Role of Sensory Input from the Lungs in Control of Muscle Sympathetic Nerve Activity

During and After Apnea in Humans

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Running head: lung inflation reflex and sympathetic activity

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Abstract

We reasoned that if the lung inflation reflex contributes importantly to apnea-induced sympathetic activation such activation would be attenuated in bilateral lung transplant recipients (LTX). We measured muscle sympathetic nerve activity (MSNA; intraneural electrodes), heart rate, mean arterial pressure, tidal volume, end-tidal CO₂, and arterial oxygen saturation in 7 LTX and 7 healthy control subjects (CON) before, during, and after 20-sec end-expiratory breath holds. Our evidence for denervation in LTX was: 1) greatly attenuated respiratory sinus arrhythmia and 2) absence of cough reflex below the level of the carina. During apnea, the temporal pattern and the peak increase in MSNA were virtually identical in LTX and CON (347±99 and 359±46% of baseline, p>0.05). In contrast, the amount of MSNA present in the first 5 sec after resumption of breathing was greater in LTX vs. CON (101±4 vs. 38±7% of baseline, p<0.05). There were no between-group differences in apnea-induced hypoxemia or hypercapnia, hemodynamic or ventilatory responses. Thus, cessation of the rhythmic sympathoinhibitory feedback that normally accompanies eupneic breathing does not contribute importantly to sympathetic excitation during apnea. In contrast, vagal afferent input elicited by hyperventilation-induced lung stretch plays an important role in the profound, rapid sympathetic inhibition that occurs following resumption of breathing after apnea.

Key words: pulmonary stretch receptors, lung transplantation, chemoreflex, baroreflex
Introduction

The mechanisms responsible for the sympathetic nervous system activation caused by apnea remain a matter of debate. There is substantial evidence that hypoxia- and hypercapnia-induced chemoreflex stimulation play an important role in the sympathetic excitation that begins shortly after the onset of the apnea (8; 15). In addition, some authors propose a role for a pause in the sympathoinhibitory influence of lung inflation in causing increased sympathetic nerve traffic during apnea (14-16).

It is unclear, however, how absence of lung stretch could be an important contributor to the marked, progressive increase in sympathetic outflow that continues for the duration of the apnea. Lung inflation, which profoundly inhibits sympathetic outflow within a breath, has very little long-term influence on sympathetic activity (12; 17). Therefore, a cessation of tidal lung inflation would not be expected to contribute to the sustained sympathetic activation caused by apnea. In addition, vagally mediated respiratory reflexes such as the Hering-Breuer reflex are weak in humans relative to other species and they exert their inhibitory influence only at large tidal volumes (7; 12).

We tested the hypothesis that removal of the rhythmic pulmonary afferent input that accompanies eupneic breathing is an important determinant of apnea-induced sympathetic activation by comparing the muscle sympathetic nerve activity (MSNA) responses to breath holds in bilateral lung transplant recipients (LTX) and healthy control subjects (CON). We reasoned that if lung stretch contributes importantly to apnea-induced sympathetic activation, such
sympathetic activation would be attenuated in patients who have undergone bilateral lung transplantation, an operation that severs the afferent neural connections between the lung and the central nervous system.

**Methods**

*Subjects.* Seven bilateral lung transplant recipients, three women and four men, participated in this study. Their mean age was $39\pm4$ years, and their mean post-transplantation time was $25\pm10$ (SD) months. The mean body mass index was $25\pm3$ kg/m$^2$. Inclusion criteria included absence of heart failure or dialysis-dependent renal failure, and the absence of cough reflex below the carina on bronchoscopy. Transplant subject characteristics are detailed in Table 1. In 3 LTX with insulin-dependent diabetes mellitus, we assessed foot sensation using Semmes-Weinstein monofilaments (11) and measured orthostatic heart rate and blood pressure responses to exclude the presence of sensory or autonomic neuropathy.

