NOCTURNAL NON-INVASIVE VENTILATION FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A FINAL BREAKTHROUGH?

Summary of Presentations from a ResMed-Sponsored Satellite Symposium, held at the 24th ERS Congress, Munich, Germany, on 8th September 2014

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MEETING SUMMARY

Prof Windisch opened the symposium on the efficacy of non-invasive ventilation (NIV) in the treatment of chronic obstructive pulmonary disease (COPD). Dr Jean-Louis Pepin summarised the evidence for efficacy of NIV in subgroups of COPD patients. Dr Thomas Köhnlein focused on a recently-published randomised trial showing a major reduction in mortality following NIV aimed at a marked reduction in carbon dioxide pressure ($PaCO_2$), while Dr Michael Dreher illustrated the place of NIV in patients with recent exacerbations.

Introduction

Professor Wolfram Windisch

Prof Windisch welcomed the audience to the ResMed-sponsored satellite symposium on NIV for COPD. The audience were invited to engage in discussion with the speakers at the end of each presentation.

NIV for Stable COPD: Which Phenotypes can Benefit?

Doctor Jean-Louis Pepin

There is a plethora of data from clinical trials supporting acute in-hospital use of NIV. However, the evidence for domiciliary use of NIV for stable COPD is comparatively weak and there are discrepancies in mortality data between individual randomised controlled trials. Despite this, in

several European countries, chronic hypercapnic respiratory failure (CHRF) due to COPD is a common indication for domiciliary NIV.[1]

Data from the general population of COPD patients are inconclusive. In a recent study by McEvoy et al.,[2] patients with hypercapnic COPD were randomised to receive either nocturnal NIV and long-term oxygen therapy, or long-term oxygen therapy alone. Only a small improvement in survival was demonstrated at the cost of a possible worsening in quality of life (QoL). Furthermore, the survival benefit was only demonstrated in the adjusted and not the unadjusted analysis, bringing its validity into question.[2] In another trial, unselected patients with COPD were treated with NIV or standard care. Immediately, or several weeks after exacerbation, there was an improvement in blood gases but no survival advantage in the NIV-treated group. However, it is likely that the adverse effect of acute respiratory failure in terms of prognosis outweighed any benefit of NIV in this setting.[3]

Results from a recent trial suggest that a subgroup of patients with stable COPD do respond to NIV. The study compared NIV aimed at a 20% reduction in partial $PaCO_2$ with standard care and showed a substantial improvement in survival and QoL in the NIV group.[4] When considering the appropriate use of NIV, it is important to understand that COPD is not a homogenous condition. The two most common phenotypes are respiratory COPD, characterised by low body mass index (BMI), severe respiratory COPD, and hyperinflation; and systemic COPD with less airway obstruction but with multiple comorbidities often including overlap syndrome (COPD and obstructive sleep apnoea [OSA]). COPD subtypes are associated with different prognoses and causes of hospitalisation, as reported in a recent study showing that all-cause mortality was higher in exacerbations of severe respiratory COPD.[5] In the systemic COPD subgroup, the main reason for hospitalisation was cardiovascular, while patients with the respiratory phenotype were more likely to be admitted due to COPD.[5] These differences in prognosis and phenotype may underlie differences in the response to NIV.

In patients with overlap syndrome, a classical picture of OSA during non-rapid eye movement (REM) sleep, and oxygen desaturation and increased transcutaneous CO_2 during REM sleep, is frequently observed.[6] A study by Marin et al.[7] revealed increased all-cause mortality and hospitalisation due to exacerbation in patients with overlap syndrome compared to those with COPD alone. In patients whose OSA was treated with NIV, the increases in mortality and exacerbation-related hospitalisation were ameliorated. A more recent study indicates that the survival benefit of NIV is restricted to hypercapnic patients, with no benefit in normocapnic patients.[8]

NIV settings are more difficult to adjust in severe respiratory COPD with hyperinflation, and thus, the response to NIV may be affected in this patient subgroup. Asynchronous ventilation caused by inappropriate settings in these patients appears to result in progressively increased hyperinflation and discomfort upon waking. In a study by Adler et al.,[9] calibrated adjustments resulted in decreased pressure support and tidal volume, with increased respiratory rate. These changes were associated with improvements in daytime $PaCO_2$, morning dyspnoea, and sleep quality.

