Non-invasive ventilation in patients with severe chronic obstructive pulmonary disease and lung emphysema (COPD)

Study Protocol
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Organisation of this study:
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Section 1
Introduction:
Chronic obstructive pulmonary disease (COPD) is one of the most common diseases in the western world (prevalence in 2000: 2–5% of the population) [1]. The total cost of this disease is estimated to be Euro 4.5 billion for a country like Germany [2]. The prevalence will increase in the coming years, mainly due to the growing number of elderly people. Apart from modern pharmacological treatment strategies, combined with improved physiotherapy and long-term oxygen therapy, there has been no significant change in the prognosis of patients with moderate or severe COPD [3].

The key problems in COPD are chronic inflammation and obstruction of the small airways. This results in markedly elevated air-flow resistance and work of breathing. The lung develops enlarged air spaces (emphysema) with a reduction of alveoli and respiratory surfaces. Consequences include flattening of the diaphragm and alterations in the thoracic skeleton. Patients with advanced COPD experience insufficiency of the muscular ventilatory pump, which may decompensate if the load overcomes the capacity of the muscles. In addition, an un-naturally high proportion of the cardiac pump volume must be allocated to the demands of the ventilatory muscles.

Hypercapnia, and later hypoxaemia, are indicators of an overloaded ventilatory pump. In the advanced stages of COPD, altered blood gases might occur first during exercise or during sleep, as well as at rest [4].

Theoretically, non-invasive ventilation (NIV) could be a treatment option for patients with advanced COPD and ventilatory pump insufficiency. Mechanical non-invasive
ventilation provides support for the ventilatory muscles and might counterbalance the elevated intrinsic positive end-expiratory pressure (PEEP) [5]. In Germany, the number of patients currently treated with NIV is estimated to be 3,600 [6]. COPD patients might represent the highest portion of this cohort. Although the number of patients with COPD receiving NIV grows continuously (in Europe), only a small number of well-designed studies have been published to date [7,8,9,10]. In contrast to the widespread opinion of many clinicians, none of these studies demonstrated a significant survival benefit of long-term use of NIV in patients with COPD [11].

The ‘National Task Force for Non-invasive ventilation and weaning’ [Arbeitsgemeinschaft Heimbeatmung und Respiratorentwöhnung e.V.], an interdisciplinary working group in Germany, intends to perform a clinical trial of long-term NIV in patients with COPD. This project will be performed in co-operation with the ‘German Society for Pulmonary Medicine’ [Deutsche Gesellschaft für Pneumologie], and the ‘German National Foundation for Pulmonary Medicine’ [Deutsche Lungenstiftung e.V.]. The results of this trial will provide a basis for future decisions on the application of NIV in patients with severe COPD. Regarding the significant amount of human and financial resources for this treatment, this study might have an important impact on the further use of NIV, at least in Germany. Due to the absence of valid data on the long-term use of NIV, reimbursement systems in the United States and in Canada do not fund this treatment. Unless otherwise proven, the same will happen in Europe in the coming years.

This study tests the hypothesis that long-term use of NIV (>1 year) reduces all-cause mortality in patients with moderate or severe COPD and hypercapnia. Other parameters investigated will be the course of the disease (measured by the number of exacerbations and the use of medical resources), exercise capacity, and quality of life (see below).

All investigators and physicians participating in this study accept the guidelines for ‘Good Clinical Practice’ [12] and the ‘Declaration of Helsinki’ [13]. Written approval of the local ethic committee is a pre-requisite for all investigators and co-investigators. Patients can be enrolled into this study if they had been completely informed about all aspects of the trial, and after signing the informed consent.

Quality criteria:
Prospective, randomised, controlled, multicentre study with a PROBE design.

Comment: PROBE design: The local investigators (co-investigators) cannot be blinded for the intervention (NIV or non-NIV). It is obvious whether the patient is in the intervention group (NIV) or in the control group (non-NIV). During the study and at the end of the study, data from all participants will be evaluated by an ‘evaluation-committee’. The evaluation-committee is completely blinded for the intervention. See Hansson L. et al, Blood Pressure 1992;1:113-119 for further details.

For this study, the PROBE design will be performed as follows: An independent assistant will collect data at the local centres from patients’ notes and case report forms (CRFs). The assistant will fill in so called ‘Master CRFs’ and encode the treatment modality. All data will be analysed from the Master CRFs by a central evaluation committee. This design allows an independent analysis of the study data. The PROBE design is suitable for all interventions which cannot been blinded. Sham treatment of the control group can be avoided, and the number of patients needed for the trial can be reduced.
**Research Questions:**
1. Can long-term application of NIV in patients with moderate or severe COPD – in addition to standard treatment – reduce all-cause mortality by improving or normalising hypercapnic respiratory insufficiency?
2. Does additional NIV treatment reduce morbidity, measured by the rate of exacerbations, utilisation of medical services, exercise capacity, and quality of life?

