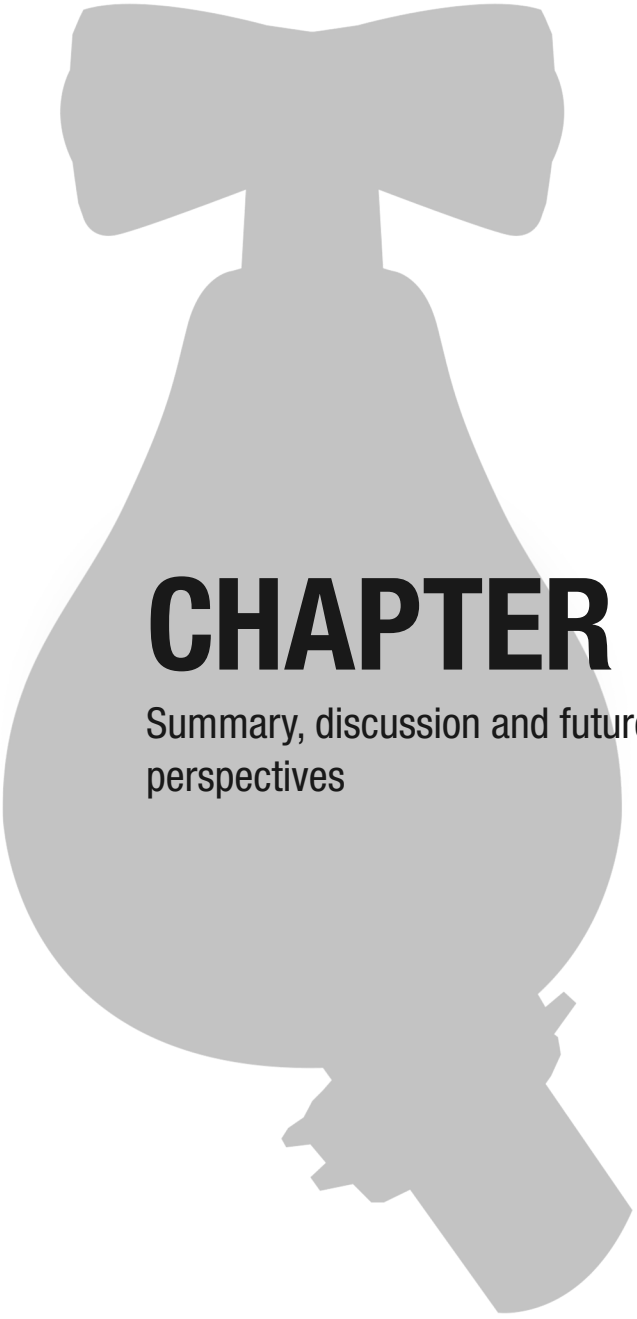

CHAPTER 7

Summary, discussion and future perspectives

SUMMARY

This thesis is about the effects of chronic NIV in COPD patients with chronic hypercapnic respiratory failure. In the first part, we systematically present what has been published in the field of stable COPD.

The second part of this thesis focuses on the results of the RESCUE trial, in which we investigated the effects of nocturnal NIV in patients who remained hypercapnic after having received ventilatory support for acute respiratory failure.

In **chapter 2** a meta-analysis and systematic review of all studies on nocturnal NIV in severe stable COPD are presented according to guidelines set up by the Cochrane Collaboration. We obtained individual patient data of seven studies. These studies were divided into two different groups: those with follow up after three months and after 12 months of NIV. The analysis of the 245 patients showed no consistent clinically or statistically effect on gas exchange, exercise tolerance, health-related quality-of-life (HRQL), lung function, respiratory muscle strength or sleep efficiency after three months of nocturnal NIV. The two new long term studies did not show significant improvements in blood gases, HRQL or lung function after 12 months of nocturnal NIV.

In **chapter 3**, we elaborate on some concerns considering a systematic review on NIV in severe stable COPD.[1] Although we believe that the review constitutes a timely and major contribution, we feel the authors conclusion are too optimistic as they were based mainly on the nonrandomized controlled trials in this field. Also, heterogeneity was present as studies were pooled with different lengths of follow up and type of ventilation (day or nocturnal NIV). In addition, we emphasize the need for proper monitoring (especially during the night) to achieve effective ventilation and the potential effects of higher inspiratory pressures to achieve normocapnia.