Seven healthy individuals served as control subjects. The control volunteers were 3 women and 4 men, aged $30\pm6$ years, with a mean body mass index of $24\pm2$ kg/m$^2$. All subjects were normotensive and free from cardiovascular, pulmonary, and neurological disease as evaluated by history and physical examination. All subjects provided informed consent, and the experimental protocol was approved by the University of Wisconsin Health Sciences Human Subjects Committee.
General procedures. All studies were carried out with the subjects awake, in the supine position. All physiologic variables were recorded continuously on paper (model TA 4000; Gould, Cleveland, OH) and on videotape (Vetter, Rebersburg, PA). The signals were also routed to a computer for off-line analysis of the data.

Respiratory variables. Subjects breathed through a leak-free nasal mask to which a pneumotachograph (model 5719; Hans Rudolph, Kansas City, MO) was attached for measurement of tidal volume (V₁) and breathing frequency. Minute ventilation was calculated by multiplying V₁ by breathing frequency. End-tidal CO₂ tension (PETO₂) was sampled from the mask and measured by a gas analyzer (model CD3; Ametek, Pittsburgh, PA). Arterial O₂ saturation (Sao2) was measured with a pulse oximeter (Biox model 3740; Ohmeda, Madison, WI).

Cardiovascular variables. Heart rate was taken from the electrocardiogram. Arterial pressure was measured at 1-min intervals with an automated arm-cuff sphygmomanometer (Dinamap; Critikon, Tampa, FL) and also beat-by-beat using finger pulse photoplethysmography (Finapres, Ohmeda, Englewood, CO). The finger bearing the photoplethysmograph cuff was positioned at heart level and kept at the same level for the duration of the study.

Sympathetic nerve activity. Postganglionic MSNA in the right peroneal nerve was recorded directly using the microneurography technique (20). The neural signals were passed to a differential preamplifier, an amplifier (total gain=100,000), a band-pass filter (700-2,000 Hz), and an integrator (time constant=100 ms). Placement of the recording electrode within a muscle nerve fascicle was confirmed by 1) the presence of muscle twitches, but not
paresthesias, in response to electrical stimulation; 2) the pulse synchronous nature of the nerve activity; 3) the appearance of afferent activity in response to tapping or stretching of muscle, but not gentle stroking of skin, in the appropriate receptive fields; and 4) the absence of neural activation in response to a startle stimulus. Once an acceptable neural recording (pulse synchronous activity with signal-to-noise ratio >3:1) was obtained, the subject was instructed to maintain the leg in a relaxed position for the duration of the study. Sympathetic bursts were identified by computer-assisted inspection of the mean voltage neurogram. For purposes of quantification, MSNA was expressed as burst frequency (bursts/min), burst amplitude (arbitrary units) and total minute activity (burst frequency x mean burst amplitude). MSNA during the apnea and recovery periods was expressed as a percentage of the baseline level.

Experimental Protocols

Baseline recording of cardiovascular and respiratory variables and MSNA was conducted for 5 minutes. Baseline $V_T$, respiratory frequency, and $P_{ET}CO_2$ were calculated for use in measurement of respiratory sinus arrhythmia (RSA; see below).

20-Second Breath Holds. All subjects (LTX and CON) performed at least 6 breath hold maneuvers. The breath holds were 20 sec in duration and started after a tidal expiration at functional residual capacity. At the end of the 20-sec breath holds, the subjects were signaled to resume spontaneous breathing. To further assess the role of lung stretch-evoked pulmonary afferent input in post-apnea regulation of MSNA, CON performed an additional set of 6 breath holds.
after which they resumed breathing at their pre-apnea VT and frequency, thereby eliminating the enhanced lung stretch that typically occurs during this period. During this controlled-mode recovery period, the subjects were provided visual and auditory feedback so that they could maintain their pre-apnea levels of ventilation. All breath hold maneuvers were separated by at least 1 min of recovery during which PETCO2 was verified to have returned to its baseline value.

*Determination of Respiratory Sinus Arrhythmia.* RSA was evaluated in all subjects during 5-min periods of breathing at 3 levels of VT: the baseline eupneic VT, twice the eupneic level, and three-to-four times the eupneic level. The respiratory frequency was kept at baseline levels in all three maneuvers. Subjects used visual and auditory feedback to control VT and frequency. PETCO2 was maintained at baseline levels during all trials by supplementation of the inspired CO2. Within each breath, the heart rate at the beginning of inspiration was subtracted from the highest heart rate during inspiration. For each subject, the inspiratory peaks in heart rate were determined by averaging all breaths during the 5-min trials at each VT.