In a recent prospective observational cohort study directly comparing patients with respiratory or systemic COPD, the rate of hospitalisation and death was lower in patients with systemic COPD than in the respiratory COPD group. Despite reasonably high adherence rates in both groups, as indicated by time spent on NIV, patients with systemic COPD had significantly longer mean daily use of NIV (6.9 versus 5.5 hours/day, respectively; Figure 1).[10] Data from a recently-published meta-analysis suggest that changes in daytime $PaCO_2$ are related to the duration of NIV.[3] These differences in adherence may partly explain differences in response to NIV.

Studies investigating the efficacy of NIV should not focus solely on mortality as an endpoint. In patients with recurrent acidotic exacerbations of COPD, NIV reduced the number and duration of admissions as well as the total days spent in hospital. These beneficial effects were associated with cost reductions of >50%.[11]

In summary, stable COPD patients are not a homogeneous population, and thus the question of whether these patients respond to NIV requires refinement. Prognostic differences and distinct causes of death and hospitalisation are apparent between phenotypes of stable COPD patients, and studies indicate that these subgroups may respond differently to NIV. Differences in adherence are also likely to have a role in determining the response to NIV in terms of both efficacy and overall

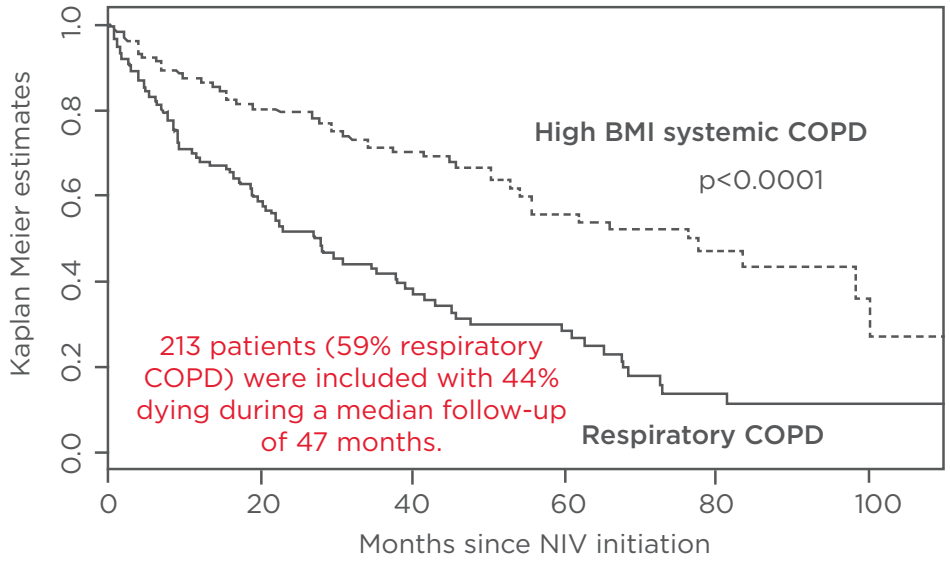
mortality. Researchers should not focus solely on mortality as an outcome and should be aware of other considerations such as cost reductions associated with NIV use. The above considerations suggest that future randomised trials should focus on subgroups of COPD patients who have a higher likelihood of response to NIV. Data from prospective registries, such as the European Home Mechanical Ventilation Registry, which is focused on domiciliary NIV, will be useful in directing future research.

Home NIV for COPD: a Final Breakthrough?

