Effects of Nocturnal Noninvasive Mechanical Ventilation on Heart Rate Variability of Patients With Advanced COPD*

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Background: **Cardiovascular comorbidities have a negative impact on the health status and prognosis of patients with COPD. We determined whether nocturnal noninvasive (positive) mechanical ventilation (NIMV) can improve heart rate variability (HRV), decrease circulating natriuretic peptide levels, and improve functional performance of patients with very advanced COPD.**

Methods: **A randomized, double-blind, parallel controlled trial was conducted in 23 participants with stable but advanced COPD. Participants received standard medical therapy plus nocturnal NIMV or standard medical therapy plus sham NIMV for 3 months.**

Results: **After 3 months of NIMV therapy, the 24-h triangular interpolation of N-N intervals increased from 322 to 473 ms ($p = 0.034$), the 24-h HRV index (HRVI) increased from 21.8 to 29.9 ms ($p = 0.035$), nocturnal HRVI increased from 6.1 to 8.0 ms ($p = 0.026$), and the SD of the average N-N interval increased from 37 to 41 ms ($p = 0.020$). None of these indexes changed significantly in the control group. Additionally, compared with the control group, the pro-atrial natriuretic peptide levels declined significantly in the NIMV group ($p = 0.013$).**

Conclusions: **NIMV applied nocturnally over 3 months may improve HRV, reduce circulating natriuretic peptide levels, and enhance the functional performance of patients with advanced but stable COPD. While not definitive due to small sample size, these data suggest that nocturnal NIMV may reduce the impact of cardiac comorbidities in COPD patients.**

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Key words: controlled clinical trial; COPD; heart rate; heart rate variability; inspiratory positive pressure ventilation; natriuretic peptides

Abbreviations: ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; CI = confidence interval; CPAP = continuous positive airway pressure; EPAP = expiratory positive airway pressure; HRV = heart rate variability; HRVI = heart rate variability index; IPAP = inspiratory positive airway pressure; NIMV = nocturnal noninvasive (positive) mechanical ventilation; pro-ANP = pro-atrial natriuretic peptide; pro-BNP = pro-brain natriuretic peptide; RMSSD = square root of the mean squared differences of successive N-N intervals; SDANN = SD of the average N-N interval; SDNN = SD of the R-R interval for normal beats; SDSD = SD of differences between adjacent N-N intervals; TINN = triangular interpolation of N-N intervals

It is well recognized that cardiovascular diseases often coexist with COPD and are a source of morbidity and mortality in COPD patients.[1,2] In patients with mild COPD, cardiac disorders are the leading causes of hospitalization, accounting for 42 to 48% of all hospitalizations.[1] Having ECG signs of previous myocardial infarction or ischemia increases the risk of mortality in COPD by 42% compared with COPD patients without such changes.[3] The presence of atrial fibrillation and ventricular arrhythmias of any kind increases mortality risk by 2.27-fold and 1.91-fold, respectively, in COPD.[4] Although a majority of COPD patients in the community do not have any overt signs of cardiac disease,[1–3] many appear to have subclinical cardiac abnormalities, which may add to their overall morbidity.[2]

One noninvasive method of ascertaining subclinical cardiac abnormalities is by determining heart rate variability (HRV). In the community, reduced HRV predicts mortality as well as conventional risk factors. In the postinfarction setting, depressed HRV predicts all-cause mortality better than does left ventricular ejection fraction.[5] More recently, circulating natriuretic peptide levels have also been associated with increased risk of all-cause mortality even in subjects without overt cardiac disease[6] and may represent another method of identifying subclinical cardiac abnormalities. Intriguingly, advanced COPD has also been associated with elevated natriuretic peptide levels[7] and reduced HRV[8,9] in a severity-dependent fashion.[10] Interestingly, positive pressure ventilation has been shown to have beneficial effects on HRV and natriuretic peptide levels.[11,12] Whether application of nocturnal noninvasive (positive) mechanical ventilation (NIMV) in COPD can improve these cardiac end points is unknown. We implemented a randomized controlled trial to determine whether nocturnal NIMV applied for 3 months can do the following: (1) improve HRV; (2) decrease circulating levels of plasma natriuretic peptides; and (3) enhance functional performance of patients with severe but stable COPD.