*Data Analysis*

For each breath hold trial, 5-sec averages were computed for mean arterial pressure (MAP; 1/3 pulse pressure + diastolic pressure), MSNA (bursts/min × mean burst amplitude), heart rate, and VT during 1 min of pre-apnea baseline, 20 sec of the apnea, and 1 min of post-apnea recovery. Average values for the 6-10 breath hold trials performed by each subject were used in computation of group mean values. Differences in MSNA, MAP, heart rate, and VT before, during, and
After the breath holds were compared by 2-way (group by time) repeated-measures analyses of variance with Newman-Keuls post hoc tests. Changes in arterial $O_2$ saturation and $P_{ET}CO_2$ were compared by unpaired t-test. $P<0.05$ was considered statistically significant. Unless otherwise noted, values presented are means±SEM.

**Results**

The absence of vagal innervation of the lung in LTX was verified using two methods: 1) the absence of cough reflex below the level of the carina, as verified by the transplant pulmonologist, and 2) the absence of RSA.

**Respiratory Sinus Arrhythmia**

In CON, we observed a significant increase in heart rate during inspiration, which was proportional to $V_T$ (Figure 1). In contrast, there was no significant change in heart rate during inspiration in any of the 3 levels of $V_T$ in LTX, confirming the absence of RSA. Tidal volumes during the RSA determination, expressed as absolute values, were the same in LTX and CON ($p>0.05$); however, the percentages of inspiratory capacity were larger in LTX vs. CON during baseline eupneic breathing and twice the baseline $V_T$ ($p<0.05$; Table 2).

**Apnea-Induced Sympathetic Activation**

*MSNA responses during apnea.* MSNA increased progressively during breath holds in both groups of subjects and reached a maximum in the last 5 sec of the 20-sec apnea (Figure 2). The peak values were $347±99\%$ of baseline in LTX group and $359±46\%$ of baseline in CON. There were no between-group
differences in the amount of sympathetic activation at any 5-sec interval during the 20-sec breath hold (p>0.05).

**MSNA during the post-apnea recovery period.** In both groups of subjects, MSNA fell abruptly after resumption of breathing (Figures 2 and 3). In CON, MSNA fell below baseline during the first two 5-sec intervals of the post-apnea recovery period (38±7 and 43±17%; p<0.05 vs. baseline). In contrast, in LTX, MSNA was not different from baseline at any time during the post-apnea recovery period (p>0.05). MSNA was lower in CON vs. LTX throughout the entire 20-sec recovery period (Figure 3).

**Effect of post-apnea hyperventilation on MSNA in control subjects.** CON performed a second set of breath holds in which they returned to pre-apnea VT and frequency upon termination of apnea in order to limit the amount of lung stretch. MSNA decreased in the first 5-sec of post-apnea recovery in the controlled ventilation condition; however, it was not suppressed below baseline like it was in the first 5 sec post-apnea in the hyperventilation condition (101± 4 vs. 38±7%, p<0.05). For the rest of the recovery period, the pattern of MSNA suppression was similar between the two conditions, and MSNA remained below baseline (Figure 3).

**Heart Rate and Blood Pressure Perturbations Caused by Apnea**

The blood pressure response pattern was similar in CON and LTX (Figure 4, upper panel). During apnea, MAP increased progressively, reaching a maximum in the first 5 sec of the recovery period. MAP remained elevated
above baseline throughout the first 10 sec of the recovery period in both groups. There was no inter-group difference in the apnea-induced rise in MAP (+10±2 and +7±4 mmHg, p>0.05).

Heart rate did not change in either group during the apnea; however, in both groups heart rate rose significantly in the recovery period (Figure 4, lower panel). Although heart rates were significantly higher in the LTX vs. CON at all times during the apnea and the recovery period, the peak apnea-induced increase in heart rate was the same in the 2 groups (+6±1 and +6±2 beats/min, p>0.05).

