Hyperventilation alters arterial baroreflex control of heart rate and muscle sympathetic nerve activity

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Van de Borne, Philippe, Silvia Mezzetti, Nicola Montano, Krzysztof Narkiewicz, Jean Paul Degaute, and Virend K. Somers. Hyperventilation alters arterial baroreflex control of heart rate and muscle sympathetic nerve activity. Am J Physiol Heart Circ Physiol 279: H536–H541, 2000.—Interactions between mechanisms governing ventilation and blood pressure (BP) are not well understood. We studied in 11 resting normal subjects the effects of sustained isocapnic hyperventilation on arterial baroreceptor sensitivity, determined as the α index between oscillations in systolic BP (SBP) generated by respiration and oscillations present in R-R intervals (RR) and in peripheral sympathetic nerve traffic [muscle sympathetic nerve activity (MSNA)]. Tidal volume increased from 478 ± 24 to 1,499 ± 84 ml and raised SBP from 118 ± 2 to 125 ± 3 mmHg, whereas RR decreased from 947 ± 18 to 855 ± 11 ms (all P < 0.0001); MSNA did not change. Hyperventilation reduced arterial baroreflex sensitivity to oscillations in SBP at both cardiac (from 13 ± 1 to 9 ± 1 ms/mmHg, P < 0.001) and MSNA levels (by 37 ± 5%, P < 0.0001). Thus increased BP during hyperventilation does not elicit any reduction in either heart rate or MSNA. Baroreflex modulation of RR and MSNA in response to hyperventilation-induced BP oscillations is attenuated. Blunted baroreflex gain during hyperventilation may be a mechanism that facilitates simultaneous increases in BP, heart rate, and sympathetic activity during dynamic exercise and chemoreceptor activation.

there is evidence for considerable interactions between the mechanisms governing ventilation and those governing blood pressure (BP) control (9). These interactions have important physiological and clinical implications; however, their nature is complex and not well understood (9, 14).

What is known is that increases in BP, acting via the baroreflex, inhibit the ventilatory responses to chemoreflex activation (9). Conversely, the phases of respiration have direct short-term effects on cardiovascular control. Inspiration impairs the cardioinhibitory baroreceptor response (8, 14). Furthermore, respiration has distinct and contrasting effects on efferent sympathetic nerve traffic, which is inhibited during inspiration and enhanced during expiration (7, 20). Vagolytic effects of inspiration contribute to sinus arrhythmia, with relative tachycardia during inspiration and heart rate slowing during expiration (2, 6, 14).

Whereas there is considerable evidence of short-term breath-by-breath ventilatory-cardiovascular interactions within the phases of ventilation, there is limited information on the effects of sustained changes in ventilatory depth on cardiovascular control in general and on baroreflex function in particular (23). The effects of more sustained ventilatory changes on baroreflex characteristics have direct relevance to understanding cardiovascular control in physiological situations such as hyperventilation induced by exercise (18) and in pathological situations such as hyperventilation induced by hypoxia or hypocapnia (21, 22).

Effects of sustained hyperventilation on arterial baroreceptor gain are unknown. The effects of hyperventilation-induced reduction in baroreflex function may facilitate simultaneous increases in BP, heart rate, and sympathetic activity during dynamic exercise (13, 18) and chemoreceptor activation (21, 22). We therefore tested the hypothesis that hyperventilation impairs arterial baroreceptor gain in humans. We used the interaction between oscillations in systolic BP (SBP) generated by respiration and the accompanying changes in R-R interval (RR) (15) as an index of baroreceptor sensitivity to investigate whether changes in respiratory frequency and respiratory depth altered the responses of heart rate to changes in BP. In addition, direct intraneural recordings of sympathetic nerve traffic to muscle blood vessels [muscle sympathetic nerve activity (MSNA)] were obtained in all subjects to determine whether any changes in baroreceptor control during hyperventilation were restricted to the sinus node or also affected baroreflex modulation of peripheral sympathetic nerve traffic (1).

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METHODS

Subjects. We studied 11 normal subjects (10 males, 1 female) with a mean age of 26 yr (range 19–37 yr). None was taking any medications. Informed written consent was obtained from all subjects. The Human Subjects Review Committee approved the study.

Measurements. SBP was measured continuously at the finger level (Finapres, Ohmeda 2300, Englewood, CO). An electrocardiogram, respiration (pneumograph), oxygen saturation (Nellcor N-100 C Pulse Oxymeter), and end-tidal CO₂ (Hewlett-Packard 47210A Capnometer) were recorded on a Gould 2800 S recorder. Minute ventilation was determined using a Kozak flow-volume turbine module (Vacumetrics). Breathing was performed via a mouthpiece with the use of a nose clip to ensure exclusive mouth breathing. Sympathetic nerve activity to muscle blood vessels was recorded continuously by obtaining multiunit recordings of postganglionic sympathetic activity, measured from a nerve fascicle in the peroneal nerve posterior to the fibular head (7). Electrical activity in the nerve fascicle was measured using tungsten microelectrodes (shaft diameter 200 μm, tapering to an non-insulated tip of 1–5 μm). A subcutaneous reference electrode was inserted 2–3 cm away from the recording electrode, which was inserted into the nerve fascicle. The neural signals were amplified, filtered, rectified, and integrated to obtain a mean voltage display of sympathetic nerve activity.

