Protocol

RECOVER

REsearch in COPD: the additional value of noninvasive VEntilation on Rehabilitation

NIPPV/ Revalidatie bij COPD

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Background

Several randomised controlled trials in patients with stable Chronic Obstructive Pulmonary Disease (COPD) have demonstrated that pulmonary rehabilitation (PR) improves dyspnoea, exercise tolerance, and health-related quality of life[1]. Research in this field has been important in our department for several years. The first study in this respect was started in 1986 comparing outpatient rehabilitation with rehabilitation in the community in patients with severe COPD[2]. This study showed that rehabilitation supervised by a physical therapist in the community is effective for a long period in contrast to outpatient rehabilitation. In 1990 the second study started showing that positive initial benefits of home based rehabilitation on quality of life can be maintained for 18 months if the patients visit the local physical therapist once a month [3].

However, less positive effects of rehabilitation have been reported in the more severe patients[4]. Because of dyspnoea due to inspiratory muscle fatigue patients may not receive an adequate training stimulus, and therefore rehabilitation might be less effective. In these more severe patients alternative therapies are needed. These non-pharmacological treatments include nutritional suppletion, oxygen therapy, lung transplantation, lung volume reduction surgery and ventilatory support.

The last few years a discussion within the 4 home mechanical ventilation centres (HMV) in the Netherlands has been started about the role of chronic ventilatory support in end-stage COPD. Theoretically, it might be effective because: 1) a resetting of the respiratory centre may reduce daytime $PaCO_2$; 2) a better internal milieu (pH, PaO_2, $PaCO_2$) may improve peripheral muscle function; 3) resting the respiratory muscles during the night may increase their daytime strength and endurance; 4) a reduction in the number of nocturnal arousals may improve the quality of sleep. Nevertheless, none of these mechanisms has been proven and currently there is no evidence that NIPPV should be given to stable patients with COPD. While several randomised controlled trials (RCT's) on NIPPV have been published with different outcomes [5-10], a recent meta-analysis did not show beneficial effects on blood gasses, lung function, respiratory muscle function and walking distance [11]. In contrast several uncontrolled studies did show clear benefits from NIPPV on gas-exchange, dyspnoea and quality of life. Possible reasons for these conflicting outcomes are differences in: 1) selection of patients, 2) adequacy of ventilatory support, 3) length of ventilatory support. Interestingly, it seems that studies with a positive outcome included mainly patients with hypercapnia, suggesting this as an important selection criterion [12]. Our hypothesis is that long term NIPPV in hypercapnic patients with COPD may improve the effects of rehabilitation at home regarding health status, ADL function, dyspnoea and exercise tolerance. Secondly, we like to elucidate the exact mechanisms why NIPPV might be effective in this group of patients.

Methods

Patients

We will include COPD patients (Tiffeneau index < 70%) who are hypercapnic (with a PCO_2 > 6.0 kPa at rest without oxygen) with symptoms of dyspnoea on exertion or a reduced exercise capacity. Patients have to be aged between 18 and 76 years old. We exclude patients with cardiac or neuromuscular diseases limiting a successful rehabilitation, patients with obstructive sleep apnea syndrome (AHI > 10), patients with previous exposure to chronic NIPPV, and patients who underwent a pulmonary rehabilitation program in the last 18 months.
We will include 100 patients in our study.

Study design

At baseline the patients are evaluated for all parameters at Beatrixoord (described in the measurements section). From that time point all patients will receive 3 months optimal pharmacological treatment only, without rehabilitation or ventilatory support (control period). After 3 months the patients are randomized for group A or B, using the principle of minimization for FEV_1, $PaCO_2$ and BMI. The use of minimization will provide treatment groups very similar for several variables even in small samples and, therefore, it will prevent a possible imbalance of important variables between the 2 groups [13]. Minimization takes place for: FEV_1 (≤ 1.2 L or > 1.2 L), $PaCO_2$ (≤ 7.0 kPa or > 7.0 kPa) and BMI (≤ 30 kg/m^2 or > 30 kg/m^2). We anticipate that NIPPV is more effective in patients with less severe airway obstruction and more signs of hypoventilation possibly due to obesity.

Figure 1

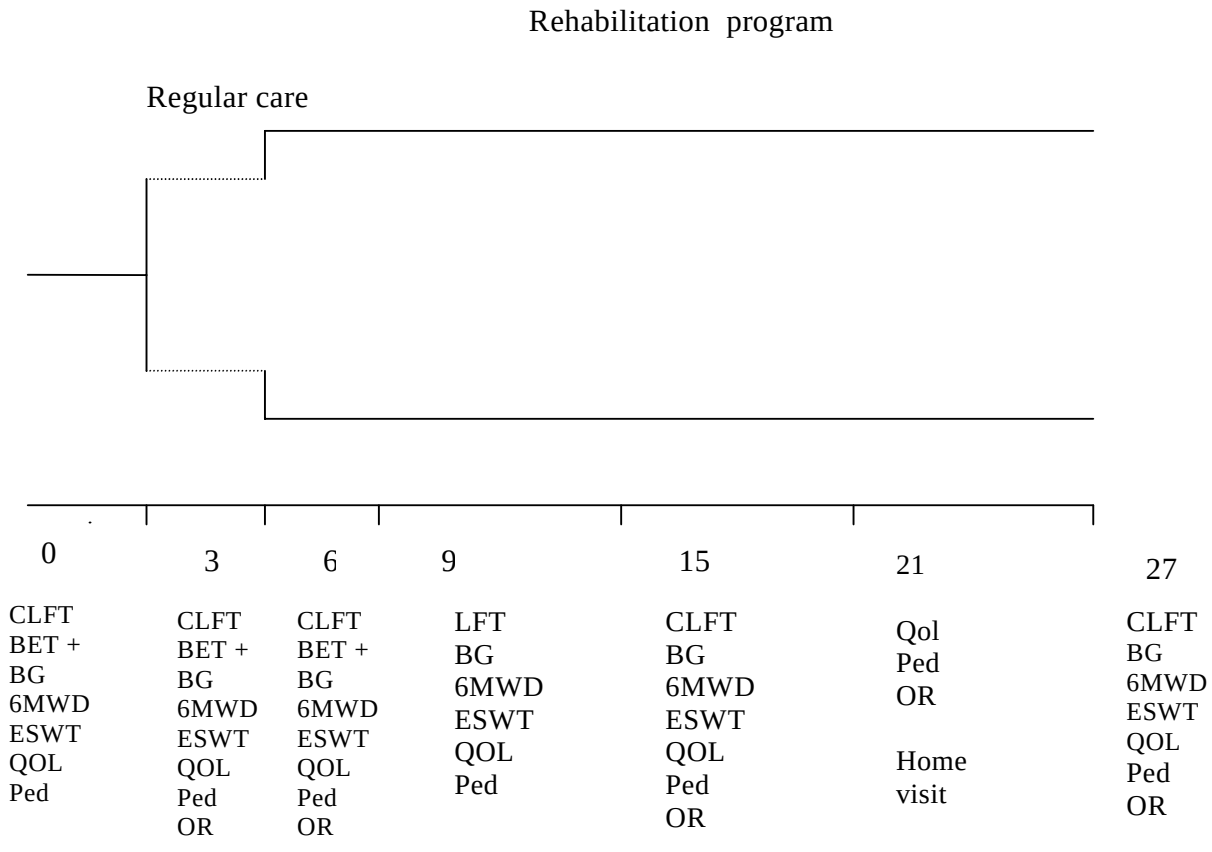

Figure 1 shows the time planning of the various measurements done during the study.

Measurements

The following measurements will be done at the various time points (see figure 1):

- Lung function (CLFT: complete lung function testing/ LFT: only spirometry and PImax)
- BG: arterial blood gas testing
- Bicycle ergometer test (BET)
- 6-minute walking distance (6-MWD)
- Endurance shuttle walk (ESWT)
- Quality of life (QoL)
- Pedometer: walking distance/ activity for a week at home (Ped)
- Polygraphy
- Overnight registration (OR)
    - In the patients in group A, an overnight arterial blood gas registration will be performed before and after institution on NIPPV (at 3 months) and then after 3 months ventilation (at 6 months). At 15, 21 and 27 months an overnight oxycapnography is performed.
    - In the patients from group B an oxycapnography is performed at 3 months, at 15, 21 and 27 months.

Group A

Patients in Group A will undergo a rehabilitation program with non-invasive ventilatory support at night.
After the first 3 months of regular care (control period), the patients are assessed at the rehabilitation center. Firstly all measurements will be repeated. Thereafter they are admitted to the university hospital. In the University Medical Center Groningen, firstly a continuous blood gas registration during the night without NIPPV is performed. Thereafter, the patients will start the ventilatory support. It takes normally 7-10 days for patients to adjust to the ventilator. When the patients are able to sleep comfortable with the ventilator for at least 6 hours per night, a second blood gas registration during the night is done, while now on NIPPV.
Thereafter the patients are send to the rehabilitation center and will start the rehabilitation program in a clinical or an outpatient setting, depending on the individual situation. This part of the rehabilitation program has a duration of 3 months. Afterwards the patients continue their exercises in the community supervised by a trained physical therapist during the next 21 months.
During the study period a specialized nurse of the home mechanical ventilation center supervises the ventilatory support. She visits the patients at least one time next to the measurement moments (T21).

Group B

These patients will follow an identical program as the patients allocated to group A except that they do not receive ventilatory support. After 3 months regular treatment they will

undergo control measurements in the rehabilitation center. Thereafter they can start with the rehabilitation program immediately.
Patients in this group can always contact the investigators or the rehabilitation center if they have problems or questions related to the program. These patients will also be visited at home (T21).

Rehabilitation programme[14-28]

The investigator has set up the programme. The rehabilitation programme consists of a 3-months inpatient or outpatient hospital programme followed by a 21 months programme in the community.

The in-hospital/ outpatient programme

The participants will follow a rehabilitation programme of 3 months in the rehabilitation centre Beatrixoord, Haren or a comparable programme in their hometown, in a clinical or outpatient setting. This programme consists of strength training of the lower and upper limbs, endurance training of the lower limbs, inspiratory muscle training, breathing exercises, education and psychosocial support; the latter depending on the individual patient.

Patients start with upper and lower limb exercises, 3 times a week, for 3 weeks, on a multigym apparatus. The sessions consisted of dynamic strengthening exercises of the m pectoralis, the m biceps brachii, the m triceps brachii, the m deltoideus, the quadriceps, and the hamstrings. The patients will exercise initially at 70% of their initial one repeat maximum (e.g. the maximum resistance patients were able to move over a full range at the initial test) for 10 movements, repeated for a total of 2 series per session. This is increased until 3-4 series of 10 movements can be made. After this the resistance is increased every 3 sessions with 5% 1 RM [17-21].

After 3 weeks patients will start with a program of 9 weeks consisting of walking, cycling, and inspiratory muscle training. In order to make this exercise program easier to attain for our patients, this part of the program is added after 3 weeks strength training

The cycle ergometer training consists of 2 times a week 30 minutes bicycling according to an interval-based exercise program, as described by Vogiatisz et al [22]. The patients start with cycling for 1 minute at 100% of the peak work rate achieved at the incremental ergometer test at 3 months, this alternated by 1 minute at 20% peak work rate. After 2 weeks the work rate is increased to 120%, after 4 weeks to 140%.
When the patients are able to achieve 140% according to the above mentioned scheme, the cycle periods are increased 30 seconds each 2 training sessions, so that the patients cycle at 140% for 11/2 min, interspersed with 1 minute rest etc.

The patients walk on the level for twice a week. Initially they walk 10 minutes per session. The duration of the sessions is increased with 5- 10 minutes every week until the patients are able to walk 30 minutes per session. The speed of walking is adjusted in order to achieve a maximum Borg score of approximately 80% of the maximum Borg score at the initial 6 MWD.

The patients receive inspiratory muscle training 5 days a week. It consists of 30 minutes training on an inspiratory threshold device on an interval basis with 2 minutes loaded breathing, followed by 1 min rest. The patients start with 30% of their initial PImax, increasing with 5-10% per session until 70% Pimax is reached. Every time when a new PImax is measured, the training intensity is adjusted to 60% of the measured PImax [23-28].

The patients also participate in group education sessions. Information is given about the disease, various strategies of treatment, use of medication, ways of coping with the disease, the role of rehabilitation, and how to recognise an exacerbation.
Next to this they are thought breathing exercises, e.g. training lip-pursing techniques, expiratory abdominal augmentation, and synchronisation of thoracic and abdominal movement, receive nutritional counselling by a dietist and if necessary psychosocial support.

The community based programme

The first 3 months of the outpatient programme the patients will visit a physical therapist twice a week, for 30 minutes each time. The following 18 months the patients will visit the therapist once a week.
In these sessions the participants will exercise under supervision of the therapist. The exercise training will consist of 20 minutes cycle endurance training and 10 minutes inspiratory muscle training, both according to the principle described above.
After the in-hospital programme an incremental cycle ergometer test was performed. Next to this we adjusted the intensity of the exercise periods for the coming home rehabilitation period to at least 100% of this new value. Intensity was increased with 20 % every 3 weeks again to a maximum of 140%. Wen 140% was reached exercise time was increased with 30 seconds per week so that patients exercised 11/2 minute interspersed with 1 minute rest, 21/2 minute exercise with 1 minute rest etc.

Inspiratory muscle training intensity was also adjusted after testing was performed.

Next to this the patients will exercise at home, on the days they do not visit the physical therapist, for 30 minutes a day, 3-5 days a week. These training sessions will consist of 30 minutes walking or cycling.

Patients and therapist noted all activities in a diary.

Ventilatory support

Non-invasive ventilation was supplied through a pressure cycled ventilator, applying both inspiratory and expiratory pressure to the patient (BiPAP; Respironics, INC., Murrysville, PA, USA) through a standard nasal mask of the proper size. The ventilator was set in a spontaneous/ time mode (S/T) at the maximal tolerated inspiratory positive airway pressure (IPAP) and at an expiratory positive airway pressure (EPAP) starting at 4 cm H_2O. When needed O_2 was added with a nasal catheter inside the mask to obtain a saturation of 90%, assessed by pulse oxymetry.
Ventilatory support was delivered at least 6 hours a night.

Outcome parameters

Polygraphy

An overnight polygraphy will be performed in patients with a BMI ≥ 30 or patients who have complaints of snoring or apnea's during the night to exclude an obstructive sleep apnea syndrome

Lung Function

Total lung capacity (TLC), residual volume (RV), forced expiratory volume (FEV_1), inspiratory vital capacity (IVC), diffusion capacity were measured at the initial evaluation (T0), after 3 months, after 6 months, after 15 months and after 27 months. After 9 months we measured FEV_1 and IVC only.
Static lung volumes were measured by means of a whole body plethysmograph. FEV_1 and IVC were measured by means of a pneumotachograph. Predicted values were derived from the ERS [29].
Pulmonary function was measured after bronchodilatation.

Respiratory muscle strength

Respiratory muscle strength was measured at the initial evaluation, after 3, 6, 9, 15 and 27 months.
Peak inspiratory mouth pressure (P.Pimax) was measured with the pressure transducer of the pneumotachograph. All patients were seated, wore a noseclip and carried out their maximal inspiratory pressure manoeuvres from RV, against a closed shutter through an oval flanged mouthpiece with a leak of 2.0 mm to prevent the use of the buccinator muscles.
Before each measurement the pressure transducer was calibrated; ambient pressure was used as zero level. The highest achievable pressure was recorded.

Bicycle ergometer test

The Bicycle ergometer test was performed at 0, 3 and 6 months. Prior to the exercise test, limited lung function testing was performed (FEV_1). The exercise test was performed on a cycle ergometer using a 1-min incremental cycle exercise protocol. The test was performed without oxygen supplementation, **with the exception when oxygen saturation decreased to less than 85% in rest, when oxygen was substituted during cycling**. A brachial catheter was inserted for periodically sampling of blood gas analysis of Ph, PaO_2 and $PaCO_2$. Samples were taken at rest and then every 2 minutes, the last sample after 2 minutes of recovery. Patients respired through a mouthpiece and wore a noseclip during the test. Minute ventilation (VE), oxygen uptake (VO_2), and carbon dioxide output (VCO_2) were measured every 30 s from analysis of the expirate by a computerised system. Heart frequency was measured and arterial oxygen saturation was recorded.
First, recordings were made during breathing at rest for 5 minutes. The exercise test started with 1 min unloaded pedalling at 60 cycles/min, followed by a 1-min incremental protocol at 5-10 Watt load increment/min, until discomfort or exhaustion was reported. The maximum workload was defined as the highest work level reached and maintained for a full minute. Prior to and during the exercise training the subjects were asked to estimate leg effort and the effort required to breathe, using a Borg category scale. During the exercise the Borg scale was kept in front of the participant and the subject was asked to rate effort at two-minute intervals

and at peak exercise. Immediately afterwards, participants were asked about the reason why they had to stop.

6-minute walking distance

The patients walk indoor as far as possible during 6 minutes. Encouragement was given every 30 seconds, containing the words “you are doing fine, go on. After 2 and after 4 minutes it was told to the patient he was 2 and 4 minutes on his way. Before and after the test patients were asked to estimate the degree of breathlessness they experienced on a Borg scale.

Shuttle walk test

The endurance shuttle walk test (ESWT) was set up according to the way Revill et al described [30]. Firstly the patients performed an incremental shuttle walk test (ISWT). From the incremental shuttle walking test the VO_2 peak can be predicted as Singh et al showed [31]. At baseline, we choose the best fitting tape with the walking speed for the endurance shuttle walk test corresponding to 85% of the predicted VO_2 peak, calculated with the ISWT.
The patients performed the endurance shuttle walk test twice to avoid learning effects. After the rehabilitation (T6) the first test was performed at the same walking speed as the initial test, while the test was performed at a speed adjusted to the ISWT performed at that particular visit. After T6, the first test was performed at baseline walking speed, the second test at post-rehabilitation walking speed. A cut of time of 20 minutes was chosen, although the patients were unaware of any time limit.
The test was performed on a 10 m course on a flat corridor demarcated by cones. Patients were instructed to walk along the course, turning around the cones at either end in time with the signals from the audio tape.
Before and after the test patients were asked to estimate the degree of breathlessness they experienced on a Borg scale

Quality of life

Quality of life was measured by the chronic respiratory questionnaire (CRQ) [32, 33], the Maugeri Respiratory Failure questionnaire (MRF-28) [34], and the Severe Respiratory Insufficiency questionnaire (SRI) [35].

The CRQ contains 20 items. It measures physical function and emotional function divided into four dimensions: dyspnoea, fatigue, emotion, and mastery. Physical function is assessed by asking the patients to quantify their dyspnoea during 5 frequently performed activities in daily life. They are asked to choose 5 activities from a list of 25 activities or they can mention activities not on the list. Physical function is also assessed by 4 items related to fatigue and energy level. Emotional function, including the emotion and mastery dimensions, include questions about frustration, depression, anxiety, panic, and fear for dyspnoea.

The MRF-28 contains of 7 schedules related to dyspnoea during daily activities, impairments in daily activities and relations; memory; depression; emotions; problems with treatment and an overall score for general health and respiratory health.

The SRI was developed to measure health-related quality of life in patients receiving home mechanical ventilation. It contains 8 subscales related to respiratory complaints, physical functioning, attendant symptoms and sleep, social relationships, anxiety, psychological well-being, social functioning and a summary scale.

Dyspnoea

Borg score:
Before, during and after the incremental cycle ergometer test and the 6-MWD test dyspnoea was measured with the Borg scale, a 10-point scale using descriptive terms to anchor responses.

Baseline and transitional dyspnoea index [36 , 37]
Dyspnoea at baseline was assessed by the BDI, which contains 3 domains (functional impairment (FI), magnitude of task (MT) and magnitude of effort (ME). The score ranges for each domain from 0 to 4 (no impairment); with the baseline total score ranging from 0 to 12. Changes in dyspnoea were measured using the TDI. The TDI score ranges from –3 (major deterioration) to +3 (major improvement) for each domain with the TDI total score from –9 to +9

Activities of daily living

The Groningen activity and restriction scale (GARS) [38,39] , was used to assess disability in personal care and domestic activities. It consists of 18 items covering different domains of daily living.

Mood state

The hospital anxiety and depression scale (HADS) was used to assess mood state. It contains of 14 items, which produce separate scores for anxiety and depression.

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