Doctor Thomas Köhnlein

The genesis of the Non-invasive Ventilation in Severe COPD trial (NCT00710541), summarised here, was the disconnect between clinical experience and the results of previous trials showing a lack of efficacy for NIV in stable COPD.[4] The investigators took a novel approach by focusing their hypothesis on achieving the marked reduction in hypercapnia that they believed would be required in order for NIV to show efficacy, and thus improve survival in patients with advanced, stable hypercapnic COPD. The primary outcome was overall mortality. Secondary outcomes included blood gases, changes in hypercapnia, oxygenation, 6-minute walking distance, and QoL measures.

The trial was a multicentre parallel-group study powered at 150 patients per group with a 1-year follow-up. Inclusion criteria included COPD in Global Initiative on Obstructive Lung Disease (GOLD)-Stage 4; $PaCO_2$ 7 kPa (51.8 mmHg) or higher, and pH >7.35, assessed during spontaneous breathing; and a stable disease state with no change in medication for ≥4 weeks. These criteria were aimed at recruiting a patient population at low risk of exacerbation or hospitalisation, with moderate-to-severe COPD and ventilatory insufficiency, ruling out any other respiratory disorders. Investigators set themselves the challenging target of achieving a sustained 20% reduction in hypercapnia after 1 hour of spontaneous breathing, post-NIV. Ventilator settings were left to investigator discretion and patients were asked to use their machines for ≥6 hours per day. In total, 195 patients were randomised, 93 patients in the control arm received standard care, and 102 patients in the intervention group received standard care plus NIV aimed at a 20% reduction in hypercapnia (Figure 2).



No. of patients at risk

Non-Obese	111	61	30	17	6	2
Obese	102	81	57	35	17	4

Figure 1: Rate of hospitalisation and death following initiation of NIV.
NIV: non-invasive ventilation; BMI: body mass index; COPD: chronic obstructive pulmonary disease.
Borel JC et al.[10]

