Carotid baroreflex function during and following voluntary apnea in humans


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Muenter Swift, N., M. J. Cutler, P. J. Fadel, W. L. Wasmund, S. Ogoh, D. M. Keller, P. B. Raven, and M. L. Smith. Carotid baroreflex function during and after voluntary apnea in humans. Am J Physiol Heart Circ Physiol 285: H2411–H2419, 2003. First published July 31, 2003; 10.1152/ajpheart.00139.2003.—Muscle sympathetic nerve activity (MSNA) and arterial pressure increase concomitantly during apnea, suggesting a possible overriding of arterial baroreflex inhibitory input to sympathoregulatory centers by apnea-induced excitatory mechanisms. Apnea termination is accompanied by strong sympathoinhibition while arterial pressure remains elevated. Therefore, we hypothesized that the sensitivity of carotid baroreflex control of MSNA would decrease during apnea and return upon apnea termination. MSNA and heart rate responses to −60-Torr neck suction (NS) were evaluated during baseline and throughout apnea. Responses to +30-Torr neck pressure (NP) were evaluated during baseline and throughout 1 min postapnea. MSNA and heart rate responses to −60-Torr neck suction (NS) were evaluated during baseline and throughout apnea. Responses to +30-Torr neck pressure (NP) were evaluated during baseline and throughout 1 min postapnea. Apnea did not affect the sympathoinhibitory or bradycardic response to NS (P > 0.05); however, whereas the cardiac response to NP was maintained postapnea, the sympathoexcitatory response was reduced for 50 s (P < 0.05). These data demonstrate that the sensitivity of carotid baroreflex control of MSNA would be attenuated during apnea. We propose a transient rightward and upward resetting of the carotid baroreflex-MSNA function curve during apnea and that return of the function curve to, or more likely beyond, baseline (i.e., a downward and leftward shift) upon apnea termination may importantly contribute to the reduced sympathoexcitatory response to NP.

SYMPATHETIC NERVE ACTIVITY; NECK SUCTION; NECK壓URE

MUSCLE SYMPATHETIC NERVE ACTIVITY ( MSNA ) increases progressively during apnea, and apnea termination is associated with an immediate and profound sympathoinhibition (13, 14, 18, 21, 24, 32, 33, 45). The mechanism(s) of the postapneic sympathoinhibition is unclear; potential contributors include the normalization of blood gases, activation of the lung inflation reflex, and baroreflex activation.

The importance of chemoreflex activation to the apnea-induced sympathoexcitation has been well demonstrated (13, 18, 21, 32). It follows that the postapneic sympathoinhibition is therefore due, in part, to blood gas normalization; however, our laboratory (22) has recently demonstrated that chemoreflex unloading is not important to the postapneic sympathoinhibition.

The apnea-induced sympathoexcitation leads to a significant increase in arterial pressure (13, 14, 17, 18, 21, 27, 33, 41, 45), which typically peaks postapnea due to the latency of MSNA translating into increased vascular resistance and blood pressure (43). The rise in arterial pressure during apnea would be expected to inhibit MSNA via the arterial baroreflexes, yet MSNA greatly increases throughout apnea. Thus the sympathoinhibitory input from the arterial baroreflexes appears to be overridden during apnea by sympathoexcitatory mechanisms such as the chemoreflex and lack of stimulation to the pulmonary stretch afferents. However, upon apnea termination, MSNA is strongly inhibited (13, 14, 18, 33, 45), even when the chemoreflex stimuli are maintained (22). These findings suggest that the role arterial baroreceptors play in the dynamics of MSNA control may differ profoundly between the conditions of apnea and apnea termination. The balance of inputs to the sympathoregulatory centers of the medulla may be altered upon apnea termination, such that sympathoinhibitory input from the arterial baroreceptors predominates.