**Outcome parameters:**
Primary outcome parameter:
- All-cause mortality with or without NIV.
Secondary outcome parameters:
- Rate of acute COPD exacerbations (definition: requirement for emergency treatment, treatment with antibiotics or oral steroids; see comments below).
- Rate of office visits (Primary Care Physician and Pneumologist).
- Number of days in the hospital.
- Number of days in an Intensive Care Unit.
- Number of endotracheal intubations.
- Exercise capacity (distance in the 6 minute walking test).
- Dyspnoea Score at rest and after 6 minutes’ walking.
- Quality-of-life questionnaires: St. George’s Respiratory Questionnaire (SGRQ), Severe Respiratory Insufficiency Questionnaire (SRI; Dr. Windisch, Freiburg/Germany), Short Form (SF)-36.
The following parameters will also been monitored:
- Spirometry, body plethysmography, diffusion capacity, ventilatory pump parameters (Pi0,1; Pimax), blood gases, haematocrit.
- Safety parameters: Skin lesions from the mask, conjunctivitis.

Comment: There is no universally-accepted definition for acute exacerbation from COPD in the literature. Only the criteria ‘emergency treatment’, ‘prescription of antibiotics’, and ‘prescription of steroids’ are objective, and these events can be reported by the patient.

The number of secondary outcome parameters has been reduced as much as possible to avoid false positive results because multiple statistical testing. Measurement of the ventilatory pump parameters might not be available at all centres.

**Section 2 Protocol**

**Design:**
Two groups will be investigated (parallel-group design with an intervention group and a control group) with >150 patients in each arm (see figure on page 4). Both groups will receive optimised medical treatment for COPD, including long-term oxygen therapy, if indicated (see National Guidelines for the treatment for COPD, published by the Deutsche Atemwegsliga and the Deutsche Gesellschaft für Pneumologie [14], and GOLD Components of care, Component 3 and 4, management of stable COPD/acute exacerbation [15]; see also National Guidelines for long term oxygen treatment published by the Deutsche Gesellschaft für Pneumologie [16]).

In the **control group**, standard medical treatment will be performed as outlined in the aforementioned guidelines. Regular in-hospital assessment of the patients will be performed as described below. NIV is not to be used in control group patients, except for an acute
exacerbation of COPD when NIV is permitted as an interim measure to avoid endotracheal intubation [17,18,19]. This exception is allowed, if PCO$_2$ at rest is $\geq 10$ kPa ($\geq 74$ mmHg), measured during room air breathing. In patients on long-term oxygen treatment, the measurement must be performed during inhalation of oxygen in the prescribed dose.

Comment: NIV as an acute treatment must be permitted in the control group because it would be unethical to allow early intubation of such patients.

In the intervention group, the same standard treatment will be implanted as in the control group. In addition, NIV will be applied for $\geq 6$ hours per day [20].

Inclusion criteria:
- Moderate or severe COPD with ventilatory pump insufficiency (GOLD stage IV [15]); stable disease for $\geq 4$ weeks prior to randomisation. COPD can have any cause (smoking, alpha-1 antitrypsin deficiency, etc). Smokers can be included.
- Capillary pCO$_2$ of 7 kPa (51.8 mmHg) to a maximum of 10 kPa (74 mmHg), combined with a pH of $\geq 7.35$. These measurements must be made after 30 minutes of breathing room air in sitting position. Patients on long-term oxygen treatment must inhale oxygen in their prescribed dose.
- Only patients aged $\geq 18$ years can be included.
- Written information about all aspects of the study must be provided for each patient. Written informed consent prior to implementation of any part of this protocol is necessary for inclusion.


**Exclusion criteria:**
- Patients with a pCO$_2$ > 10 kPa (>74 mmHg). These patients can be re-evaluated for inclusion after 4 weeks.
- Diseases of the lung or thorax apart from COPD: advanced pulmonary fibrosis, advanced bronchiectasis, active tuberculosis, post-tuberculosis syndrome, pneumonia, severe kyphoscoliosis, tracheostomy, neuromuscular diseases, or any other disorder, which might result in elevated pCO$_2$.
- Patients on NIV.
- Body mass index $\geq 35$ kg/m$^2$.
- Severe cardiac disease, NYHA class IV, instable angina, severe cardiac arrhythmia, especially of ventricular origin (atrial fibrillation is not an exclusion criterion).
- Malignancy
- Disorders of the basal brain nerves with derangement of swallowing, or reflexes of swallowing and choking.
- Local derangement of the face, skin, tongue, upper airways, larynx and upper oesophagus.
- Severe chronic diseases except COPD that would limit the ability of the patient to follow the study schedule.

