Influence of Lung Volume on Sympathetic Nerve Discharge in Normal Humans

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The purpose of this study was to determine the influence of tidal volume, breathing pattern, and beginning lung volume on the modulation of efferent, muscle sympathetic nerve activity (MSNA) in humans. In seven supine, healthy subjects, we measured MSNA (microneurography of the right peroneal nerve) and beat to beat arterial blood pressure during 1) low-frequency breathing \( (f_b=12 \text{ breaths/min}) \) at tidal volumes \( (V_T) \) of 30\% (control), 50\%, and 70\% of inspiratory capacity and with inspiratory time-to-total breath time ratios \( (T_i/T_{TOT}) \) of 0.3–0.5 (control), <0.3, and >0.5; and 2) simulated exercise hyperpnea \( (f_b=40 \text{ breaths/min}; V_T=60–70\% \text{ inspiratory capacity}; \text{minute ventilation} \approx 90 \text{ l}) \). To optimize our ability to discern modulatory effects, breathing was performed during three conditions of heightened MSNA: nonhypotensive \( (<20 \text{ mm Hg}) \) lower-body negative pressure, isometric handgrip exercise, and posthandgrip vascular occlusion (ischemia). \( \text{PETCO}_2 \) was maintained at normal levels by adjusting the \( F_{\text{CO}_2} \). Within-breath modulation of MSNA was observed during control tidal breathing with approximately 65\% of the burst frequency occurring during the expiratory phase. Deep, low-frequency breathing potentiated this modulatory influence \( (p<0.05 \text{ versus control}) \) and produced near-complete sympathoinhibition from onset-mid inspiration to early-mid expiration. Increasing (slow inspiration) and decreasing (fast inspiration) \( T_i/T_{TOT} \) shifted the onset of sympathoinhibition occurring later (greater change in volume) and earlier (less change in volume) during inspiration, respectively. In two subjects who performed deep breathing from an elevated beginning lung volume, the sympathoinhibition was observed earlier in the inspiratory period and with less change in volume compared with control. These within-breath modulatory effects did not appear to be due solely to changes in arterial pressure. Sustained low- or high- (“exerciselike”) -frequency deep breathing did not alter total minute MSNA compared with control breathing. These results demonstrate that the depth and pattern of breathing, and possibly the starting lung volume, exert marked influences on the within-breath modulation of MSNA in humans. Our findings also suggest that these modulatory effects may be mediated, at least in part, by pulmonary stretch reflexes. (Circulation Research 1990;67:130–141)

In anesthetized laboratory animals with intact vagi, inflation of the lungs causes reflex reductions in sympathetic nerve activity and vascular resistance in a number of tissues including skin, skeletal muscle, heart, kidney, and gut.\(^1\)–\(^6\) The afferent limb of the reflex is by way of the vagus nerve and, possibly, via sympathetic afferents.\(^3\)

During normal breathing in conscious, resting humans, Hagbarth and Valbo\(^7\) reported that efferent, postganglionic muscle sympathetic nerve activity (MSNA) could be observed throughout the breath cycle but that it occurred most frequently during expiration. Recently, Eckberg and colleagues\(^8\) reported that MSNA is highest at end-expiration and lowest at end-inspiration during quiet, normal breathing in humans. Taken together, these findings indicate that lung inflation exerts a modulatory influence on central sympathetic neural outflow under resting conditions. If so, lung inflation could have an even greater effect on sympathetic regulation during exercise and other acute stress states in which both ventilation and sympathetic outflow are augmented.

The purpose of the present study was threefold. First, we wished to extend previous findings in

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humans by determining the influence of tidal volume, breathing pattern, and beginning lung volume on the "within-breath" modulation of sympathetic neural discharge. Second, we wanted to determine whether sustained changes in breathing pattern and/or depth produced corresponding changes in total sympathetic outflow over the course of both inspiration and expiration. Finally, since some forms of physical stress (e.g., large-muscle exercise) result in marked increases in both breathing rate and depth, we sought to determine if sympathetic neural outflow was altered during "exerciselike" (i.e., hyperpneic) breathing.

To address these aims, we made intraneural (microneurographic) measurements of MSNA in conscious humans while systematically varying their breathing. To improve our ability both to discern the modulatory effects of breathing and to apply our findings to certain acute physiological states such as exercise, the studies were performed under three different conditions of experimentally heightened sympathetic nerve activity.

