Delta SaO_2$) and intercept B ($VE=S(SaO_2-B)$). During both HCVR and HVR, $P_{ET}CO_2$, breathing frequency (fr) and tidal volume (Vt) were recorded on an analogue chart recorder (Servogor 122 AC; Kipp & Zonen).

Airway resistance (R_{aw}) and specific airway conductance (sG_{aw}) were determined using body plethysmography (Masterlab Pro; Jaeger Würzburg).

Respiratory muscle strength was determined by $P_i$max and $P_e$max, measured at RV and TLC respectively. $P_i$max and $P_e$max were defined as the highest plateau-value out of three reproducible measurements with a maximum variability of 10%.[23]

Exercise performance was determined by six-minute walking distance (6MWD) under standardized conditions. [24, 25] Patients were encouraged every two minutes by the

investigator. Patients were allowed to rest during the test. 6MWD was expressed in terms of total walking distance.

6.3.4 Statistical Analysis

Statistical analyses were performed using statistical software (SPSS for Windows; Version 11.0; SPSS; Chicago, IL). Descriptive data are presented as mean ± standard deviation (SD) or as number (percentage). The acetazolamide group was compared to the placebo group using the Mann-Whitney-U-test for two independent samples. Within groups baseline was compared to the effects after three, respectively six months using Wilcoxon matched-paired signed-rank test.

6.4 Results

Table 1. *Patients' characteristics.*

Variables	Mean Acetazolamide	Mean Placebo	*p*-value
Number	7	8	
Gender, Male	3 (42.9)	5 (62.5)	
Age, years	67.0 ± 11.5	65.6 ± 8.4	0.2
BMI, $kg.m^{-2}$	26.2 ± 4.2	27.4 ± 4.6	0.7
Current smoking, y	2 (28.6)	2 (25.0)	
Packyears	33.0 ± 17.8	25.8 ± 18.6	0.5
FEV_1, % predicted	38.4 ± 16.1	35.4 ± 6.7	0.7
FEV_1/VC, %	31.4 ± 8.7	31.1 ± 7.6	0.9
IC, % predicted	95.1 ± 12.0	89.4 ± 14.3	0.4
R_{aw}, $kPa.sec.L^{-1}$	1.0 ± 0.2	0.7 ± 0.4	0.2
$P_i$max, % predicted	96.8 ± 36.8	107.0 ± 38.9	0.1
$P_e$max, % predicted	108.6 ± 24.6	108.9 ± 28.8	0.4
$P\,aCO_2$, mmHg	49.5 ± 2.3	47.3 ± 2.3	0.06
$P\,aO_2$, mmHg	60.8 ± 3.8	62.3 ± 6.8	0.8
HCVR, $L.min^{-1}.mmHg$	0.6 ± 0.2	0.6 ± 0.3	0.9
HVR, $L.min^{-1}.\%$	-0.02 ± 0.1	-0.3 ± 0.6	0.6

Data are presented as mean ± SD or number (percentage). BMI: body mass index. FEV_1: forced expiratory volume in-one-second. FEV_1/IVC: forced expiratory ratio. IC: Inspiratory Capacity. R_{aw}:

airway resistance. $P_i$max: maximum inspiratory pressure. $P_e$max: maximum expiratory pressure. $PaCO_2$: carbon dioxide tension. P-value < 0.05: significant difference in means between groups. Y (yes): parameter is present in subject.

Fifteen chronic hypercapnic COPD patients (15 male; mean age 67.4 ± 8.8 years) completed the study. Seven patients (3 male; mean age 67.8 ± 10.1 years) had received acetazolamide. Groups did not differ significantly between each other. Further characteristics are shown in Table 1.

6.4.1 Long-term effects of acetazolamide on arterial blood gas values and ventilation

Acetazolamide significantly decreased pH after three months, as well as after six months in comparison to placebo. (Table 2)

Table 2. *Long-term effects of acetazolamide on arterial blood gas values and ventilatory parameters.*

Variables	Acetazolamide			Placebo		
	Baseline	3 months	6 months	Baseline	3 months	6 months
pH	7.38 ± 0.01	7.32 ± 0.02 *	7.33 ± 0.05	7.40 ± 0.02	7.39 ± 0.02 ^	7.39 ± 0.01 #
BE	4.9 ± 1.8	-0.9 ± 2.1 *	1.4 ± 2.5	3.8 ± 0.7	3.9 ± 1.1 ^	3.4 ± 1.0
*P*aCO_2, mmHg	49.5 ± 2.3	48.0 ± 2.3	48.0 ± 3.8	47.3 ± 2.3	47.3 ± 3.8	47.3 ± 3.0
*P*aO_2, mmHg	60.8 ± 11.3	59.3 ± 5.3	65.3 ± 10.5	62.3 ± 6.8	62.3 ± 6.0	64.5 ± 8.3
HCVR, L.min^{-1}.mmHg	0.6 ± 0.2	0.3 ± 0.2	0.6 ± 0.3	0.6 ± 0.3	0.7 ± 0.3	0.8 ± 0.4
HVR, L.min^{-1}.%	-0.3 ± 0.1	-0.9 ± 0.2	-0.2 ± 0.02	-0.3 ± 0.6	-0.2 ± 0.2	-0.5 ± 0.9

*Data are presented as mean ± SD (Standard Deviation) or number (%). *p< 0.01 (acetazolamide: baseline versus 3 months) ^p<0.01 (3 months: acetazolamide versus placebo) #p<0.05 (6 months: acetazolamide versus placebo)*

The negative change in BE was significantly greater in acetazolamide after three months, compared to placebo. After six months the difference did not reach statistical significance. (Table 2) This was also the case for [HCO3-]. Arterial carbon dioxide tension (PaCO2) tended to be reduced (49.5 ± 2.3 mmHg at baseline versus 48.0 ±

2.3 mmHg) after three months of acetazolamide. However, this did not reach statistical significance. (p=0.09) The effect on PaCO2 was not statistical significantly different from the placebo-group. (p=0.7) After six months of treatment PaCO2 was 48.0 ± 3.8 mmHg in the acetazolamide group. Acetazolamide did not have a statistical significant effect on arterial oxygen tension (PaO2). HCVR and HVR did not improve after treatment with acetazolamide. (Table 2)

6.4.2 Effects of metabolic acidosis on other parameters

Table 3 shows that acetazolamide did not affect airway resistance, respiratory muscle strength, or exercise tolerance in terms of 6 minute walking distance.