All variables were recorded on a Macintosh Quadra 900 Computer (Apple Computer, Cupertino, CA) with a MacLab 8/s data acquisition system (AD Instruments, Milford, MA) and an IBM 433DX/T computer.

Protocol and interventions. Respiration was paced at 0.19, 0.27, and 0.32 Hz with the use of a metronome throughout the experiment, which allowed us to determine effects of hyperventilation on baroreceptor control over a wide range of respiratory frequencies. Moreover, the use of different frequencies of breathing at normal ventilatory depth gave us the opportunity to ensure that the changes in baroreflex sensitivity during hyperventilation were due to hyperventilation itself and not secondary to changes in central command (4). Measurements were taken during each of the following six interventions in random sequence: 1) 10-min baseline periods of stable ventilation while subjects breathed room air at 0.19, 0.27, and 0.32 Hz (controlled breathing); and 2) 10-min periods of maximal voluntary exercise-like hyperventilation at 0.19, 0.27, and 0.32 Hz while subjects breathed room air with CO₂ added to maintain isocapnia.

Data analysis. Sympathetic bursts were identified by a careful inspection of the mean voltage neurogram, and sympathetic activity was calculated as bursts per minute. The amplitude of each burst was determined, and sympathetic activity was calculated as bursts per minute multiplied by mean burst amplitude and expressed in arbitrary units (au). The absolute amplitude of MSNA depends on voltage amplification, which varies from one subject to another but is kept constant during every experiment. Modifications in MSNA during hyperventilation were therefore calculated as percentages of changes from values recorded during normal ventilation. A single trained observer (P. van de Borne) made measurements. The intra- and interobserver variability was 4.3 ± 0.3% and 5.4 ± 0.5%, respectively.

Analog-to-digital conversion was performed over 10 min at 300 samples/s for the electrocardiogram, BP, MSNA, and respiratory signals. The data were then analyzed off-line with a personal computer (IBM 433DX/T).
to 99 ± 0.2% (P < 0.0001) and shortened RR (from 947 ± 18 to 855 ± 11 ms, P < 0.0001). Sympathetic inhibition during inspiration resulted in a decrease in MSNA burst frequency from 27 ± 3 to 24 ± 2 bursts/min during hyperventilation (P < 0.001, Fig. 1). However, MSNA suppression during large inspirations was followed by an increase in sympathetic burst amplitude during expiration. As a result, integrated sympathetic activity (sum of burst amplitude/min) did not decrease significantly during hyperventilation (−8 ± 7% vs. normal breathing, P = 0.24).

Hyperventilation increased the magnitude of respiratory oscillations in SBP from 2 ± 0.3 to 9 ± 1 mmHg² (P < 0.0001), in RR from 1,481 ± 387 to 1,908 ± 277 ms² (P < 0.01), and in MSNA by 194 ± 26% (P < 0.01, Fig. 1).

Paired comparison of the α index during controlled breathing and isocapnic hyperventilation revealed a blunted baroreflex response to the enhanced respiratory BP fluctuations during hyperventilation for control of both the sinus node (from 13 ± 1 to 9 ± 1 ms/mmHg, n = 30, P < 0.001) and sympathetic outflow to muscle blood vessels (by −37 ± 5% vs. normal breathing, n = 24, P < 0.0001) (Fig. 2). Changes in respiratory frequency alone, in the absence of hyperventilation, did not affect baroreceptor control of either heart rate (P = 0.22 by ANOVA) or MSNA (P = 0.59 by ANOVA).

Hyperventilation impaired baroreceptor modulation of the sinus node (P = 0.02 by ANOVA) and sympathetic outflow (P = 0.0003 by ANOVA) at all breathing frequencies, but did less so at 0.19 Hz for arterial baroreceptor sensitivity of the sinus node (13 ± 2 vs. 10 ± 1 ms/mmHg, n = 11, P = 0.19 by paired t-test) (Fig. 3). Hyperventilation reduced the α index for SBP and RR from 12 ± 2 to 9 ± 1 ms/mmHg (P < 0.01) and from 11 ± 1 to 7 ± 1 ms/mmHg (P < 0.05) when subjects breathed at 0.27 and 0.32 Hz, respectively. Hyperventilation also decreased the α index for SBP and MSNA by −24 ± 8% (P < 0.05), −32 ± 9% (P < 0.01), and −56 ± 5% (P < 0.001) when subjects breathed at 0.19, 0.27, and 0.32 Hz, respectively.

