Augmented sympathetic neural response to simulated obstructive apnoea in human heart failure

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ABSTRACT

Sleep apnoea in heart failure increases mortality risk, possibly as a result of greater activation of the sympathetic nervous system. In healthy subjects, simulated central apnoeas (holding breath) and obstructive apnoeas (Mueller manoeuvres) increase muscle sympathetic activity equally, primarily through chemoreceptor stimulation. In heart failure, however, Mueller manoeuvres cause greater reductions in blood pressure than breath holds. We hypothesized that in heart failure, the summation of arterial baroreceptor unloading and chemoreceptor stimulation would increase sympathetic activity more during obstructive than central apnoeas. Healthy human subjects and heart failure patients (seven of each) performed 15-s breath holds and 15-s Mueller manoeuvres. Breath holds evoked a progressive increase in muscle sympathetic nerve activity in both groups, but had no effect on blood pressure. In healthy subjects, breath holds and Mueller manoeuvres caused equal peaks in sympathetic activity. In contrast, in heart failure patients, Mueller manoeuvres caused a progressive decrease in blood pressure ($P < 0.05$) and greater increases in sympathetic activity than breath holds ($P < 0.01$). In heart failure, simulated obstructive apnoea elicits greater increases in sympathetic activity than simulated central apnoea, due to its additional hypotensive effect. These present findings offer novel insight into the potential role of sleep apnoea in augmenting sympathetic activity and accelerating disease progression in heart failure.

INTRODUCTION

Sleep-related breathing disorders afflict the majority of patients with heart failure owing to left-ventricular systolic dysfunction [1,2]. When present, central sleep apnoea (CSA) and obstructive sleep apnoea (OSA) affect survival adversely and independently [3,4]. Augmented sympathetic nervous system activity is one potential mechanism for accelerated disease progression and premature mortality in such patients [5–7].

Key words: baroreceptor reflex, blood pressure, heart failure, hypoxia, sleep apnoea, sympathetic nervous system.
Abbreviations: AoiPtm, aortic intra-thoracic transmural pressure; CPAP, continuous positive airway pressure; CSA, central sleep apnoea; MSNA, muscle sympathetic nerve activity; OSA, obstructive sleep apnoea; $P_{aCO_2}$, partial pressure of arterial CO$_2$; $P_{aO_2}$, partial pressure of arterial O$_2$; $P_{es}$, oesophageal pressure.

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Disturbances in the regulation of sympathetic and vagal nerve traffic in heart failure by cardiopulmonary and arterial baroreceptor reflexes, in response to altered cardiac and systemic haemodynamics, have been documented extensively in awake subjects [5–11]. CSA and OSA can increase sympathetic outflow further through additional, non-baroreflex-mediated mechanisms. Decreases in the partial pressure of arterial O₂ (Pao₂) and increases in the partial pressure of arterial CO₂ (Paco₂) during apnoea are two chemical sympatho-excitatory stimuli whose interaction is additive. Cessation of sympathetic nerve activity (MSNA), achieving the identical peak value at their termination. Because supplemental sympathetic nerve activity (MSNA), achieving the identical peak value at their termination. Because supplemental sympathetic nerve activity (MSNA), achieving the identical peak value at their termination.

Several groups have studied the time course and magnitude of haemodynamic and neural responses to OSA, or to simulated obstructive (by Mueller manoeuvres) or central (by breath holds) apnoeas in the awake state in subjects with normal left-ventricular systolic function [13,15,17,18]. Morgan et al. [13] reported that 20-s breath holds and Mueller manoeuvres (i.e. the abrupt inspiratory generation of negative intra-thoracic pressure) elicit progressive increases in muscle sympathetic nerve activity (MSNA), achieving the identical peak value at their termination. Because supplemental O₂ attenuated this sympathetic activation to the same extent during both interventions, these authors concluded that peripheral chemoreceptor excitation was the predominant stimulus to sympathetic outflow during both breath holds and Mueller manoeuvre.