In **chapter 4** we first first give an overview of the results of our Cochrane meta-analysis on nocturnal NIV in stable COPD. In the second part, we describe three important subgroup analyses we performed within the nocturnal NIV group based on the individual patient data we gathered. We found that improvements in $PaCO_2$ after three months were statistically greater in the following patients:

- those who received IPAP levels of 18 cm H_2O and higher
- those who used ventilation on average for more than 5 hours per night
- those with baseline hypercapnia levels of over 55 mmHg (7,3 kPa)

Several studies (similar to the RESCUE trial described in the next two chapters) are currently still taking place in Europe (or were at the time of publication of chapter 6), in which the effects of nocturnal NIV are investigated after an episode of acute respiratory failure requiring ventilatory support in hospital. With this in mind, we wanted to compare which questionnaire is the most appropriate for this specific group.

In **chapter 5** the comparison and assessment of four HRQL questionnaires is described in terms of reliability, validity and multiple regression analysis. We found that the CCQ, CRQ, MRF-28 and the SRI are all reliable and valid in hospitalized patients with CHRF who are still hypercapnic after ending ventilatory support for an acute exacerbation. Overall, the SRI performed best when analyzing the distribution of scores, floor and ceiling effects, construct validity, and explained proportion of variance. For this reason, and since the SRI also contains a psychological domain, we recommend using this questionnaire in patients with severe end-stage COPD and chronic HRF.

In **chapter 6A** we describe the results of the RESCUE study, in which we compared the effects of 12 months of nocturnal NIV with standard therapy in COPD patients who remained hypercapnic after ventilatory support for acute respiratory failure. Two hundred and one patients were randomized in hospital, after which measurements were performed at baseline and after 3, 6 and 12 months. When comparing nocturnal NIV to standard therapy we concluded the following:

- nocturnal NIV does not prolong the time to readmission for respiratory causes or death, the primary outcome of the study.
- nocturnal NIV does improve daytime $PaCO_2$ and nocturnal transcutaneous $PaCO_2$.
- nocturnal NIV does not improve survival, number of respiratory readmissions, number of exacerbations, lung function, HRQL, mood state, daily activity levels or dyspnoea.

Chapter 6B contains our reply to the correspondence of Borel et al[2] who suggest looking at certain subgroups of COPD in future research. They found that survival was better in obese COPD patients than in non-obese patients on NIV. In our reply we agree with the authors that that this subgroup seems to respond better to NIV and that future studies should focus on this certain group as well. Although our population was different we still want to further explore our group of mainly non-obese COPD patients and try and find characteristics of subgroups of responders. This is because we believe that even in these patients responders to chronic NIV can be found.

GENERAL DISCUSSION

Nocturnal NIV in stable COPD

The Cochrane update[3] did not show any significant difference between nocturnal NIV and standard therapy alone (sometimes including LTOT) in stable hypercapnic COPD, which is in line with the original review.[4] However, by adding three new studies to the existing four, individual patient data of in total 245 patients was gathered giving this update more statistical power. The original meta analysis found a (non-significant) decrease of 1.5 mmHg in $PaCO_2$ after three months of NIV. In the update, six studies now contributed to this outcome and with data from 162 patients and $PaCO_2$ showed a trend towards near significance with a decrease of 2.5 mmHg and a 95% confidence interval (CI) only just exceeding zero (95% CI -5.28 to 0.29). A decrease of 2.5 mmHg in $PaCO_2$ would be of clinical significance. PaO_2 after 3 months showed a slightly smaller improvement and again with CI's just over zero. Similarly, the non-significant improvement of 27.7 meters in the 6 minute walking distance (6MWD) could be of clinical value as it does reach the clinically minimal important difference of 26 meters.[5] However, 6MWD data was gathered from only three studies totaling 40 patients. Altogether, it is unfortunate that all five short term RCT's with data after three months provided only small sample sizes, making it impossible to draw any firm conclusions other than that nocturnal NIV cannot be recommended routinely in stable hypercapnic COPD.

Although as mentioned, we were able to include three more studies, of which two long-term studies[6,7] to the update, both with considerably more patients per trial, still no significant differences were found for their common outcomes: arterial blood gasses, lung function and HRQL. Two aspects are of interest.

Firstly, both long-term studies separately did not show clear evidence for improvements in the standard clinical outcomes but interestingly McEvoy[7] did find a survival benefit when adjusting for baseline differences like $PaCO_2$, PaO_2 and HRQL. This was however at the cost of a worsening in HRQL. The lack of clear benefits on arterial blood gasses during spontaneous breathing for both trials, (but also the short-term trials of our meta analysis on NIV in stable COPD) can possibly be attributed to the common denominator; that is low inspiratory pressures (average IPAP was 13 and 14 cm H_2O respectively).

Secondly, in Clini's study,[6] HRQL was significantly different between groups only when measured by the MRF questionnaire, not by the St. George, a general respiratory questionnaire. And again, also in the study by McEvoy,[7] differences in HRQL were found only in one of the two questionnaires (the Short Form Health Survey (SF36)[8] and not in the St. George. This is quite surprising as the SF36 is a generic HRQL questionnaire, not specific for COPD, let alone patients with respiratory failure. The importance of using sensitive questionnaires that are more specific for the target population alongside the more general questionnaires is underlined, such as the SRI in **chapter 5**.

During the writing of this thesis, a new study on NIV in stable COPD was published and reaffirms both points mentioned above. The RCT by Kohnlein and colleagues[9] randomized 195 patients with chronic hypercapnic failure to either long-term NIV or standard therapy, making it the largest study in the field of stable COPD. An important new aspect in the delivery of NIV was that it was targeted to reduce baseline $PaCO_2$ by at least 20% or more, or achieve $PaCO_2$ values lower than 6.5 kPa (48.1 mmHg). Also, high back-up ventilation and high IPAP levels were the preferred method, suggesting controlled ventilation, however assisted ventilation was accepted. Mean IPAP was 21.6 cm H_2O (EPAP 4.8 cm H_20), with a mean backup frequency of 16.1. Mean compliance to NIV was 5.9 hours per day.

The authors show a considerable benefit in survival after 1 year for the NIV group with a 12% mortality rate in the NIV group vs. 33% in the control group. Other significant benefits in favor of NIV were $PaCO_2$, pH, SaO_2, bicarbonate, FEV_1 and HRQL. Benefits were seen on the summary scores of both the SRI and St. George and on a subscale of the SF-36 (General Health Perception)). Again, these results stress the added value of using higher levels of IPAP and disease- or subgroup-specific questionnaires.

Nocturnal NIV after acute respiratory failure

As explained in the introduction, there might be a specific subset of patients which could benefit from NIV, i.e. those patients with severe COPD and recurrent admissions requiring acute NIV.[10] Two randomised controlled studies recently investigated the effects of nocturnal NIV in patients with acute-on-chronic respiratory failure.[11,12] Although these studies were very different in study design, both did show significant benefits of NIV on their primary outcome, that is, respiratory deterioration requiring mechanical ventilation. Unfortunately, Cheung et al's[11] primary effect size was not clearly defined and Funk et al[12] did not find improvement on secondary outcomes such as all-cause readmission and exacerbation frequency, thereby limiting the clinical impact of their findings.

So in summary, positive results of NIV have recently been reported for patients with stable COPD[9] as well as patients with acute-on-chronic respiratory failure.[11,12] So why did we not find clinical benefits of NIV in the RESCUE study?[13] Three different aspects are important in this respect.

1. Target population

One explanation could be that we did not include the right target population[14] and the following items are of relevance.

a. Chronic respiratory failure

We aimed to include only patients who remained hypercapnic after cessation of NIV for acute respiratory failure (ARF). However, when looking at blood gas levels after 3 months, we noticed that not only the NIV but also the control group showed similar improvements in daytime $PaCO_2$. The natural recovery of this aspect of the disease partially led to inclusion of a subgroup of patients who did not persist in having chronic respiratory failure

(CRF). In other words, we included a mixed cohort of acute-on-chronic respiratory failure but also patients with only ARF. This was unintended of course, but difficult to prevent in any such trial. Currently, a trial in the UK is taking place (UK HoT-HMV, Clinical trials.gov: NCT00990132) which is quite similar in design and patient population to the RESCUE study. In this trial, LTOT is compared to LTOT alongside chronic NIV at home in COPD patients post acute hypercapnic exacerbation. Two inclusion criteria are of importance in this respect (and different compared to those of the RESCUE) 1) Acute hypercapnic exacerbation of COPD at least two weeks previously and 2) Chronic hypercapnia ($PaCO_2$ >7 kPa). This trial is estimated to be completed in December 2014.