Table 3. *Long-term effect of acetazolamide on airway resistance, respiratory muscle strength and exercise tolerance.*

Variables	Acetazolamide		Placebo	
	Baseline	*6 months*	*Baseline*	*6 months*
R_{aw}, kPa.sec.L^{-1}	1.0 ± 0.2	1.0 ± 0.2	0.7 ± 0.4	0.7 ± 0.4
$P_i$max, % pred	96.8 ± 36.8	107.0 ± 38.9	108.6 ± 24.6	108.9 ± 28.8
$P_e$max, % pred	107.9 ± 10.2	109.0 ± 11.2	108.2 ± 24.1	104.2 ± 21.5
6MWD, meters	353.2 ± 63.4	355.6 ± 62.2	422.3 ± 35.8	412.2 ± 17.4

Data are presented as mean ± SD (Standard Deviation). No statistical significant differences were found between variables.

6.5 Discussion

Long-term administration of acetazolamide in chronic hypercapnic COPD patients induced a metabolic acidosis after three, as well as after six months. Arterial carbon dioxide tensions tended towards a decrease after three months of treatment with acetazolamide. Six months administration of acetazolamide did not affect arterial oxygen and carbon dioxide tensions, or hypercapnic and hypoxic ventilatory responses, respiratory muscle strength, respectively exercise tolerance.

Acetazolamide has been shown to be an effective short-term respiratory stimulant for hypercapnic COPD patients in previous studies. However, most studies focused on

short-term effects of acetazolamide. Van de Ven et al.[11] studied the effect of one week treatment with acetazolamide 250 mg b.i.d. in 16 normocapnicCOPD patients (FEV_1 28.8 ± 9.6% predicted; $PaCO_2$ 39.8 ± 2.3 mmHg) and 17 hypercapnic COPD patients (FEV_1 24.3 ± 7.0% predicted; $PaCO_2$ 47.4 ± 3.8 mmHg). A siginificant metabolic acidosis was induced in both groups. pH decreased from 7.42 ± 0.02 to 7.35 ± 0.01 in normocapnic, respectively from 7.39 ± 0.02 to 7.32 ± 0.02 in hypercapnic COPD patients.[11] pH in our study decreased similarly after treatment with acetazolamide (pH 7.38 ± 0.01 at baseline, respectively 7.32 ± 0.02 after three months of acetazolamide). In the study of van de Ven et al.[11] $PaCO_2$ decreased siginificantly in boths groups after acetazolamide ($PaCO_2$ from 39.8 ± 2.3 mmHg to 35.3 ± 3.0 mmHg in normocapnic COPD patients, respectively from 47.3 ± 3.8 mmHg to 45.0 ± 5.3 mmHg in hypercapnic COPD patients). In our study $PaCO_2$ decreased from 49.5 ± 2.3 mmHg to 48.0 ± 2.3 mmHg after three months of acetazolamide. The effect was as small as in the study by van de Ven et al.[11] However, in our study it did not reach statistical significance, which was probably due to a small number of patients. The number of patients in the study by van de Ven et al. was also small, but a cross-over design was used in their study.[11] Another study that investigated the effect of *one week* treatment of acetazolamide was a study in 53 hypoxemic COPD patients by Vos et al.[12] In this study $PaCO_2$ decreased significantly by 3.8 mmHg on average.[12]

A *two-week* effect of acetazolamide 250mg b.i.d. was studied by Wagenaar et al.[10] In their group of 12 stable chronic hypercapnic COPD patients (mean age 68.0 ± 2.0 years, FEV_1 33.0 ± 4.0% predicted), $PaCO_2$ significantly decreased from 47.3 ± 1.5 mmHg to 42.0 ± 1.5 mmHg.[10] In comparison to our study, the short-term effect of acetazolamide on $PaCO_2$ was larger.

In our study we did not find a long-term effect of acetazolamide on PaO_2. In the study by van de Ven et al.[11] a small but significant effect was found on PaO_2 in normocapnic COPD patients. PaO_2 increased from 68.3 ± 4.5 mmHg to 71.3 ± 6.0 mmHg. The effect on PaO_2 in hypercapnic COPD patients was not statistically significant.[11] In the study by Wagenaar et al.[10] PaO_2 significantly improved from 65.3 ± 2.3 mmHg to 75.0 ± 3.0 mmHg after acetazolamide. An improvement of 11.3 mmHg was found by Vos et al.[12]

Hacki et al.[26] investigated short-term effects (3 days), as well as long-term effects (4.5 months; range 1-7 months) of acetazolamide (250mg b.i.d.) in COPD patients with hypoxemia (PaO_2 48.8 ± 5.3 mmHg) and hypercapnia ($PaCO_2$ 50.3 ± 3.8 mmHg).[26]

During the short-term phase a cross-over design was used. PaO_2 significantly increased to 57.8 ± 6.8 mmHg after acetazolamide, followed by a drop in PaO_2 to 52.5 ± 6.0 mmHg after cross-over took place to placebo. Hacki et al.[26] investigated the long-term effect by randomizing five patients to the acetazolamide group. After 4.5 months on average, the long-term effect on PaO_2 remained the same (PaO_2 59.3 ± 2.3 mmHg), whereas a significant decrease in PaO_2 was seen in the placebo group (PaO_2 45.8 ± 8.3 mmHg).[26]

In our study we did not find any long-term effects of acetazolamide o hypercapnic, respectively hypoxemic ventilatory responses. In study of van de Ven et al.[11] no significant effect was seen either on hypercapnic ventilatory responses. Wagenaar et al.[10] did not find a statistical significant effect on HCVR after acetazolamide. However, HVR increased significantly from -1.5 ± 0.4 $L.min^{-1}$.% to -3.0 ± 0.8 $L.min^{-1}$.% in their group of chronic hypercapnic COPD patients.[10] In a study of five healthy men, HCVR increased after three doses of 500mg acetazolamide every 6 hours.[27] Bashir et al.[28] found an increase of HCVR of 1.8 ± 0.4 $L.min^{-1}$.mmHg to 2.2 ± 0.3 $L.min^{-1}$.mmHg in healthy subjects. The differences in results between normal subjects and severe COPD patients could be due to the fact that COPD patients with chronic CO_2 retention have a decreased ventilatory response to hypercapnia.[3] Moreover, COPD patients are relatively more on the flat part of the metabolic hyperbola, or the $PaCO_2$ versus minute ventilation curve.[2,3,29]

Metabolic acidosis has been related to a decrease in strength of myocardial muscles[30], and peripheral muscles[31] in men, and a decrease in strength of respiratory muscles in dogs.[32] However, controversial results exist.[17,18] In a study by Brijker et al.[18] in healthy men, no effect was seen on respiratory, respectively peripheral muscle strength in metabolic acidosis. We also could not find an effect of metabolic acidosis induced by acetazolamide on respiratory muscle function.