Materials and Methods

Subjects

We recruited study participants from specialists' clinics at the University of Alberta Hospital. To qualify for the study, patients had to meet the following entry criteria: (1) clinical diagnosis of COPD; (2) age $\geq$ 40 years old; (3) $\geq$ 10-pack-year history of cigarette smoking; (4) FEV_1/FVC ratio $<$ 70% and postbronchodilator FEV_1 $<$ 70% of predicted. Patients were excluded if they had the following conditions: (1) coexisting medical conditions that made survival for at least 6 months unlikely; (2) refusal to participate; (3) cognitive impairment that made it impossible to obtain informed consent; (4) clinical history of left ventricular heart failure; or (5) apnea-hypopnea index $\geq$ 20 on a home-based sleep apnea test (Embletta PDS; Medcare; Reyjkavik, Iceland). All patients provided written informed consent. Ethics approval was obtained from the University of Alberta and the University of British Columbia Research Ethics Boards.

Study Design

We employed a randomized, double-blind, parallel-group design. Recruited patients were randomly assigned to receive either standard medical therapy for COPD plus nocturnal NIMV or standard medical therapy plus sham NIMV therapy for 3 months. Randomization occurred at a central site by one individual who was unaware of patients' clinical status. All outcome measurements were performed and interpreted by personnel who were blinded to the treatment allocation of patients. Following randomization, participants started on either nocturnal NIMV or sham therapy. All participants spent at least 4 h of NIMV/sham training at the University of Alberta Hospital Sleep Disorders Laboratory, during which patients were properly fitted with a mask (either with a nasal mask [UltraMirage; ResMed; Posway, CA] or a full-face mask [Mirage; ResMed] depending on patient preference), and the appropriate ventilator settings were set. Patients received NIMV via a ResMed VPAP II machine with a heated humidifier (HumidAire; ResMed). The patients were initially started on an inspiratory positive airway pressure (IPAP) of 8 cm H_2O and an expiratory positive airway pressure (EPAP) of 4 cm H_2O. The IPAP was titrated up in increments of 2 cm H_2O until the highest IPAP tolerated by the patient or 20 cm H_2O was reached, whichever came first. The EPAP remained at 4 cm H_2O. All the other available settings were reviewed and adjusted according to the patient's needs and preferences. All ventilatory assist devices contained a computer chip, which activated only when negative (inspiratory) flow was detected downstream. The counter was set to zero hours at the commencement of the study. For patients with arterial oxyhemoglobin saturation of $<$ 90% despite nocturnal NIMV, supplemental oxygen was entrained to maintain arterial oxyhemoglobin saturation of $\geq$ 90%. For those assigned to sham therapy (*ie*, control subjects), they were treated using a continuous positive airway pressure (CPAP) device (S7Elite; ResMed) set at 4 cm H_2O. The other components of the protocol were exactly the same as those for the NIMV study arm. Information on the hours of use from the NIMV or the sham machines was downloaded at the end of the 12 weeks of follow-up. Downloads were performed using software (AutoScan version 3.4; ResMed). Study patients were seen in person at baseline, 1 month, and 3 months for a clinical assessment and to troubleshoot any problems with the machine. Detailed measurements of physiologic end points were conducted at baseline and at 3 months. The baseline characteristics of the two groups are summarized in Table 1.

Measurements

Spirometry was performed with a rolling seal spirometer, according to published American Thoracic Society standards and as previously described.[13] Maximal inspiratory and expiratory pressures were measured by a calibrated manometer. The best of four attempts was documented. Arterial blood gases were measured from blood obtained from the radial artery during midafternoon with the patient breathing room air. A 6-minute walk

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Table 1—*Baseline Characteristics of the Study Patients

Characteristics	Control Subjects (n = 10)	NIMV (n = 11)	p Value
Age, yr	66.6 ± 9.7	64.1 ± 10.6	0.565
Male gender, No. (%)	6 (60)	4 (36)	0.395
Body mass index, kg/m^2	26.2 ± 6.4	28.2 ± 7.2	0.513
FEV_1, L	0.7 ± 0.2	1.0 ± 0.4	0.064
FEV_1, % predicted	24.8 ± 7.0	37.6 ± 17.7	0.045
PaO_2, mm Hg	60.7 ± 8.3	59.3 ± 10.1	0.729
$PaCO_2$, mm Hg	43.1 ± 4.9	45.2 ± 13.5	0.640
Supplemental O_2, L/min	2.4 ± 1.1	2.2 ± 1.7	0.736
24-h heart rate at baseline	86.8 ± 10.0	88.1 ± 10.1	0.760
24-h heart rate at 3 mo	86.7 ± 7.9	86.6 ± 11.1	0.974
C-reactive protein, mg/L†	0.92 ± 1.34 (2.5)	1.33 ± 1.15 (3.8)	0.453
6-min walk distance, m	343 ± 48	262 ± 100	0.115
Compliance, hours per night	5.3 ± 4.4	3.7 ± 3.4	0.339
Inhaled β_2 agonists or anticholinergics, %	100	100	1.0
Inhaled corticosteroids, %	100	100	1.0
Oral corticosteroids, %	60	64	1.0
Antihypertensives, %	10	0	0.476
Statins, %	20	9	0.587

