Respiratory Modulation of Muscle Sympathetic Nerve Activity in Patients With Chronic Heart Failure

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Background—Sympathoexcitation and respiratory instability are closely related to worsening of chronic heart failure. To elucidate the dynamic nature of respiratory modulation of sympathetic activity in patients with heart failure, we studied within-breath variation of muscle sympathetic nerve activity (MSNA) under various ventilatory volumes.

Methods and Results—MSNA, blood pressure, and respiratory flow were recorded in 23 patients with left ventricular ejection fraction ≤45\%. Within-breath suppression of MSNA (neural silence) was found in 11 patients (MSNA bursts: 71±10/100 heartbeats) but not in the remaining 12 patients (MSNA bursts: 88±8/100 heartbeats). Patients without neural silence had a smaller tidal volume (391±70 versus 267±75 mL/m², P<0.01) and a higher respiratory rate (15±2 versus 19±4 breaths/min, P<0.01) during spontaneous respiration than those with neural silence. The relationship between tidal volume and minimal amplitude of MSNA bursts in each breath was obtained during random-interval breathing and fitted by an exponential function. The curve of patients without neural silence was shifted to the right and upward, which suggests that a greater tidal volume was required to suppress MSNA (227±70 versus 437±195 mL/m², P<0.01).

Conclusions—Sympathoexcitation in patients with chronic heart failure is closely related to both a decrease in resting tidal volume and an attenuated sympathoinhibitory effect of lung inflation reflex. (Circulation. 2001;104:418-423.)

Key Words: nervous system, sympathetic ■ norepinephrine ■ heart failure ■ lung

Chronic heart failure is characterized by enhanced sympathetic nerve activity and cardiorespiratory disarrangement. However, mechanisms for sympathoexcitation in this syndrome remain unclarified. Recent clinical studies demonstrated a high prevalence of respiratory instability, such as rapid and shallow respiration and periodic breath, which were closely related to sympathoexcitation in patients with heart failure. Experimentally, the brainstem respiratory oscillator is known to be coupled with the central sympathetic network in the modulation of sympathetic neural outflow. In normal subjects, Seals et al found that vagally mediated lung stretch reflex is the primary mechanism by which within-breath variation of muscle sympathetic nerve activity (MSNA) is augmented at high tidal volume (TV) ventilation. Recently, Naughton et al reported that rapid, shallow respiration was frequently accompanied by a higher degree of sympathetic activity in patients with heart failure. However, the dynamic nature of the relationship between ventilation and sympathetic nerve activity remains unclear on a breath-by-breath basis in patients with heart failure. It is also unknown whether sympathetic nerve activity in patients with shallow respiration could be fully suppressed when they breathe as deeply as patients with a normal respiratory pattern do.

To elucidate the respiratory modulation of sympathetic nerve activity in heart failure, we examined within-breath variation of MSNA in patients with chronic heart failure. For this purpose, we recorded instantaneous respiratory flow simultaneously with MSNA under the conditions of various respiratory patterns while patients were asked to breathe at random intervals. The use of random-interval respiration as a controlled broad-band input has a great advantage in that this method enables us to identify the dynamic and complete nature of the coupling between respiration and MSNA.

Methods

Study Populations
The present study included 23 patients with stable heart failure (18 men and 5 women) with left ventricular ejection fraction ≤45\% determined by radionuclide or contrast ventriculography. New York Heart Association functional class was I in 5, II in 14, and III in 4 patients. Each patient’s quality of life was quantified by a specific activity scale on questionnaires for ordinary physical activities. Thirteen patients had dilated cardiomyopathy, and 10 had previous myocardial infarction (Table 1). Patients with lung disorders, atrial fibrillation, unstable angina, left bundle-branch block, recent coronary angioplasty or revascularization, and previous treatment with β-blockers were excluded. Patients were allowed to continue all their medications other than β-blockers. All patients gave informed consent.