Therefore, the purpose of the present study was to determine whether carotid baroreflex (CBR) function changes with apnea and apnea termination. Application of 5-s pulses of −60-Torr neck suction (NS) was performed during baseline and at the beginning, middle, and end of end-expiratory apnea to determine whether the sympathoinhibitory response of the CBR diminished with apnea. Application of 5-s pulses of +30-Torr neck pressure (NP) was performed during baseline and throughout 1 min of postapneic recovery to assess the sympathoexcitatory response of the CBR during postapneic sympathoinhibition. We applied only an increase in carotid sinus transmural pressure during apnea because MSNA is so elevated that further increases would be difficult to observe; similarly, we applied only a decrease in carotid sinus transmural pressure during postapneic recovery because MSNA is very low postapnea and further inhibition would be

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difficult to measure, as MSNA is often at or near zero. We hypothesized that the sensitivity of CBR control of MSNA would decrease during apnea and return upon apnea termination.

METHODS

Subjects. This study was approved by the University of North Texas Health Science Center Institutional Review Board. Ten volunteers (3 women and 7 men, age: 21–30 yr, weight: 75.7 ± 3.5 kg, means ± SE) participated in the study after giving written informed consent. All subjects completed a medical history/health questionnaire to establish good health. Female subjects tested negative for pregnancy and a medical history/health questionnaire to establish good health. Subjects were not studied during menses to eliminate potential confounding effects of menses on fluid metabolism, blood volume, and cardiovascular function. Subjects were asked to abstain from vigorous exercise and alcohol for 24 h before the study start time and from caffeine for 12 h before the study start time.

Measurements. Heart rate was obtained using a standard limb-lead ECG. Arterial blood pressure was measured non-invasively from beat-to-beat photoplethysmographic recordings at the finger (Finapres blood pressure monitor 2300, Ohmeda; Englewood, CO). This method has been validated against direct arterial pressure recordings (16, 25). A respiratory monitoring band was placed around the subject’s abdomen (Grass Instruments; West Warwick, RI), allowing investigators to monitor breathing frequency and to ensure that all apneas were performed at end-expiration and that all NS/NP pulses were delivered at end-expiration. Pulse oximetry at the finger assessed oxygen saturation (SaO2; DS-100A Durasensor, Nellcor Puritan Bennett; Pleasanton, CA). Subjects were also fitted with an airtight mouthpiece and three-way Rudolph valve connected to a Douglas bag containing a gas mixture of 13% O2–87% N2, which subjects inhaled during baseline to maximize O2 desaturation with apnea.

Efferent sympathetic nerve instrumentation. Effector MSNA was directly measured from the peroneal nerve at the popliteal fossa using standard microneurographic techniques (2, 32). Two sterile tungsten microelectrodes (tip diameter 5–10 μm, 35 mm long, Frederick Haer; Bowdoinham, ME) were inserted; one was inserted into the peroneal nerve for recording of MSNA, and the other served as a reference. Microelectrodes were inserted without local anesthesia because they are so small they do not cause appreciable pain when inserted and because anesthesia might affect local nerve function. A signal processing system rectified and integrated the nerve signal and amplified it ~9 × 106 times (University of Iowa Bioengineering, Iowa City, IA). Pulse synchrony of bursts and reproducible activation during apnea, and the lack of response to skin stroking or startle stimuli, confirmed recording of muscle, and not skin, sympathetic nerve activity.

Carotid baroreflex function. We altered carotid baroreceptor activation and deactivation via the delivery of suction and pressure to an airtight chamber enclosing the anterior portion of the neck. This method of assessing CBR function was first described by Ernsting and Parry (9) and later simplified and improved by Eckberg and colleagues (5). Subjects were fitted with a cushioned, malleable lead collar, which encased the anterior two-thirds of the neck. A pressure of +30 Torr and a suction of ~60 Torr were generated by a manually controlled, variable pressure source and delivered through large-bore two-way solenoid valves (Asco; Florham Park, NJ) to the neck chamber. A pressure transducer (Validyne Engineering; Northridge, CA) measured neck chamber pressure.