**Study population:**
Patients to be included into this study must be clinically stable since for $\geq$ 4 weeks, with no exacerbations according to the above criteria. No change of COPD medication or change in oxygen flow rate can have taken place during this 4-week period. Patients can be recruited from outpatient chest clinics or as inpatients provided they meet the inclusion and exclusion criteria. Pulmonary specialists co-operating with the study centres will be invited to provide suitable patients.

**Size of the cohort:**
Patients eligible for this study have a 1-year probability of mortality of 20–22% \cite{8,21}. NIV could reduce 1-year mortality by 30% (alpha 5%, beta 20%; power 100% - beta = 80%). The estimated sample size for the trial was **150 subjects per arm (300 in total)**.

**Observation period:**
All patients included in this study will be observed for $\geq$ 1 year. If the recruitment of patients takes 1–2 years, the mean observation period will be 1 to 1.5 years. The study start date is 1 February 2004 (zero time). The study will be closed when $\geq$ 150 patients in each arm had been enrolled and observed for $\geq$ 12 months.

**Section 3 – Schedule of the study**

**Study centres:**
In each participating centre, one co-investigator and at least one other physician must be responsible for the trial. The co-investigator must apply for approval from the local ethics committee. The co-investigator is responsible for conducting the study in the local centre according to the protocol. The number of included patients must be high enough to ensure that $\geq$ 14 patients had been included and treated according to the protocol for at least one year. This number (e.g. 7 subjects in the intervention group and 7 subjects in the control group) must be achieved 2 years after approval of the local ethics committee.

The local centre will be closed if no patient has been included into this study 3 months after local ethics committee approval.
Screening of patients:
- All patients with moderate or severe COPD at each study centre are eligible for enrolment in this study.
- Inclusion and exclusion criteria must be checked, using data from the patient’s notes and by interviewing the patient. The baseline pCO₂ must be measured under the conditions described above. The interval between measurement of pCO₂ and randomisation must not exceed 24 hours.
- Complete information about the necessity and requirements for this study must be provided to each patient.
- The physician and the patient must both sign the informed consent form.
- Randomisation (see below). Day 0 (Day Zero) is determined with randomisation.

Comment: All physicians from the participating hospitals are obliged to screen and include all patients who might be suitable for this study. The concern of some physicians that a patients with long-standing, severe COPD might be randomised into the control group, and therefore not receive NIV, is completely unacceptable. With the current knowledge about the effects of long-term NIV in COPD, non-screening of patients and treating them with NIV outside the study would be unethical.

Randomisation Procedure:
Randomisation can be planned if a patient fulfils all inclusion criteria and does not meet any exclusion criteria. Written informed consent must have been signed. Randomisation is performed by telephone contact with the study organisation in Hannover. One representative is available 24 h per day/7 days per week by mobile phone. The variables ‘intervention group’ or ‘control group’ will be randomised in the first step. For each participating centre, randomisation lists will be held in Hannover, and block randomisation will provide equal numbers of patients in both treatment groups. If a patient is randomised into the intervention group, the type of ventilator will be randomised in a second step. The size of the randomisation lists are determined prior to the start of the study, but these lists are not accessible to the participating centres.

Modes of ventilation:
NIV must be performed according to the guidelines of the “National Task Force for Non-invasive ventilation and weaning” [20,22]. Only ventilators supplied by the study sponsors can be used for this study. Each centre will hold a pool of ventilators, which will be refilled by the manufacturer or their local representatives. The patient will have the ventilator on loan for the first three months. Three months after randomisation, the study centres will apply for reimbursement of the costs of ventilator, masks and accessories.

Comment: Previous concepts, e.g. a loan period for the complete study period cannot be accepted by the sponsors. If the results of this study are negative for NIV, no reimbursement applications could be made. The sponsors accept the current version only.

As described above, the ventilator will be centrally randomised. The device to be used first is not to be determined by the study centre. Only if the randomised ventilator cannot been adapted to the patient, can another of the sponsors’ ventilators be used. The study organisation must be informed about any switch of a ventilator. Patients will be ventilated via conventional nasal masks or full face masks. Customised masks are allowed, but this must be managed and paid for by the local study centre.
Modes of ventilation: pressure-driven ventilation, with the highest possible degree of unloading the ventilatory muscles of the patient, is the target [23].