Subjects and Methods

Subjects

Seven subjects (six males and one female) aged 22–35 years participated in this study after providing their written, informed consent. All subjects were normotensive (arterial blood pressure less than 140/90 mm Hg) and were free of overt cardiopulmonary disease as assessed by medical history and by an electrocardiogram at rest. All experimental procedures and protocols were approved by the Institutional Committee for Research on Human Subjects.

Measurements

Recordings of efferent, postganglionic sympathetic nerve activity to nonactive skeletal muscle (MSNA) in the lower leg (peroneal or anterior tibialis muscle) were made using the microneurographic method as described in detail previously. A tungsten electrode was inserted percutaneously into a fascicle of the right peroneal nerve just posterior to the fibular head, and the position was adjusted until an adequate recording of multunit sympathetic traffic was obtained. A reference electrode was inserted near the fibular head approximately 1–3 cm from the recording electrode. Both electrodes were connected to a differential preamplifier and amplifier from which the signal could be routed through a band-pass filter (bandwidth, 700–2,000 Hz). The filtered signal was passed through a resistance-capacitance network (time constant, 0.1 seconds) from which a rectified and integrated mean voltage display was obtained and recorded (ES 1000, Gould Instruments, Cleveland). Only neurograms of efferent MSNA were accepted based on previously described criteria.

For each subject, the MSNA recording was examined for at least 10 minutes before starting the experimen-
Measurements were also made during normal breathing conditions (i.e., $f_b=12$ breaths/min, $V_T=30\%$ IC, normal FRC) immediately before (control) and immediately after (recovery) the period of hyperpnea.

End-tidal CO$_2$ was maintained within 3–5 mm Hg of control levels during all breathing maneuvers by adding CO$_2$ to the inspired air as needed.

**Background Conditions**

The breathing patterns described above were performed during the following background conditions of heightened MSNA: 1) a nonhypotensive level (<20 mm Hg) of lower body negative pressure (suction); 2) isometric handgrip exercise performed at 30% of maximal voluntary force with the right arm, and 3) posthandgrip ischemia (vascular occlusion) induced by inflation of a blood pressure cuff on the upper right arm to 250 mm Hg immediately before the cessation of handgrip exercise. Because an augmented, yet steady-state, level of MSNA could be maintained for a prolonged period of time during lower body suction without discomfort to the subject, all of the maneuvers described above were performed during this background condition. During postexercise ischemia, a heightened, steady-state level of MSNA could be maintained for only a few minutes before the discomfort became extreme. Because of this time constraint, subjects were not able to perform all combinations of the low-frequency (i.e., $f_b=12$ breaths/min) breathing maneuvers or the simulated exercise hyperpnea protocol during this background condition. The same was true for handgrip exercise per se, which could only be maintained for approximately 2–5 minutes. During this period, MSNA never attained a plateau. MSNA was unchanged from control during the initial phase of exercise and then increased in a progressive, time-dependent manner until the force could no longer be maintained at the required level as reported previously.$^{15}$ In general, baseline MSNA (i.e., during quiet rest) was low in this small group of healthy, young subjects. Therefore, a portion of the breathing maneuvers was performed in only four of the subjects during a resting background.

**Data Analysis**

Bursts of MSNA were determined by visual inspection of the mean voltage neurogram; all microneurographic recordings were analyzed by the same investigator (D.R.S.). Depending on the specific comparison, the frequency (bursts per minute), average amplitude (millimeters), and total activity (calculated as the product of bursts per minute and average burst amplitude per minute and presented in arbitrary units) for MSNA was determined as previously described.$^{5,15}$

Two types of analyses were performed. First, in four subjects a within-breath analysis was performed in which the point of occurrence of each sympathetic "burst" during each breath cycle was determined, and a frequency histogram of burst occurrence over all of the individual breaths throughout a particular breathing condition was generated. The point of occurrence for each burst was determined with respect to 1) the percentage of the total inspiratory or expiratory time elapsed from the beginning of inspiration or expiration, respectively, within the breath cycle; 2) the absolute level of tidal volume above baseline (end-expiratory) volume during inspiration or expiration (expressed as both liters of $V_T$ and as percent IC). These determinations were made on a "real time" basis and after the neurogram was corrected for the estimated nerve conduction delay. The latter correction was estimated from the subject's height as described by Fagius and Wallin.$^{16}$ Because of the limited amount of data and the generally low activity obtained during quiet rest, the within-breath analysis was not performed on the few recordings made during this background condition. Because MSNA is highly correlated with the diastolic, but not with the systolic, arterial blood pressure,$^{11,17}$ both the absolute level of diastolic pressure and the point in the breath cycle at which it occurred was determined for each pressure wave. Thus, the objective of this analysis was to provide insight into the within-breath modulation of MSNA and diastolic blood pressure.