*Data are presented as mean ± SD unless otherwise indicated.
†Data are presented as log-transformed mean ± SD (geometric mean).

test was performed along a flat indoor hallway using standard procedures.[14] During the baseline measurement, we performed two walk tests and used the average values in the analysis. All walks were performed at room air under standardized conditions at the same time of the day by the same study member blinded to the patient's assignment.

Holter Monitoring

All of the study participants underwent 24-h Holter monitoring with an ambulatory three-channel ECG recorder with an R-R interval sampling frequency of ≥ 256 Hz (model 483 Holter SSR Digicorder; Delmar Avionics; Irvine, CA). All Holter recordings were performed off NIMV or CPAP. The data were sampled digitally and transferred to a microcomputer for the analysis of HRV. After the transfer of the ECG data to a microcomputer, the R-R interval series were edited both manually and automatically. Only recordings with at least 20 h of data and with > 85% of qualified sinus beats were included in the analysis of HRV. We used the methods recommended by the Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology to perform the time-series analyses. All data analyses were performed using software (Accuplus; Del Mar Avionics; Irvine, CA).[15] The SD of all normal-to-normal R-R intervals and the geometric HRV indexes were computed as time domain measures from the recording period. The time domain analyses were expressed in geometric measures (HRV index [HRVI]; triangular interpolation of N-N intervals [TINN]), and in standard measures (SD of the average N-N interval [SDANN]; SD of the R-R interval for normal beats [SDNN]; square root of the mean squared differences of successive N-N intervals [RMSSD]; SD of differences between adjacent N-N [SDSD]). Geometric measures require a reasonable number of N-N intervals to construct the geometric pattern. Thus, in accordance with the task force recommendations,[15] we used the entire 24-h recordings to determine TINN and HRVI. Both TINN and HRVI reflect long-term changes in HRV. For standard measures, which reflect short-term variations in HRV, the recordings were classified into daytime (from 7:30 AM to 9:30 PM) and nighttime (from midnight to 7:00 AM) periods. These data are summarized in Tables 2, 3.

Natriuretic Peptide Measurements

A blood sample was obtained during daytime with the subjects in a sitting position using standard venipuncture techniques. Blood specimens were centrifuged immediately, and plasma was stored at – 70°C without any freeze/thaw cycles until the natriuretic peptide levels were measured. Both N-terminal components of pro-atrial natriuretic peptide (pro-ANP) and pro-brain natriuretic peptide (pro-BNP) were measured from plasma using highly sensitive quantitative immunoassays (Biomedica; Biomedica Medizinprodukte GMBH; Vienna, Austria). All measurements were made in triplicate and averaged. The lower limits of detection for these assays were 50 pg/mL for pro-BNP and 50 fmol/mL for pro-ANP. The average interassay coefficients of variation were 11.2% for pro-BNP and 4.7% for pro-ANP. To assess the effects of NIMV on inflammatory parameters, we measured serum C-reactive protein levels at baseline and after 3 months of therapy using a highly sensitive using commercially available solid-phase sandwich enzyme-linked immunosorbent assay kits (α Diagnostics; San Antonio, TX). All samples were measured in triplicate.