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TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sympathetic Neural Silence</th>
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<tr>
<td></td>
<td>Present (n=11)</td>
</tr>
<tr>
<td>Age, y</td>
<td>55±11</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>8/3</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>58±13</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>5</td>
</tr>
<tr>
<td>II</td>
<td>5</td>
</tr>
<tr>
<td>III</td>
<td>1</td>
</tr>
<tr>
<td>SAS, Mets</td>
<td>6.2±1.3</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
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<tr>
<td>DCM</td>
<td>6</td>
</tr>
<tr>
<td>Prior MI</td>
<td>5</td>
</tr>
<tr>
<td>CTR, %</td>
<td>51±5</td>
</tr>
<tr>
<td>LVEDD, mm/m²</td>
<td>36±3</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>38±9</td>
</tr>
<tr>
<td>MSNA</td>
<td></td>
</tr>
<tr>
<td>Bursts/min</td>
<td>48±9</td>
</tr>
<tr>
<td>Bursts/100 heartbeats</td>
<td>71±10</td>
</tr>
<tr>
<td>End-expiratory apnea,</td>
<td></td>
</tr>
<tr>
<td>bursts/15 heartbeats</td>
<td>15±1</td>
</tr>
<tr>
<td>PRA, ng · mL⁻¹ · h⁻¹</td>
<td>3.1±3.5</td>
</tr>
<tr>
<td>Aldosterone, ng/dL</td>
<td>8.2±3.5</td>
</tr>
<tr>
<td>NE, pg/mL</td>
<td>248±165</td>
</tr>
</tbody>
</table>

Values are mean±SD. NYHA indicates New York Heart Association; SAS, specific activity scale; DCM, dilated cardiomyopathy; MI, myocardial infarction; CTR, cardiothoracic ratio; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; PRA, plasma renin activity; and NE, plasma norepinephrine.

Measurements
All measurements were performed with subjects supine and in a resting state, as reported previously. Blood pressure was determined by noninvasive tonometry (Jentow 7700, Colin), which was capable of providing accurate analog pressure tracing. Respiratory flow was measured continuously on a breath-by-breath basis with the thermal dissipation technique (AE-280, Minato). Multunit recording of efferent postganglionic sympathetic nerve activity to the skeletal muscle district was obtained with a microelectrode inserted directly into the left peroneal nerve posterior to the fibular head. The nerve signal was amplified by 100 000, fed through a band-pass filter (500 to 5000 Hz), and integrated with a custom nerve-traffic analysis system (NeuropackΣ MEB-5504, Nihonkohden). Integrated nerve activity was recorded serially together with blood pressure, ECG, and respiratory flow on digital tape (RD-130TE, TEAC Corp) for later analysis.

To evaluate baseline cardiac function, we examined arterial blood gases, chest radiograph, and 2D echocardiogram in all patients, and cardiac catheterization was performed in 21 patients. Ventilatory activity and forced expiratory volume were measured in all patients, and functional residual volume was evaluated in 13 patients. In all patients, blood was drawn from the antecubital vein with the subject at rest for measurements of plasma renin activity and plasma concentrations of aldosterone and norepinephrine.

Respiratory Control
According to the method of Berger et al., patients were asked to initiate a breath with each tone of a series of auditory clues. The random sequence of tones (0.06 to 0.5 Hz, mean 0.25 Hz) was generated by a computer and recorded on cassette tape for playback during each experiment. Although respiratory intervals were controlled, patients were allowed to comfortably control the depth and shape of each breath throughout the examination. Consequently, long beep intervals resulted in a deep and long inflation of the lungs.

Study Protocol and Data Analysis
Baseline recordings of ECG, blood pressure, respiratory flow, and MSNA were performed while patients lay quietly without respiratory control, after which they held their breath for 15 seconds in the end-expiratory phase without producing a Valsalva effect on blood pressure. Figure 1A illustrates a distinct respiratory periodicity of MSNA accompanied by sympathetic neural silence. MSNA began to decrease from a minimum in early expiration and reached a maximum during the early- to mid-inspiratory phase. We defined the inspiration-related neural silence as the decline of neural activity below 15% of maximum amplitude during eupneic breath. Sympathetic neural silence was observed in 11 patients but not in the remaining 12 patients (Figure 1B). The same set of measurements was repeated under random-interval breathing for 8 minutes.

