Respiratory correlates of muscle sympathetic nerve activity in heart failure

Matthew T. NAUGHTON*, John S. FLORAS†, M. Atiar RAHMAN†, Munir JAMAL‡ and T. Douglas BRADLEY‡
*Alfred Hospital, Commercial Road, Prahran, Victoria 3181, Australia, †Suite 1614, Mount Sinai Hospital, 600 University Avenue, Toronto, Ontario, Canada MSG 1X5, and ‡Eaton North, 10th Floor, Room 212, Toronto General Division, Toronto Hospital, 200 Elizabeth Street, Toronto, Ontario, Canada MSG 2C4

ABSTRACT

1. Sympathetic activation in congestive heart failure indicates a poor prognosis. Haemodynamic correlates of increased sympathetic nerve traffic to muscle (MSNA) and to the heart have been well characterized, but these account for only 50 to 60% of the variance in sympathetic activity between patients.

2. In healthy subjects, breathing pattern modulates MSNA and positive airway pressure consistently increases MSNA. However, in patients with heart failure, the influence of spontaneous breathing pattern and of short-term application of nasal continuous positive airway pressure on MSNA have not been described.

3. Spontaneous breathing frequency, tidal volume, end-expiratory lung volume, PCO₂ and MSNA were recorded, along with blood pressure, heart rate and stroke volume in 14 men with congestive heart failure of idiopathic or ischaemic origin (left ventricular ejection fraction < 35%). Measurements were made during baseline rest, followed by 45 min of either nasal continuous positive airway pressure applied at 10 cmH₂O (n = 9), or spontaneous breathing, in the absence of nasal continuous positive airway pressure (time control; n = 6).

4. At baseline, there was a significant positive correlation between MSNA burst frequency and breathing frequency (r = 0.758, P = 0.001), and an inverse correlation between MSNA burst incidence and tidal volume (r = -0.705, P = 0.005). These relationships were independent of left ventricular ejection fraction, stroke volume or cardiac output.

5. Nasal continuous positive airway pressure increased end-expiratory lung volume, but had no effect on breathing frequency, tidal volume or MSNA.

6. In patients with congestive heart failure, there is a significant independent and previously unrecognized correlation between spontaneous breathing pattern and MSNA; patients with rapid shallow breathing exhibit the highest degree of sympathetic activation. In distinct contrast to healthy subjects, the short-term application of nasal continuous positive airway pressure at 10 cmH₂O does not increase MSNA in congestive heart failure.

Key words: heart failure, positive airway pressure, sympathetic nervous system.
Abbreviations: AOI/Ptm., intrathoracic aortic transmural pressure during systole; CHF, congestive heart failure; MSNA, muscle sympathetic nerve activity; NCPAP, nasal continuous positive airway pressure; Poes, oesophageal pressure; PtCO₂, transcutaneous PCO₂; Vb, minute ventilation; VT, tidal volume.
Correspondence: Dr John S. Floras, Suite 1614 Mount Sinai Hospital, 600 University Ave., Toronto, Ontario, Canada MSG 1X5.
INTRODUCTION

Because of its adverse implications for disease progression and survival, the contribution of sympathetic nervous system activation to the pathophysiology of congestive heart failure (CHF) has received considerable attention [1]. However, our current understanding of mechanisms by which neurohumoral excitation arises in patients with CHF is incomplete [1–3]. Haemodynamic factors, such as impaired stroke work index, increased left ventricular end-diastolic pressure and increased pulmonary artery pressures, correlate significantly with both increased muscle sympathetic nerve activity (MSNA) and cardiac noradrenaline spillover [4–7]. However, these variables only account for approximately 50–60% of the observed variance in these measures of sympathetic tone among patients with CHF.

Sympathetic outflow to the heart and periphery can be modulated by the central respiratory rhythm generator [8]. In healthy subjects, breathing patterns and, in particular, tidal volume (VT) exert a major influence on sympathetic nerve traffic to muscle [9,10]. Whether a similar relationship pertains in heart failure is unknown, and the influence of the spontaneous respiratory rate on MSNA has not been determined in either animal or human studies. However, recent observations in our laboratory suggest that spectral coherence between variations in breathing and MSNA may be similar in normal subjects and patients with heart failure [11].