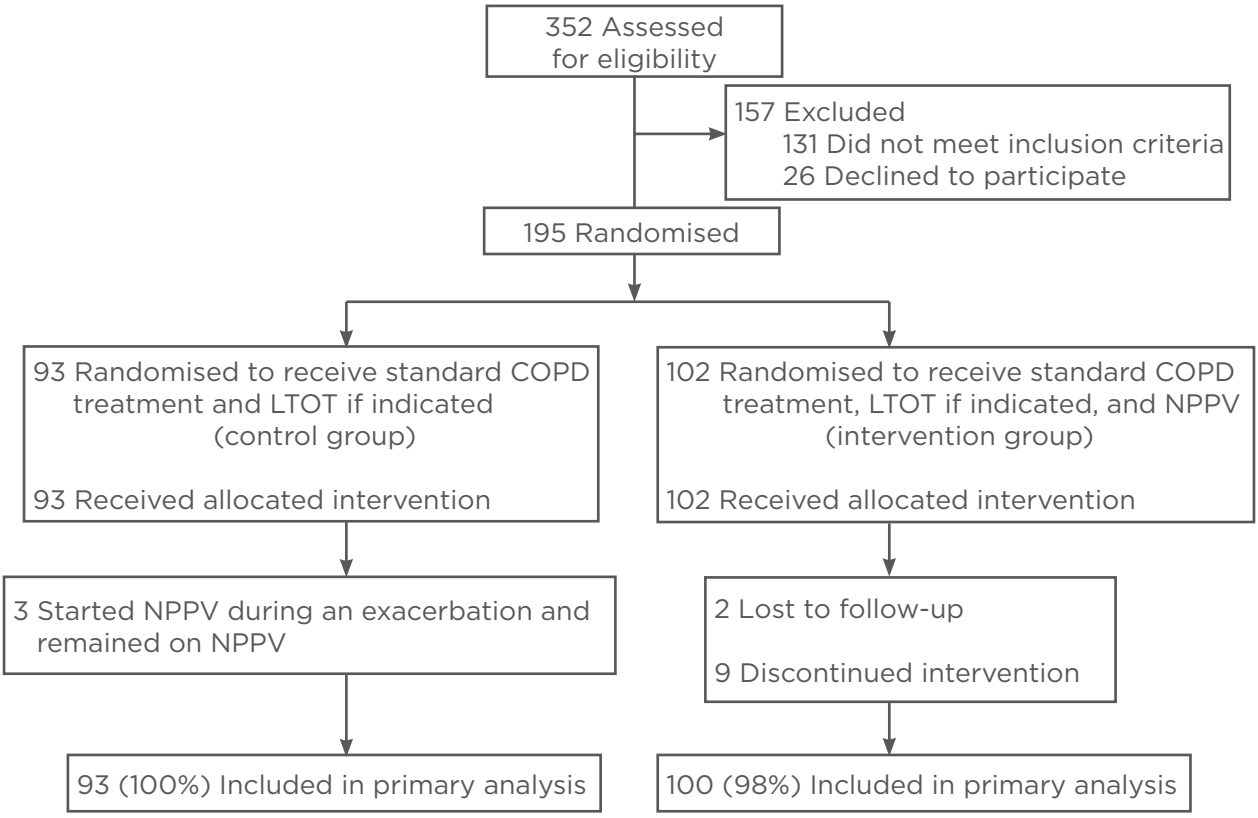


Figure 2: Patient disposition through the randomised controlled trial of non-invasive ventilation versus standard care.

COPD: chronic obstructive pulmonary disease; LTOT: long-term oxygen therapy; NPPV: non-invasive positive pressure ventilation.

Köhnlein T et al.[4]

Patients were well balanced in terms of baseline characteristics: predominantly male, with a mean age of approximately 64 years. Mean BMI was 24–25 kg/m^2 and there were no cases of obesity hypoventilation syndrome.[12] Lung function was as expected for GOLD–Stage 4 patients (forced expiratory volume in 1 second [FEV_1] 26-28% of predicted), patients were not acidotic, and baseline $PaCO_2$ was 7.7 kPa and 7.8 kPa in the control and intervention groups, respectively (approximately 58 mmHg). Both groups showed elevated bicarbonate (HCO_3-) levels (approximately 34 mmol/L), indicative of chronic hyperventilation. Approximately 65% of patients in each group were on long-term oxygen at baseline.

After 1 year of treatment, patients receiving NIV had mean inspiratory and expiratory pressures of 21.6±4.7 and 4.8±1.6 cmH_2O, respectively. The mean back-up frequency was 16 breaths/minute, with 70 of the 102 ventilated patients having back-up frequency settings indicative of controlled ventilation (≥14 breaths/minute). The mean daily duration of NIV was 5.9±3.1 hours, slightly below target.

There was a marked reduction in $PaCO_2$ (≈16%) after 14 days, which remained stable for the duration of the trial but did not reach the desired 20% threshold (Figure 3). Notably, the 14 days during which ventilation settings were calibrated was the period during which the reduction in $PaCO_2$ occurred in the intervention group, and there was little change after this period despite ventilation throughout the study. It is also worth noting that there was a slight improvement in $PaCO_2$ in the control group, perhaps due to improved compliance with standard care.

There was a statistically and clinically significant 35-metre (14%) increase in 6-minute walking distance in the intervention group, which was evident after 14 days, and it remained relatively stable throughout the study.[13] There was no meaningful change in health-related QoL (measured using the St George's Respiratory Questionnaire

[SGRQ]) in the control group, but there was a small, but clinically relevant, 5-point improvement in SGRQ score in the intervention group. The mental component of the generic Short Form-36 questionnaire also showed a statistically significant improvement in the intervention group, but there was no change in the physical summary score. The Severe Respiratory Insufficiency (SRI) questionnaire is specifically designed to assess health-related QoL in patients receiving either invasive or non-invasive long-term ventilation. An improvement in the SRI score, similar to that seen in previous studies, was achieved in the intervention group.[14] In summary, QoL improvements were documented using disease-specific tools, which are more likely to reflect true changes in QoL.[14]