**Respiratory Responses Caused by Apnea**

The $V_t$ of the first post-apneic breath was the same in LTX and CON when expressed in absolute terms (1.49±0.25 and 1.62±0.25 liters) and also when expressed as a percent of inspiratory capacity (52±3 and 48±8%) (both p>0.05).

Baseline $SaO_2$ was the same in LTX and CON (96.4±0.3 and 97.0± 0.3%). Likewise, the nadir in saturation following the apnea was the same in the two groups (93.6 ± 0.6% and 94.0 ± 0.7%) (both p>0.05).

$P_{ET}CO_2$ was lower at baseline in LTX vs. CON (35±2 vs. 41±1 mmHg, p<0.05). The average $P_{ET}CO_2$ for the first 10 sec of recovery, expressed as a percentage of the baseline value, was the same in the two groups (94±2 and 93±3%, p>0.05).
Discussion

In this study we found that sympathetic activation during apnea was similar in pattern and in amplitude in lung-denervated and neurally intact humans. We conclude that withdrawal of the sympathoinhibitory influence of eupneic lung inflation does not contribute significantly to sympathetic activation during apnea. In contrast, the profound, rapid decrease in MSNA that coincides with resumption of breathing was attenuated in lung-denervated subjects. Thus, pulmonary vagal afferent input, activated by post-apnea hyperventilation, does contribute to the prompt suppression of MSNA below baseline immediately post-apnea. The following discussion outlines the assumptions and evidence that underlie these conclusions.

Sympathetic Activation during Apnea

Release from the sympathoinhibitory effect of lung inflation is frequently cited as a potential contributor to the increase in sympathetic outflow caused by apnea (14-16). We reasoned that if afferent input from pulmonary stretch receptors were an important cause of sympathetic activation during apnea, such sympathetic activation would be diminished in recipients of bilateral lung transplantation, an operation that severs the pulmonary branches of the vagus nerves. Because we saw no difference in the amount or pattern of sympathetic activation during apnea in the lung transplant recipients and control subjects, we conclude that apnea-induced sympathetic activation is not dependent on intact pulmonary vagal innervation.
This conclusion is predicated on the assumption that the lungs of LTX we studied were, in fact, vagally denervated. We previously documented the absence of the Breuer-Hering reflex in LTX who ranged from 20-49 months post-transplantation (7). In contrast, other investigators reported restoration of the noxious sensations produced by intravenous injection of lobeline (a pulmonary C fiber stimulant) one year after bilateral lung transplantation (2). Even though the majority of our subjects were studied more than one year after lung transplantation, we consider it unlikely that reinnervation can explain our findings. First, mechanical probing of the mainstem bronchi at the time of bronchoscopy failed to elicit a cough in any subject. Second, respiratory sinus arrhythmia was greatly attenuated in our LTX (Figure 1). In fact, the amount of within-breath fluctuation in heart rate that remained was not \( V_T \)-dependent and was not much greater in magnitude than that seen after heart transplantation, an operation that results in denervation of the sinus node (19). Although it is possible that the cardiac branches of the vagus nerves could be mechanically stressed during lung transplantation, they should not be severed or permanently damaged. Previously, we demonstrated normal cardiac innervation in LTX by showing an immediate 9-28\% increase in heart rate in response to atropine infusion (19). We believe that LTX in the present study had intact cardiac vagi because they all demonstrated normal heart responses to apnea.

Finally, 3 out of 7 of LTX in our study had insulin-dependent diabetes, a condition associated with autonomic neuropathy (5). We were concerned that diabetes-associated damage to sympathetic vasoconstrictor fibers could have
decreased baseline MSNA or attenuated the increase in MSNA evoked by apnea in these subjects. In addition, diabetic neuropathy could have impaired parasympathetic control of sinoatrial node function, making it impossible to assess RSA. We consider it unlikely that diabetic neuropathy influenced our findings for the following reasons. First, the baroreflex-activated increase in heart rate that occurs with standing, which is mediated by withdrawal of cardiac parasympathetic outflow, was normal in these subjects (1; 6). Second, the blood pressure response to standing was intact, indicating normal sympathetic activation in the muscle, skin, and splanchnic circulations (1, 5). Finally, the magnitude of the inspiratory peak in heart rate (1.6±0.6 and 2.2±0.8 beats/min at the highest VT) and the increase in MSNA during apnea (464±215 and 260±73% of baseline) were not reduced in LTX with diabetes vs. those without diabetes.