The primary objective of these experiments was to test the hypotheses that MSNA burst frequency in heart failure is directly related to breathing frequency, and that MSNA burst incidence (a time-independent variable derived from the number of bursts per 100 cardiac cycles) is inversely related to VT. Our secondary objective was to test the hypothesis that an acute increase in intrathoracic pressure as generated by nasal continuous positive airway pressure (NCPAP), will suppress MSNA. When administered nocturnally over a period of weeks to months to patients with CHF complicated by central sleep apnoea, NCPAP lowers nocturnal urinary noradrenaline excretion and daytime plasma noradrenaline concentrations [12]. These sympato-inhibitory responses can be attributed to attenuation of central sleep apnoea, apnoea-related hypoxia and arousals from sleep, but may also be due to the direct and reflex effects of increased intrathoracic pressure in CHF.

In subjects with normal ventricular function and filling pressures, a positive end-expiratory pressure of 10 cm.H2O or more increases MSNA [13,14]. This effect can be considered an appropriate reflex response to unloading of low- and high-pressure mechanoreceptor afferents by reductions in intracardiac and aortic arch transmural pressures, and to the fall in cardiac output caused by a drop in preload. However, the cardiac output of patients with CHF is relatively insensitive to reductions in preload, but responsive to decreases in afterload. NCPAP might reduce rather than increase MSNA reflexively in such patients through several alternative mechanisms, acting alone or in concert. These include reductions in atrial, ventricular or pulmonary artery transmural pressures [15] (i.e. three well-documented correlates of increased MSNA and cardiac noradrenaline spillover in CHF) [16,17]; increases in stroke volume and cardiac output [16,18,19]; increases in end-expiratory lung volume [20] (thereby activating pulmonary stretch receptors with inhibitory effects on sympathetic outflow [9,21]); or by altering breathing frequency [9,10].

In our previous experiments in patients with CHF studied while awake, the short-term application of NCPAP increased time and frequency domain indices of parasympathetic activity [20]. There was a trend towards an immediate decrease in the spectral index for cardiac sympathetic nerve activity derived from heart rate variability, but this was not significant, and not sustained 30 to 45 min into the application of this intervention. However, in CHF there are serious limitations to the use of heart rate spectral analysis as a means of estimating sympathetic nerve traffic to the heart or periphery [22]. We therefore examined the effects of NCPAP on MSNA, measured directly using microneurography, in patients with CHF.

METHODS

Subjects

Fourteen male patients were recruited on the following basis: CHF due to ischaemic or idiopathic dilated cardiomyopathy, present for at least 6 months, chronic exertional dyspnoea despite medical therapy, a left ventricular ejection fraction < 35% measured by 99mTc equilibrium radionuclide angiography, sinus rhythm and no previous exposure to NCPAP. Patients refrained from caffeinated beverages and alcohol for 24 h before the study. This protocol was approved by our University’s Human Subjects Review Committee and all subjects gave their informed consent.

Respiratory variables

A respiratory inductance plethysmograph (Respirtrace, Ambulatory Monitoring Inc., White Plains, NY, U.S.A.), calibrated in the DC mode by the two positions simultaneous equations method against VT from a spirometer [23,24], was used to measure VT, NCPAP-induced changes in end-expiratory lung volume, respiratory rate and minute ventilation (VE). Transcutaneous PCO2 (PtcCO2) was measured continuously by a capnograph (Kontron Medical, F. Hoffman LaRoche, Basle, Switzerland) [25]. Intrathoracic pressure was assessed by oesophageal pressure (Poes) measured from an oeso-
phageal balloon catheter system attached to a pressure transducer (Validyne MP 45 ± 50 cm H₂O, Northridge, CA, U.S.A.) [16]. Arterial blood gas tensions were measured before the study.