These findings may not pertain to patients with depressed ejection fractions, in whom ventricular systolic performance is highly afterload-dependent. Indeed, we have demonstrated that the abrupt generation of negative intra-thoracic pressure at the onset of a Mueller manoeuvre lowers systemic blood pressure (BP) and induces greater reductions in cardiac output in patients with left-ventricular systolic dysfunction than in age-matched control subjects [19]. In contrast, breath holds had no effect on BP or cardiac output in either cohort. We reasoned that unloading of arterial baroreceptors by the Mueller manoeuvre should elicit a reflex increase in MSNA in heart failure that would interact in an additive fashion with the sympathetic neural response to a breath hold. Therefore, the primary objective of the present investigation was to test the hypothesis that, in contrast with control subjects, increases in MSNA elicited by Mueller manoeuvres in patients with left-ventricular systolic dysfunction exceed those induced by breath holds. If so, those aspects of disease progression caused by increased sympathetic activity may be accentuated in patients with OSA, as compared to those without sleep-related breathing disorders. More importantly, abolition of those adverse effects specific to OSA could explain, in part, the rapid reversal of systolic dysfunction that follows the initiation of nocturnal continuous positive airway pressure (CPAP) as therapy [19-21].

This reasoning presupposes that arterial baroreflex regulation of MSNA is competent in heart failure. Because the baroreflex control of heart rate is attenuated [7,22], it has been generally assumed that the arterial baroreflex modulation of MSNA is similarly impaired in heart failure [10,11]; however, a substantial body of recent evidence indicates that the reflex regulation of MSNA is intact in heart failure and is rapidly responsive to changes in diastolic BP [8,9,23]. The abrupt generation of negative intra-thoracic pressure at the onset of obstructive apnoea will stimulate cardiopulmonary and intra-thoracic baroreceptors by increasing cardiac and aortic transmural pressures [24,25]. These mechanical stimuli inhibit MSNA reflexively in healthy young subjects performing the Mueller manoeuvre [13,18]. Whether the Mueller manoeuvre induces similar acute suppression of MSNA in subjects with impaired ventricular systolic function is unknown. Therefore, a secondary objective of the present investigation was to compare the gain of aortic baroreceptor reflex suppression of MSNA at the onset of the Mueller manoeuvre in heart failure and control subjects.

**METHODS**

**Subjects**

Seven patients (four with ischaemic cardiomyopathy and three with idiopathic dilated cardiomyopathy) and seven healthy control subjects matched for age, sex and body mass were studied. The protocol received institutional ethics review committee approval confirming conformity with the Declaration of Helsinki, and all subjects provided written informed consent. Patient inclusion criteria were: (i) congestive heart failure of ≥ 6 months’ duration; (ii) chronic exertional dyspnoea despite appropriate drug treatment; (iii) stable clinical status and medications for ≥ 1 month; (iv) resting left-ventricular ejection fraction < 40% (by radionuclide angiography or echocardiography); and (v) sinus rhythm. Exclusion criteria included myocardial infarction, unstable angina or cardiac surgery within the preceding 3 months.

**Procedures**

Intra-thoracic pressure was derived from oesophageal pressure (Pₐₐ) [26], Thoraco-abdominal movements and tidal volumes were measured by respiratory inductance plethysmography (Respitrace, Ambulatory Monitoring Inc., White Plains, NY, U.S.A.) [27,28]. Oxyhaemoglobin saturation was monitored by pulse oximetry (Oxyshuttle®, Sensormedics Corp., Anaheim, CA, U.S.A.). BP was measured continuously using digital photoplethysmography (Finapres, 2300 Ohmeda, Englewood,
CO, U.S.A.) with the arm horizontal. Heart rate was determined from an electrocardiogram. MSNA was recorded from an electrode inserted into the peroneal nerve [29].

Protocol
Subjects were studied awake and in the supine position while wearing a nose clip and mouthpiece [30]. Baseline measurements were acquired during quiet breathing. Breath holds and Mueller manoeuvres were performed at the end of expiration and were sustained for 15 s. A 21-gauge needle was inserted into the mouthpiece, creating a small air-leak, to prevent closure of the glottis during the Mueller manoeuvre. Subjects generated an intra-thoracic pressure of −30 mmHg during the Mueller manoeuvre, which was calibrated with visual feedback of oesophageal pressure. After several practice trials, four breath holds and four Mueller manoeuvres were performed in random order, each separated by 3 min of regular breathing.

Data analysis
Aortic intra-thoracic transmural pressure (AoIPtm) during systole or diastole was calculated as the difference between simultaneous measurements of BP and Peso. Systolic and diastolic BP, systolic and diastolic AoIPtm, and heart rate were analysed for each cardiac cycle. MSNA was quantified in terms of burst frequency, burst incidence (bursts per 100 heart beats), burst amplitude and as integrated MSNA (burst incidence × burst amplitude).