Our finding that lung transplantation did not affect sympathetic activation during apnea is perhaps predictable, based on several previous reports. First, intact pulmonary vagal afferents are not required for within-breath modulation of MSNA at eupneic levels of breathing in humans (13). Second, while respiration affects the within-breath timing of MSNA (4; 12), it does not influence the steady-state quantity of sympathetic traffic (12). We previously found that increases in VT and in respiratory motor output were without effect on sympathetic minute activity (12; 17). Other investigators have shown that interruption of the pulmonary branches of the vagi in conscious rabbits did not alter the steady-state level of renal sympathetic nerve activation produced by exposure to hypoxia (10).
Many investigators have demonstrated within-breath modulation of MSNA during eupneic breathing in humans—i.e. inspiration, even at eupneic VT, causes sympathetic inhibition (4; 12; 17). Thus, we speculate that removal of this inhibition during apnea in our subjects must have had an excitatory effect on MSNA, during the first absent breath, at least. However, this excitation, if present, must have been too small to be distinguished from the accumulating chemoreflex stimulation and was clearly not dependent on vagal feedback from the lungs.

If no role can be demonstrated for absence of lung inflation, what mechanism is responsible for the increase in sympathetic activity during apnea? We (8) and others (15; 16) have demonstrated that chemoreflex stimulation is the primary mechanism of sympathetic activation caused by apnea. In the present study, there were no between-group differences in chemical stimuli produced by 20-sec apnea: the nadir SaO2 and the amount of desaturation caused by apnea were the same in LTX and CON. Although our methods did not allow measurement of apnea-induced PCO2 build-up, the fact that post-apnea hyperventilation was of the same magnitude in the two groups suggests that the chemical stimuli were, in fact, equivalent.

*Sympathetic Inhibition after Resumption of Breathing*

In contrast to the virtually identical patterns of sympathetic activation during apnea in denervated and intact subjects, we found that sympathetic inhibition in the immediate post-apnea hyperventilation period was attenuated in LTX vs. CON. During this brief hyperventilatory phase, VT increased and PETCO2
fell to the same extent in the two groups; however, post-apnea sympathoinhibition was delayed and reduced in magnitude in LTX.

In both groups, MSNA fell precipitously in the first 5 sec after apnea termination, probably as the result of immediate shut-off of carotid sinus nerve activity by rapid normalization of blood gases (9). The normalization of SaO₂ after the resumption of breathing followed the same time course in LTX and CON, suggesting that chemical stimuli in the recovery period were equivalent. Post-apnea MAP responses were comparable in the two groups. Despite these similarities, MSNA was significantly lower in CON vs. LTX at all times during recovery period. MSNA was significantly lower than baseline in the first 10 sec following apnea in CON but not LTX. These findings suggest that the profound, immediate suppression of MSNA below baseline that occurred after resumption of breathing was dependent on an intact pulmonary stretch reflex.

This prompt inhibition of MSNA observed within the first post-apnea breath in CON, which has been reported by previous investigators (21), was not evident in LTX or in neurally intact subjects when they volitionally suppressed post-apnea hyperventilation. This immediate inhibition cannot be explained by chemo- and baroreflex mechanisms because the nadir of MSNA occurred prior to normalization of blood gases and it preceded the maximal rise in blood pressure. Taken together, these findings indicate that the immediate post-apnea suppression of MSNA below the baseline level is critically dependent on vagal feedback from the lungs.
We also observed a less abrupt, less pronounced post-apnea inhibition of MSNA that was evident even in the absence of pulmonary afferent innervation and in the absence of hyperventilation. This delayed sympathoinhibition had a time course consistent with resolution of chemoreflex activation following the normalization of blood gases and baroreflex activation caused by the apnea-induced blood pressure rise. Following 20-sec apneas in anesthetized cats, marked inhibition of renal sympathetic nerve activity accompanies a precipitous decline in carotid sinus nerve activity between the first and second post-apnea breaths (9). In LTX and in CON who suppressed post-apnea hyperventilation, the nadir of this delayed decrease in MSNA followed the peak in blood pressure by approximately 5 sec, a time course that is consistent with baroreflex activation (18). Thus, we propose that the slower-onset, less pronounced post-apnea MSNA inhibition is attributable to chemoreflex and baroreflex mechanisms.