Comment: Highest possible unloading of the ventilatory muscles means to reduce the patient’s own respiratory efforts as much as possible. This can be judged by clinical observation only. This can be achieved by assisted, but preferably by controlled ventilation.

Ventilators provided by the sponsors allow pressure-driven ventilation only.

**Target of ventilation:** Reduction of pCO₂ during spontaneous breathing by ≥20% or to <6.5 kPa (<48.1 mmHg). If possible, the lower normal range for pCO₂ should be targeted.

As described above, the baseline pCO₂ must be measured under stable conditions. The interval between measurement of blood gases and randomisation may be ≤24 hours. After randomisation, patients in the intervention group start acclimatisation with NIV. NIV can be adapted over a period of 14 days after randomisation. Blood gas measurements for the target pCO₂ is taken after ≥2 hours of ventilation, or preferably after overnight ventilation. There must be an interval of 60–120 minutes between the end of NIV and measurement of blood gases.

**Proposed invention with NIV:** initiate ventilation with pressure support ventilation (PSV) or pressure controlled ventilation (PCV), using an inspiratory pressure of 15 mbar and PEEP of 4 mbar. Elevate inspiratory pressure in 2 mbar increments until the expiratory volume reaches a maximum. Vary PEEP according to the clinical situation (PEEP might range from 0 to 6 mbar). If the minimum pressure setting of 15/5 mbar cannot been tolerated by the patient, the inspiratory pressure can be reduced in 2 mbar increments. This is expected for a very small number of patients only. The inspiratory flow must be high, the same is necessary for the pressure rise after inspiratory triggering.

Comment: The application of PEEP is recommended, but not mandatory. If the patient tolerates a very low inspiratory pressure only, the PEEP should be reduced to maintain enough ‘driving pressure’.

The investigator is free to select the (minimum) breathing frequency. Setting of the minimum frequency below or above the frequency of spontaneous breathing determines whether assisted or controlled ventilation is performed. The maximum unloading of the ventilatory muscles is achieved with controlled breathing. During adaptation to NIV, a sufficiently high number of blood gas measurements has to be performed for safety reasons.

The setting of the ventilator is primarily guided by the pCO₂. Oxygenation should improve at the same time. Additional oxygen can be inserted into the breathing circuit if necessary.

Comment: The setting of the ventilator, as described above, is not strictly determined. Only the targets of ventilation (PCO2 reduction) are mandatory for every investigator. If the target of ventilation cannot been reached until 14 days after randomisation, the study organisation has to be contacted.

Patients on long-term oxygen treatment will receive oxygen via nasal cannula during ventilation-free intervals. During ventilation, oxygen will be inserted into the breathing circuit. The flow rate of oxygen during ventilation must be determined by blood gas measurements.
In all follow-up visits, ventilator settings must be optimised. If the targets of ventilation are not reached during the course of the study, new settings of the ventilator must be tested. If this is unsuccessful, the study organisation has to be contacted.

**Documentation:**
The documentation of all relevant data must be made in Case Report Form (CRF) for this study. Data will be transferred to master CRFs by assistants for further analysis.

**Study Schedule:**
All measurements taken during this study will be performed in hospitalised patients. This applies for both the intervention and control groups.

**The time point of randomisation is Day Zero.**

Intervention group: Clinical assessment, obtaining of data by interviewing and measurements (see Outcome parameters). Documentation of data into the CRFs. Optimisation of medical treatment if necessary. Introduction to NIV. Patients should be adapted to NIV under supervision of a physician. Measurement of blood gases as required. The ventilatory targets should be achieved. Adaptation of the patient to NIV starts on Day Zero and might take up to 14 days.

> Comment: Adaptation of NIV might take up to 8 hours. This amount of time must be available. Several study patients can be observed at the same time. Some patients may have a quick initial improvement of blood gases without reaching the final ventilatory target. These patients may be discharged and readmitted on day 14.

Control group: Clinical assessment, obtaining of data by interviewing and measurements (see Outcome parameters). Documentation of data into the CRFs. Optimisation of medical treatment if necessary.

**Clinical assessment after 14 days (from Day Zero):**
Intervention group: Clinical assessment, obtaining of data by interviewing and measurements (see Outcome parameters). Documentation of data into the CRFs. Optimisation of medical treatment if necessary. Critical assessment of NIV (compliance?; technique?). Optimisation if necessary. The run time of the ventilator will be recorded from the hour meters. Measurement of blood gases. The target of ventilation must be achieved 14 days after start of NIV.