As the primary outcome, overall mortality was higher than expected in the control group (Figure 4), but there was a highly significant reduction in mortality in the intervention group after 1 year (12% versus 33%, respectively). Although it should be noted that the study is somewhat underpowered, this signal is clear enough to indicate a decisive survival advantage with chronic NIV treatment in patients with stable hypercapnic COPD. Investigators have continued to follow patients and the survival advantage appears to persist up to 5 years, although these data should be viewed with caution given the small population size and the fact that the study was not powered for this duration of follow-up. It is notable that the majority of the between-group difference in mortality rate occurred during the first month of the study, similar to the pattern seen for other outcomes; survival lines remained approximately parallel from month 6 onwards throughout the remainder of the extended follow-up.

These data show a clear survival signal with NIV when treatment is aimed at achieving a marked reduction in $PaCO_2$. Further studies building on these results will help to better define the place of this NIV strategy in the treatment of stable COPD.

One major point covered during the discussion, following the above presentation was why the control group mortality rate was so high. Currently there is no clear answer; indeed it was found later that the Data Safety Monitoring Board had considered stopping the trial early, but did not believe that the trend of high mortality in control patients would continue. All patients were followed until the 1-year time point or death, and there was no clear signal from death certificates or from medical reports despite numerous pneumonias, cardiac arrests, and infections.

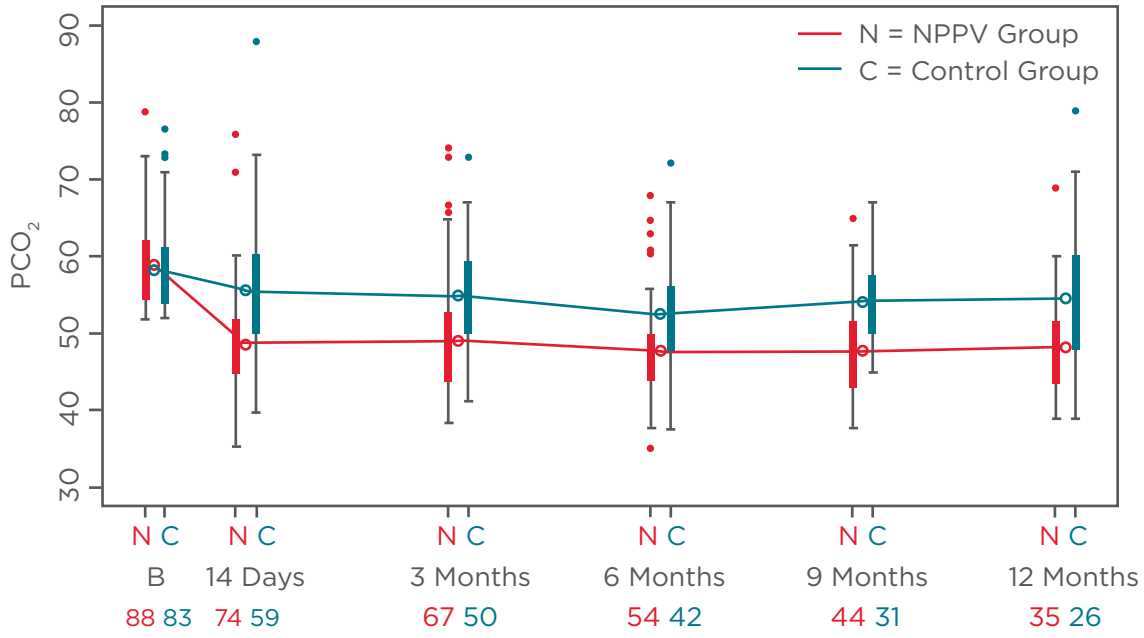


Figure 3: Change in $PaCO_2$ in NIV versus standard care in patients with stable COPD.
NPPV: noninvasive positive pressure ventilation; NIV: non-invasive ventilation; COPD: chronic obstructive pulmonary disease; $PaCO_2$: partial pressure of carbon dioxide.
Köhnlein T et al.[4]