Baseline values were averaged over 1 min of normal breathing prior to these respiratory manoeuvres. Responses during breath holds and Mueller manoeuvres were expressed as a percentage of the baseline. Average beat-by-beat values for all variables were calculated during the first, second and final 5-s intervals of the breath holds and the Mueller manoeuvres, and during the 5-s interval immediately after their release.

Baseline data in heart failure and control subjects were compared using two-tailed unpaired t tests. To determine the independent effects of intra-thoracic pressure and time on the haemodynamic variables of interest, mean values during baseline, the first, second and final 5 s of each breath hold and Mueller manoeuvre, and subsequent recovery, were compared using a two-way ANOVA and the Student–Newman–Kuels test. A P value < 0.05 was considered significant. Results are expressed as means ± S.E.M.

RESULTS

Subject and protocol characteristics
Patients reported New York Heart Association Class II symptoms and had marked impairment of left-ventricular systolic function (mean ejection fraction, 24 ± 6%). They were receiving digoxin (n = 5), diuretics (n = 6), angiotensin-converting enzyme inhibitors (n = 6), vaso-dilators (n = 2), β-blockers (n = 2), and amiodarone (n = 2) as therapy. Age, body-mass index, BP, AoIPtm, and heart rate were similar in the two cohorts, but baseline MSNA was greater in the heart failure group (P < 0.01) (Table 1).

Oxyhaemoglobin saturation did not fall below 91% during either breath holds or Mueller manoeuvres, and was similar at the end of both interventions in controls (95.2 ± 0.7 versus 95.8 ± 0.4%) and heart failure subjects (92.3 ± 0.8 versus 92.8 ± 0.6%). Controls and heart failure subjects generated similar Peso values during the Mueller manoeuvres (−28.8 ± 1.4 mmHg and −28.4 ± 1.9 mmHg respectively). Figure 1 illustrates Peso, BP and MSNA during a breath hold and a Mueller manoeuvre in one of these heart failure patients.

Responses to breath holds
Breath holding had no effect on systemic BP or on AoIPtm in either control or heart failure subjects (Figures 2 and 3). Heart rate decreased in the controls (P < 0.05), but not in heart failure subjects.

In healthy subjects, breath holds had no significant effect on MSNA burst amplitude, but burst frequency, incidence, and integrated activity rose progressively over the course of this voluntary apnoea, and fell promptly to baseline on resumption of breathing. In the heart failure group, integrated MSNA also increased significantly by the end of the breath hold, and returned to baseline afterwards; however, this increase was less intense than in control subjects, and achieved through a different mechanism: an increase in mean burst amplitude rather than MSNA burst frequency or incidence (Figures 4 and 5).

Responses to Mueller manoeuvres
The Mueller manoeuvre had no effect on systolic or diastolic BPs in control subjects. In contrast, the systolic and diastolic BPs of heart failure patients fell significantly at the start of this intervention, declined progressively

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<th>Table 1 Baseline characteristics of the subjects</th>
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<td>Controls (n = 7)</td>
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<td><strong>Age (years)</strong></td>
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thereafter, and displayed incomplete recovery on resumption of breathing (Figure 2). Heart rate increased significantly during the Mueller manoeuvre in both groups \((P < 0.05)\).

In healthy subjects, the Mueller manoeuvre elicited marked, immediate, and sustained increases in both systolic and diastolic AoIPtm. Both BP and AoIPtm returned promptly to baseline values during the recovery period. In the heart failure group, systolic and diastolic AoIPtm also rose at the onset of the manoeuvre, but these responses were not sustained. AoIPtm had returned to the baseline value by the last 5–10 s of the Mueller manoeuvre and, in contrast to healthy subjects, systolic AoIPtm fell below baseline upon its release (Figure 3).

MSNA exhibited a triphasic response in both groups, with an initial abrupt suppression of MSNA burst frequency, incidence, and integrated activity, followed by a progressive rise over the following 10 s to a peak that was significantly above baseline values, and a prompt recovery on resumption of breathing. The key difference between these two groups resided in MSNA burst frequency, incidence, and integrated activity.
amplitude, which increased significantly above baseline at the end of the Mueller manoeuvre in heart failure patients, but not in healthy subjects (Figures 4 and 5).