To determine whether alterations in breathing influenced MSNA over a longer period of time (e.g., over a breath cycle or cycles), a between-condition analysis was performed on the data from all seven subjects. The total amount of MSNA was determined over all of the breaths within a specific breathing condition and expressed as minute activity. The same analysis was also performed for diastolic pressure. This analysis allowed comparisons of MSNA and blood pressure in one breathing condition versus another. Only those trials performed during lower body suction and postexercise ischemia were used for this analysis because these two interventions produced augmented, but steady state, levels of MSNA, whereas during handgrip exercise MSNA never attained steady-state levels.

Differences in MSNA or diastolic pressure in inspiration versus expiration within a specific breathing condition and differences between different breathing conditions were determined with an analysis of variance for repeated measures designs. Specific differences were assessed using Scheffe's test. Differences were considered to be significant at $p<0.05$. All values presented are mean±SEM.

**Results**

**Background Conditions**

Lower body suction (37.5±1.0 bursts/min), handgrip exercise (32.4±2.5), and postexercise ischemia (31.8±1.4) produced 89–123% increases in the minute frequency of MSNA compared with normal, resting conditions (16.8±1.4) ($p<0.05$) (Figure 1). Thus, each of our three stimuli resulted in a markedly enhanced baseline level of MSNA from which the
potential modulatory effects of breathing could be more optimally studied.

Within-Breath Analysis

During low-frequency, normal tidal breathing (VT=30% IC) in all three background conditions, on average MSNA burst frequency was 89% higher during expiration than during inspiration (24.5±2.6 versus 13.0±2.7 bursts/min, p<0.05), suggesting that a modulatory effect was present. However, distinct periods of sympathoinhibition were not consistently observed within the breath cycles at this level of tidal breathing (Figures 2–5).

In contrast, during each of the three heightened MSNA background conditions, deep, low-frequency tidal breathing (i.e., VT=50–70% IC, fs=12 breaths/min, normal Ti/TTOT) produced a distinct within-breath modulation of MSNA (Figures 2, 4, and 5). In general, an inhibition of MSNA was observed from mid-inspiration to mid-late expiration. After correcting for the estimated nerve conduction delays, the inhibition was shifted, occurring from onset-mid inspiration (i.e., ≤40% IC, ΔVT ≤1.2) to early-mid expiration (Figures 3–5).

This marked within-breath inhibition of MSNA was observed during tidal breathing at both the 50% and 70% IC levels. If the differences in burst frequency between the inspiratory and expiratory phases of each breath are used for comparison, the magnitude of the inhibitory effect on MSNA was quite similar for the two levels of deep breathing. Burst frequency was 202% higher during expiration versus inspiration during the 50% IC trials (29.3±4.5 versus 9.7±2.5 bursts/min, p<0.05) and 226% higher during expiration in the 70% IC trials (27.9±3.9 versus 8.5±1.4 bursts/min, p<0.05) (difference between 50% and 70% IC, NS). The fact that these expiratory-inspiratory differences for MSNA were significantly greater than the corresponding differences during control tidal breathing (p<0.05) suggests that the modulation of MSNA was much greater during deep breathing than during normal breathing.

During deep, low-frequency breathing, increasing the Ti/TTOT (thus reducing the mean inspiratory flow rate) delayed the onset of the inhibition of MSNA, occurring later during the inspiratory period and with a greater increase in lung volume (Figures 2, 3, and 5). Decreasing the Ti/TTOT had the opposite effect; the onset of the inhibition occurred earlier during inspiration and with less of an increase in lung volume (often no sympathetic activity could be seen even during early inspiration) (Figures 2 and 3). On average, during breathing at a normal Ti/TTOT, the onset of the inhibition occurred at a change in volume of 0.75–1.0 l, whereas the onset was observed at a change in volume of approximately 2.2 and 0.3 l during the increased and decreased Ti/TTOT conditions, respectively.