The responses to NS/NP pulses are affected by the point in the cardiac and respiratory cycles in which they are delivered (3, 5–8, 19, 38); thus the timing of NS/NP pulses in relation to these two cycles was kept constant throughout the study. The timing of each NS/NP pulse in relation to the cardiac cycle was computer controlled such that each pulse was initiated precisely 50 ms after the R-wave of the ECG and was maintained for 5 s. The timing of each NS/NP pulse in relation to the respiratory cycle was controlled manually by an investigator who observed the respiratory signal. It is important to note that each neck pulse was under both manual and computer control, such that upon manual activation, the computer then initiated the neck pulse 50 ms after the next R-wave. During the nonapneic portions of the protocol (i.e., baseline and postapnea), when subjects reached approximately the last fourth of expiration, the computer-controlled neck pulse was triggered to activate after the next R-wave. Thus the actual initiation of the neck pulses occurred anywhere from the last part of expiration to the first part of inspiration, depending on the subject’s heart rate. Only those neck pulses actually initiated during end-expiration (i.e., the nadir in the respiratory signal, at which time subjects were at functional residual capacity) were included in the data analyses. During apnea, because the respiratory signal was static (at functional residual capacity), manual activation of the neck pulse was based strictly on time relative to the start of the apnea (timing details are given in Protocol). In this way, all neck pulses were delivered at functional residual capacity.

Protocol. These studies were performed with subjects in the supine position. Subjects were instrumented for recording of heart rate, blood pressure, respiratory activity, and SaO2, and were fitted with a neck collar appropriate for their size. Practice NS/NP pulses were then performed to verify both a tight seal and encasement of the carotid bifurcation within the neck chamber, based on heart rate responses. The collar was then removed, for comfort’s sake, while the subject was instrumented for recording of MSNA. The neck collar was then reapplied in the same position, the subject was fitted with the mouthpiece, and normal resting respiratory frequency was determined. A computer sound file was then used to guide the subject to maintain respiratory frequency at the resting frequency throughout the protocol. Eight repetitions of the following procedure were then performed: 1) 1 min of baseline breathing of a 13% O2–87% N2 gas mixture (to maximize O2 desaturation with apnea); 2) a 20-s end-expiratory apnea; and 3) 1 min of recovery. Subjects controlled respiratory frequency during baseline and recovery and were asked to maintain a consistent tidal volume during baseline (i.e., subjects were asked to avoid taking any irregular breaths, such as a sigh, so that all breaths were as similar as possible, not only in terms of duration but also in terms of depth). This was monitored via the respiratory signal, which was displayed on the computer screen along with all other signals. If a subject did take an irregular breath, that section of data was avoided and not used for analysis. Subjects were allowed to increase tidal volume as necessary after apnea. Neck pulses were randomly delivered as follows during six of the repetitions: 1) NS/NP ~35 s into baseline; 2) NS during either the first third of apnea (A1; 1–7 s), the second third of apnea (A2; 7–13 s), or last third of apnea (A3; 13–19 s); and 3) NP during the first postapneic expiration and then repeatedly throughout recovery, with a minimum of 5 s between the termination of one pulse and the initiation of the next. Thus three NS and three NP pulses were performed during baseline; two NS pulses were performed at each third of apnea (A1–A3), and up to six NP pulses were obtained for each of
the following time points in recovery: 1–10 s (first recovery; R1), 11–20 s (second recovery; R2), 21–30 s (third recovery; R3), 31–40 s (fourth recovery; R4), 41–50 s (fifth recovery; R5), and 51–60 s (sixth recovery; R6). Neck pulses delivered during A1, A2, and A3 were manually activated at 1, 7, and 13 s into apnea, respectively, such that the entire neck pulse occurred during the appropriate third of apnea. If an error in NS/NP timing occurred, additional repetitions were performed as necessary so that at least two correctly timed NS/NP pulses were obtained for each time point for each subject. Only NS was applied during apnea because MSNA is so high that additional increases due to NP would be difficult to measure; likewise, only NP was delivered during recovery because postapneic sympathoinhibition would make responses to NS difficult to observe and measure because MSNA is often at or near zero. The remaining two repetitions served as controls and consisted of the same procedure of baseline, apnea, and recovery, but with no delivery of NS/NP pulses. These two controls were placed randomly within the eight repetitions.