**Summary and Conclusions**

In this study, we describe a 2-phase MSNA response to apnea: 1) a marked, progressive increase during the breath hold; 2) a profound inhibition of MSNA to below baseline that occurs immediately after resumption of breathing and gradually resolves during the next 15-20 sec. Our data demonstrate that intact sensory innervation of the lungs is not required for the sympathetic excitation during apnea. In contrast, vagal afferent input evoked by lung stretch plays a significant role in the profound sympathetic inhibition that immediately follows resumption of breathing.
Acknowledgments

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References


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Figure Legends

Figure 1. Respiratory sinus arrhythmia was determined in the lung transplant (LTX) (open circles) and control (CON) subjects (filled circles) while they breathed at 1, 2, and 3-4 times their baseline tidal volumes. Heart rate increased during inspiration in both groups; however, this increase was smaller in LTX vs. CON at all tidal volumes (see Table 2). In CON, higher volumes were associated with greater inspiratory increases in heart rate, whereas this relationship was not observed in LTX.

*P<0.05, heart rate x tidal volume interaction
† P<0.05, LTX vs. CON at a given tidal volume

Figure 2. Five-sec averages of muscle sympathetic nerve activity (MSNA) in response to breath holds in lung transplant recipients (LTX) and control subjects (CON). During the breath hold (indicated by vertical dashed lines), there was no between-group difference in the pattern or degree of MSNA increase. Immediately after release of the breath hold, MSNA fell abruptly in both groups. MSNA was suppressed below baseline during the first 20 sec of recovery in CON. In LTX, MSNA was not different from baseline at any time during the recovery period.

* P<0.05 vs. baseline
† P<0.05, LTX vs. CON
Figure 3. Muscle sympathetic nerve activity (MSNA), mean arterial pressure (MAP) and tidal volume in control subjects (CON) with spontaneous (filled circles) and controlled (open triangles) breathing in the post-apnea recovery period. Data from lung transplant recipients (LTX; open circles) are shown for reference. In the first 5-sec interval of controlled recovery, MSNA decreased, but was not suppressed below the baseline level (105±32%) as it was in the spontaneous recovery condition (38±7%). At 10 sec after apnea termination, MSNA was suppressed below baseline to the same extent in both conditions. For the remainder of the 20-sec recovery period, MSNA was not significantly different from baseline in either condition and was comparable in the 2 conditions.

* P<0.05 vs. baseline
‡P<0.05, spontaneous vs. controlled recovery in CON

Figure 4. Mean arterial pressure and heart rate responses to breath hold in denervated (LTX; open circles) and control (CON; filled circles) groups. Baseline blood pressures and heart rates were higher in LTX vs. CON; however, there were no differences in the pattern or amplitude of blood pressure or heart rate responses during or after the breath hold.

* P<0.05 vs. baseline
† P<0.05, LTX vs. CON
Table 1. Characteristics of lung transplant recipients. All subjects received immunosuppressive regimens of cyclosporine (n=5) or tacrolimus (n=2), mycophenolate, and prednisone.

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<th>Reason for Transplant</th>
<th>Time post Transplant (months)</th>
<th>Diabetes? (Y/N)</th>
<th>FEV₁/FVC (%)</th>
<th>FVC (% predicted)</th>
<th>Creatinine (mg/dl)</th>
<th>BMI (kg/m²)</th>
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Table 2. Inspiratory capacities and tidal volumes during respiratory sinus arrhythmia determinations in control subjects (CON) and lung transplant recipients (LTX). IC, inspiratory capacity; $V_T$, tidal volume

*p<0.05, LTX vs. CON

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Inspiratory Increase in Heart Rate

![Graph showing heart rate changes across different tidal volumes for CON and LTX groups.](image-url)

Figure 1
Figure 2

- Tidal Volume (liters)
- MSNA (% baseline)

CON (n=7) vs. LTX (n=7)
Figure 4