**Comparison of responses to breath holding and Mueller manoeuvres**

In healthy subjects, the principal difference between these two interventions was the immediate inhibition of MSNA and the sustained increase in diastolic AoIPtm evoked by the Mueller manoeuvre (Figures 2–5). In contrast, in the heart failure patients, systolic BP was significantly lower throughout the Mueller manoeuvre, diastolic BP was significantly lower during the final 10 s, and diastolic AoIPtm significantly greater during the first 10 s. After the first 5 s, systolic AoIPtm fell significantly below baseline values (Figures 2 and 3). As with control subjects, MSNA burst incidence and integrated activity, which did not change during the first 5 s of the breath hold, were suppressed significantly at the start of the Mueller manoeuvre; however, in marked contrast with those with normal ventricular function, MSNA burst amplitude and integrated MSNA were significantly greater during the final 5 s of the Mueller manoeuvre than during the corresponding breath holding (Figures 4 and 5).

**Aortic baroreceptor reflex regulation of muscle sympathetic nerve activity**

To estimate the gain of aortic baroreceptor reflex inhibition of MSNA, we related the change in MSNA (response) from baseline, during the first 5 s of the Mueller manoeuvre, to the corresponding change in diastolic AoIPtm (stimulus). There was no evidence for attenuated baroreflex gain in the congestive heart failure group, whether expressed in terms of changes in MSNA burst incidence (–1.5 ± 0.4 bursts·100 beats·min⁻¹·mmHg⁻¹ in controls versus –2.9 ± 1.5 bursts·100 beats·min⁻¹·mmHg⁻¹ in heart failure subjects; \( P = 0.4 \)), frequency (–0.9 ± 0.3 bursts·min⁻¹·mmHg⁻¹ versus –1.9 ± 1.0 bursts·min⁻¹·mmHg⁻¹ in heart failure; \( P = 0.3 \)) or as relative change in integrated MSNA (–0.6 ± 0.3 % versus –1.5 ± 0.8 % baseline/mmHg in heart failure; \( P = 0.2 \)).

**DISCUSSION**

Sympathetic nervous system activation in heart failure has adverse implications for prognosis [5,6]. It is therefore important to develop a more complete understanding of the mechanisms responsible for this process. By having subjects perform 15-s Mueller manoeuvres and breath holds, we simulated the mechanical and some of the chemical effects of obstructive and central apnoea respectively, without introducing the confounding influences of profound hypoxia, sleep state, or arousal. Our objective in these experiments was to test the hypothesis that increases in MSNA elicited by the Mueller manoeuvre exceed those induced by a breath hold in patients.
with left-ventricular systolic dysfunction, but not in age-matched healthy control subjects.

In control subjects, breath holds and the Mueller manoeuvre elicited virtually identical increases in MSNA burst frequency and integrated MSNA. These findings indicate that previous observations in healthy young individuals [13] also pertain in older late-middle-aged subjects. In contrast, those with heart failure: (i) were not able to maintain their BP in the face of brief increases in left-ventricular afterload, i.e. AoIPtm, induced by the Mueller manoeuvre; (ii) responded to this hypotensive stimulus with significantly greater integrated MSNA after 15 s of a Mueller manoeuvre than after 15 s of a breath hold; and (iii) achieved this increase via augmentation of mean MSNA burst amplitude, rather than MSNA burst frequency.

Both the amplifying effect of apnoea on changes in MSNA, elicited by falls in \( P_{aO_2} \) and \( P_{aCO_2} \), and the haemodynamic and sympathetic responses to breath holds and Mueller manoeuvres have been characterized extensively in subjects with normal ventricular function [13,14,18,31]. By the conclusion of both the breath holds and the Mueller manoeuvres, sympathetic nerve firing rates were significantly higher than the baseline values (Figures 4 and 5). Our findings in control subjects are therefore consistent with those of previous investigators, (Figures 4 and 5). Our findings in control subjects are therefore consistent with those of previous investigators, that many of these improve cardiac and autonomic function, and circulatory regulation, they could have reduced, rather than accentuated differences in MSNA responses between the heart failure and control groups. The abrupt generation of negative intra-thoracic pressure at the onset of the Mueller manoeuvre should also suppress MSNA [13,24,18]. The aortic baroreceptor reflex gain with respect to MSNA was similar in the two groups, whether expressed in terms of changes in MSNA burst incidence or frequency, or as the relative change in integrated MSNA per mmHg change in diastolic aortic transmural pressure. These findings are consistent with the concept that aortic baroreflex regulation of MSNA is not impaired in heart failure [8,9,23].