An increase in $PaCO_2$ has been found to associated bronchodilatation[33] and a subsequent decrease in airway resistance in normal subjects and asthmatics.[34] Therefore, we also hypothesized that induction of metabolic acidosis by acetazolamide might affect airway resistance. Subsequently, the possible effect of acetazolamide on ventilatory parameters and airway resistance could have an effect on exercise tolerance. Since we did not find an effect of acetazolamide on these parameters, it is not surprisingly no effects on exercise tolerance were found either.

However, carbonic anhydrase is an enzyme, which is present widespread throughout the body, including the kidney[35,36], red cells[15,36], capillary vascular endothelium, the brain[35], and the central and peripheral chemoreceptors[35]. Due to complex interactions between these tissues, the actual respiratory response is not always easy to predict. The main increase in respiratory drive by acetazolamide, however, is thought to be caused by induction of a metabolic acidosis, generated by renal inhibition of the carbonic anhydrase enzyme. But some authors suggest that is not just the "pH-effect" that increases the ventilatory drive, but that the efficacy of acetazolamide depends also on local "carbonic anhydrase effects". Low doses of acetazolamide inhibit a membrane-bound isozyme in red cells, also located in the lung and the brain. Partial inhibition of this isozyme leads to a local tissue CO_2 retention, causing an additional stimulating effect on ventilation, whether metabolic acicodosis is present or not. The fact that we did not find any long-term effects of acetazolamide, besides induction of a metabolic acidosis, implicates that these local effects may not play a susbstantial role in ventilation, or that compensatory mechanisms occur that counteract the effects. In a study by Skatrud et al.[37] among COPD patients responders to acetazolamide were compared to non-responders. They found that non-responders were the patients with the most severe airway obstruction (FEV_1 < 24%). One could hypothesize that induction of metabolic adidosis by acetazolamide in severe COPD patients causes an additional stimulus for ventilation on chemoreceptor level, but that these patients are simply not capable of improving blood gas values due to impaired lung function parameters. Due to a small number of patients we were not able to do a subgroup analysis to investigate responders versus non-responders in this study.

This study was conducted to determine the effects of long-term administration of acetazolamide on ventilatory parameters. Hypercapnic respiratory failure in severe COPD patients has been associated with a higher mortality risk. Acetazolamide is a respiratory stimulant that acts by inducing a metabolic acidosis. Improving survival by lowering the $PaCO_2$ in chronic hypercapnic COPD patients implicates that acetazolamide should be given for a longer period of time. However, in our study we were not able to demonstrate a long-term effect of acetazolamide on ventilatory parameters. Therefore, in this study no clinical benefit of long-term administration of acetazolamide in stable chronic hypercapnic COPD patients was shown. Considering the fact that we did not find any negative effects of acetazolamide, it may be

concluded that acetazolamide can be used safely in chronic hypercapnic COPD patients.

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Chapter 7

Summary and Conclusions

7.1 Introduction

Hypercapnic respiratory failure in patients with severe chronic obstructive pulmonary disease (COPD) results from alveolar hypoventilation, due to an imbalance between the load on the ventilatory pump and its capacity.[1] The capacity of the pump depends, among others, on chemoreceptor drive[2], the strength and endurance of the respiratory muscles[3], the degree of hyperinflation, and on the acid-base status of the muscles. Under normal circumstances the respiratory system maintains a homeostasis of the acid-base equilibrium. Hypercapnia causes a respiratory acidosis, which in turn stimulates central and peripheral chemoreceptors, increases ventilation and, subsequently, should lower arterial carbon dioxide tensions. However, when hypercapnia becomes chronic, pH tends to normalize due to renal compensatory mechanisms. Chronic hypercapnia has been shown to have several negative systemic effects: it has been shown to affect cellular tissue[4], the cardiovascular system (impaired contractility of cardiac and vascular smooth muscle[5], decrease in systemic vascular resistance[6]), and the central nervous system[4] (cerebral vasodilation, increased intra-cranial pressure). Moreover, chronic hypercapnia has been related to a poor survival in these patients. Five-year survival of a cohort of 85 COPD patients, admitted to the hospital for an acute exacerbation of the disease, was 11% for the COPD patients that were chronic hypercapnic at entry-time, respectively 33% and 28% for normocapnic and reversible hypercapnic COPD patients.[7] By pharmacologically inducing an acute metabolic acidosis in chronic hypercapnic COPD patients, an additional stimulus of the ventilatory drive could occur. This could diminish hypercapnia and might ultimately improve survival of these patients. Short-term studies (up to 14 days) have shown that induction of acute metabolic acidosis improves arterial carbon dioxide tensions in chronic hypercapnic COPD patients.[8,9] The long-term effect of metabolic acidosis on ventilation in chronic hypercapnic COPD patients has not been studied yet.

Metabolic acidosis, however, has been associated with decreased respiratory muscle strength. Since hypercapnic respiratory failure may be sustained by impaired respiratory muscle function, it was also the question what the net-effect on ventilation would be in chronic hypercapnic COPD patients.