Data analyses. The integrated neurogram was manually inspected for each subject. The minimum and maximum signal processing software (Windaq, Dataq Instruments; Akron, OH). MSNA bursts were identified according to appearance and timing relative to the previous (one removed) R-wave of the ECG. Relative baseline (i.e., zero activity) was set by selecting a section of the neurogram in which no bursts occurred, calculating the signal average of that section, and setting that average equal to zero. The area of each burst was then calculated relative to that zero baseline.

MSNA and heart rate responses to NS/NP were averaged for each time point for each subject. Timing of MSNA bursts was adjusted to correct for nerve conduction delay (11). Only MSNA bursts associated with diastoles occurring within 2.5 s of stimulus initiation were used in the quantification of the MSNA responses, as it has been shown that the MSNA response to carotid baroreceptor loading and unloading is transient, lasting only 1–2 bursts and then returning to baseline activity, despite continued baroreceptor loading/unloading (7, 26, 42, 44). The cutoff criterion for whether or not a diastole (and its associated MSNA burst) was included in the analysis was chosen by the investigators to be the second downslope in the blood pressure profile, i.e., after the dichrotic notch. In other words, if the 2.5-s cutoff line fell in the middle of a blood pressure pulse, that pulse was included in the analysis only if the 2.5-s line occurred after the dichrotic notch. The entire MSNA burst associated with that diastolic pressure was then included in the analysis; MSNA bursts were never partially counted. MSNA was calculated as total activity (sum of areas of bursts) rather than burst frequency, as burst amplitude and duration are greatly increased during apnea and these increases would not be reflected in burst frequency. The integrated MSNA signal was originally measured in volts; therefore, total activity was originally in volts squared. Each value of total activity was multiplied by 10,000 for the convenience of working with whole numbers and was calculated as both units per heartbeat and units per second. MSNA data analyses yielded the same results for MSNA per heartbeat and MSNA per second, so MSNA is reported here only as total activity per heartbeat. Because of high interindividual variability in nerve activity, MSNA was normalized such that each subject’s baseline activity equaled 100 U/heartbeat, and MSNA at all other time points was quantified as a percentage of this baseline.

To determine the MSNA response to NS/NP, MSNA associated with the first 2.5 s of NS/NP was compared with MSNA during the time-matched, respiratory cycle-matched controls in which no neck pulse was delivered. For example, if a subject’s average time of NS delivery during baseline was 37 s into baseline, the investigator would begin the control files at the end-expiratory period nearest 37 s into baseline. Change in MSNA due to NS/NP was thus calculated as the average MSNA during the first 2.5 s of NS/NP minus the average MSNA during the time-matched, respiratory-matched controls. The reason for using the time-matched control files to determine MSNA responses rather than using MSNA just before NS/NP delivery is because physiological variables are constantly changing during apnea: for example, MSNA 10 s into apnea is not an appropriate control for MSNA during NS delivered 13 s into apnea, because between 10 and 13 s into apnea, SaO₂ falls, arterial pressure increases, and MSNA increases. Thus, in these circumstances, a time-matched control file is more appropriate. Heart rate responses were similarly calculated as the minimum and maximum heart rates during NS and NP, respectively, minus the average heart rate during time- and respiratory-matched controls. Heart rates were relatively stable during control files in which no neck pulse was delivered; thus analysis of minimum and maximum heart rates during NS and NP control files, respectively, yielded the same results. Only comparisons with the average heart rates during control files are reported.

Statistical analyses were divided into two parts: CBR responsiveness to NS at baseline and throughout apnea and CBR responsiveness to NP at baseline and throughout recovery. Two-way repeated-measures ANOVA was used to determine the effect of time (i.e., baseline, three apnea time points, and six recovery time points) and NS/NP on dependent variables and whether an interaction existed between the two factors (i.e., does apnea or recovery from apnea affect the response to NS/NP?). If significance was found, post hoc multiple-comparison Tukey tests were performed to determine where specific differences existed. All statistical analyses were performed at a significance level (α) of 0.05. All data are expressed as means ± SE.