**Blood pressure and cardiac output**
Systemic blood pressure was measured at 1-min intervals with an automatic sphygmomanometer (Physio-Control Lifestar 200, Redmond, WA, U.S.A.). Heart rate was determined from lead II of an ECG. Stroke volume and cardiac output were determined by echocardiographic-Doppler ultrasound (Ultramark 4, Advanced Technology Laboratories, Bothell, WA, U.S.A.) [26]. With patients in the supine position, maximum instantaneous aortic flow velocity was measured in the ascending aorta using continuous-wave Doppler (2.25 MHz) directed through the suprasternal window. Stroke volume was calculated from the product of the mean time–velocity integral and the cross-sectional area of the aortic annulus orifice (A), calculated as $A = \pi(D/2)^2$ where D is the diameter of the aortic annulus obtained from a prior parasternal long-axis view. The mean time–velocity integral was obtained from 30–60 successive cardiac cycles, a time period sufficient to include inspiratory and expiratory phases of the respiratory cycle. Cardiac output was calculated from the product of stroke volume and heart rate. Stroke volume index and cardiac index were derived by accounting for body surface area.

**Microneurography**
Multi-unit recordings of post-ganglionic MSNA were obtained with a unipolar tungsten electrode inserted into muscular fascicles of the peroneal nerve, posterior to the fibular head. The raw neurogram was amplified (by 20 000–70 000), filtered (at a bandwidth of 700–2000 Hz), rectified and integrated (time constant 0.1 s) to obtain a mean voltage display of MSNA. Bursts arising from muscle were differentiated from those arising from skin sympathetic nerves using accepted criteria [27].

**Protocol**
Eight patients were administered NCPAP, the next five were studied as time controls, and one patient was studied twice, under both experimental conditions. Thus, a total of nine NCPAP and six time control studies were performed. A 15-min baseline recording was obtained followed either by a 45-min time period during which subjects breathed through a nasal mask with no pressure applied (time control group) or during which 10 cmH₂O of NCPAP (BiPAP®, Respironics Inc, Murrysville, PA, U.S.A.) was applied via a tight fitting nasal mask with the mouth closed (NCPAP group). All patients breathed through their noses throughout the experiments. Since none of the patients had been previously exposed to NCPAP, it was applied for 45 min, first, to determine its immediate and sustained effects on breathing pattern and MSNA and, second, to minimize any potential effects of mask discomfort or anxiety.

**Data acquisition and analysis**
$V_e$, $P_{oes}$, ECG, heart rate and integrated MSNA were recorded on a strip chart (Gould model 2800S, Cleveland, OH, U.S.A.). Intrathoracic aortic transmural pressure during systole ($AOI_{tm_{sys}}$) was determined by subtracting $P_{oes}$ during systole from systolic blood pressure, as previously described [14]. Respiratory rate, $V_T$, $V_e$, end-expiratory lung volume, $P_{aco_2}$, $AOI_{tm_{sys}}$, heart rate, stroke volume index and cardiac index were averaged over 2-min intervals at the end of the baseline periods, and at 15 and 45 min during the control or NCPAP periods.

Microneurographic recordings were analysed by a visual count of bursts occurring during the last 5 min of baseline and during the first 15 min (immediate) and last 15 min (sustained) of the 45-min NCPAP or time control intervals. The mean inter-observer variability in counting sympathetic nerve bursts in our laboratory is 3.9% and the mean intra-observer variability is 4.5% [28]. MSNA was expressed both as burst frequency (bursts/min) and, to adjust for the pulse synchronous nature of MSNA, as burst incidence (bursts/100 heartbeats). To test the hypothesis that the two time-dependent variables, MSNA burst frequency and respiratory frequency, would be directly related and that the two time-independent variables, MSNA burst incidence/100 cardiac cycles and $V_T$, would be inversely related, these two relationships were examined separately by least squares linear regression analyses. In addition to respiratory frequency and $V_T$, other factors that could potentially influence MSNA, such as left ventricular ejection fraction, stroke volume index, cardiac index, $P_{aco_2}$ and $P_{aco_3}$ were entered into multiple stepwise linear regression analyses as independent variables. Baseline data in the control and NCPAP groups were compared using unpaired $t$-tests. Within-group comparisons between baseline and either the 15- or 45-min time control or NCPAP periods were performed using analyses of variance for repeated measures and post-hoc Tukey’s tests. A $P$-value of < 0.05 was considered statistically significant. Results are expressed as means ± S.E.M.

**RESULTS**

**Patient characteristics**
The two groups were comparable for age, body mass index, left ventricular ejection fraction, New York Heart Association HA functional class and medications (Table 1). The aetiology of CHF was similar in both groups. The
Table 1 Patient characteristics

| Abbreviations: CHF, congestive heart failure; IsCM, ischaemic cardiomyopathy; IDCM, idiopathic dilated cardiomyopathy; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; V̇E, forced tidal volume; FVC, forced vital capacity; FEV₁/FVC, forced expiratory volume in 1.0 s; ACE, angiotensin-converting enzyme. There were no significant differences between the two groups with respect to any of the baseline variables. |
|---|---|
| **Control group (n = 6)** | **NCPAP group (n = 9)** |
| Age (years) | 59.5 ± 1.5 | 55.0 ± 3.2 |
| Body mass index (kg/m²) | 25.4 ± 1.3 | 27.4 ± 1.4 |
| NYHA (class) | 4 ± 2 | 4.5 |
| LVEF (%) | 109 ± 13 | 77 ± 8 |
| FEV₁/FVC (%) normal | 110 ± 12 | 80 ± 8 |
| FEV₁/FVC (%) normal | 92 ± 3 | 95 ± 3 |
| PaCO₂ (mmHg) | 89 ± 5 | 94 ± 6 |
| PaO₂ (mmHg) | 37 ± 1 | 36 ± 3 |
| pH | 7.43 ± 0.01 | 7.48 ± 0.02 |
| Medications (% patients) | | |
| Diuretics | 5 (83) | 7 (78) |
| Digoxin | 5 (83) | 8 (89) |
| ACE inhibitors | 6 (100) | 9 (100) |
| Vasodilators | 2 (33) | 6 (47) |
| Antiarrhythmics | 1 (17) | 1 (11) |
| β-blockers | 1 (17) | 1 (11) |

degree of cardiac impairment was moderate to severe, as indicated by a mean left ventricular ejection fraction of approximately 20% in both groups.

Satisfactory V̇r signals were obtained in all control patients and eight of the nine NCPAP patients. There were no significant differences in baseline respiratory rate, V̇r, V̇t or PETCO₂ between the groups (Table 2). In addition, no significant differences in heart rate, systolic or diastolic blood pressure, stroke volume index, cardiac index, AOIPtm or MSNA were observed at baseline between the control and NCPAP groups (Table 3).

Relationship between cardiorespiratory variables and MSNA under resting conditions

Figure 1 illustrates V̇t and MSNA in two patients with CHF. MSNA is greater in the patient with a rapid shallow pattern of breathing than in the patient with a slower, deeper pattern of breathing. In Figure 2 individual data for all patients are plotted. During quiet recumbent rest there was a significant positive correlation between MSNA burst frequency and respiratory frequency (r² = 0.57; P = 0.001) and a significant inverse correlation between MSNA burst incidence and V̇t (r² = 0.50; P = 0.005). Multiple stepwise linear regression analyses indicated that respiratory frequency was the only significant independent correlate of MSNA burst frequency and V̇t the only independent correlate of MSNA burst incidence. In particular, there was no relationship between MSNA and either left ventricular ejection fraction or stroke volume index or cardiac index in these patients.

Effects of NCPAP on cardiorespiratory variables and MSNA

As shown in Table 2, there was no change in respiratory rate, V̇r, V̇t, PETCO₂ or end-expiratory lung volume over the first or last 15 min of the time control period (i.e. in the absence of NCPAP). Similarly, NCPAP had no immediate or sustained effect on respiratory rate, V̇r, V̇t or PETCO₂. However, end-expiratory lung volume was increased over the entire 45-min NCPAP period (P < 0.01) (Table 2).

There were no significant changes in heart rate, systolic or diastolic blood pressure, stroke volume index, cardiac index or AOIPtm over the first or last 15 min of the time control period (Table 3). NCPAP did not change systolic or diastolic blood pressure, stroke volume index or cardiac index, but caused a significant immediate decrease in AOIPtm that was sustained into the last 15-min interval of the 45-min application (P < 0.05). In the single subject who was studied twice, MSNA was 90 bursts/100 cardiac cycles at baseline: 88 during the first

Table 2 Respiratory data

| Abbreviations: RR, respiratory rate; V̇t, tidal volume; V̇̇, minute ventilation; PETCO₂, transcutaneous PCO₂; ΔEELV, change in end-expiratory lung volume compared with baseline. There were no significant differences between the two groups at baseline with respect to any of these variables. **P < 0.01 compared with baseline within NCPAP group. |
|---|---|
| **Control (n = 6)** | **NCPAP 10 cmH₂O (n = 9)** |
| Baseline | First 15 min | Last 15 min | Baseline | First 15 min | Last 15 min |
| RR (breaths/min) | 15 ± 2 | 13 ± 2 | 14 ± 2 | 16 ± 2 | 14 ± 2 | 15 ± 2 |
| V̇t (ml) | 377 ± 85 | 423 ± 127 | 369 ± 80 | 476 ± 90 | 542 ± 89 | 456 ± 30 |
| V̇̇ (l/min) | 5.3 ± 0.9 | 4.8 ± 0.8 | 4.7 ± 0.8 | 7.2 ± 0.8 | 7.7 ± 1.1 | 7.2 ± 1.1 |
| PETCO₂ (mmHg) | 35 ± 3 | 35 ± 3 | 35 ± 3 | 36 ± 2 | 35 ± 2 | 35 ± 1 |
| ΔEELV (ml) | 0 ± 0 | 0 ± 0 | 67 ± 10 | 0 ± 0 | 639 ± 94** | 637 ± 137** |

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Table 3  Haemodynamics and muscle sympathetic nerve activity

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<th>Control</th>
<th>NCPAP</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>First 15 min</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>67 ± 5</td>
<td>67 ± 5</td>
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<tr>
<td>Systolic BP (mmHg)</td>
<td>111 ± 7</td>
<td>113 ± 7</td>
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<tr>
<td>Diastolic BP (mmHg)</td>
<td>72 ± 5</td>
<td>74 ± 5</td>
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<tr>
<td>Stroke volume index (m1/m2)</td>
<td>26 ± 7</td>
<td>27 ± 7</td>
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<tr>
<td>CI (l/min/m2)</td>
<td>1.68 ± 0.42</td>
<td>1.70 ± 0.40</td>
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<tr>
<td>AOIPtms (mmHg)</td>
<td>114 ± 8</td>
<td>115 ± 6</td>
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<tr>
<td>MSNA (bursts/min)</td>
<td>51.7 ± 5.7</td>
<td>51.4 ± 6.5</td>
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<tr>
<td>MSNA (bursts/100 heart beats)</td>
<td>77.3 ± 6.7</td>
<td>76.5 ± 7.4</td>
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DISCUSSION

These observations demonstrate, for the first time, a correlation between the spontaneous pattern of breathing and MSNA in patients with CHF. Specifically, the higher the respiratory frequency, and the lower the tidal volume, the higher the MSNA. Accordingly, patients with rapid, shallow breathing, a pattern commonly observed in CHF [12,29,30], seem unable to suppress central sympathetic outflow, and exhibit the greatest degree of sympathetic activation with a burst incidence often approaching 100%. These relationships between breathing frequency, tidal volume and MSNA were independent of haemodynamic variables such as ejection fraction, stroke volume, cardiac output and blood pressure, and the extent to which these respiratory factors were related to the variance in MSNA among these patients with heart failure (57% for breathing frequency; 50% for tidal volume) was quantitatively similar to the relationship between haemodynamic factors and sympathetic nervous activity documented previously by other groups [4–6]. Thus, respiratory factors should also be considered when evaluating mechanisms responsible for sympathetic nervous system activation in patients with CHF.
Respiratory periodicity in MSNA has been well documented in healthy subjects with normal ventricular function [31]. Stimulation of pulmonary vagal afferents by an increase in $V_t$ by lung inflation can inhibit central sympathetic outflow to peripheral vascular beds, while reduced $V_t$ or voluntary apnoea has the opposite effect [9,27,32,33]. Increasing breathing frequency from 10 to 20 breaths/min causes a significant increase in that component of the heart rate variability power spectrum conventionally attributed to cardiac sympathetic nerve activity in both healthy subjects and patients with heart failure [34]. The low frequency/high frequency ratio in the systolic blood pressure variability spectrum is also augmented significantly by doubling breathing frequency in heart failure, but not in normal subjects [34]. Our recent demonstration of similar spectral coherence between the variability of breathing and the variability of MSNA in subjects with normal and impaired ventricular function suggested that these respiratory patterns could influence MSNA in patients with CHF [11].