7.2 Predictors of survival of chronic hypercapnic COPD patients

Hypercapnia may be sustained or augmented by a lowered respiratory muscle strength and as well as a lowered ventilatory response to hypercapnia. It was hypothesized that these factors would also be related to a poor prognosis in chronic hypercapnic COPD patients. In **chapter three** a cohort of 47 chronic hypercapnic COPD patients (28 male; mean age 66.3 ± 6.7 years) was followed for 3.8 years on average. The overall survival rate was 61.8%. Of all patients, 55.6% died of acute-on-chronic respiratory failure due to an exacerbation of COPD. After optimal correction for age and gender, an increased mortality risk was found in current smokers (Hazard Ratio (HR) 7.0; 95%-CI) [1.4-35.5]) and in patients with co-morbidity (HR 5.5; [1.7-18.7]). Co-morbidity was present in 38.3% of the patients. Most common co-morbidities were cardiovascular diseases (17.0%), diabetes mellitus (14.9%), and hypertension (8.5%). Survival rate was better in COPD patients who were less hypoxemic (HR 0.6 per 5 mmHg PaO_2; [0.4-1.0]).

Respiratory muscle strength and ventilatory responses to hypercapnia did not predict survival in chronic hypercapnic COPD patients. Hypercapnia itself tended to be less severe in survivors, however without statistical significance (HR 2.0 per 5 mmHg $PaCO_2$; [0.9-4.3]).

Factors that are known to be predictors of survival in normocapnic COPD patients, such as FEV_1 and BMI, did appear to no longer affect survival once these patients had become chronic hypercapnic.

Therefore, therapeutic interventions in this subgroup of COPD patients should focus on smoking cessation programs, treatment of co-morbidities and improvement of arterial blood gas values.

7.3 The effect of acute metabolic acidosis on respiratory and peripheral muscle function

As mentioned before, respiratory muscle fatigue contributes to hypercapnic respiratory failure. By inducing an acute metabolic acidosis we could stimulate ventilation and reduce hypercapnia. However, acidosis can also deteriorate muscle contractility. Consequently, a potential beneficial effect of an additional ventilatory stimulation might be counteracted by a deterioration of the respiratory muscle function. On the other

hand, metabolic acidosis may lower airway resistance (R_{aw}) and, therefore, decrease hyperinflation. Hyperinflation causes a shortening of the respiratory muscles, displacing them to a less advantage position on the length-tension curve. A decrease in R_{aw} could subsequently lead to a increase in muscle strength. In order to obtain insight in these possible counteractive mechanisms, and the net effect on blood gas values, we induced acute metabolic acidosis (ΔBE -3.1 mmol.L^{-1}) in 15 healthy subjects (4 male; age 33.2 ± 11.5 years; FEV_1 108.3 ± 16.2% predicted), 15 asthma patients (5 male; age 62.8 ± 6.8 years; FEV_1 101.6 ± 15.3% predicted) and 14 normocapnic COPD patients (9 male; age 62.8 ± 6.8 years; FEV_1 50.0 ± 11.8% predicted) (**chapter four**). Acute metabolic acidosis did not deteriorate respiratory muscle function, nor endurance time of the respiratory muscles in an endurance threshold loading test in either subgroup ($P_i$max 124.2 % predicted in placebo, versus 121.1% predicted in metabolic acidosis; Endurance time 508.8 seconds in placebo, respectively 519.4 seconds in metabolic acidosis). No effect was seen on peripheral muscle strength and endurance either. The fact that we did not find any differences between groups suggests that the muscles of COPD patients, which are characterized by peripheral muscle dysfunction, a shift from slow-twitch type I fibers toward fast-twitch type II fibers, and an altered metabolic capacity, are not necessarily more fatigueable.

Metabolic acidosis decreased R_{aw} (R_{aw} 0.4 kPa.sec.L^{-1} in placebo, versus 0.3 kPa.sec.L^{-1} in acidosis; p-value 0.003). This small effect on airway resistance, however, was not followed by an effect on respiratory muscle function.

Acute metabolic acidosis decreased arterial carbon dioxide tensions in COPD patients ($PaCO_2$ 41.3 mmHg in placebo, versus 39.8 mmHg in metabolic acidosis (p-value 0.04)). In healthy subjects and in asthmatic patients no such effect was found. A possible explanation for this result could be that COPD patients are more on the horizontal part of the metabolic hyperbola ($PaCO_2$ versus ventilation), since baseline $PaCO_2$ was relatively lower in asthma patients and healthy subjects, compared to COPD patients (baseline $PaCO_2$ 37.5 ± 3.8 mmHg in healthy subjects, 36.8 ± 3.0 mmHg in asthma patients, respectively 41.3 ± 3.8 mmHg in COPD patients (p = 0.01)). This would mean that at higher levels of $PaCO_2$, small increases in minute ventilation would have greater lowering effect on $PaCO_2$, than at lower levels of $PaCO_2$.

7.4 Induction of acute metabolic acidosis in chronic hypercapnic COPD patients

By inducing an acute metabolic acidosis in COPD patients who are chronically hypercapnic, the decrease in pH could add to the stimulation of central and peripheral chemoreceptors. This could augment ventilation and subsequently lower arterial carbon dioxide tensions and improve arterial oxygen tensions.

Ammonium chloride (NH_4Cl) induces an acute metabolic acidosis by decreasing plasma bicarbonate [HCO_3^-] concentration. In nine chronic hypercapnic COPD patients (7 male; age 65.3 ± 8.5 years; FEV_1 35.6 ± 8.6% predicted; $PaCO_2$ 48.0 ± 3.0 mmHg) metabolic acidosis was induced by drinking an oral solution containing NH_4Cl and licorice (**chapter five**). Base excess (BE) was 4.3 ± 0.8 $mmol.L^{-1}$ in placebo, respectively 1.5 ± 2.0 $mmol.L^{-1}$ after ingestion of NH_4Cl. This acute metabolic acidosis lowered $PaCO_2$ (48.8 mmHg ± 3.0 mmHg in placebo, versus 47.3 ± 2.3 mmHg in acute metabolic acidosis). The slopes of the ventilatory responses to hypercapnia, respectively hypoxemia did not change during an acute metabolic acidosis. No effects were found on airway resistance or respiratory muscle strength.

After 7 days of ingesting NH_4Cl once a day, no chronic effect was seen on arterial blood gas values. BE was no longer lowered after ingestion of NH_4Cl (BE 2.1 ± 1.8 $mmol.L^{-1}$ after NH_4Cl, versus 3.5 ± 1.2 $mmol.L^{-1}$ in placebo). However, an acute-on-chronic effect was found on BE. But this effect was too small to have a subsequent effect on other ventilatory parameters.