RESULTS

Ten volunteer subjects were enrolled in the study, but the data for two subjects were not analyzed due to technical difficulties. A sample tracing of one subject’s raw data is depicted in Fig. 1. The strength and brevity of the MSNA response to NS during apnea are well illustrated, as is the postapneic attenuation of the MSNA response to NP, which was observed in all subjects. The characteristic apnea-induced sympathoexcitation and postapneic sympathoinhibition are also well illustrated and occurred in all subjects.

Effect of apnea and apnea termination on MSNA responses to NS/NP. The effects of apnea and apnea termination on MSNA responses to NS/NP are shown in Figs. 2 and 3. Apnea alone increased MSNA above baseline activity (P = 0.02), with the only significant difference occurring between baseline and A3 (P = 0.015; Fig. 2). NS decreased MSNA during baseline and apnea (P = 0.003), and there was no interaction between time and NS (P = 0.127). In other words, time point (i.e., whether a subject was at baseline or in a particular phase of apnea) did not affect the MSNA response to NS. Therefore, despite the strong sympathoexcitatory effect of apnea, the sensitivity of CBR control of MSNA was preserved.
Postapneic recovery was associated with decreased sensitivity of CBR control of MSNA (Fig. 3). A significant interaction existed between time and NP on MSNA (P = 0.036). In other words, time point (i.e., whether a subject was at baseline or in a particular phase of recovery from apnea) significantly affected the MSNA response to NP. NP significantly increased MSNA at baseline (P = 0.006), but this sympathoexcitatory effect of NP was not detectable statistically after apnea termination (R1–R3; P = 0.588). Although the MSNA response to NP showed a clear trend for recovery at R4 and R5, the sympathoexcitation did not reach statistical significance (P = 0.086). Only during the last 10 s of postapneic recovery (R6) was the MSNA response to NP again statistically significant (P = 0.004).

**Effect of apnea and apnea termination on heart rate responses to NS/NP.** The effects of apnea and apnea termination on heart rate responses to NS/NP are shown in Figs. 4 and 5. NS significantly affected heart rate (P = 0.014), as did time (P = 0.043; Tukey: A1 vs. A3, P = 0.041). There was no interaction between the

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Fig. 1. Sample tracings of raw data from a single representative subject. Nerve signal has not been corrected for conduction delay. A: responses to −60-Torr neck suction (NS) delivered during the last third of apnea (A3) as well as responses to +30-Torr neck pressure (NP) delivered during the first postapneic expiration (R1). During apnea, muscle sympathetic nerve activity (MSNA) bursts occurred with each heartbeat (HB), and NS completely abolished a single burst (arrow). NP was unable to elicit a MSNA response postapnea. B: the same subject during a time-matched control in which no NS/NP pulses were delivered. MSNA bursts occurred with every heartbeat during A3, and MSNA was completely inhibited upon apnea termination. NCP, neck chamber pressure.

Fig. 2. MSNA response to −60-Torr NS at baseline and throughout apnea [first to last third of apnea (A1–A3)]. Apnea significantly increased MSNA, and NS significantly reduced MSNA, but no interaction existed between the two. Thus, although apnea caused a significant increase in MSNA, this did not affect the sympathoinhibitory response to NS. *Significantly less than the time-matched control (P < 0.05); †significantly greater than baseline (P < 0.05).
two factors \( P = 0.107 \). Thus, as with MSNA, apnea did not affect the heart rate response to NS.

A significant interaction between time and NP existed in heart rate responses during postapneic recovery \( P = 0.028 \). However, post hoc analyses determined that NP significantly increased heart rate at all time points (baseline through R6, all \( P < 0.01 \)). Thus, unlike MSNA, the sensitivity of CBR control of heart rate was preserved after apnea termination.