b. Level of hypercapnia

Another important factor for selection of the right type of patient, is the level of hypercapnia. The mean $PaCO_2$ at baseline of the RESCUE population was 7.9 and 7.7 kPa for the NIV and control group respectively, we set our inclusion at $PaCO_2$ > 6.0 kPa (45 mmHg). As detailed above, some patients spontaneously became normocapnic, in fact 26% did. It is questionable if patients with mild hypercapnia or even normocapnia benefit from NIV. In **chapter 4** we found a significant difference in change in $PaCO_2$ after 3 months of NIV in patients with a baseline $PaCO_2$ of at least 7.3 kPa (55 mmHg) when compared to patients with lower baseline $PaCO_2$. The positive results from Kohnlein et al[9] are consistent with this assumption of better effects in more hypercapnic patients: although targeting a different subgroup, they included patients with a $PaCO_2$ of 7.0 kPa (51.9 mmHg) or higher. Mean $PaCO_2$ was 7.8 at baseline for both groups. This could also have been a factor in the lack of benefits found in the two long-term studies by Clini[6] and McEvoy[7] as they included patients with baseline $PaCO_2$ levels of around 6.7 and 7.1 kPa.

c. Obesity and COPD

As COPD is a heterogeneous disease, different groups show different probabilities for health-related events and different mortality rates. This has led to phenotyping as a way to identify patient groups with unique prognostic or therapeutic characteristics.[15] Two phenotypes were recently investigated by Borel et al[16] to see what impact NIV had on them. The 'respiratory COPD' phenotype is characterized by severe airflow limitation without obesity. The other 'systemic COPD' exhibits less airway flow obstruction but a higher proportion of obesity and more cardiovascular and metabolic comorbidities. The main objective of Borel et al was to assess the relationship between daily NIV use and hospitalization for acute exacerbation or death in both obese COPD (BMI>30 kg/m^2) and non-obese COPD patients (BMI<30 kg/m^2). Mean IPAP in the total group was 19 cm H_2O, EPAP 7.6 cm H_2O with a mean back up rate of 11. They show that the non-obese COPD subtype was associated with a higher rate of death or hospital readmission than obese COPD after 3 years of NIV (58% vs. 27%). Not only did non-obese COPD patients exhibit poorer prognosis, but also a lower mean daily use of NIV than obese-COPD patients. Within the obese subgroup, adherence to NIV was associated with better prognosis (a significant improvement was found when NIV was used for > 5 hours per day).

However, for the whole group, the use of NIV above 9 hours per day predicted poor outcomes and was associated with an increased risk of death or readmission for acute exacerbation. As explained in **chapter 6**, although we did not exclude severe obesity we did minimize for this, leading to a similar mean BMI in both groups of around 25 kg/m^2. As our patients all showed marked airflow limitation, and most were non-obese, the majority of our patients can be classified as the 'respiratory COPD' phenotype, making our results consistent with the results of Borel et al.[16] We agree with their suggestion that future studies should focus on subgroups like obese COPD, but we also believe that within our subgroup of non-obese COPD, responders to NIV can be identified.

2. IPAP

As mentioned earlier, the lack of benefit of NIV found in the studies on stable COPD which were included in the meta analysis could perhaps be attributed to the low ventilator settings. The results from **chapter 4** strengthen this assumption. As the study by Meecham Jones and colleagues[17] with a median IPAP of 18 cm H_2O was the only short term study in our meta analysis with significant effects on daytime $PaCO_2$, we chose this as cut-off point to compare different levels of IPAP on change in $PaCO_2$ after3 months. Patients who received IPAP levels of 18 cm H_2O and higher indeed showed a statistically greater improvement in $PaCO_2$ after 3 months. But caution is warranted as number of patients were small (n=78).

Duiverman and colleagues[18,19] investigated the effects of NIV in addition to an extensive rehabilitation program in stable COPD and found a significant decrease in $PaCO_2$ after 3 and 24 months when compared to rehabilitation alone. Mean IPAP at 3 months was 20 cm H_2O and 23 cm H_2O at 24 months with a mean EPAP and RR of 6 and 18 respectively. However there was no relationship between the level of IPAP and the amount of change in $PaCO_2$ suggesting that the extreme pressures sometimes given with high-pressure NIV are perhaps not really of additional benefit. The recent study of Kohnlein[9] with positive results after giving moderately high IPAP of around 21 cm H_2O endorses this theory (although one should not forget that they also used a high back-up rate).