In two subjects, deep breathing from an elevated baseline level of lung inflation shifted the onset of the sympathoinhibition so that it occurred earlier during the inspiratory phase and with less of an increase in lung volume compared with the normal condition (i.e., similar to that seen in the decreased Ti/TTOT condition; Figure 6). In one of the subjects, the inhibition was shifted such that it occurred from the very onset of inspiration (Figure 6, subject 1).

In general, during the low-frequency breathing trials, diastolic blood pressure increased with inspiration and decreased during expiration (Figures 2, 4, and 5). The magnitude of the increase with inspiration was greater during deep breathing than during normal tidal breathing. However, during deep breathing the diastolic blood pressure at end-expiration tended to fall below the corresponding level during normal breathing. Thus, the average diastolic pressure throughout the entire breath was generally similar for normal and deep tidal breathing.
Between-Conditions Analysis

The values for MSNA (burst frequency, average amplitude, and total activity) and diastolic blood pressure were quite similar during the low-frequency breathing trials at 50% versus 70% IC; therefore, the data from these deep breathing trials were pooled and compared with that obtained during the control VT trials. The average tidal volume during the control VT T/TOT trials was 0.83±0.06 liters and during the increased VT trials averaged 2.32±0.14, 2.28±0.19, and 2.29±0.23 liters, respectively, for the control, increased, and decreased T/TOT conditions (all p<0.05 versus control VT value).

During enhanced, steady-state sympathetic baseline conditions (LBNP and postexercise ischemia) when the T/TOT was normal (f_b=12 breaths/min), the minute burst frequency of MSNA tended to be slightly lower (9–13%) during deep breathing versus control tidal breathing (p<0.05 for postexercise ischemia background only; Table 1). The burst frequency was also slightly, but significantly, lower (16–22%) during deep breathing with an increased T/TOT compared with control breathing (p<0.05, both backgrounds). MSNA burst frequency was similar during control tidal breathing versus deep breathing with a decreased T/TOT (NS). However, because the average amplitudes of the sympathetic bursts tended to be greater (6–16%) during deep breathing compared with control tidal breathing (p<0.05 only for the normal T/TOT conditions), the “total” minute MSNA was not different during increased VT versus control breathing in any of the T/TOT conditions. The average diastolic blood pressure was quite similar during control breathing and deep breathing under all T/TOT conditions (all NS, Table 1).

During high frequency, increased tidal volume breathing (i.e., simulated exercise hyperpnea, f_b=40 breaths/min, ΔVT=2.2±0.2 liters), on average the burst frequency and total activity of MSNA and the diastolic blood pressure were quite similar compared with the corresponding values measured during the preceding (control) and subsequent (recovery) normal breathing periods (f_b=12 breaths/min, VT=0.7±0.1 liters) (all NS, Table 2). The minute frequency of MSNA was 15–28% lower in three of the subjects and was 12–32% higher in the other two subjects during hyperpneic breathing.
compared with control. The total minute activity of MSNA was 11–19% lower in three of the subjects and was 31–35% higher in the other two subjects during hyperpneic versus control breathing.

Discussion
The present findings support the concept that there is within-breath modulation of sympathetic neural outflow during normal tidal breathing in humans. Our results obtained under conditions of experimentally heightened muscle sympathetic outflow extend this fundamental observation in several ways. First, our data indicate that this modulatory effect is markedly enhanced during deep, low-frequency breathing and that the breath pattern (duty cycle), the beginning lung volume (level of FRC), and the rate of change in lung volume all exert important influences. Second, in contrast to this striking within-breath modulation, we found that sustained changes in the depth and pattern of low-frequency breathing do not alter the total minute activity of sympathetic discharge to skeletal muscle.

Third, our findings suggest that total minute muscle sympathetic activity is not influenced by hyperpneic (exercise-like) breathing.

Within-Breath Modulation of MSNA During Low-Frequency Breathing

The results of the present study confirm previous observations of a within-breath modulation of MSNA during low-frequency, normal tidal breathing in humans.7,8 As in these earlier reports, we found that most of the sympathetic activity occurred during the expiratory phase of the breathing cycle. Our results are also consistent with previous reports of inhibition of preganglionic and postganglionic sympathetic nerve activity during experimentally induced lung inflations in anesthetized and/or decerebrate, vagally intact laboratory animals.2–6