**DISCUSSION**

We hypothesized that the sensitivity of CBR control of MSNA diminishes with apnea, as MSNA and arterial pressure concomitantly increase during apnea. In addition, due to the sympathoinhibition postapnea while arterial pressure remains elevated, we hypothesized that the sensitivity of CBR control of MSNA returns upon apnea termination. However, both hypotheses were refuted. The CBR maintained the ability to decrease MSNA in response to -60-Torr NS throughout apnea, even during the last third of apnea, when strong sympathoexcitatory stimuli were present. After apnea termination, the CBR was unable to elicit a significant increase in MSNA in response to +30-Torr NP; however, this effect was transient, and normal baroreflex response had returned by the end of the postapneic recovery minute. In contrast to the sympathetic arm of the CBR, cardiac responses to NS/NP were preserved both during apnea and after its termination. These heart rate responses to brief NS/NP are predominately mediated by parasympathetic nerve activity (4).

Resetting of the CBR-MSNA function curve has been demonstrated with exercise (10). Fadel et al. (10) showed that the CBR-MSNA function curve reset to the higher arterial pressure and the higher MSNA induced by exercise (i.e., a rightward and upward shift in the curve) but that the properties of the CBR-MSNA function curve were unchanged. While the present study did not attempt to model the entire CBR-MSNA function curve, we propose that a similar resetting is occurring with apnea (Fig. 6). During baseline resting conditions, the operating point is located near the onset mean arterial pressure (MAP) for sympathoexcitation (26) (point B in Fig. 6). Baseline application of -60-Torr NS produced essentially complete sympathoinhibition in our subjects (98 ± 2% decrease in MSNA); however, the absolute change in MSNA was relatively small, due to low baseline sympathetic tone (Fig. 2). Apnea caused approximately a 10-mmHg increase in MAP. If the CBR-MSNA function curve did not reset during apnea, the rise in MAP would be expected to significantly reduce MSNA (30). However, at the end of apnea, MSNA increased >10-fold, consistent with a rightward and upward resetting of the CBR-MSNA.

**Fig. 3.** MSNA response to +30-Torr NP at baseline and throughout postapneic recovery (first to sixth periods of recovery [R1–R6]). There was a significant interaction between time and NP. Post hoc multiple-comparison Tukey analyses revealed that NP significantly increased MSNA at baseline and R6 but not at R1 through R5. Thus transitory attenuation of the sensitivity of carotid baroreflex control of MSNA appears to occur postapnea. *Significantly greater than the time-matched control (\( P < 0.05 \)).

**Fig. 4.** Heart rate response to -60-Torr NS at baseline and throughout apnea (A1–A3). NS significantly decreased heart rate at all time points. Thus apnea did not affect the bradycardic response to NS. bpm, Beats per minute. *Significantly less than the time-matched control (\( P < 0.05 \)).

**Fig. 5.** Heart rate response to +30-Torr NP at baseline and throughout postapneic recovery (R1–R6). NP significantly increased heart rate at all time points. Thus the sensitivity of carotid baroreflex control of heart rate was preserved after apnea termination. *Significantly greater than the time-matched control (\( P < 0.05 \)).
function curve (Fig. 6, dashed curve). NS of ~60 Torr during the last third of apnea produced a significant sympathoinhibitory response, with the absolute decrease in MSNA being even greater than at baseline due to the high MSNA during apnea (Fig. 2). From these results, we hypothesize that the operating point of the CBR-MSNA function curve may have moved leftward (i.e., further from saturation and closer to threshold), as hypothetically presented as point A3 in Fig. 6. However, it is important to note that our data do not identify the exact location of the operating point on the function curve, only that some degree of leftward movement was likely. Nonetheless, the much higher MSNA during apnea suggests that the baroreflex, relative to baseline, can now function more effectively to reduce MSNA and vascular resistance in the face of a hypertensive challenge.