Taking it one step further is the newer approach of high inspiratory pressures (28 cm H_2O) and respiratory rates called high-intensity (Hi) NIV. The aim of this more controlled type of ventilation is to maximally decrease $PaCO_2$. Several uncontrolled studies[20] have been performed in Germany and found improved blood gasses, lung function but equally important also that patients were able to tolerate this more aggressive form of ventilation. Although air leakage is bigger with Hi-NIV, Dreher and colleagues[21] showed in an RCT that this did not reduce sleep quality when compared to the more conventional approach of ventilation with lower IPAP and respiratory rates (low-intensity NIV). As survival was not compared, it would be interesting to see if Hi-NIV also shows benefits in that area.

One, small, randomized, cross-over trial[22] performed in 12 patients with stable COPD however, challenges the view of requiring high back up rates in Hi-NIV to achieve physiological and clinical improvements. It compared Hi-NIV with high-pressure NIV (high pressure and low back up rates) and did not find a difference in ventilator adherence and other secondary outcomes. However, the trial duration of both forms of NIV were relatively short (6 weeks) and the drop-out rate was relatively high.

3. Compliance

The positive results from the study by Kohnlein,[9] can perhaps also be attributed to the level of compliance to NIV as mean adherence was 5.9 hours per day. This would be in line with our results from **chapter 4** where we found that the improvement in $PaCO_2$ after 3 months was statistically greater in those patients who used ventilation on average for more than 5 hours per night. The study by Duiverman et al[18] showed similar results with a correlation between the change in $PaCO_2$ after 3 months and the number of hours on NIV per day.

FUTURE STUDIES AND PERSPECTIVES

The RESCUE study has provided new insights specifically for the timing of initiation of chronic NIV in patients with COPD. It seems that patients who have received NIV for ARF, first need time to recover at home (without NIV), before being reassessed for chronic NIV. This to be able to exclude the patients with only acute respiratory failure.

Based on data from the RESCUE study and all studies discussed in this chapter, it seems the effects of chronic NIV are better in certain groups of COPD patients. Further research should consider the following suggestions:

- Both patients with stable COPD and patients treated for acute respiratory failure seem to benefit from NIV, but research suggests NIV may only be beneficial if they remain chronically hypercapnic. In patients treated for ARF, this can be investigated by measuring $PaCO_2$ during a run-in period of 6 weeks to 3 months to check if hypercapnia is still present before commencing with chronic NIV trial. A run-in period of 4 weeks for stable COPD patients would be sufficient.

- As the level of hypercapnia seems to determine the effectiveness of chronic NIV, an inclusion criteria for patients could be that when they are stable, $PaCO_2$ needs to be at least 7.0 kPa or higher.

- Research suggests patients need to be ventilated sufficiently. We would recommend a protocol for the ventilator settings with IPAP levels of at least 18 cm H_2O alongside a high back up rate to achieve a substantial reduction in $PaCO_2$ of 20%. Patients could be adviced to use the ventilation for at least 5 hours or more per day.

- When measuring HRQL in COPD patients with hypercapnic respiratory failure, we would propose to use the highly specific SRI questionnaire alongside a more general COPD questionnaire.

Studies that are of importance for the future:

- Further studies on the different phenotypes of COPD and how they react to NIV are necessary. Especially the phenotype of 'systemic COPD' with obesity seems to be a group that could benefit more from NIV than others.

- Valuable studies are those that focus on the underlying mechanisms of why NIV works in some COPD patients. Following Kohnleins positive results it was stated that when NIV is effective by means of reducing $PaCO_2$, that it improves survival and HRQL.[23] But a direct association between $PaCO_2$ and survival was not investigated or tested, making the statement perhaps a bit too strong. After all, other mechanisms could be the cause of this survival benefit. For instance, FEV_1 was also significantly improved. A hypothesis is that higher IPAP could lead to less inflammation.

This in turn would lead to less oedema which could have led to better ventilation and thereby improving FEV_1. Trials need to be performed that are powered to further analyze these mechanisms and associations.

- The potential of using electromyography (EMG) techniques during NIV should be further explored. With surface EMG, respiratory muscle activity can be measured in a non-invasive way.[24,25] Using EMG techniques during NIV should give more insight into the work of breathing with different levels of IPAP or ventilation modes for instance.
- To keep patient groups as homogeneous as possible, in the past certain co-morbidities in NIV trials were excluded. Therefore the effects of co-morbidities in COPD patients on NIV have not yet been investigated thoroughly, although they have been shown to occur frequently and have an important impact on COPD prognosis.[26]

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