> Comment: For the intervention group, the first 14 days are the training period. The ventilation target and use of NIV for ≥6 hours per day should be achieved. At day14, “critical” blood gases measurements are made to determine whether pCO₂ is reduced by ≥20% from baseline or to <6.5 kPa (48.1 mmHg).

Control group: Clinical assessment, obtaining of data by interviewing and measurements (see Outcome parameters). Documentation of data into the CRFs. Optimisation of medical treatment if necessary.

**Clinical assessment after 90 days (from Day Zero):**
The assessment may be performed between day 80 and day 100.

Intervention group: Same procedure as at day 14. Application for cost reimbursement for the ventilator and for the masks. The local study centre decides whether or not the ventilator will be prescribed. The patient must be treated sufficiently by clinical criteria.

> Comments: If ventilation targets are not met, efforts must be made to change ventilator settings and improve the ventilation technique. Even if these measures are not successful, the patient remains in the study. Long-term NIV can be continued and the ventilator prescribed if the patient meets the requirements of the local centre for
Control group: Same procedure as day 14.

**Clinical assessment after 180 days (from Day Zero):**
The assessment may be performed between day 160 and day 200.
Same procedure as day 14.

**Clinical assessment after 270 days (from Day Zero):**
The assessment may be performed between day 250 and day 290.
Same procedure as day 14.

**Clinical assessment after 360 days (from Day Zero):**
The assessment may be performed between day 340 and day 380.
Same procedure as day 14.

The clinical assessments are continued every 90 days with an allowed variation of ±20 days.

**Telephone assessments:**
All patients are contacted by telephone monthly (day 30, 60, 120, 150, etc from Day Zero). Patients will be interviewed about acute exacerbations (see definition above), number of visits to their Primary Care Physician or Pneumologist; number of days in the hospital, number of days in an Intensive Care Unit, endotracheal intubations, medication. There are 8 telephone calls per patient each year.

To ensure reliable contact with the patient, the telephone number of at least one other person in their family will be recorded. This is especially important in case a study participant dies.

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**Section 4 Data Analysis**
For analysis of the data, a group-sequential method (standard statistical method) will be applied. Data analysis is planned at 12 and 18 months after Zero Time. Both per-protocol and intention-to-treat analyses will be performed. The intention-to-treat analysis includes all patients who had been included into the study and is the primary endpoint. The per-protocol analysis is restricted to patients who fulfil all requirements of the protocol. The most frequent reason for protocol violence will be too short ventilator run times, and inadequate changes in the pCO$_2$ during NIV. In the control group, a high number of acute interventions might
become an important confounding factor. The patient will not be included in the per-protocol analysis if ≥7 acute interventions had been necessary. An ‘acute intervention’ is defined as a hospitalisation with >20 hours of ventilation, independent of whether it is invasive or non-invasive ventilation.

Repeated data analysis during the study allows early recognition of large effects of the intervention relatively early. In case of problems with patients’ compliance or other major problems or side effects, the protocol can be modified or the study can be terminated. All data analysis during the study will be associated with an Alpha adjustment of 1%.

The total duration of the study is estimated to be three years. The mean observation time for each patient is estimated on 1 to 1.5 years.

The level of significance for the primary outcome parameter (mortality; Kaplan-Meier analysis) is set at 5%. For secondary parameters, the level will be set at 1%. Quality-of-life questionnaires will analysed using variance analysis, and dichotomizations in scores is made (i.e. >8 or <8 points of improvement in the SGRQ) are provided.

Section 4.1 Publication
It cannot be guaranteed that all investigators and co-investigators will be mentioned in a publication. At least the principal investigator from each institution will be listed in a publication of the study results. The first author of a study publication will be Dr. Thomas Köhnlein, Hannover, Germany.

Section 5 Appendix
Study organisation, protocol development:
Professor Dr. Tobias Welte, Otto-von-Guericke -University of Magdeburg, Magdeburg, Germany, Head of the Department of Pulmonary and Intensive Care Medicine.
Dr. Thomas Köhnlein, Research Fellow, same institution.
Estimated time consumption per patient and year:
Inclusion into the study (identification of patients, confirmation of inclusion and exclusion criteria, patient information, etc.): 1 hour.
Introduction of NIV: 8 hours
Five regular clinical assessments: 7.5 hours (1.5 hours each)
8 telephone calls: 4 hours (0.5 hours each)
Total time commitment: 20 hours per patient per year. In addition, time for education, familiarisation with the protocol, and documentation must be allowed.
References: