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Long-term Controlled Trial of Nocturnal Nasal Positive Pressure Ventilation in Patients With Severe COPD*

Ciro Casanova, MD; Bartolome R. Celli, MD, FCCP; Lina Tost, MD; Estanislao Soriano, MD; Juan Abreu, MD; Valle Velasco, MD; and Francisco Santolaria, MD

Study objectives: To determine the 1-year efficacy of noninvasive positive pressure ventilation (NPPV) added to long-term oxygen therapy (LTOT) in patients with stable severe COPD.

Patient selection and methods: We prospectively randomized 52 patients with severe COPD (FEV$_1$ < 45%) to either NPPV plus “standard care” (96% patients with LTOT) or to standard care alone (93% patients with LTOT). The outcomes measured included the following: rate of acute COPD exacerbations; hospital admissions; intubations; and mortality at 3 months, 6 months, and 12 months. The patients were also evaluated at 3 months and 6 months for dyspnea using the Medical Research Council and Borg scales, gas exchange, hematocrit, pulmonary function, cardiac function with echocardiogram, and neuropsychological performance.

Results: One-year survival was similar in both groups (78%). The number of acute exacerbations was similar at all time points in patients receiving NPPV, compared with control subjects. The number of hospital admissions was decreased at 3 months in the NPPV group (5% vs 15% of patients, p < 0.05), but this difference was not seen at 6 months (18% vs 19%, respectively). The only beneficial differences were observed in the Borg dyspnea rating, which dropped from 6 to 5 (p < 0.039), and in one of the neuropsychological tests (psychomotor coordination) for the NPPV group at 6 months.

Conclusions: Our study indicates that over 1 year, NPPV does not affect the natural course of the disease and is of marginal benefit in outpatients with severe COPD who are in stable condition. (CHEST 2000; 118:1582–1590)

Key words: COPD; noninvasive mechanical ventilation; respiratory failure

Abbreviations: EPAP = expiratory positive airway pressure; FRC = functional residual capacity; IPAP = inspiratory positive airway pressure; LTOT = long-term oxygen therapy; MEP = maximal expiratory pressure; MIP = maximal inspiratory pressure; NPPV = noninvasive positive pressure ventilation; OSAS = obstructive sleep apnea syndrome; P$_{0.1}$ = mouth occlusion pressure; RV = residual volume; TLC = total lung capacity

The clinical course of COPD is characterized by a high morbidity and mortality despite long-term oxygen therapy (LTOT). Recent alternative therapies, including lung transplantation and lung volume reduction surgery, can only be undertaken in a small number of patients, and there is no demonstration of improved long-term survival rate. Noninvasive positive pressure ventilation (NPPV) administered via a nasal mask has proven useful in treating restrictive extrapulmonary respiratory insufficiency and in many patients with severe COPD and acute respiratory failure. Theoretically, NPPV could also be beneficial in patients with severe stable COPD, through several mechanisms. It could improve nocturnal ventilation, decrease the end-expiratory lung volume and hence the level of dynamic hyperinflation (auto-positive end-expiratory pressure), and improve the response of the respiratory center to CO$_2$. It could also decrease upper-airway resistance and improve the quality of sleep. In addition, NPPV could improve respiratory muscle function by resting the respiratory muscles.
ever, the efficacy of this form of therapy in patients with airflow obstruction who are in stable condition remains controversial because the published reports, with a small number of patients and with short follow-up time, have shown conflicting results.

We therefore completed a prospective randomized controlled trial to assess the efficacy of nocturnal NPPV vs conventional standard treatment in patients with stable severe COPD. We analyzed at 3 months and 6 months the effects of NPPV on dyspnea, arterial blood gases, pulmonary function, and neuropsychological, hematologic, and hemodynamic parameters (systemic arterial pressure and pulmonary artery pressure by echocardiography). Furthermore, we followed up the patients at 3 months, 6 months, and 12 months to assess the influence of NPPV on COPD morbidity (acute exacerbations, intubation rate, and hospital admissions) and mortality.

Materials and Methods

Patient Selection

Eighty patients with severe COPD from the pulmonary clinics of two hospitals in the Canary Islands (Hospital Clinico and Hospital Nuestra Señora de La Candelaria, Canary Islands, Spain) were asked to participate in the study, which was approved by the humans study committee at both institutions. All patients signed the informed consent and were enrolled between 1995 and 1997. The patients were included if they met the following criteria: age from 45 to 75 years, smoking history of >20 pack-years, FEV1 < 45% of predicted, FEV1/FVC < 70%, total lung capacity (TLC) ≥ 80% predicted, and a stable clinical state (no acute exacerbation for 3 months prior to the initiation of the study). Patients were excluded if they had the following: a 15% increase in FEV1 after the administration of an inhaled bronchodilator (n = 12); refusal to stop smoking (n = 9); obstructive sleep apnea syndrome (OSAS); index of apneas-hypopneas > 10 episodes per hour; n = 3; other etiologies of chronic airway obstruction (bronchiectasis and cystic fibrosis; n = 2); active and important coexisting medical conditions, such as left ventricular failure (n = 2). The results of arterial blood gas tests were not used as criteria for enrollment.

The 52 patients who met the study criteria were randomized by an independent office into two groups using a table of random numbers. Twenty-six patients were maintained on standard treatment, and the other 26 patients received nocturnal nasal ventilation with bilevel positive pressure ventilation added to their treatment.

Standard Treatment

The patients were evaluated and followed up at least every 2 months in the pulmonary clinic. Bronchodilators were adjusted to achieve optimal symptomatic control. Antibiotics and corticosteroids were administered during the episodes of acute exacerbation. Hospitalizations were advised for patients with the most severe episodes. The patients were encouraged to remain active. Forty-nine patients were receiving supplemental oxygen, which had been prescribed at the clinics because of resting hypoxemia (PaO2 < 55 mm Hg).

Initial Evaluation

Spirometry was completed with a constant-volume body plethysmograph (Materlab; Jaeger, Germany) following the guidelines of the American Thoracic Society. The static pulmonary volumes (residual volume [RV], functional residual capacity [FRC], and TLC) were also measured using standard methods. The reference values were those of the European Community for Steel and Coal. The pulmonary transfer of carbon monoxide was determined with a single-breath test. The maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were measured at the mouth during a maximal respiratory effort at RV and TLC, respectively. Values were compared with the prediction equations of Morales et al. proposed by the Spanish Society of Respiratory and Thoracic Surgery. We also measured the mouth occlusion pressure (P0.1) and the ΔP0.1/end-tidal CO2, using the method recommended by Cherniak. Arterial blood gas measures at rest were obtained from the radial artery (AVL-945; Graz, Austria) with the patient in the seated position between 1 h and 3 h after having withdrawn oxygen in the control group, or this plus the ventilatory support in the patients assigned to NPPV. Dyspnea was assessed using the Medical Research Council and modified Borg dyspnea scales. At the time of initiation of the study, there were no validated health-related quality-of-life questionnaires in the Spanish language. Therefore, we chose a group of neuropsychological tests that have been validated in that language. A psychiatrist blinded to the treatment conducted the tests. The tests assessed a wide range of neurobehavioral functions, including attention and concentration tests, visual memory, verbal memory, association capacity and learning capabilities, construction praxis (Strub and Black test adapted from Peña-Casanova), and gestural praxis as described by Luria. Standard administration and scoring procedures were utilized for all neuropsychological measures. A cardiologist blinded to treatment performed the assessment of cardiac function. An echocardiographic Doppler study was performed from the parasternal projection. The pulmonary arterial pressure was calculated from the gradient of the systolic pressure peak between the right ventricle and the right atrium added to normal right atrial pressure.

To rule out the coexistence of OSAS, all the patients were screened with a nocturnal respiratory polysomnography (Apneascreen Type I; Jaeger). This test continuously recorded oxygen saturation and heart rate by pulse oximetry, oronasal flow by thermistor, body activity, and position. During this study, the patients maintained their normal oxygen flow. In doubtful cases, a full polysomnogram was completed. Sleep studies were staged according to the Rechtschaffen and Kales method. OSAS was defined as an apnea-hypopnea index ≥ 10 episodes per hour. The patients included in the study had a mean ± SD apnea-hypopnea index of 3 ± 1.5 episodes per hour without arousals.

Institution of Mechanical Ventilation

For those patients randomized to NPPV, ventilation was initiated as an inpatient and administered via a standard nasal positive airway pressure mask using a bilevel pressure ventilation system (model DP-90: Taema; Antony Cedex, France). The ventilation system used in our study has a highly sensitive electrical trigger that senses very small changes in airflow in the nasal mask. The ventilator was set in the spontaneous mode. We targeted an expiratory positive airway pressure (EPAP) of 4 cm H2O and an inspiratory positive airway pressure (IPAP) of at least 8 cm H2O above EPAP in an attempt to reach the higher pressure, as was the case in the majority of our patients. Adequate mechanical ventilation was attempted by closely observing the patient during the day and the night. Once the mask was
comfortably adjusted, the pressures were adjusted to achieve a visual decrease in accessory muscle use,6 20 a decrease in perception of dyspnea,10 13 and a 20% decrease in respiratory rate.5 6 20 Subsequently, the patients were observed in the hospital for at least 2 nights. The ventilatory pressure settings were adjusted to maintain the target goals. During NPPV, oxygen was delivered using a cannula attached to a port on the nasal mask. Oxygen flow was titrated to achieve a minimum oxygen saturation ≥ 90%. The highest required level was 6 L/min. All patients and their relatives were informed on the proper use of mechanical ventilation. The patients were discharged from the hospital only after the investigators had been assured that ventilation was adequate and that proper training was completed. Twenty-five patients in the NPPV group and 24 patients in the control group received long-term home oxygen therapy. Within 48 h of hospital discharge, technically skilled personnel performed the installation of the apparatus in the patient’s home. During the first 3 weeks, close contact was maintained with the patient in order to ensure good coupling with the ventilator during sleep.

Clinical Course and Outcomes

The outcomes and clinical course were evaluated with personal interviews. In the case of failure to attend an appointment, the patient or relatives were contacted by telephone. All patients were contacted at all follow-up points. The number of respiratory exacerbations was recorded. Acute exacerbation was defined as an increase in dyspnea, cough, and sputum production, or change in the character and color of the sputum where the patient required a medical evaluation.30 We also recorded all hospital admissions, episodes of endotracheal intubation, and all pulmonary or extrapulmonary causes of death at 3 months, 6 months, and 12 months.

Statistics

Survival was assessed by Kaplan-Meier actuarial curve analysis. A power analysis using death as the outcome variable showed that 20 subjects in each group would have a 92% chance of proving a 10% difference if there was one. Therefore, 26 patients in each arm of the trial were more than enough to test the hypothesis. After the study, a post hoc power analysis using the 1-year mortality value showed that there would have been no difference in mortality independent of the number of patients recruited into the study. Comparison of the other outcomes was completed using Student’s t test and two-way analysis of variance for repeated measures using the Statistical Package for Social Sciences (SPSS/PC; SPSS; Chicago, IL). Differences were considered statistically significant at values of p < 0.05.

RESULTS

Patient Characteristics

The 52 patients were randomized into one group treated with NPPV (n = 26) and a control group (n = 26). In spite of the encouragement, five patients from the treatment group did not tolerate ventilation within the first 3 weeks. All complained about pressures being too high. Another patient stopped participation after a significant aortic stenosis was diagnosed at a follow-up echocardiography. Two patients from the control group also abandoned the trial because of abnormal echocardiographic findings detected during routine follow-up. Therefore, the study was completed in 44 patients (84%): 20 in the NPPV group and 24 in the control group. Inclusion of the patients who did not complete the trial (intent to treat) did not affect any of the outcomes.

All patients in the treated group were men. Only one woman was included in the control group. All patients were white. Patients in the NPPV group were younger than those in the control group (64 ± 5 y vs 68 ± 4 y, respectively; p = 0.005). The body mass index and LTOT time were similar in both groups. There were no differences in FVC (62 ± 17% predicted in control subjects and 59 ± 15% in NPPV patients); FEV 1 (31 ± 7% predicted in control subjects and 29 ± 8% in NPPV patients); lung volumes; respiratory muscle strength (MIP and MEP); and blood gas analyses between groups (Table 1).

Ventilator Tolerance and Compliance

The average time of ventilation was 6.2 h/d at the third month and sixth month, and decreased slightly (5.9 h/d) during the following 6 months. These numbers were obtained from the quotient of the total number of hours of apparatus use (electrical time counter, which measures the number of hours since the moment the machine is turned on) and the number of days from the time the ventilator was installed at home. Although it would have been more accurate to use ventilators that also monitor the actual pressure delivered, they were not available when the study was performed. Eleven percent of our patients had a compliance rate < 3 h/d. All

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*Data are presented as mean ± SD unless otherwise indicated. BMI = body mass index; M = male; F = female. †Significant difference is in comparison with control group (p = 0.005).
patients reached an IPAP of at least 12 cm H$_2$O and an EPAP of 4 cm H$_2$O, with the exception of two patients who reached an IPAP of 10 cm H$_2$O and could not tolerate higher pressure. The mean IPAP pressure achieved was 12 ± 2 cm H$_2$O.

**Morbidity and Mortality**

There were no significant differences in the number or severity of the acute exacerbations. The number of hospital admissions and episodes of endotracheal intubations were lower for the NPPV group during the first 3 months (Fig 1, *upper panel*) but this difference was not statistically significant. This difference was not observed at 6 months and 1 year (Fig 1, *lower panel*). Survival at all points during a 1-year follow-up was similar for both groups (Fig 2). Two patients in the NPPV group died during the first 3 months (one from sudden death, and one from a respiratory tract infection) and two died during the last 6 months (one from prostate carcinoma, and one from a respiratory tract infection). During the same period (12 months), there also were four deaths in the control group (one from a respiratory tract infection, another one from a stroke, and two sudden deaths). From the group of patients who did not tolerate NPPV treatment, only one patient died (unknown cause) between the sixth month and the 12th month.

**Physiologic Outcomes**

**Respiratory Parameters:** There were no significant changes in the arterial blood gas tests results, FEV$_1$, FVC, lung volumes (TLC, FRC, RV/TLC), and muscular strength (MIP and MEP). The $P_{0.1}$ decreased significantly in the NPPV group by the third month ($p = 0.035$), but this difference was not observed at sixth month. The $\Delta P_{0.1}/\Delta CO_2$ did not change during our study. No patients showed a deterioration in blood gas measures or pulmonary function test results while receiving nasal ventilation (Table 2).

**Hemodynamic Parameters:** The levels of BP and hematocrit were normal and did not change throughout the study. For the seven patients in the NPPV group in whom all the echocardiographic measurements at all time points were available, the right ventricle/right atrium systolic gradient was elevated in the treated group at baseline, compared with the six control subjects ($p = 0.004$). It decreased significantly by the third month ($p = 0.009$) and was

![Figure 1](image_url)
nearly significant by the sixth month (p = 0.09). The rest of the hemodynamic parameters did not differ between groups.

Dyspnea improved significantly (p = 0.035, Medical Research Council scale; p = 0.039, Borg scale) in the NPPV group by the third month. By the sixth month, the difference was less evident and only the evaluation with the Borg scale continued to show significant differences (p = 0.033; Table 2). These changes were not seen in the control group.

Neuropsychological Tests: The compliance was excellent (93%). We only found significant improvement in the treatment group in one of the psychomotor coordination tests (specifically, the right postures sequence at the sixth month; p = 0.024; Table 3).

Subgroup Analysis

To determine if any clinical or functional variable could predict an improvement associated with NPPV, we independently analyzed subgroups of patients in each of the following conditions: PaO2 < 50 mm Hg (n = 41), PaCO2 > 50 mm Hg (n = 12; < 50%), and compliance with the ventilator treatment of ≥ 5 h/d (n = 16). This analysis did not reveal any significant differences.

Discussion

To our knowledge, this prospective study is the largest and longest prospective, randomized, controlled trial of NPPV in patients with stable severe COPD. In addition, it is the only one that analyzes the influence of NPPV on 1-year morbidity and mortality. Over this time, we were unable to demonstrate an important benefit of NPPV when added to standard treatment. There was an improvement in the Borg dyspnea scale and in one neuropsychological test at 6 months, but the clinical importance of these changes appeared minimal.

Our results support the studies that demonstrated little benefit of NPPV in patients with stable severe COPD, and contradict some of those with more favorable results. To our knowledge, there are only six published prospective, randomized trials. All of them have in common a high intra-individual and inter-individual variability when the efficacy of NPPV is analyzed. The differences may stem from the way in which the studies were conducted. Three of them have a follow-up time of < 2 weeks, and the other followed up the patients for only 3 months. Ours is the first study following up patients for 1 full year.

None of the short follow-up studies demonstrated benefits on gas exchange, and Renston et al documented an improvement in dyspnea (Borg scale) and in the walk test, whereas Mezzanotte and coworkers showed an improvement in MIP and in the electromyographic activity of the diaphragm. Although suggestive of some short-term beneficial physiologic effect, the clinical importance of these findings remains speculative.

This difference in results is more evident in the studies with longer follow-up time (3 months). With the exception of Morales et al, who used continuous positive airway pressure, bilevel positive pressure-type ventilation was used in all of the other studies. The different results cannot be attributed to differences in disease severity, as the degree of airflow obstruction in the patients in the studies was similar. Strumpf et al in 19 patients and Gay et al in 13 patients showed no difference between the baseline and posttreatment values in respiratory muscle strength, pulmonary function tests, arterial blood gas measures, or dyspnea. Similar to our results, in the largest of those studies, there was an improvement in some neuropsychological parameters after treatment, but this was not associated with any clinically detectable change. In contrast, Morales et al found an improvement in dyspnea, which was related to an increase in MIP and a decrease in RV that is difficult attribute to the continuous positive airway pressure treatment. It is unlikely that reversible airways disease accounted for the decrease in lung volume, the improvement in dyspnea, and the increase in MIP, as there was no change in FEV1 after treatment. However, an effect on respiratory muscle fatigue can be documented only if there is no change in resting lung volume, a finding that was not observed in that study.

The most quoted positive study is the one by Meecham Jones et al, which had a run-in period and a 3-month follow-up time. As in our study,

![Cumulative Survival](#)

**Figure 2.** One-year survival was similar in patients with severe COPD after oxygen treatment alone and oxygen plus NPPV.
patients in the control group received supplemental treatment with oxygen, an important component in the treatment of patients with COPD, and a factor that was not clearly detailed in all the other studies. In contrast to our negative results, Meecham Jones et al.\textsuperscript{12} reported improvements in daytime gas exchange, sleep quality, and health-related quality of life, but no change in pulmonary function. The differences between this and all the other studies, including ours, are difficult to explain. It is not due to lung mechanics, as the degree of airflow obstruction in all the studies was similar. In both studies, oxygen was supplemented in treated and control groups and great care was devoted to the correct implementation of ventilatory support, as shown by a high overall patient compliance. Perhaps the most important difference is the initial level of gas exchange dysfunction (hypoxemia and hypercapnia). Indeed, both components of the arterial blood gas measures showed worse values in the patients described by Meecham Jones et al.\textsuperscript{12} The effect of baseline hypoxemia can be discarded because oxygen was closely titrated in all patients. That leaves the level of hypercapnia as the most important difference between both studies. The patients in the Meecham Jones et al.\textsuperscript{12} study had higher mean levels of Pa\textsubscript{CO\textsubscript{2}}. In an attempt to test this hypothesis, we analyzed all of our outcomes stratifying the patients by their CO\textsubscript{2} level, but this failed to reveal any benefit even in the patients with Pa\textsubscript{CO\textsubscript{2}} > 50 mm Hg. Although the number of hypercapnic patients in our series was small, our results are consistent with the results of the study of Gay et al.,\textsuperscript{13} in which the patients had a level of Pa\textsubscript{CO\textsubscript{2}} similar to the patients treated by Meecham Jones et al.\textsuperscript{12}

Another possible factor that may explain the difference between the studies was the level of ventilatory pressure utilized and its consequences on effective ventilation. Whereas we used levels of IPAP that fall within the clinically tolerated range (IPAP of around 12 cm H\textsubscript{2}O), this level is lower than that utilized by Meecham Jones et al.\textsuperscript{12} (close to 18

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*Data are presented as mean ± SD unless otherwise indicated. All volumes are expressed as percent of predicted values. MRC = Medical Research Council; ΔP\textsubscript{R}0/ΔCO\textsubscript{2} = hypercapnic response.

†Significant difference is in comparison with control group (p = 0.033).
cm H$_2$O). However, we did use higher EPAP (4 cm H$_2$O vs 1.9 cm H$_2$O). Overall, our ventilatory pressures were significantly higher than those used by others, 13,35 and similar to those used by Strumpf et al. 10 We began treatment in the hospital and attempted to provide adequate ventilation by achieving a decrease in baseline respiratory rate and decreased accessory muscle use. 5,29 We tailored the pressure to the patient’s perception of dyspnea and overall comfort. Higher pressures were not well tolerated; indeed, the patients who refused to continue NPPV did so because they believed the ventilatory pressure was too high, an observation that was frequently reported in at least two of the studies. 10,13 Although we do not believe that poor ventilation at night was a factor that affected our outcomes, it certainly remains a possibility.

Finally, one other potential difference between our patients and those of Meecham Jones et al. 12 was the degree of sleep-related hypopnea/apneic episodes. We excluded patients who had > 10 hourly episodes of hypopneas during the sleep study. Indeed, our patients only had 3.5 episodes per hour per night, whereas those treated by Meecham Jones et al. 12 had an average of 10 episodes per hour. Although unlikely, this small difference could help explain the difference between the two studies.

The results of all of the trials suggest that if NPPV is to be implemented, it may need to be used only in selected patients capable of tolerating the higher pressures and with close nighttime monitoring. However, if the treatment is applicable only to a small proportion of patients with COPD, its clinical applicability is limited at best.

It could be said that our control patients should have received a sham treatment. Initially, we tried sham NPPV in the control group (the first four patients) but could not continue its use due to nasal discomfort. Because one of the previous randomized trials used sham controls and found no differences between control and treated patients, 13 we believed it was unjustified to submit patients to a 1-year trial of an uncomfortable machine without a theoretical benefit.

The most important contribution of our study is that we extended our treatment and evaluation for 1 year. After 6 months, we only found an improvement in the Borg scale and in the right posture sequence. Although the improvement in dyspnea may be important in the quality of life of patients with severe COPD, 38 we should keep in mind the possible placebo effect of NPPV. The right posture sequence, which might reflect the function of an area in the brain very sensitive to oxygen, 38 was the only test among the 20 neuropsychological parameters that showed a significant improvement. We believe that this single test change is best explained by chance alone; although statistically significant, it carries little clinical relevance.

Our study is unique in that it evaluated 1-year mortality. The patients in the NPPV group were on average 4 years younger, but if anything, this should favor mortality in the NPPV group. It could be argued that the number of patients in the study was too small to detect changes in mortality. However, we completed a power analysis choosing a 1-year 10% mortality difference between groups, based on a study 39 that suggests this to be the death rate for patients with severe COPD, and found that 20 patients in each group were enough to detect that change. In addition, a post hoc power analysis using the observed mortality in our study showed that there would be no mortality differences independent of the number of patients enrolled. It is possible that 1 year is not enough time to determine the mortality of patients with COPD. However, our finding is supported by that of Muir et al. 40 who, in abstract form, reported no difference in overall mortality at 4 years in 123 patients randomized to NPPV plus oxygen, vs oxygen therapy alone.

We consider the number and severity of respiratory infections to be of great relevance. There were fewer hospital admissions and intubations in the NPPV group at 3 months, but the difference was not statistically different. Furthermore, this finding disappeared after 6 months. We believe that disease-specific health-related quality of life would have been a desirable outcome to measure, but at the time of the study, there were no tools validated in the Spanish language. However, we did use validated neuropsychological tests. The changes observed in dyspnea and neuropsychological testing were minimal, and very much in agreement with the findings of Strumpf et al. 10 We also addressed utilization of health-care resources by evaluating the number of hospital admissions, a very important outcome given the ever-debated problem of health-care cost. 51 The lack of significant benefit in any of these areas constitutes an incentive to reevaluate the use of NPPV in patients with stable COPD. We did not find any selected subgroups, based on gasometric criteria, respiratory function, and treatment compliance, that specifically benefit from NPPV treatment. It is possible, but highly unlikely, that a bigger patient sample size could be necessary to demonstrate small differences.

We conclude that NPPV with bilevel-type ventilation in the spontaneous mode when used in addition to LTOT has limited efficacy in patients with stable severe COPD. Perhaps a large, multicenter trial aimed at patients with important hypercapnia and without sleep apnea should be implemented. The
results of the large, multicenter trial in Europe\textsuperscript{41} could help clarify this debate. If we could develop technology that may better unload the ventilatory pump, such treatment may result in a more significant benefit. However, it is possible that NPPV may have little impact on a system that, in patients in chronic stable condition, is functioning at its optimal level.

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