Modulation of central sympathetic outflow by input from the brainstem respiratory rhythm generator [8] probably contributes to the coherence between these spontaneous fluctuations in breathing and MSNA, whereas the inverse relationship between burst incidence and $V_t$ can be explained, in part, by a sympatho-inhibitory response to stimulation of pulmonary stretch receptors with vagal afferents [9,19]. An example of inspiratory modulation of MSNA is shown in Figure 1 (left panel). In addition, high left-sided filling pressures and pulmonary congestion can cause both sympatho-excitation [4,5] and rapid, shallow breathing [29,30] through stimulation of sympatho-excitatory atrial and pulmonary vascular afferents, and pulmonary J-receptors, respectively. If this were the case in our patients, both high MSNA and the pattern of rapid shallow breathing may simply reflect elevated cardiac filling pressures and pulmonary congestion. Alternatively, it is possible that increased sympathetic nervous system activity and circulating catecholamines stimulated rapid shallow breathing [35]. Thus, rapid shallow breathing may not be the cause of increased MSNA, but may simply be an outward manifestation of its presence in CHF.

Immediate and sustained responses to the short-term application of 10 cmH$_2$O of NCPAP were examined specifically because we have previously shown that this level of pressure has beneficial effects on both mechanical and neural factors in patients with CHF. Systolic left ventricular transmural pressure (an index of afterload) decreases, stroke volume increases, and time and frequency domain indices of parasympathetic nervous system activity are augmented by 10 cmH$_2$O of CPAP [16,18–20]. These mechanical and neural responses to NCPAP raised the possibility that this intervention might also inhibit MSNA reflexively by increasing end-expiratory lung volume and stroke volume, or by reducing breathing frequency.

In healthy subjects, stimulation of cardiac baroreceptors by increasing filling pressures causes reflex reductions in MSNA [28,36]. In the context of these well-documented observations, the consistent demonstration of short-term NCPAP responses was expected. However, in our CHF patients, a significant reduction in MSNA occurred only after 10 min of NCPAP, with no significant change in breathing frequency or tidal volume. It is possible that a 10 cmH$_2$O CPAP may not be sufficient to cause a reflex inhibition of MSNA in our patients. Alternatively, our CHF patients may have a baroreflex dysfunction that prevents the development of a reflex inhibition of MSNA by NCPAP.

**Figure 2** Relationships of MSNA and respiratory pattern at baseline among the 14 patients in whom satisfactory tidal volume recordings were obtained

In one of the patients tidal volume was not obtained so that only 14 points are shown in the tidal volume–MSNA plot. The left panel shows the significant direct correlation of MSNA burst frequency with respiratory rate ($r^2 = 0.57$), and the right panel the significant indirect correlation of MSNA burst incidence and tidal volume ($r^2 = 0.50$).
of significant positive relationships between left ventricular end-diastolic, atrial or pulmonary artery pressures, on the one hand, and either MSNA or transcardiac noradrenaline spillover [4–7], would appear paradoxical. Our primary hypothesis was that short-term increases in intrathoracic pressure induced by NCPAP might inhibit efferent MSNA reflexively by reducing cardiac or pulmonary vascular transmural pressures. If so, this would be consistent with the recent demonstration by Kaye et al. [15] of a reduction in transcardiac noradrenaline spillover in patients with severe CHF when pulmonary artery and cardiac transmural pressures were lowered acutely by an infusion of sodium nitroprusside. In addition, our secondary hypothesis was that if NCPAP reduced respiratory rate and increased sodium nitroprusside. In addition, our secondary hypothesis was that if NCPAP reduced respiratory rate and increased ventilation, it might also reduce MSNA through an effect on breathing pattern.