During the first 10 s postapnea, MAP remained elevated and MSNA was almost completely inhibited. The sympa-thoexcitatory response to +30-Torr NP was clearly reduced relative to baseline during the first 30 s postapnea; however, the mechanism for this remains unclear. One possible explanation is that the CBR-MSNA function curve reset back to baseline upon apnea termination, with the operating point hypotheti-cally at point R1b in Fig. 6. This would partially explain the reduced sympathoexcitatory response to NP at R1, as the operating point would now be located on the relatively flat portion of the curve. However, this cannot fully explain the postapneic reduction in CBR-MSNA response to a decrease in carotid sinus transmural pressure. Sympathoexcitatory response to +30-Torr NP was reduced at recovery R1–R3, showed a trend for recovery at R4 and R5, and had regained baseline function by R6 (Fig. 3). If the location of the operating point on the flat part of the function curve were the sole explanation for the reduced baroreflex responsiveness, then MAP would be expected to follow a similar time course of recovery to baroreflex function, returning to baseline pressures at approximately R6. However, MAP had returned to pressures not significantly different from baseline by R2 (Fig. 7). Thus some other sympathoinhibitory mechanism would have to be present postapnea to fully explain the results. Alternatively, and perhaps more likely, it is possible that the CBR-MSNA function curve transiently resets down-ward and leftward of baseline after apnea termination (Fig. 6, dotted curve). This would explain the decreased MSNA response to NP even after MAP had returned to baseline. Such a downward shift of the CBR-MSNA function curve has been demonstrated after dynamic exercise in humans (12).

Van de Borne and colleagues (40) have demonstrated that isocapnic, increased tidal volume breathing leads to an attenuation of the sensitivity of arterial baroreflex control of MSNA. In addition, Macefield and Wallin (20) noted that the duration of sympathoinhibition and abnormal respiration postapnea were similar, suggesting that ventilation is importantly involved in postapneic sympathoinhibition. In the present study, subjects controlled respiratory frequency throughout the protocol but were allowed to increase tidal volume as necessary postapnea. Thus elevated tidal volume could potentially explain the reduced MSNA response to NP postapnea, perhaps by resetting the CBR-MSNA function curve to a position downward and leftward from preapneic baseline. Unfortunately, we do not have tidal volume data; only respiratory movements were recorded via a respiratory monitoring band. Therefore, we cannot determine whether increased tidal volume and decreased CBR-MSNA function were correlated in our subjects. Nevertheless, our data demonstrate that the sensitivity of baroreflex control of
MSNA is attenuated immediately postapnea; this is consistent with resetting of the reflex back to, or even beyond, the preapnea state (Fig. 6) and may also involve modulation by ventilation or other inputs such as the cardiopulmonary baroreceptors. Regardless, the abruptness of the sympathoinhibition at apnea termination (22, 45) strongly implies that the altered baroreflex sensitivity during recovery from apnea is mediated by central nervous system modulation of the reflex and not modulation at the baroreceptors.

The bradycardic response to −60-Torr NS was not altered during apnea, nor was the tachycardic response to +30-Torr NP altered during postapneic recovery. A previous study (46) determined that hypoxia decreased cardiac baroreflex sensitivity; we did not find a change in cardiac baroreflex function with decreased SaO2, which fell to 91 ± 1% at the A3 time point. However, differences exist between the two studies that could explain the different results. Ziegler et al. (46) measured cardiac baroreflex sensitivity during breathing of a 15% O2 gas mixture, which decreased SaO2 to 90% or below in their subject groups, comparable with SaO2 in our subjects at the end of apnea. However, their subjects were respiring, whereas ours were in apnea. Hypoxia during respiration significantly increases heart rate (13, 15, 28, 29, 34–36, 39, 47) and did so in their study, but hypoxia during apnea decreases heart rate (47). During the last third of apnea, our subjects had slightly, but not significantly, decreased heart rates compared with baseline. Thus the hypoxia-induced tachycardia present in the subject population of Ziegler et al. (46) could have counteracted the bradycardic response to phenylephrine-induced increases in pressure.

The decreased MSNA response to NP postapnea accompanied by the maintenance of the heart rate response indicates a disassociation between the sympathetic and cardiac parasympathetic branches of the CBR. Wallin and Eckberg (42) have suggested that central nervous system processing of arterial baroreceptor input is different for parasympathetic and cardiac parasympathetic branches of the reflex, based on their observation of different degrees and time courses of adaptation of these two branches to the same baroreceptor stimulus. Recently, Cui and colleagues (1) utilized infusions of vasoactive drugs to demonstrate increased sensitivity of baroreflex control of MSNA but not of heart rate during the cold pressor test. Additionally, Narkiewicz et al. (23) reported impairment of the sympathetic but not the cardiac branch of the arterial baroreflex in obstructive sleep apnea patients, independent of hypertension, obesity, and age. Interestingly, the MSNA baroreflex impairment was selective for hypertensive but not hypertensive stimuli (23). We also found impairment of the sympathetic but not the cardiac response to CBR deactivation; however, this impairment was transient and occurred postapnea in healthy individuals. Nonetheless, it is interesting to note the similarities in the results of these two studies, and it raises the possibility that the transient postapneic reduction in CBR-MSNA responsiveness to CBR deactivation may eventually translate into a permanent baroreflex impairment in patients experiencing repetitive apneas each night.

Study limitations. Subjects breathed a 13% O2-87% N2 gas mixture during baseline data collection. As discussed above, Ziegler et al. (46) have demonstrated that breathing a hypoxic gas reduces cardiac baroreflex sensitivity. However, during baseline baroreflex measurements in the present study, the subjects’ SaO2 averaged 96 ± 1%, essentially equivalent to the SaO2 during normoxia in the study of Ziegler et al. (46). A reduction in baroreflex sensitivity was noted in their subjects at SaO2 values of 90% and below. Thus it is doubtful that baroreflex function was affected by the mild oxygen desaturation during baseline.

During baseline and postapneic recovery, NS/NP pulses were delivered during respiration, whereas during apneic application of NS, no respiration was present. Responses to carotid baroreceptor stimulation have been shown to be affected by the point in the respiratory cycle in which the stimuli are applied (6–8, 38). To minimize these effects, NS/NP pulses delivered during respiration were applied only at end-expiration, as all apneas were held at end-expiration. However, it remains possible that the difference in respiratory state between baseline and apnea affected the responses to NS. This seems unlikely, however, because no change in CBR function was found from baseline throughout apnea.

The present study assessed responses to only an increase in carotid sinus transmural pressure (NS) during apnea and to only a decrease in carotid sinus transmural pressure (NP) during postapneic recovery. Although the MSNA responses are consistent with resetting of the CBR function curve, as proposed in Fig. 6, we were unable to model the complete reflex function curve at each time point. However, modeling is not feasible because MSNA is so high during apnea that further increases due to NP would be difficult to observe; likewise, additional sympathoinhibition due to NS postapnea would be difficult to measure because MSNA is already at or near zero.

Finally, application of NS/NP tests CBR function only. MAP remained elevated during the first 10 s postapnea and was still slightly, though not significantly, elevated during the second 10 s postapnea. Therefore, during postapnea R1 and R2, sympathoinhibitory input from the aortic baroreflex was potentially counteracting the sympathoexcitatory input from the CBR during application of NP. This could partly explain the decreased MSNA response to NP postapnea. Studies have suggested that when the aortic and carotid baroreceptors are sending conflicting input to sympathoregulatory centers, the loaded baroreceptors dominate the response (31, 37). However, in neither study were the loaded baroreceptors the aortic baroreceptors, as was the case postapnea in the present study. As discussed above, MAP had returned to baseline by R3 (and was not significantly different from baseline at R2); thus sympathoinhibitory input from
aortic baroreceptors cannot explain the decreased MSNA response to NP at R3.

In conclusion, we found that sympathoinhibitory responses to −60-Torr NS did not diminish with apnea, whereas sympathoexcitatory responses to +30-Torr NP were reduced after apnea termination but recovered within 1 min. In addition, heart rate responses to −60-Torr NS and +30-Torr NP were not affected by apnea or its termination, respectively. We hypothesize a rightward and upward resetting of the CBR-MSNA function curve with apnea, similar to that seen with exercise (10), as well as shifting of the operating point away from saturation and toward threshold. Return of the CBR-MSNA function curve to, or more likely beyond, baseline (i.e., a downward and leftward shift of the curve) upon apnea termination may contribute importantly to the postapneic reduction in sensitivity of CBR control of MSNA; however, full understanding of the mechanism(s) remains unclear.

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