In comparison to acetazolamide, the effect of NH_4Cl is not as strong on ventilation as is the effect of acetazolamide. The latter has been shown to reduce $PaCO_2$ by 5.3-6.0 mmHg in hypercapnic COPD patients. The effect of acetazolamide on ventilation could, therefore, be more likely to its “carbon anhydrase effect”, than on its “pH-effect”. The effect of NH_4Cl was too small to affect airway resistance, dynamic hyperinflation or exercise-tolerance in terms of six minute walking distance. Moreover, NH_4Cl only had an acute effect on the acid-base equilibrium. Therefore, it seems that NH_4Cl is not a clinically relevant additional respiratory stimulant in chronically hypercapnic COPD patients.

7.5 The long-term effect of acetazolamide on ventilation in chronic hypercapnic COPD patients

To decrease hypercapnia, and subsequently improve survival in chronic hypercapnic COPD patients, drugs inducing a metabolic acidosis could, theoretically, be beneficial if given for longer periods of time. In **chapter six** acetazolamide was compared to placebo in 15 chronic hypercapnic COPD patients (mean age 67.0 ± 11.5 years; FEV_1 38.4 ± 16.1% predicted for the acetazolamide group, respectively 65.6 ± 8.4 years and 35.4 ± 6.7% predicted for the control group) during a period of six months. Acetazolamide caused a significant metabolic acidosis after three (BE decreased from 4.9 ± 1.8 to -0.9 ± 2.1 $mmol.L^{-1}$ in acetazolamide, versus 3.8 ± 0.7 to 3.9 ± 1.1 $mmol.L^{-1}$ in placebo), as well as after six months of treatment (BE 1.4 ± 2.5 $mmol.L^{-1}$). Arterial carbon dioxide tension tended to be lower after three months of acetazolamide ($PaCO_2$ from 49.5 ± 2.3 mmHg to 48.0 ± 2.3 mmHg), however this did not reach statistical significance (p=0.09). Chronic administration of acetazolamide did not affect arterial oxygen tensions, ventilatory responses, or respiratory muscle strength. Therefore, in this study it remains uncertain whether long-term administration of acetazolamide has a clinical benefit for chronic hypercapnic COPD patients.

7.6 General conclusion

Chronic hypercapnic respiratory failure in COPD patients has been associated with lower survival rates. Short-term induction of an acute metabolic acidosis in these patients has been shown to improve ventilatory parameters.[8,9] If long-term induction of a metabolic acidosis could have a similar effect on ventilation as in these short-term studies, this could be beneficial for chronic hypercapnic COPD patients in terms of survival rates. However, metabolic acidosis has also been associated with decreases in respiratory muscle strength. Considering the fact that decreases in respiratory muscle strength could augment or sustain hypercapnic respiratory failure, the net effect of metabolic acidosis on ventilatory parameters in these patients is uncertain. Therefore, in this thesis we were interested in answering two main questions: 1) does induction of metabolic acidosis have a long-term effect on ventilation? and 2) is this effect not counteracted by a negative effect of metabolic acidosis on respiratory muscle strength and endurance? With respect to the first question, the answer,

unfortunately, cannot be found in this thesis. In our study of long-term administration of acetazolamide we did not find an effect on arterial blood gas values or on ventilatory responses. However, due to a small number of patients, we cannot draw definite conclusions from this study. Not only a larger number of patients should be investigated, but also further investigations of long-term physiological effects of acetazolamide on chemoreceptor level are needed. Nevertheless, we were able to confirm that inducing an acute metabolic acidosis is an effective way of stimulating ventilation during short periods of time. Ammonium chloride was found to be able to improve arterial blood gas values by inducing a metabolic acidosis. However, the effect was a small one. And therefore, it is not clear whether ammonium chloride will be a clinical important substitute for acetazolamide. Further studies, comparing acetazolamide to ammonium chloride are needed.

In our study of acetazolamide we did not investigate the effect of acetazolamide on survival of chronic hypercapnic COPD patients. However, the question rises whether hypercapnia is really a *cause* of lower survival rates, or that two parameters are solely associated through other parameters. Clini et al.[10] found that after non-invasive positive pressure ventilation of chronic hypercapnic COPD patients, daytime $PaCO_2$ improved, but this did not improve survival rates. Therefore, the question would be whether our goal should be to improve arterial blood gas values, in order to improve survival, or that we should focus on adjusting the cause of hypoventilation (i.e. ventilation-perfusion mismatch, airway obstruction, etc.), and not sec on decreasing hypercapnia.

Regarding the second question, we did not find a negative effect of metabolic acidosis on respiratory muscle strength or endurance. Therefore, we can conclude that metabolic acidosis can be induced safely and we should not be afraid of negative effects on muscle function, and secondarily on ventilation. Moreover, the respiratory muscle strength and endurance of COPD patients is probably not as impaired as is often suggested.