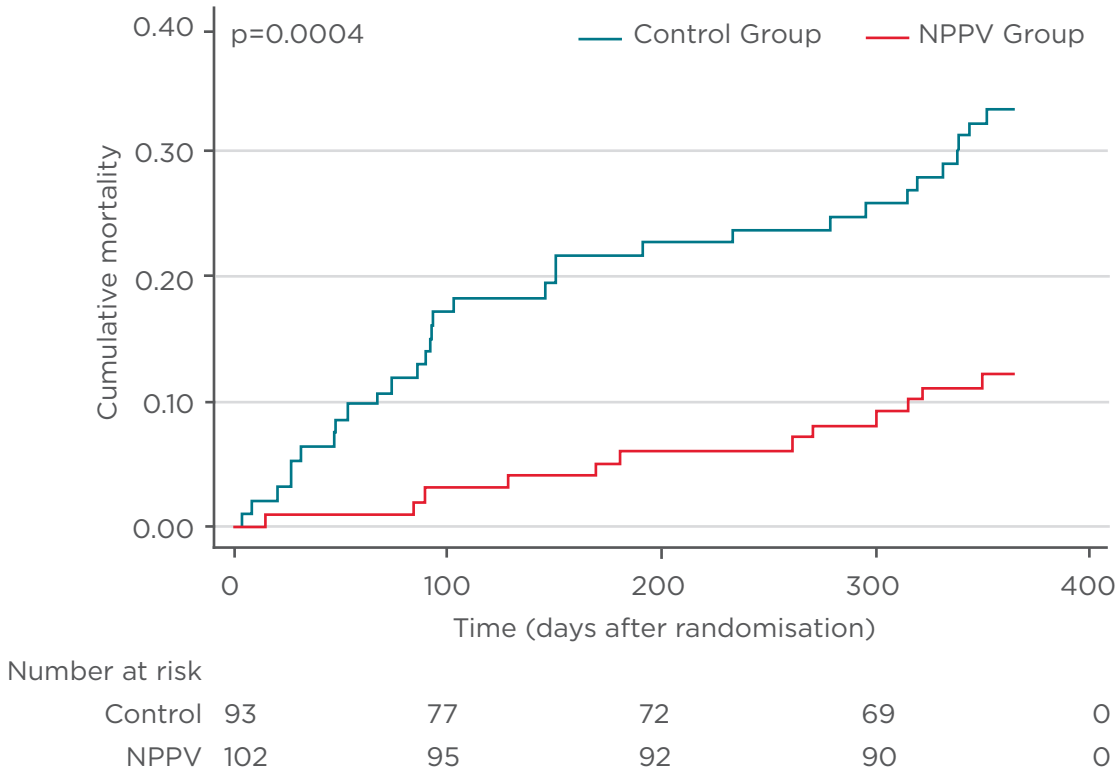


Figure 4: Overall mortality for treatment with NIV versus standard care in stable COPD.
NIV: non-invasive ventilation; COPD: chronic obstructive pulmonary disease; NPPV: noninvasive positive pressure ventilation.
Köhnlein T et al.[4]

Some deaths were attributed to COPD in general, but no specific cause of death was documented in these patients. Indeed, the issue of what ultimately causes death in COPD patients is a difficult topic. The underlying cause of death is often difficult to identify and the precision of medical reports, at least in the above German setting, is currently inadequate for this purpose.

Case Reports: What can we Learn from Daily Practice?

Professor Michael Dreher

In order to illustrate what can be learned about treating COPD from daily practice, two case studies were presented. The first case was that of a 72-year-old male patient, a former smoker, with COPD in GOLD Stage 4. FEV_1 was 19% of predicted, total lung capacity (TLC) was 137% predicted (indicative of severe emphysema), and exacerbations were frequent. The patient had received 6 years of domiciliary NIV by 2009, a year in which he was admitted to hospital eight times with acute hypercapnic respiratory failure (AHRF). The mortality risk in such a patient with very severe COPD and more than bi-monthly hospitalisations is extremely high, particularly given of the link between repeated exacerbations and increased mortality.[15] The patient refused to be transported to hospital without continuous ventilation from his own device during incidents of acute exacerbation he would administer ventilation for 18–24 hours/day.