As reported previously, analog data of ECG, blood pressure, respiratory flow, and MSNA were played back from the digital tape and digitized at 1000 Hz per channel by an analog-to-digital converter (DT31-EZ, Data Translation Inc) and stored on a hard-disk memory system (Optiplex-GXMT, Dell Computer Corp). Systolic and diastolic pressures were identified from each beat of the arterial pressure signals. Instantaneous ventilatory volume was calculated from the integration of respiratory flow. TV was calculated from the peak of instantaneous ventilatory volume in each breath. The amplitude of MSNA was expressed as percentage of the maximum value of MSNA in each patient. Instantaneous ventilatory volume, MSNA, and diastolic blood pressure were splined and sampled at 4
Hz. Nerve conduction delay of the lung stretch reflex could result in changes in the timing of sympathetic suppression within the respiratory cycle when the breathing pattern changed. To determine the optimal timing to measure maximal neural suppression, we examined a cross-correlation function from instantaneous ventilation to MSNA during random-interval respiration and found the reflex latency caused by nerve conduction delay and central processing in each patient. The amplitude of MSNA bursts, which were advanced by the delay time, was plotted against the corresponding TV in each breath. The individual relationship between TV and MSNA was fitted to the monoexponential function (SigmaPlot 5.0, SPSS Inc) as follows:

\[ MSNA = 100 \times \exp(-TV/Tc) \]

where 100 represents the maximum amplitude of MSNA. The exponential parameter Tc defines the entire profile of the exponential function and corresponds to TV for 63.2% suppression of MSNA. These fittings yielded a good correlation coefficient \( r = 0.91 \pm 0.05 \).

Statistical Analysis
All data are expressed as mean±SD. Differences in variables between groups were examined with unpaired \( t \) tests and \( \chi^2 \) tests. The level of statistical significance was set at \( P<0.05 \).

Results
Baseline Hemodynamics
Clinical and hemodynamic features and respiratory function are shown in Tables 1, 2, and 3. The groups were comparable for age, body weight, and distribution of the origin of cardiac dysfunction. Similarly, there were no significant differences in resting left ventricular ejection fraction, heart rate, blood pressure, cardiac output, and pulmonary and systemic vascular resistance between the 2 groups. However, patients without neural silence had a larger left ventricular end-diastolic dimension and cardiorthoracic ratio than those with neural silence. Although there were no significant differences in vital capacity, forced expiratory volume, and functional residual volume, patients without neural silence showed a tendency to a decline in arterial carbon dioxide partial pressure (Table 3). Functional capacity (as assessed by New York Heart Association functional class and specific activity scale) was significantly reduced in patients without neural silence compared with those with neural silence.

<table>
<thead>
<tr>
<th>TABLE 2. Baseline Hemodynamics</th>
<th>Sympathetic Neural Silence</th>
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<tbody>
<tr>
<td></td>
<td>Present (n=10)</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>75±13</td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td>76±27</td>
</tr>
<tr>
<td>RAP, mm Hg</td>
<td>6±4</td>
</tr>
<tr>
<td>PAP, mm Hg</td>
<td>19±9</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>11±6</td>
</tr>
<tr>
<td>CI, L ( \cdot ) min(^{-1}) \cdot m(^{-2})</td>
<td>2.9±0.8</td>
</tr>
<tr>
<td>PVR, dyne ( \cdot ) s ( \cdot ) cm(^{-5})</td>
<td>166±121</td>
</tr>
<tr>
<td>SVR, dyne ( \cdot ) s ( \cdot ) cm(^{-5})</td>
<td>1600±663</td>
</tr>
</tbody>
</table>

Values are mean±SD. HR indicates heart rate; MBP, mean blood pressure; RAP, mean right atrial pressure; PAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; and SVR, systemic vascular resistance.

Within-Breath Variation of MSNA
Mean burst incidence of MSNA was 71±10 bursts/100 heartbeats in patients with sympathetic neural silence and 88±8 bursts/100 heartbeats in those without neural silence. Similarly, plasma norepinephrine level was significantly higher in patients without neural silence than in those with neural silence (Table 1). There were, however, no significant differences in plasma renin activity and plasma aldosterone concentration between the 2 groups. When the breath was held for \( \approx 15 \) seconds in the end-expiratory phase, MSNA bursts appeared almost every heartbeat, even in patients with neural silence (Figure 1A). Consequently, burst incidence of MSNA during end-expiratory apnea was almost comparable between the 2 groups (Table 1). Patients without neural silence showed a distinct suppression of MSNA by deep inspiration immediately after the respiratory pause (Figure 1B).