7.7 References

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Chapter 8

Samenvatting en Conclusies

8.1 Introductie

Hypercapnisch respiratoir falen in patiënten met ernstig chronisch obstructief longlijden (COPD) is het gevolg van alveolaire hypoventilatie, veroorzaakt door een onbalans tussen de belasting op de ventilatoire pomp en zijn belastbaarheid.[1] De belastbaarheid van de pomp is afhankelijk van, onder andere, de chemoreceptor drive[2], de kracht en het uithoudingsvermogen van ademhalingsspieren[3], de mate van hyperinflatie, en van de zuur-base status van de spieren. Onder normale omstandigheden streeft het ademhalingsregelsysteem naar een homeostase van het zuur-base evenwicht. Hypercapnie veroorzaakt een respiratoire acidose, wat op zijn beurt de centrale en perifere chemoreceptoren stimuleert, daardoor neemt de ventilatie weer toe, hetgeen vervolgens tot een vermindering van de arteriële koolzuurspanning leidt. Echter, wanneer de hypercapnie chronisch wordt, treedt een normalisatie van de pH op ten gevolge van renale compensatiemechanismen. Van chronische hypercapnie zijn verscheidene negatieve effecten aangetoond: zo tast het, onder andere, weefsel aan[4], het cardiovasculaire systeem (vermindering van contractiliteit van cardiaal en vasculair glad spierweefsel[5], afname in systemische vasculaire weerstand[6]), en tast het het centrale zenuwstelsel aan[4] (cerebrale vasodilatie, toename intra-craniële druk en vermindering prikkelbaarheid). Bovendien is chronische hypercapnie gerelateerd aan een vermindere levensverwachting van deze patiënten. De vijfjaars-overleving van een cohort van 85 COPD patiënten, opgenomen in een ziekenhuis wegens een acute exacerbatie van de ziekte, was 11% voor de COPD patiënten met chronische hypercapnie ten tijde van opname, respectievelijk 33% en 28% voor COPD patiënten die normocapnisch of reversibel hypercapnisch waren.[7] Door op farmacologische wijze een metabole acidose te induceren in chronisch hypercapnische COPD patiënten, zou een additionele stimulus van de ventilatoire drive kunnen optreden. Hierdoor zou de mate van hypercapnie kunnen afnemen waardoor uiteindelijk de levensverwachting van deze patiënten bevorderd zou kunnen worden. Korte termijn studies (tot 14 dagen) hebben aangetoond dat het induceren van acute metabole acidose, de arteriële koolzuurspanning van chronsich hypercapnische COPD patiënten verbetert.[8,9] De lange termijneffecten van geïnduceerde metabole acidose op de ademhaling van chronisch hypercapnische COPD patiënten is tot op heden nog niet onderzocht.

Metabole acidose is echter ook geassocieerd met een afname van de kracht van ademhalingsspieren. Aangezien hypercapnisch respiratoir falen in stand gehouden kan worden door een verminderde kracht van adehalingsspieren, was ook de vraag wat het netto effect op ventilatie zou zijn bij chronisch hypercapnische COPD patiënten.

8.2 Voorspellers van levensverwachting in chronisch hypercapnische COPD patiënten

Hypercapnie kan in stand gehouden, alsmede verergerd worden, door zowel een afname in de kracht van ademhalingsspieren, als een afname in de ventilatoire respons op hypercapnie. De hypothese was dat deze factoren gerelateerd zouden kunnen zijn aan de prognose van chronisch hypercapnische COPD patiënten. In **hoofdstuk drie** wordt een cohort van 47 chronisch hypercapnische COPD patiënten beschreven (28 mannen; gemiddelde leeftijd 66.3 ± 6.7 jaar), die gedurende gemiddeld 3.8 jaar zijn gevolgd. Zij werden behandeld met “usual care” volgens de internationale GOLD-standaard. De overall overleving was 61.8%. Van alle patiënten overleed 55.6% ten gevolge van acuut-op-chronisch respiratoir falen, veroorzaakt door een exacerbatie COPD. Na toepassing van optimale correctie voor leeftijd en geslacht werd een verhoogd mortaliteitsrisico gevonden in huidige rokers (Hazard Ratio (HR) 7.0; 95%-BI) [1.4-35.5]) en in patiënten met comorbiditeit (HR 5.5; [1.7-18.7]). Comorbiditeit was aanwezig bij 38.3% van alle patiënten. De meest voorkomende comorbiditeiten waren cardiovasculaire aandoeningen (17.0%), diabetes mellitus (14.9%), en hypertensie (8.5%). De levensverwachting was hoger in COPD patiënten die minder hypoxisch waren (HR 0.6 per 5 mmHg PaO_2; [0.4-1.0]).
De kracht van ademhalingsspieren en de ventilatoire responsen op hypercapnie waren geen voorspellers van de levensverwachting van chronisch hypercapnische COPD patiënten. Hypercapnie zelf neigde minder ernstig te zijn in overlevers, echter dit bereikte geen statistische significantie (HR 2.0 per 5 mmHg $PaCO_2$; [0.9-4.3]).
Factoren waarvan bekend is dat ze de overleving voorspellen in normocapnische COPD patiënten, zoals de FEV_1 en BMI, bleken geen effect meer te hebben op de levensverwachting zodra deze patiënten chronisch hypercapnisch geworden waren.

Dientengevolge zouden therapeutische interventies, in deze subgroep van COPD patiënten, gericht moeten zijn op stoppen met roken programma's, de behandeling van comorbiditeiten en het verbeteren van arteriële bloedgas waarden.

8.3 Het effect van acute metabole acidose op de spierfunctie van ademhalingsspieren en perifere spieren

Zoals eerder vermeld draagt zwakte en vermoeidheid van ademhalingsspieren bij aan hypercapnisch respiratoir falen. Door een acute metabole acidose te induceren zouden we de ademhaling kunnen stimuleren en de hypercapnie kunnen verminderen. Echter, acidose kan tevens de contractiliteit van spieren verslechteren. Een potentiëel gunstig effect van een additionele ventilatoire stimulatie zou dus tegengewerkt kunnen worden door een afname van het functioneren van ademhalingsspieren. Anderzijds is het zo dat metabole acidose de luchtwegweerstand (R_{aw}) kan doen verminderen en op die manier de mate van hyperinflatie kan doen afnemen. Hyperinflatie verkort de ademhalingsspieren waardoor ze verplaatst worden naar een verminder gunstige positie op de lengte versus kracht curve. Een afname in R_{aw} zou zo kunnen leiden tot een toename in spierkracht. Om inzicht te verkrijgen in de mogelijk tegengestelde mechanismen en het netto effect op bloedgas waarden, induceerden we acute metabole acidose (ΔBE -3.1 mmol.L^{-1}) in 15 gezonde vrijwilligers (4 mannen; leeftijd 33.2 ± 11.5 jaar; FEV_1 108.3 ± 16.2% voorspeld), 15 astma patiënten (5 mannen; leeftijd 62.8 ± 6.8 jaar; FEV_1 101.6 ± 15.3% voorspeld) en 14 normocapnische COPD patiënten (9 mannen; leeftijd 62.8 ± 6.8 jaar; FEV_1 50.0 ± 11.8% voorspeld) (**hoofdstuk vier**). Acute metabole acidose verminderde kracht noch uithoudingsvermogen van ademhalingsspieren in een zogenaamde "endurance threshold loading test" in geen van de subgroepen ($P_i$max 124.2 % voorspeld in placebo, versus 121.1% voorspeld in metabole acidose; Endurance tijd 508.8 seconden in placebo, respectievelijk 519.4 seconden in metabole acidose). Er werd ook geen effect waargenomen op kracht en uithoudingsvermogen van perifere spieren. Het feit dat we geen verschillen gevonden hebben tussen groepen suggereert dat de dysfunctionerende spieren van COPD patiënten, gekarakteriseerd door een verminderde kracht van perifere spieren, een verschuiving van slow-twitch type I vezels naar fast-twitch type II vezels, en een veranderde metabole capaciteit, niet per definitie vermoeibaarder zijn.