In the control subjects, increases in diastolic and systolic AoIPtm were sustained throughout the Mueller manoeuvre, yet after its initial suppression MSNA increased rapidly over the next 10 s to achieve terminal values equal to those evoked by the breath hold. This finding indicates that sympathetic activation elicited by the summation of chemoreceptor stimulation and apnoea overrides this intra-thoracic aortic baroreflex-mediated sympatho-inhibition.

In contrast, the heart failure patients could not maintain their BP when faced by this sudden increase in afterload (i.e. systolic AoIPtm) (Figure 2). Consequently, in this group the Mueller manoeuvre also caused a progressive decrease in diastolic BP, which unloaded extra-thoracic (carotid sinus) baroreceptors that inhibit reflexly sympathetic outflow. At the onset of the manoeuvre the summation of responses to aortic baroreceptor loading and carotid baroreceptor unloading resulted in net sympatho-inhibition, as would be anticipated from previous investigations of this interaction in healthy subjects [25]. Over the next 10 s, diastolic AoIPtm returned to baseline levels, whereas stroke volume [19] and diastolic BP decreased further. As a result, the extra-thoracic baroreceptors were unloaded profoundly by the fall in systemic diastolic BP by the end of the Mueller manoeuvre, and this sympatho-excitatory stimulus was no longer countered by increased intrathoracic aortic baroreceptor discharge. The summation of chemoreceptor-mediated sympatho-excitation during apnoea, and arterial baroreceptor unloading due to systemic hypotension, absent in healthy subjects, can explain why MSNA burst amplitude and integrated MSNA during the final 5 s of the Mueller manoeuvre were significantly higher than corresponding values during breath holds in the heart failure group.

Several of the heart failure patients were receiving medication that had negative chronotropic actions, effectively precluding a definitive interpretation of heart rate responses to breath holds and Mueller manoeuvres in this group. These drugs were not withdrawn, to ensure that the present findings would be relevant to the clinical scenario of apnoea in heart failure. Because several of these improve cardiac and autonomic function, and circulatory regulation, they could have reduced, rather than accentuated differences in MSNA responses between the heart failure and control groups. The abrupt generation of negative intra-thoracic pressure at the onset of the Mueller manoeuvre should also suppress MSNA.
by stimulating a group of cardiopulmonary receptors that elicit a net sympato-inhibitory response [7]. Because cardiopulmonary reflex regulation of MSNA differs from arterial baroreflex regulation of MSNA, in that the former is impaired in human heart failure [9,10], the simultaneous engagement of these two inhibitory reflexes might evoke less inhibition of MSNA in that cohort, but this was not observed.

Attenuation of excessive sympathetic nervous system activity remains an important therapeutic goal in heart failure [7]. If a significant proportion of this sympathetic activation, especially during sleep, is triggered by co-existing apnoea in addition to altered haemodynamics, then this particular stimulus may be amenable to suppression by specific therapy of both obstructive and central apnoea [16,28]. The pattern of sympathetic activation elicited by the Mueller manoeuvre in the present study is similar to that recorded during OSA in subjects with normal ventricular function [15,17]. In such subjects, MSNA is increased, but this can be suppressed with long-term abolition of OSA by CPAP [33]. Moreover, the fall in BP evoked by the Mueller manoeuvre is analogous to the hypotension caused by obstructive apnoeas during sleep in patients with systolic dysfunction [34]. In heart failure patients with OSA, CPAP improves left-ventricular function within 1 month of treatment [20,21].

The presence of CSA in heart failure also has adverse prognostic implications. These can be attributed, in part, to the elevated sympathetic activity that accompanies this breathing disorder [3,4,16,28]. The effects of breath holds on MSNA (Figures 4 and 5) are similar to those noted during CSA in heart failure. Alleviation of CSA, either with O₂ or CPAP, reduces adrenergic activity [28,35], and in a recent small, randomized trial, those who adhered to CPAP therapy experienced a significant reduction in the combined rate of death and cardiac failure [34]. Our results underscore the importance of identifying sleep-related breathing disorders in patients with heart failure and suggest that OSA may be a more potent acute stimulus than central apnoea to sympathetic activation, because of its additional adverse haemodynamic consequences [19].

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