Statistical Analysis

The NIMV group was defined as those who were assigned to NIMV. The control group was composed of individuals who were assigned to sham therapy and two individuals who agreed to participate but declined to use any of the machines. Continuous variables were compared between the NIMV and control groups using a Student *t* test, and dichotomous variables were compared using a χ^2 test. For nonnormally distributed variables, normality was achieved through logarithmic transformation. For time trend analysis within each group, a paired *t* test was used to compare 3-month data to those obtained at baseline. For the intergroup

Table 2—*Twenty-Four-Hour Measurement of Geometric Measures and Nighttime Recordings of Standard Measures of HRV at Baseline and After 3 Months of Treatment

Variables	Control, ms			NIMV, ms			
	Baseline	3 mo	p Value†	Baseline	3 mo	p Value†	p Value‡
Total TINN	444 ± 144	405 ± 140	0.242	322 ± 104	473 ± 258	0.034	0.010
Total HRVI	27.3 ± 9.9	26.1 ± 8.4	0.457	21.8 ± 7.3	29.9 ± 15.1	0.035	0.017
Night SDNN	69.6 ± 22.8	75.8 ± 31.3	0.412	63.0 ± 24.8	89.9 ± 42.9	0.021	0.262
Night RMSSD	25.5 ± 13.1	27.6 ± 12.4	0.663	28.3 ± 20.0	29.6 ± 22.1	0.898	0.829
Night SDSD	20.0 ± 8.0	18.9 ± 7.7	0.807	20.1 ± 13.3	21.2 ± 15.7	0.866	0.819
Night SDNN index	35.1 ± 21.0	37.3 ± 24.2	0.742	37.1 ± 25.4	41.1 ± 31.6	0.717	0.916
Night SDANN	52.2 ± 19.4	60.9 ± 25.3	0.507	46.6 ± 17.0	73.6 ± 31.7	0.020	0.191

*Data are presented as mean ± SD.
†Within-group comparison.
‡Between-group comparison.

comparisons, a mixed model was used to take into account within-group and between-group variances (Proc Mixed, version 9.1; SAS Institute; Cary, NC). In this model, we controlled for age, gender, and baseline percentage of predicted FEV_1. A p value < 0.05 (two tailed) was considered statistically significant. Continuous variables are reported as mean ± SD, unless otherwise specified.

Results

There were 23 subjects who were enrolled in the study, but 2 subjects refused any nocturnal therapy following randomization and were excluded from the main analysis. There were no significant differences in any of the other parameters measured at baseline between the NIMV and control groups except for baseline FEV_1, which was significantly higher in the group that received NIMV ($p = 0.045$). The mean IPAP delivered was 15.5 ± 4.2 cm H_2O for the NIMV group ($p < 0.001$ compared to control group). The EPAP was fixed at 4 cm H_2O.

HRV

Over the 3 months, the subject's 24-h heart rate did not change significantly. In the control group, the heart rate changed by − 0.10 ± 6.8 beats/min; in the NIMV group, the heart rate changed by − 0.89 ± 5.6 beats/min ($p = 0.788$ for the comparison between the control and NIMV groups). After 3 months of treatment, some indexes of HRV increased significantly. Overall, compared with changes in the control group, the group that received NIMV had significant increases in the geometric measures of HRV (*ie*, TINN, HRVI). The 24-h TINN increased from 322 to 473 ms ($p = 0.034$). In the control group, the 24-h TINN did not change significantly (from 444 to 405 ms; $p = 0.242$). Similarly, the 24-h HRVI increased from 21.8 to 29.9 ms in the NIMV group ($p = 0.035$); whereas in the control group, the 24-h HRVI did not change significantly (from 27.3 to 26.1 ms; $p = 0.453$). The standard measures were separated into nighttime and daytime measurements. In the nighttime assessment, there was a significant increase in SDNN ($p = 0.021$) and SDANN ($p = 0.020$) at 3 months compared to baseline recordings in the NIMV group. There were no significant changes in the standard HRV measures during daytime (Table 3).

In a secondary analysis, we included the two subjects who did not receive any nocturnal therapy into the control group. The nighttime SDANN comparison, which had been insignificant in the main

Table 3—*HRV During Daytime Recordings at Baseline and After 3 Months of Treatment*

Variables	Control Group, ms			NIMV, ms			
	Baseline	3 mo	p Value†	Baseline	3 mo	p Value†	p Value‡
Day SDNN	73.1 ± 26.5	76.0 ± 29.2	0.943	69.6 ± 30.3	77.5 ± 36.1	0.597	0.773
Day RMSSD	27.1 ± 9.1	24.6 ± 8.5	0.718	22.5 ± 11.1	22.5 ± 14.3	0.861	0.225
Day SDSD	18.9 ± 5.9	18.0 ± 5.0	0.835	16.7 ± 8.1	16.9 ± 11.0	0.947	0.305
Day SDNN index	30.4 ± 11.8	29.3 ± 10.9	0.573	32.4 ± 18.5	33.3 ± 20.3	0.659	0.666
Day SDANN	70.2 ± 23.1	73.1 ± 24.7	0.557	58.5 ± 23.9	69.0 ± 30.7	0.308	0.719

*Data are presented as mean ± SD.
†Within-group comparison.
‡Between-group comparison.

analysis (p = 0.191), became significant after the inclusion of the two subjects (p = 0.048). For geometric measures, the inclusion or exclusion of the two subjects made no material difference to the results.