Metabole acidose verminderde R_{aw} (R_{aw} 0.4 kPa.sec.L^{-1} in placebo, versus 0.3 kPa.sec.L^{-1} in acidose; p-waarde 0.003). Dit kleine effect op luchtwegweerstand werd echter niet gevolgd door een effect op spierfunctie van ademhalingsspieren.
Acute metabole acidose verminderde de arteriële koolzuurspanning in COPD patiënten (*P*aCO_2 41.3 mmHg in placebo, versus 39.8 mmHg in metabole acidose (p-waarde 0.04)). In gezonde vrijwilligers en astma patiënten werd een dergelijk effect niet waargenomen. Een mogelijke verklaring hiervoor zou kunnen zijn dat COPD patiënten zich meer op het horizontale deel van de metabole hyperbool (*P*aCO_2 versus ventilatie) bevinden, aangezien de uitgangswaarde *P*aCO_2 relatief lager was in astma patiënten en in gezonde vrijwilligers, in vergelijking met COPD patiënten. (uitgangswaarde *P*aCO_2 37.5 ± 3.8 mmHg in gezonde vrijwilligers, 36.8 ± 3.0 mmHg in astma patiënten, respectievelijk 41.3 ± 3.8 mmHg in COPD patiënten (p = 0.01)). Dit betekent dat bij hogere waarden van *P*aCO_2, kleine toenames in ademminuut volume grotere effecten op verlaging van de *P*aCO_2 zouden hebben dan bij lagere waarden van de *P*aCO_2.

8.4 Inductie van acute metabole acidose in chronisch hypercapnische COPD patiënten

Door een acute metabole acidose te induceren in COPD patiënten met chronische hypercapnie, zou de afname in pH kunnen bijdragen aan de stimulatie van centrale en perifere chemoreceptoren. Hierdoor zou de ventilatie kunnen toenemen en vervolgens de arteriële koolzuurspanning kunnen afnemen en de arteriële zuurstofspanning kunnen verbeteren.
Ammonium chloride (NH_4Cl) induceert een acute metabole acidose door de plasma bicarbonaat [HCO_3^-] concentratie te verlagen. In negen chronisch hypercapnische COPD patiënten (7 mannen; leeftijd 65.3 ± 8.5 jaar; FEV_1 35.6 ± 8.6% voorspeld; *P*aCO_2 48.0 ± 3.0 mmHg) werd metabole acidose geïnduceerd door het drinken van een NH_4Cl- en drop-bevattende hoestdrank (Mixtura Resolvens®) (**hoofdstuk vijf**). Base excess (BE) was 4.3 ± 0.8 mmol.L^{-1} in placebo, respectievelijk 1.5 ± 2.0 mmol.L^{-1} na inname van NH_4Cl. Deze acute metabole acidose verlaagde de *P*aCO_2 (48.8 mmHg ± 3.0 mmHg in placebo, versus 47.3 ± 2.3 mmHg in acute metabole acidose). De hellingen van de ventilatoire responsen op hypercapnie, respectievelijk hypoxie, toonden geen verandering gedurende acute metabole acidose. Op

luchtwegweerstand of spierkracht van ademhalingsspieren werden geen effecten waargenomen.
Na 7 dagen NH_4Cl eenmaal daags te hebben ingenomen, werd geen chronisch effect gevonden op arteriële bloedgas waarden. BE daalde niet meer na langdurige inname van NH_4Cl (BE 2.1 ± 1.8 mmol.L^{-1} na NH_4Cl, versus 3.5 ± 1.2 mmol.L^{-1} in placebo). Echter, er werd wel een acuut-op-chronisch effect gezien op BE. Dit effect was kennelijk te klein om een aanvullend effect op andere ventilatoire parameters te veroorzaken.
Het effect van NH_4Cl op de ademhaling is niet zo krachtig als het effect van de carboanhydrase remmer acetazolamide op de ademhaling. Acetazolamide reduceert de *P*aCO_2 met 5.3-6.0 mmHg in hypercapnische COPD patiënten. Het effect van acetazolamide op ventilatie zou daarom mogelijk meer het gevolg kunnen zijn van zijn "carboanhydrase effect", dan van zijn "pH-effect". Het effect van NH_4Cl was te klein om luchtwegweerstand, dynamische hyperinflatie of inspanningstolerantie, in termen van zes minuten looptest, te beïnvloeden.
NH_4Cl had bovendien slechts een acuut effect op het zuur-base evenwicht. Mede daardoor lijkt het onwaarschijnlijk dat NH_4Cl een klinisch relevant additioneel ademhalingsstimulans is in chronisch hypercapnische COPD patiënten.

8.5 Het lange termijneffect van acetazolamide op ventilatie in chronisch hypercapnische COPD patiënten

Om hypercapnie te verminderen en vervolgens de levensverwachting te verbeteren, in chronisch hypercapnische COPD patiënten, zouden medicijnen die een metabole acidose induceren, theoretisch gunstig kunnen zijn indien ze gedurende langere tijd gegeven worden. In **hoofdstuk zes** is acetazolamide vergeleken met placebo in 15 chronisch hypercapnische COPD patiënten (gemiddelde leeftijd 67.0 ± 11.5 jaar; FEV_1 38.4 ± 16.1% voorspeld voor de acetazolamide groep, respectievelijk 65.6 ± 8.4 jaar en 35.4 ± 6.7% voorspeld voor de controle groep) gedurende een periode van zes maanden.
Acetazolamide induceerde een significante metabole acidose zowel na drie maanden (BE daalde van 4.9 ± 1.8 naar -0.9 ± 2.1 mmol.L^{-1} in acetazolamide, versus 3.8 ± 0.7 naar 3.9 ± 1.1 mmol.L^{-1} in placebo), als na zes maanden van behandeling (BE 1.4 ± 2.5 mmol.L^{-1}). De arteriële koolzuurspanning neigde te verminderen na drie maanden

van acetazolamide ($PaCO_2$ van 49.5 ± 2.3 mmHg naar 48.0 ± 2.3 mmHg). Dit bereikte echter geen statistische significantie (p=0.09). Chronische toediening van acetazolamide had geen effect op de arteriële zuurstofspanning, ventilatoire responsen, noch spierkracht van ademhalingsspieren. Dientengevolge blijft het na dit onderzoek de vraag, of lange termijnbehandeling met acetazolamide een klinisch gunstig effect heeft voor chronisch hypercapnische COPD patiënten.