On admission with an acute hypercapnic exacerbation in November 2009, the patient presented with no fever, no elevation in C-reactive protein (CRP) levels, increased dyspnoea, and increased time on NIV (24 hours); pH was 7.29 and $PaCO_2$ was nearly 75 mmHg. The patient had been receiving NIV for several years with an inspiratory positive airway pressure of 28.6 cmH_2O and an expiratory positive airway pressure of 4.1 cmH_2O. Inspiration time was 1 second and breathing frequency was 18 $minute^{-1}$. The patient refused entry to the intensive care unit (ICU), he was prescribed prednisolone, and was discharged after 6 days

on the respiratory ward, during which ventilation time was gradually reduced. This single case illustrates the potential for home NIV to ameliorate AHRF, with the patient effectively copying the treatment they will later receive in hospital.

Another exacerbation episode in this patient, although different from the events described above, also illustrates an important point. The patient declined admission to the ICU and, unfortunately, died. When patients have such a strong personal engagement with their treatment, it is essential to agree plans in advance on how to proceed in case of deterioration to allow the possibility of admission to ICU or other appropriate measures.

The second case was a 57-year-old male with COPD GOLD-Stage 4, who had a BMI of 17 kg/m^2, an FEV_1 36% of predicted, and a high TLC (119% of predicted). He had been on long-term oxygen for 3 years and his breathing was rapid and shallow, with a frequency of 38 minute^{-1}. The patient presented with a silent lung due to emphysema, fever, elevated CRP (156 mg/dL), and no infiltrates detected on chest X-ray. Blood gas analysis (5 L oxygen [O2]/min) showed a pH of 7.21, PaO_2 of 59 mmHg, $PaCO_2$ of 78 mmHg, and HCO_3- of 29 mmol/L, indicating AHRF with respiratory acidosis. The patient was referred to the ICU, NIV was set up, and his blood gases were controlled at $PaCO_2$ 82 mmHg and pH 7.2. He was acutely ventilated with inspiratory pressure levels incrementally increased from 15.3 to 21.4 cmH_2O, and expiratory levels incrementally increased from 4.1-6.1 cmH_2O, FiO_2 was 45%. pH significantly improved over time and $PaCO_2$ fell from 82-62 mmHg.

The patient was discharged from the ICU after 3 days with no fever and reduced CRP, dyspnoea, and breathing frequency. Blood gases (3 LO_2/min) were now at pH 7.36, $PaCO_2$ 54 mmHg, and HCO_3- 30 mmol/L, indicating CHRF. The patient was referred to the respiratory ward and overnight blood gases (2 LO_2/minute) showed a slight increase in $PaCO_2$ to 58 mmHg, with pH 7.37, PaO_2 59 mmHg, and HCO_3- 29 mmol/L. Again, these results are indicative of CHRF. The question for physicians was whether to begin domiciliary NIV. As the patient had CHRF and this was his first admission to hospital, attending physicians discharged him from the respiratory ward after 4 days with no fever, normal CRP levels, and a 3-day course of oral corticosteroids. Readmission was planned for control of blood gases and an evaluation of the need for domiciliary NIV. The patient returned to hospital after 6 weeks showing mild hypercapnia ($PaCO_2$ 46.3 mmHg). Night-time levels were slightly higher (49.8 mmHg) and it was determined that there was not an indication for domiciliary NIV.

In summary, domiciliary NIV may reduce the severity of AHRF if the treatment mirrors that likely to be received in hospital. NIV after AHRF is not necessary in all hypercapnic COPD patients, but lack of recovery after 6 weeks may be a good indicator that NIV is required.

Meeting Close

Professor Wolfram Windisch

Prof Windisch thanked the speakers for their presentations as well as the audience for their questions and discussion points. With a final thank you to ResMed for having organised the symposium, the meeting was brought to a close.

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