Despite these various considerations, NCPAP at 10 cmH\textsubscript{2}O had no effect on MSNA in these patients. On the basis of our observations during spontaneous breathing, this result might be anticipated, since NCPAP did not alter either breathing frequency or V\textsubscript{T} in these patients. In our previous experiments, the short-term application of NCPAP at this level tended to decrease the spectral index for cardiac sympathetic activity derived from heart rate variability, but this effect was not significant [20], an observation that is consistent with the present findings.

It should be emphasized that these results are in distinct contrast to two previous experiments in subjects with normal ventricular function, in whom the short-term application of 10 and 16 cmH\textsubscript{2}O end-expiratory pressure, respectively, caused a marked and sustained increase in MSNA [14,31]. Several mechanisms could account for this qualitative difference between the effects of NCPAP on MSNA in subjects with normal and impaired left ventricular function. In healthy subjects, positive airway pressure will reduce cardiac output [16,37] and increase MSNA reflexively by unloading arterial baroreceptors [38]. In addition, the simultaneous increase in intrathoracic pressure induced by NCPAP [16] will also decrease ventricular and aortic arch transmural pressures, unload aortic arch and ventricular mechanoreceptors and further increase MSNA reflexively [38]. Acute reductions in cardiac filling pressure, as may be replicated by lower-body negative pressure, will elicit an additional sympatho-excitatory response [38]. However, because it reduces left ventricular afterload (i.e. left ventricular transmural pressure during systole) in patients with CHF, NCPAP either has no effect or in some patients actually increases cardiac output [16,19]. Under these conditions, arterial baroreflex-mediated increases in MSNA will not be required to defend systemic blood pressure. This effect may be particularly pronounced in those patients with significant pericardial restraint on left ventricular filling [39]. Second, in CHF, blunting of reflex responses to acute reductions in ventricular or aortic arch transmural pressure (i.e. AOI\textsubscript{Ptm\textsubscript{sys}}) [1,2,40,41] should attenuate any reflex sympatho-excitatory responses to NCPAP arising from this mechanism. Third, NCPAP causes increases in end-expiratory lung volume (Table 2), which could cause pulmonary stretch receptor-mediated inhibition of MSNA [21] which would counteract, if not completely suppress, any sympatho-excitatory influences in CHF. Finally, reductions in pulmonary vascular or cardiac transmural pressure might selectively lower MSNA in patients with severe CHF, as observed recently for cardiac noradrenaline spillover in response to infusion of sodium nitroprusside [15]. This may be a result of suppression, by NCPAP, of sympatho-excitatory reflexes of intrathoracic origin that are ordinarily quiescent in healthy subjects [40,42–44].

Our findings lead us to two conclusions. First, in patients with CHF, rapid, shallow breathing is associated with increased MSNA, indicating a previously unrecognized relationship between spontaneous respiratory pattern and central sympathetic outflow to skeletal muscle vasculature in patients with CHF. Since the extent of sympathetic activation strongly predicts prognosis in CHF [45,46], it is important that further research be directed at identifying the mechanisms that underlie this relationship. Second, brief application of NCPAP reduced left ventricular afterload (i.e. AOI\textsubscript{Ptm\textsubscript{sys}}) without reducing cardiac output or increasing MSNA. Consequently, reductions in plasma and urinary indices of sympathetic activity due to long-term application of NCPAP, as documented previously in patients with CHF and central sleep apnoea [47], were probably caused by elimination of apnoeas, hypoxia and arousals from sleep, haemodynamic improvement and cardiac remodelling [47,48], rather than by the immediate reflex effects of this intervention.

ACKNOWLEDGMENTS

This work was supported by an Operating Grant from the Medical Research Council of Canada (MT 11607). M.T.N. and M.A.R. were supported by Research Fellowships from the Medical Research Council of Canada. J.S.F. and T.D.B. were recipients of Career Scientist Awards from the Ministry of Health of the Province of Ontario.

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Received 15 January 1998; accepted 21 April 1998