8.6 Algemene conclusie

Chronisch hypercapnisch respiratoir falen in COPD patiënten is geassocieerd met een afname van de levensverwachting. Van korte termijn inductie van een acute metabole acidose is in deze patiënten aangetoond dat het de ventilatoire parameters en bloedgas waarden verbetert.[8,9] Indien lange termijn inductie van een metabole acidose een vergelijkbaar effect zou kunnen hebben op de ademhaling, zou dit gunstig kunnen zijn voor chronisch hypercapnische COPD patiënten in termen van levensverwachting. Metabole acidose is echter ook geassocieerd met een afname van de kracht van ademhalingsspieren. Rekening houdend met het feit dat een dergelijke afname in spierkracht hypercapnisch respiratoir falen in stand zou kunnen houden, dan wel zou kunnen verergeren, is het netto effect van metabole acidose op ventilatoire parameters in deze patiënten onzeker.
In deze thesis waren wij daarom geïnteresseerd in het beantwoorden van twee voorname vragen: 1) Is er sprake van een lange termijn effect van metabole acidose op de ademhaling? en 2) wordt dit effect niet tegengewerkt door een negatief effect van metabole acidose op kracht en uithoudingsvermogen van ademhalingsspieren?
Met betrekking tot de eerste vraag moet het antwoord ons in deze thesis vooralsnog schuldig blijven. In onze studie van lange termijn toediening van acetazolamide is er geen effect gevonden op arteriële bloedgas waarden of ventilatoire responsen. Ten gevolge van een klein aantal patiënten kunnen we geen definitieve conclusies trekken uit deze studie. Niet alleen zou een groter aantal patiënten onderzocht dienen te worden, ook verder onderzoek naar lange termijn fysiologische effecten is noodzakelijk. Desalniettemin zijn we in staat geweest om te bevestigen dat inductie van een aceute metabole acidose een effectieve manier is om de ademhaling te stimuleren gedurende korte perioden. Van ammonium chloride hebben we aangetoond dat het in staat is om arteriële bloedgas waarden te verbeteren door een

metabole acidose te induceren. Dit effect was echter klein en het blijft dan ook twijfelachtig of ammonium chloride een klinisch relevante substitutie voor acetazolamide zal zijn.

In onze studie van acetazolamide hebben we niet gekeken naar het effect van acetazolamide op de levensverwachting van chronisch hypercapnische COPD patiënten. Het blijft de vraag of hypercapnie daadwerkelijk een *oorzaak* is van een afname in de levensverwachting, of dat twee parameters slechts met elkaar geassocieerd zijn via andere parameters. Clini et al.[10] hebben aangetoond dat na non-invasieve positieve druk beademing van chronisch hypercapnische COPD patiënten, de $PaCO_2$ gedurende de dag verbeterde, maar dat dit geen effect had op de levensverwachting. Dientengevolge blijft het de vraag of ons doel zou moeten zijn om de arteriële bloedgas waarden te verbeteren, om zo de overleving te verbeteren, dan wel dat we ons meer zouden moeten richten op het aanpakken van de oorzaak van de hypoventilatie (d.w.z. ventilatie-perfusie mismatch, luchtwegobstructie, etc.), en niet exclusief op het verminderen van de mate van hypercapnie.

Met het oog op de tweede vraag hebben we geen negatief effect van metabole acidose kunnen waarnemen op kracht of uithoudingsvermogen van ademhalingsspieren. Hieruit mogen we concluderen dat metabole acidose veilig geïnduceerd kan worden zonder te vrezen voor negatieve effecten op spierfunctie, dan wel ventilatie. Bovendien is uit deze studies gebleken dat de spierkracht en het uithoudingsvermogen van ademhalingsspieren van COPD patiënten niet zo aangedaan zijn, als vaak gesuggereerd wordt in de literatuur.

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Curriculum Vitae

Tessa Nizet werd op 1 juni 1976 geboren te Sittard. In 1994 behaalde zij haar V.W.O. diploma aan het Ubbo Emmius Lyceum te Stadskanaal. In dat zelfde jaar ving zij aan met de studie Biomedische Gezondheidswetenschappen aan de Katholieke Universiteit Nijmegen (thans Radboud Universiteit Nijmegen). In 1996 werd zij ingeloot voor de studie Geneeskunde aan dezelfde universiteit, waar zij in 1998 haar doctoraalexamen behaalde. De wetenschappelijke stage, getiteld "*Tremor side effects of salbutamol, quantified by a laser pointer technique*", verrichtte zij in 2000 op het Universitair Longcentrum Dekkerswald te Groesbeek, onder leiding van Prof. Dr. H.Th.M. Folgering. Hiervoor ontving zij in 2001 de aanmoedigingsprijs van de medische faculteit van de Katholieke Universiteit Nijmegen. Haar afsluitend co-schap volgde zij in Guarjila, El Salvador. In augustus 2001 startte zij haar promotie-onderzoek op de afdeling Longziekten van het Rijnstate Ziekenhuis Arnhem. In januari 2005 begon zij als arts-assistent op de afdeling interne geneeskunde van het Máxima Medisch Centrum te Veldhoven (opleider Dr. A.W.L. van den Wall Bake), in het kader van de vooropleiding tot longarts. Sinds januari 2007 is zij werkzaam als longarts in opleiding in het Rijnstate Ziekenhuis Arnhem (opleider Dr. F.J.J. van den Elshout).

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