Figure 3. Frequency histograms of muscle sympathetic nerve activity (MSNA) during the same four breathing conditions (lower body negative pressure background) for the subject presented in Figure 2. The number of breaths upon which each set of histograms is based is denoted by N. Each set shows the frequency of burst occurrence with respect to both the time during the breathing cycle (top panel) and the volume (bottom panel). The total number of bursts occurring during inspiration and expiration are shown in parentheses. MSNA units in the top panels represent the burst frequency corrected for the number of breaths in the samples. The neurograms have been corrected for estimated nerve conduction delays. Note the influence of changes in inspiratory rate on the onset of sympathoinhibition during deep breathing. T1, inspiratory time.
Our data indicate that the magnitude of this modulatory effect is greatly influenced by the depth of breathing. Specifically, after correcting for estimated nerve conduction delays, we found that an increase in VT from 30% (control) to 50% of IC produced an almost complete inhibition of MSNA from early-mid inspiration to early-mid expiration. Furthermore, the expiratory-inspiratory difference in the frequency of the sympathetic discharge was much greater during deep breathing compared with normal tidal breathing. In contrast, we did not observe any further increase in the modulatory effect of breathing on MSNA when VT was increased from 50% to 70% of IC. The within-breath sympathoinhibitory period occurred over a similar range at these two levels, and the expiratory-inspiratory difference in the frequency of sympathetic discharge was almost identical. These findings suggest that in humans the full sympathoinhibitory influence of lung inflation may occur at moderately deep levels of breathing.

In addition to the influence of the depth of breathing, our findings indicate that the pattern of breathing is also an important determinant of the within-breath modulation of MSNA (Figure 3). We found that at a particular depth of tidal breathing, slowing the rate of inspiration (i.e., increasing the T/I/TOT) delayed the onset of sympathoinhibition so that it occurred later during the inspiratory phase and with a greater change in lung volume compared with the normal T/I/TOT condition. Conversely, increasing the rate of inspiration (decreased T/I/TOT condition) shifted the onset of sympathoinhibition to an earlier point in the inspiratory phase, which was associated with less of an increase in lung volume. These observations suggest that the breathing-induced inhibition of MSNA in humans is influenced by the rate of lung inflation.

It appears that the baseline level of lung inflation may be another important factor in the modulation of sympathetic outflow during deep breathing (Figure 6). In both of our subjects who performed deep breathing from an elevated level of end-expiratory lung volume, the sympathoinhibitory period was shifted such that it occurred earlier during inspiration (even from the onset). Although these observations obviously need to be confirmed in a larger
FIGURE 5. Recording from one subject during postexercise ischemia. Left panel: Note the marked modulatory effect on muscle sympathetic nerve activity (MSNA) during the two deep breathing sequences (middle and bottom panels) that is not apparent during normal tidal breathing (top panel). Right panel: Frequency histograms of burst occurrence during normal and deep breathing for the same subject. Note the delayed onset (rightward shift) of sympathoinhibition during deep breathing with a prolonged inspiration compared with the normal inspiratory rate condition. See Figures 2 and 3 for further details.
FIGURE 6. Frequency histograms of burst occurrence during deep tidal breathing (lower body negative pressure background) from normal (top histogram for each subject) and elevated (bottom histogram for each subject) levels of end-expiratory lung volume in two subjects. Note that the period of sympahtoinhibition observed during the normal condition is shifted to the left, that is, occurs earlier during the inspiratory phase when the subjects breathed from an elevated level of end-expiratory lung volume. The total number of bursts occurring during inspiration and expiration are shown in parentheses. MSNA, muscle sympathetic nerve activity; \( f_b \), frequency of breathing; IC, inspiratory capacity; \( T_i \), inspiratory time; FRC, functional residual capacity.

TABLE 1. Effects of Changes in Tidal Volume and Inspiratory Time During Low-Frequency Breathing on Muscle Sympathetic Nerve Activity and Diastolic Blood Pressure (During Lower Body Negative Pressure and Postexercise Ischemia Backgrounds)