Natriuretic Peptide Levels

In the group that received NIMV, there was a trend toward lower pro-BNP levels in plasma after 3 months of therapy compared to baseline levels (p = 0.060). Compared with the control group, the pro-ANP levels were significantly lower after 3 months with NIMV therapy (p = 0.013) [Fig 1].

Six-Minute Walk Test

Compared to baseline, individuals who received NIMV were able to walk 30 m (95% confidence interval [CI], 2 to 57 m) further after 3 months. In contrast, there was no significant change in the walk distance in the control group (4 m; 95% CI, − 38 to 47 m; p = 0.820). However, the control subjects had greater walk distances at baseline (343 ± 48 m) than NIMV subjects (262 ± 100 m) and at 3 months (367 ± 59 m vs 311 ± 144 m; p = 0.311), although none of these comparisons were significant at the p = 0.05 level (Fig 2). There were no significant associations between changes in the 6-minute walk distance and either pro-ANP or pro-BNP levels.

Other Measurements

There were no significant changes in log-C-reactive protein levels over the 3 months in the control (p = 0.930) or the NIMV groups (p = 0.511). Daytime arterial $PaCO_2$ values were similar before and after 3 months of therapy in the control group (p = 0.728). In the NIMV group, there was a trend toward a lower daytime $PaCO_2$ (45.2 mm Hg vs 40.4 mm Hg; p = 0.083). There were no significant changes in FEV_1 in the control group (p = 0.138) or the NIMV group (p = 0.051).

Discussion

The principal finding of this study was that nocturnal NIMV for 3 months increased some indexes of HRV at nighttime and reduced circulating natriuretic peptide levels in patients with advanced but stable COPD. These data suggest that nocturnal NIMV may be able to improve certain cardiac end points in COPD. However, due to the small sample size and lack of other cardiac performance data, these findings must be interpreted cautiously.

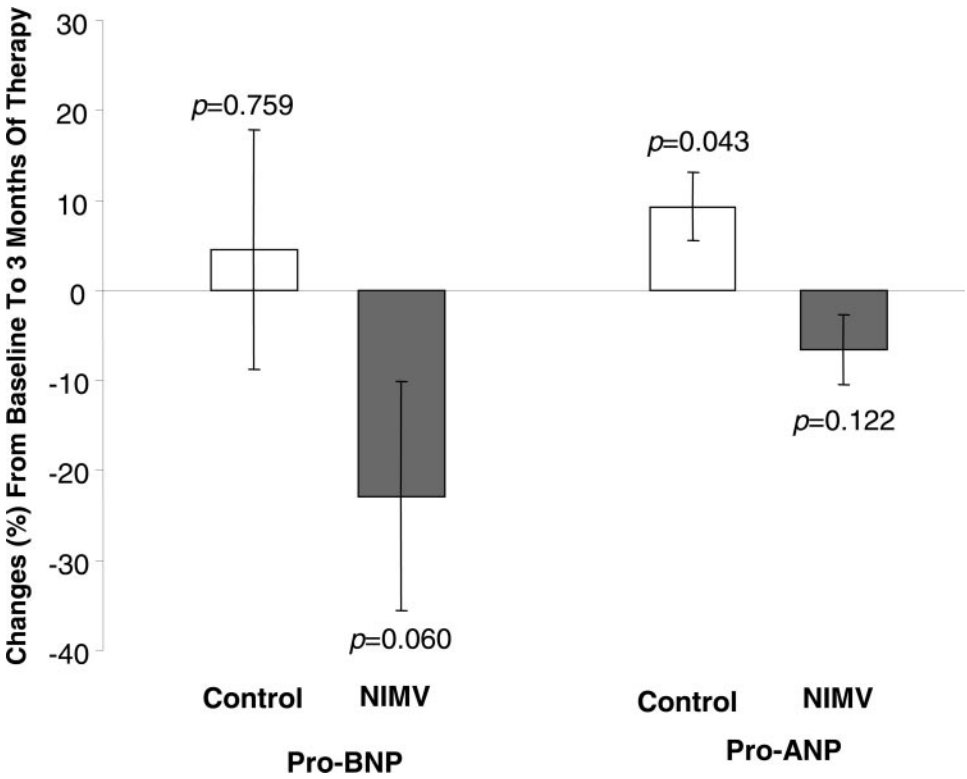

Figure 1. Changes in daytime plasma natriuretic peptide levels over 3 months in COPD patients treated and not treated with NIMV.

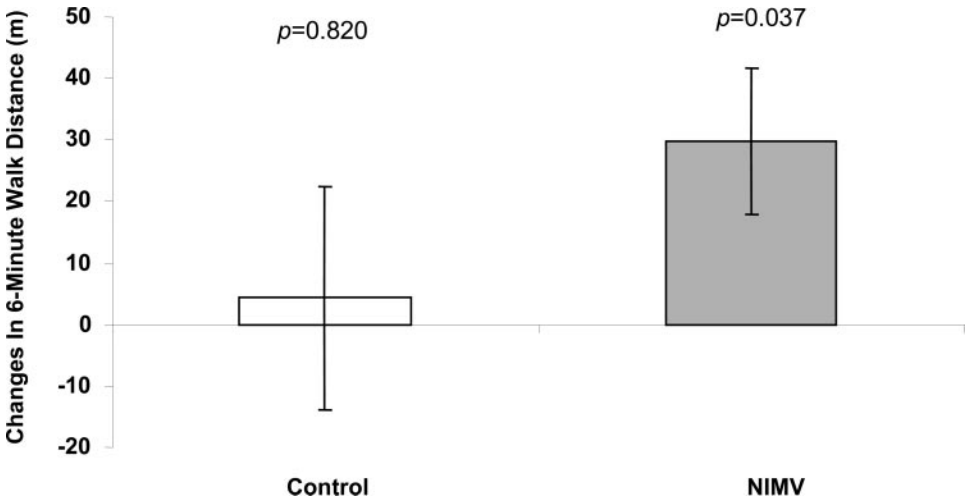

FIGURE 2. Change in 6-min walk distance over 3 months in COPD patients treated and not treated with NIMV.

There have been several randomized controlled trials that have evaluated the effects of nocturnal NIMV for chronic COPD. Similar to our findings, Garrod et al[16] (45 patients, 8 weeks) demonstrated a significant improvement in the mean shuttle walk test after 8 weeks of NIMV therapy. Meecham Jones et al[17] showed significant improvements in daytime arterial Pa_{O_2} and Pa_{CO_2}, total sleep time, sleep efficiency, overnight Pa_{CO_2}, and quality of life of COPD patients with NIMV. We extend these and other findings[18,19] by demonstrating a possible salutary effect of NIMV on HRV and circulating natriuretic peptides in severe COPD.

Although there are many factors that govern HRV, HRV provides important information regarding autonomic influences to the heart.[20,21] Generally, increased HRV reflects increased vagal modulation; reduced HRV indicates the reverse. In diseased states of the heart, HRV usually decreases[19]; with improvements in the cardiac condition, HRV increases.[22] Importantly, reduced HRV is associated with poorer prognosis. In the Framingham cohort study, for instance, a 1-SD decrement in SDNN was associated with a hazard ratio of 1.47 for new cardiac events[23] and significantly increased the risk of mortality in individuals who were free of overt cardiac disease at baseline.[24] In the Rotterdam Study,[25] subjects in the lowest quartile of SDNN relative to those with normal HRV had an 80% age- and sex-adjusted increase in the risk for cardiac mortality (hazard ratio, 1.8; 95% CI, 1.0 to 3.2). Taken together, these data suggest that HRV is a reasonable surrogate for hard clinical end points such as cardiac morbidity in the general population. It is plausible that HRV may be a surrogate of cardiac end points in COPD; however, future work is needed to validate this notion.

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are hormones of myocardial cell origin that are produced in order to maintain circulatory homeostasis.[26] ANP is secreted primarily by the atrial myocardium in response to dilation, while BNP is secreted almost exclusively by the ventricles in response to increased end-diastolic pressure or volume.[26,27] ANP and BNP gene expressions are up-regulated in states of pressure overload and their circulating levels correlate with patient symptoms (*eg*, dyspnea), sympathetic activity, endothelin and renin-angiotensin-aldosterone levels.[28] Most importantly, their plasma levels predict future risk of cardiovascular events and death.[29] For instance in the Framingham Offspring Study, Wang and colleagues[29] showed that for each 1-SD increment in log BNP levels, mortality increased by 27% and cardiovascular events increased by 28%, independent of other cardiovascular risk factors. Similar findings were observed for ANP. In view of the evolving importance of these natriuretic peptides, our finding that nocturnal NIMV reduces these levels in COPD is likely to have clinical relevance.

How NIMV improves HRV and reduces circulating natriuretic peptides in COPD patients is unclear. In certain clinical conditions (*eg*, congestive heart failure), positive pressure ventilation has been demonstrated to reduce both preload and afterload,[30] improve cardiac output,[31] and attenuate sympathetic neural activity, leading to decreased atrial and ventricular stimulation.[11] There may be other mechanisms. Future work is needed to clearly delineate these mechanisms. We also observed a statistically significant increase in the 6-min walk distance after 3 months of NIMV treatment. However, the effect was quite modest (30 m on average) and did not achieve the threshold at which patients usually notice a

subjective improvement.[14] Moreover, although statistically not significant, the NIMV group had shorter 6-min walk distance than the control group at baseline measurement. As such, we cannot discount the possibility that the observed improvement in the NIMV group was a "regression to the mean" effect.

The present study has certain limitations. Firstly, the overall sample size was modest; therefore, hard end points such as hospitalizations and mortality could not be evaluated. Moreover, the small sample size resulted in some imbalance in the baseline characteristics (*eg*, FEV_1) that could have influenced the analysis. To mitigate this possibility, we used regression techniques to adjust for confounders. Nevertheless, the findings of the present study should be interpreted cautiously. Secondly, we enrolled patients with very advanced COPD; thus, these findings cannot be generalized to the milder COPD population. Thirdly, the follow-up period was short. It is not clear whether the salutary effects on the cardiac end points observed within the three months are sustainable over a longer period of time. Fourthly, although we used a "sham" therapy to blind subjects to the assignment, it was not a true placebo. As such, complete blinding may not have been present and we cannot completely eliminate the possibility of a "placebo effect," though this seems unlikely in view of the excellent compliance observed in those assigned to sham therapy. Whether the sham therapy could have effected some positive benefits in our group of patients is uncertain. CPAP alone may unload respiratory muscles during inspiration and reduce the work of breathing.[32] Under such scenario, we could have underestimated the true effects of NIMV in our study.

In summary, the present study indicate that NIMV applied nocturnally over 3 months may improve HRV and reduce circulating natriuretic peptides in stable advanced COPD. These data suggest the possibility that nocturnal NIMV may reduce the impact of cardiac comorbidities, which add significantly to the overall morbidity and mortality of COPD patients.

References

1 Anthonisen NR, Connett JE, Enright PL, et al. Hospitalizations and mortality in the Lung Health Study. Am J Respir Crit Care Med 2002; 166:333–339

2 Rutten FH, Cramer MJ, Grobbee DE, et al. Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. Eur Heart J 2005; 26:1887–1894

3 Antonelli Incalzi R, Fuso L, De Rosa M, et al. Co-morbidity contributes to predict mortality of patients with chronic obstructive pulmonary disease. Eur Respir J 1997; 10:2794–2800

4 Fuso L, Incalzi RA, Pistelli R, et al. Predicting mortality of patients hospitalized for acutely exacerbated chronic obstructive pulmonary disease. Am J Med 1995; 98:272–277

5 Malik M, Farrell T, Camm AJ. Circadian rhythm of heart rate variability after acute myocardial infarction and its influence on the prognostic value of heart rate variability. Am J Cardiol 1990; 66:1049–1054

6 Kistorp C, Raymond I, Pedersen F, et al. N-terminal probrain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. JAMA 2005; 293:1609–1616

7 Morrison LK, Harrison A, Krishnaswamy P, et al. Utility of a rapid B-natriuretic peptide assay in differentiating congestive heart failure from lung disease in patients presenting with dyspnea. J Am Coll Cardiol 2002; 39:202–209

8 Bartels MN, Jelic S, Ngai P, et al. High-frequency modulation of heart rate variability during exercise in patients with COPD. Chest 2003; 124:863–869

9 Tukek T, Yildiz P, Atilgan D, et al. Effect of diurnal variability of heart rate on development of arrhythmia in patients with chronic obstructive pulmonary disease. Int J Cardiol 2003; 88:199–206

10 Stein PK, Nelson P, Rottman JN, et al. Heart rate variability reflects severity of COPD in PiZ α1-antitrypsin deficiency. Chest 1998; 113:327–333

11 Naughton MT, Benard DC, Liu PP, et al. Effects of nasal CPAP on sympathetic activity in patients with heart failure and central sleep apnea. Am J Respir Crit Care Med 1995; 152:473–479

12 Javaheri S. Effects of continuous positive airway pressure on sleep apnea and ventricular irritability in patients with heart failure. Circulation 2000; 101:392–397

13 American Thoracic Society. Standardization of spirometry, 1994 update. Am J Respir Crit Care Med 1995; 152:1107–1136

14 Redelmeier DA, Bayoumi AM, Goldstein RS, et al. Interpreting small differences in functional status: the six minute walk test in chronic lung disease patients. Am J Respir Crit Care Med 1997; 155:1278–1282

15 Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. Circulation 1996; 93:1043–1065

16 Garrod R, Mikelsons C, Paul EA, et al. Randomized controlled trial of domiciliary noninvasive positive pressure ventilation and physical training in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000; 162:1335–1341

17 Meecham Jones DJ, Paul EA, Jones PW, et al. Nasal pressure support ventilation plus oxygen compared with oxygen therapy alone in hypercapnic COPD. Am J Respir Crit Care Med 1995; 152:538–544

18 Casanova C, Celli BR, Tost L, et al. Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. Chest 2000; 118:1582–1590

19 Clini E, Sturani C, Rossi A, et al. The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. Eur Respir J 2002; 20:529–538

20 Akselrod S, Gordon D, Ubel FA, et al. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat to beat cardiovascular control. Science 1981; 213:220–222

21 Pomeranz B, Macaulay RJ, Caudill MA, et al. Assessment of autonomic function in humans by heart rate spectral analysis. Am J Physiol 1985; 248:151–153

22 Weber F, Schneider H, von Arnim T, et al. Heart rate variability and ischaemia in patients with coronary heart disease and stable angina pectoris: influence of drug therapy and prognostic value; TIBBS Investigators Group. Total Ischemic Burden Bisoprolol Study. Eur Heart J 1999; 20:38–50

23 Tsuji H, Larson MG, Venditti FJ Jr, et al. Impact of reduced heart rate variability on risk for cardiac events: the Framingham Heart Study. Circulation 1996; 94:2850–2855
24 Tsuji H, Venditti FJ Jr, Manders ES, et al. Reduced heart rate variability and mortality risk in an elderly cohort: the Framingham Heart Study. Circulation 1994; 90:878–883
25 de Bruyne MC, Kors JA, Hoes AW, et al. Both decreased and increased heart rate variability on the standard 10-second electrocardiogram predict cardiac mortality in the elderly: the Rotterdam Study. Am J Epidemiol 1999; 150:1282–1288
26 Suttner SW, Boldt J. Natriuretic peptide system: physiology and clinical utility. Curr Opin Crit Care 2004; 10:336–341
27 Baughman KL. B-type natriuretic peptide: a window to the heart. N Engl J Med 2002; 347:158–159
28 Patel JB, Valencik ML, Pritchett AM, et al. Cardiac-specific attenuation of natriuretic peptide A receptor activity accentuates adverse cardiac remodeling and mortality in response to pressure overload. Am J Physiol Heart Circ Physiol 2005; 289:777–784
29 Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med 2004; 350:655–663
30 Tkacova R, Liu PP, Naughton MT, et al. Effect of continuous positive airway pressure on mitral regurgitant fraction and atrial natriuretic peptide in patients with heart failure. J Am Coll Cardiol 1997; 30:739–745
31 Baratz DM, Westbrook PR, Shah PK, et al. Effect of nasal continuous positive airway pressure on cardiac output and oxygen delivery in patients with congestive heart failure. Chest 1992; 102:1397–1401
32 Petrof BJ, Kimoff RJ, Levy RD, et al. Nasal continuous positive airway pressure facilitates respiratory muscle function during sleep in severe chronic obstructive pulmonary disease. Am Rev Respir Dis 1991; 143:928–935