During spontaneous respiration, patients without neural silence displayed a significantly smaller TV and a higher respiratory rate than those with neural silence (Table 3). Consequently, TV and the burst incidence of MSNA during spontaneous respiration showed a significant inverse correlation (MSNA = \(-0.069 \cdot TV + 102, r = -0.53, P<0.01 \)). During random-interval respiration, MSNA was variably suppressed, depending on the depth of each breath (Figure 2A). The cross-correlation function from instantaneous ventilatory volume to MSNA revealed a negative peak with a lag time of 1.5±0.2 seconds but no positive peak at a lag time of 0 seconds (Figure 3). The individual TV-MSNA relationship curve determined after advancing MSNA by the latency of each patient differed substantially between the 2 groups (Figure 2B). The relationship clearly shifted to the right and upward in patients without neural silence, suggesting that a greater TV was required to suppress MSNA. The equation parameter of the exponential function, Tc, nearly doubled in patients without neural silence compared with patients with neural silence (Table 3). Breath-by-breath interaction of
instantaneous ventilatory volume, diastolic blood pressure, and MSNA during random-interval respiration was shown within a 3D framework (Figures 4 A and 4B), where MSNA was advanced by the latency time and all data were interpolated for this analysis. The amplitude of MSNA fell, along with an increase in ventilatory volume, independently of diastolic blood pressure. These figures show that greater lung inflation is required to fully suppress MSNA in patients without sympathetic neural silence compared with patients with neural silence. In both groups of patients, the effects of this lung stretch reflex were amplified as the diastolic pressure increased.

**Discussion**

The present results from patients with heart failure support the concept derived from data from normal subjects that MSNA is coupled with respiration on a breath-by-breath basis and is suppressed by lung inflation and blood pressure elevation. As shown by Naughton et al, a close inverse relationship was found in group data between TV and MSNA during spontaneous respiration, which suggests that reduced input to lung stretch receptors is one of the mechanisms responsible for augmentation of sympathetic nerve activity in patients without sympathetic neural silence. More importantly in the present study, random-interval respiration demonstrated that TV and MSNA during spontaneous respiration were positioned on the different TV-MSNA relationship curve of each patient. This relation curve was deviated rightward and upward in patients without neural silence, which suggests that these patients required greater lung inflation to suppress sympathetic nerve activity than did those with neural silence.

**Respiratory Influence on Sympathetic Nerve Activity**

Previous experimental studies showed that sympathetic nerve firings are synchronized with central inspiratory motor activity. At the same time, the increase in lung volume during inspiration activates pulmonary vagal afferents that reflexly inhibit sympathetic nerve discharge. Consequently, the relative magnitude of these 2 opposing mechanisms, which would depend on physiological state, determines the net...
Effect of Respiratory Modulation of Sympathetic Nerve Activity

In intact humans, however, Croix et al demonstrated that arterial baroreflex and lung stretch reflex are the dominant determinants of respiratory modulation of MSNA. Their findings were quite concordant with the present results from the cross-correlation analysis. MSNA was not in phase with ventilation but was suppressed by lung inflation, with a fixed delay time. This reflex delay time depends largely on nerve conduction velocity and central processing in the brain. The average delay of 1.5 seconds, determined by cross-correlation analysis, appears to accurately reflect nerve conduction delay when we consider the conduction velocity (<2.5 m/s) of nonmyelinated, slowly adapting lung C fibers, 0.3 seconds for central delay, and 1 second of the transmission delay from the brain to the leg sympathetic nerve. These data suggest that feedback mechanisms from peripheral receptors rather than central respiratory motor output would play a dominant role in the respiratory modulation of MSNA in patients with heart failure.

There are at least 4 different types of afferent stretch receptor fibers carried in the vagus: (1) slowly adapting myelinated afferents, which cause cardioacceleration at lower transpulmonary inflation pressure of <9 cm H2O (or 1/6 maximal lung expansion) and inhibit the level of inspiration (Hering-Breuer reflex); (2) rapidly adapting myelinated fibers, some of which are from irritant receptors; (3) unmyelinated, slowly adapting bronchial C fibers; and (4) unmyelinated, slowly adapting pulmonary C fibers. The latter 2 are known to elicit the cardiovascular suppression reflex at higher inflation pressures from 10 to 30 cm H2O. Cassidy et al demonstrated that the magnitude of the reflex is directly proportional to expansion of the lungs without hysteresis. Seals et al examined within-breath variation of sympathetic nerve activity in normal subjects and showed that an increase in TV from 30% to 50% of inspiratory capacity almost completely inhibited MSNA from late inspiration to mid-expiration. In the present study, the TV-MSNA relationship in each patient indicates that respiratory sympathoinhibition ability was attenuated in patients without sympathetic neural silence, as reflected by the rightward and upward shift of this relationship.

Attenuated Sympathoinhibitory Effect of Lung Stretch Reflex

The mechanisms for decreased ability to inhibit sympathetic nerve activity in heart failure remain unclear. Seals et al demonstrated that both deep and long inspiration contributed considerably to sympathetic suppression, the decline of total MSNA/min did not reach statistical significance provided respiratory rate remained unchanged. Random-interval respiration provided an opportunity to examine the effects of a wide range of blood pressures and lung inflations on MSNA and demonstrated that lung inflation suppressed MSNA more effectively as blood pressure was maintained at an elevated level. These findings suggest that arterial baroreflex and lung stretch reflex modulate MSNA independently but synergistically. However, under conditions in which central blood volume, a reservoir of left ventricular filling, is increased (as is the case in heart failure), blood pressure is little influenced by respiration and probably would affect sympathetic nerve activity.

Clinical Implications

As the heart fails, a progressive decrease in lung compliance requires a greater distending pressure for a given TV. The rapid and shallow respiration frequently observed in patients with heart failure is an adaptive mechanism that minimizes the work of respiratory muscles. However, this abnormal respiration could be viewed as a maladaptive change in terms of sympathetic neural control and effective alveolar ventilation in heart failure. Recently, application of continuous positive airway pressure (CPAP) for patients with heart failure and coexistent sleep apnea produced a significant improvement in cardiac function and heart rate variability and a significant fall in heart rate and plasma norepinephrine levels. Stimulation of pulmonary vagal afferents by CPAP-induced lung inflation is postulated as one of the mechanisms responsible for reflexively reduced cardiac sympathetic outflow. Furthermore, slow, deep respiration training has been shown to ameliorate symptoms of heart failure and to improve exercise performance in patients with heart failure. These observations indicate that training the patient to breathe deeply and slowly may have considerable clinical benefits toward restoring a normal sympathovagal balance in patients with heart failure.

Study Limitations

Within-breath modulation of MSNA could differ from overall MSNA/min because what was lost during inspiration might be gained during expiration. Although Seal et al demonstrated that both deep and long inspiration contributed considerably to sympathetic suppression, the decline of total MSNA/min did not reach statistical significance provided respiratory rate remained unchanged. Random-interval respiration allowed a parallel increase in TV and lung inflation periods with an increase in beep intervals. Therefore, the magnitude of sympathoinhibition by the depth and duration of lung inflation could not be quantified separately in the present study. From the findings of Seal et al and our findings, we assume that not only TV but also lung inflation periods with a slow respiratory rate would play an important role in the total suppression of MSNA. Second, MSNA could be modulated through arterial baroreflexes in response to respiratory variations of arterial pressure, because arterial baroreflex control of sympathetic nerve activity is preserved in heart failure. Random-interval respiration provided an opportunity to examine the effects of a wide range of blood pressures and lung inflations on MSNA and demonstrated that lung inflation suppressed MSNA more effectively as blood pressure was maintained at an elevated level. These findings suggest that arterial baroreflex and lung stretch reflex modulate MSNA independently but synergistically.
less than in normal subjects. Third, we cannot exclude the possibility that the cardiopulmonary baroreflex in response to cardiac filling pressure mediated the within-breath variation in MSNA. In contrast to the arterial baroreflex, the cardiopulmonary baroreflex is known to be attenuated in patients with heart failure and possibly has little, if any, influence on within-breath variation of MSNA.\textsuperscript{30}

**Conclusions**

Sympathoexcitation in heart failure is complex and multifactorial and could be ameliorated via multiple approaches. In patients with heart failure, an increased sympathetic nerve activity was closely related both to a decreased input to lung inflation reflex, ie, rapid and shallow respiration, and to an attenuated sympathoinhibitory effect of the lung stretch reflex, presumably due to counteraction of other sympathoexcitatory mechanisms. Additional study is warranted to elucidate whether respiratory training to teach patients to breathe slowly and deeply could ameliorate sympathoexcitation in patients with heart failure.

**Acknowledgments**

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