<table>
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<tr>
<th></th>
<th>Normal ( V_{ti} )</th>
<th>Normal ( T_i/T_{TOT} )</th>
<th>Normal ( V_{ti} )</th>
<th>Normal ( T_i/T_{TOT} )</th>
<th>Normal ( V_{ti} )</th>
<th>Normal ( T_i/T_{TOT} )</th>
<th>Normal ( V_{ti} )</th>
<th>Normal ( T_i/T_{TOT} )</th>
<th>Increased ( V_{ti} )</th>
<th>Normal ( T_i/T_{TOT} )</th>
<th>Increased ( V_{ti} )</th>
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<th>Increased ( V_{ti} )</th>
<th>Normal ( T_i/T_{TOT} )</th>
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<td><strong>Lower body negative pressure</strong></td>
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<td>Frequency (bursts/min)</td>
<td>35.6±1.4</td>
<td>32.4±1.4</td>
<td>34.8±1.3</td>
<td>29.2±1.4*</td>
<td>35.0±1.6</td>
<td>34.7±1.9</td>
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<td>Mean amplitude (units)</td>
<td>22.9±1.2</td>
<td>25.4±1.6*</td>
<td>22.7±1.4</td>
<td>24.7±1.5</td>
<td>22.2±1.5</td>
<td>24.4±1.5</td>
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<td>Total activity (total units)</td>
<td>826±67</td>
<td>821±62</td>
<td>801±74</td>
<td>734±68</td>
<td>781±78</td>
<td>863±84</td>
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<td>DBP (mm Hg)</td>
<td>76±2</td>
<td>76±2</td>
<td>76±2</td>
<td>78±2</td>
<td>76±2</td>
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<td>Frequency (bursts/min)</td>
<td>29.3±1.5</td>
<td>25.5±1.1*</td>
<td>34.0±3.0</td>
<td>26.5±1.7*</td>
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<tr>
<td>Mean amplitude (units)</td>
<td>14.6±0.8</td>
<td>16.9±0.9*</td>
<td>14.4±1.4</td>
<td>15.2±1.4</td>
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<tr>
<td>Total activity (total units)</td>
<td>419±24</td>
<td>421±19</td>
<td>469±27</td>
<td>394±32</td>
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<td>DBP (mm Hg)</td>
<td>89±1</td>
<td>89±2</td>
<td>88±3</td>
<td>90±4</td>
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Values are mean±SEM. \( V_{ti} \), tidal volume; \( T_i/T_{TOT} \), inspiratory time; MSNA, muscle sympathetic nerve activity; DBP, diastolic blood pressure; Normal (control): \( V_{ti}=0.8 \text{ l} \); \( T_i/T_{TOT}=0.3–0.5 \); Increased \( V_{ti}=2.3 \text{ l} \); Increased \( T_i/T_{TOT}>0.5 \); Decreased \( T_i/T_{TOT}<0.3 \); \( f_b=12 \text{ breaths/min for all conditions. Note that each increased } V_{ti} \text{ condition was preceded by control breathing. Total MSNA and DBP were not different in any of the increased } V_{ti} \text{ conditions versus control. } n=5 \text{ for lower body negative pressure, and } n=4 \text{ for postexercise ischemia.}^* \)

\(^*p<0.05\) vs. control value.
TABLE 2. Effects of High-Frequency Deep Breathing (i.e., Simulated Exercise Hyperpnea) on Muscle Sympathetic Nerve Activity and Diastolic Blood Pressure during Lower Body Negative Pressure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Hyperpnea</th>
<th>Recovery</th>
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<tbody>
<tr>
<td>Frequency (bursts/min)</td>
<td>40.7±2.3</td>
<td>37.8±3.8</td>
<td>39.8±2.1</td>
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<tr>
<td>Mean amplitude (units)</td>
<td>22.3±2.3</td>
<td>25.1±1.6</td>
<td>22.7±1.8</td>
</tr>
<tr>
<td>Total activity (total units)</td>
<td>920±140</td>
<td>945±100</td>
<td>915±118</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>83±5</td>
<td>85±5</td>
<td>81±5</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Control and Recovery: f=12 breaths/min, V̇t=0.7 L, minute ventilation=8.5 L; Hyperpnea: f=40 breaths/min, V̇t=2.2 L, minute ventilation=90 L. Total muscle sympathetic nerve activity (MSNA) and diastolic blood pressure (DBP) were not different during hyperpnea versus control or recovery. See Table 1 for other details.

*p<0.05 vs. control and recovery values.

diastolic blood pressure during each phase of breathing, MSNA was markedly higher during expiration than during inspiration. This was true for the individual subjects (Figure 7a) and on average in the entire group (Figure 7b). Eckberg and colleagues19 have recently reported similar findings in humans. Thus, the modulatory effects of breathing on MSNA can be dissociated from changes in arterial blood pressure (at least statistically). This suggests that arterial baroreflexes may not be solely responsible for our observations.

Another possibility is that the modulatory effect of breathing on MSNA is mediated by cardiopulmonary baroreceptors responding to changes in cardiac filling pressure and/or contractility.20 Sustained changes in central venous pressure induced by lower body suction or saline infusion are known to produce reciprocal changes in MSNA in humans in the absence of alterations in arterial pressure.21-23 Whether the rapid and less marked changes in cardiac filling pressure produced during breathing contribute to the oscillation of MSNA observed within a single breath cycle cannot be determined from the present results.

A third possibility is that the within-breath modulation of MSNA is governed by pulmonary stretch reflexes. In anesthetized or decerebrate laboratory animals, lung inflation causes reflex inhibition of preganglionic and postganglionic sympathetic nerve traffic and vasodilation in a number of vascular beds including nonactive skeletal muscle.1-6 These effects are independent of changes in arterial blood pressure and cardiac filling pressure and thus are not mediated by cardiovascular reflexes.4,5 While our findings are suggestive of a sympathoinhibitory effect of lung inflation, we also recognize the probability of species differences. For example, in contrast to observations in anesthetized animals,24 only a relatively weak effect of lung stretch on the timing of breathing pattern has been reported in conscious humans.25 Clearly, additional experimental approaches and models will be required in the human to distinguish among the many and complex inhibitory effects on MSNA associated with lung inflation.

Effects of Sustained, Low-Frequency Deep Breathing on MSNA

If deep, low-frequency breathing exerts a strong modulatory effect on MSNA within a single breath cycle, it is possible that sustained deep breathing could influence total MSNA over the entire breath cycle or several cycles. If so, this could result in alterations in steady-state skeletal muscle blood flow and vascular resistance. In the present study, we addressed this issue by examining the minute activity of MSNA during the various breathing conditions. We found that the minute frequency of MSNA during deep breathing with a normal and/or a prolonged inspiratory time was, in general, slightly, but significantly, lower compared with the respective control breathing conditions; no difference was observed during deep breathing with a shortened inspiratory time (Table 1). However, total minute MSNA was not different during deep versus normal breathing under any of the conditions studied. This was due to the fact that the average burst amplitude was slightly increased during the deep compared with the normal breathing trials.

How could the minute burst frequency (and, therefore, the minute total activity) of MSNA be so similar during normal and deep tidal breathing when there was such a marked increase in sympathoinhibition during inspiration with deep breathing? The answer appears to be that the decrease in activity during the inspiratory phase of deep compared with normal tidal breathing was reversed during expiration. That is, what was "lost" during inspiration was "gained" during expiration. For example, the average burst frequencies during inspiration were 13.0 and 9.1 bursts/min for normal and deep (average of 50% and 70% IC trials) tidal breathing, respectively, a difference of approximately 4 bursts/min (see "Results"). The corresponding values during expiration were 24.5 and 28.6 bursts/min—again, a difference of approximately 4 bursts/min. The data from the frequency histograms (Figures 3–5) indicate that the greater number of sympathetic bursts in the expiratory phase during deep breathing occurred primarily toward the end of expiration. Thus, in spite of the striking within-breath modulation of MSNA observed during deep, low-frequency breathing, our data indicate that sustained breathing of this type has no effect on the total minute MSNA and, therefore, would not be expected to produce sustained changes in skeletal muscle blood flow.

Simulated Exercise Hyperpnea

During even moderate, submaximal levels of large-muscle, rhythmic exercise, V̇t increases approximately fivefold and breathing frequency increases two to three times above levels at rest.20 Considering these increases in the frequency, rate, and depth of lung inflation, one might postulate that the hyperp-
neurontic to this type of exercise might exert a sympathoinhibitory influence that would counteract the excitatory autonomic effects of central command and muscle afferent reflexes. To test this hypothesis, we had our subjects simulate a submaximal exercise hyperpnea by increasing their breathing frequency and $V_T$ to exercise-like levels. As during the low-frequency breathing trials, end-tidal CO$_2$ was maintained at control levels by adding CO$_2$ to the inspirate. We found that the minute frequency and total minute MSNA were not changed from control levels during this sustained hyperpnea (Table 2). Therefore, our findings do not support the postulate that during exercise the overall MSNA response is diminished by the associated increases in ventilation. However, temporal (within-breath) changes in MSNA will be affected by the breathing pattern and tidal volume of the accompanying hyperpnea.

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**References**


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