**DISCUSSION**

This study addressed the effects of changes in respiratory depth on baroreflex sensitivity. We have shown that hyperventilation, in the absence of hypocapnia, is
associated with an increase in BP and tachycardia but with no change in MSNA. The absence of reflex cardiac slowing and the absence of sympathetic inhibition in response to the higher BP during hyperventilation are indicative of attenuation of baroreflex control of both heart rate and sympathetic traffic. Changes in respiratory frequency alone, in the absence of hyperventilation, do not affect baroreflex gain, suggesting that the changes in baroreflex characteristics that occur during voluntary hyperventilation are a function of the hyperventilation per se and are not reflective of the effects of central command on baroreflex gain (4).

Hyperventilation and arterial baroreceptor control of heart rate and MSNA. Our findings are supportive of an earlier study (23) showing that short-lasting isocapnic hyperventilation impaired the bradycardic response to neck suction. We are, however, unaware of any previous studies examining the effects of hyperventilation on baroreflex control of sympathetic nerve activity in humans. We confirm an earlier observation that hyperventilation does not reduce sympathetic traffic (20), because complete suppression of MSNA during inspiration was compensated for by facilitation of MSNA during expiration. Our study also reveals

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that the rise in BP during hyperventilation did not elicit the expected reduction in sympathetic nerve traffic.

The mechanism of baroreflex impairment of sinus node and MSNA control during hyperventilation is not known. Whereas the absence of effects of changes in paced breathing frequency alone on baroreflex gain suggests that changes in central command are unlikely to be involved (4), several other mechanisms may be implicated. These include, first, the vagolytic effects of inspiration (2, 6). Inhibition of cardiac vagal activity during stretch of thoracic afferents would inhibit the capacity of the baroreflex to slow heart rate in response to change in BP. Second, mechanical effects of very deep breathing would influence the sinoatrial node independent of baroreflex-mediated neural mechanisms (3, 24). Third, the sigmoidal nature of the baroreflex pressure-response relationship results in an enhanced reflex response to pressure fluctuations that are close to the baroreflex set point but a diminished response to more dramatic changes in BP that occur at the less steep and less sensitive portions of the stimulus-response curve (14, 18). Thus heart rate changes in response to the very large oscillations in BP generated by hyperventilation would be relatively attenuated compared with the heart rate responses to the smaller BP fluctuations that occur during normal breathing. Finally, central interactions between pulmonary afferents and baroreflex control mechanisms may also be involved (14).

Several of the postulated mechanisms for impaired heart rate control during hyperventilation may also be operative in the impairment of the sympathetic response to BP change during hyperventilation. These include the sigmoidal nature of the baroreflex response curve and central interactions between thoracic afferents and baroreflex control mechanisms.

Implications for hyperventilation during exercise. The tachycardia and increased BP during exercise are indicative of overriding of baroreflex control mechanisms so that the baroreflexes play a permissive role in allowing simultaneous increases in heart rate despite marked increases in BP (11, 13–14, 18). The mechanisms underlying the overriding of the baroreflex during exercise are not known. Our study reveals that threefold increases in tidal volume blunt baroreflex gain. This inhibition could become even more marked during heavy exercise, when tidal volume increases nearly eightfold.

Although other factors such as muscle and joint afferents and central command relating to motor activity are likely to be involved (11, 13, 18), the present study suggests that the effects of hyperventilation per se, in the absence of large muscle exercise or joint movement, are likely to contribute to simultaneous increases in BP and heart rate during dynamic exercise.

Chemoreflex-induced hyperventilation. Both hypoxia and hypercapnia elicit increases in ventilation, accompanied by increases in BP and heart rate (21, 22). Although baroreflexes are known to inhibit chemoreflex responses (9), there are also data to suggest that the chemoreflexes may have direct effects on baroreflex function (14). The effects of hyperventilation on baroreflex gain evident in the present study, namely, inhibition of baroreflex-mediated changes in heart rate and sympathetic traffic, suggest that the simultaneous increases in BP, heart rate, and MSNA evident during hypoxia and hypercapnia may, in part, be linked to the hyperventilation per se, independent of any direct baroreflex-inhibitory influence of the chemoreflex itself.

Limitations and strengths of the study. A potential limitation of our study is that we did not directly assess baroreflex sensitivity with the standard phenylephrine method. The α index, with the use of spontaneous changes in RR in response to BP changes, however, is a widely accepted method for the assessment of arterial baroreflex control of the sinus node (1, 10–13, 15–16). Other techniques, such as the sequence method, have been reported to be more strongly correlated to the α index. However, this has not been a consistent finding, and other studies have found a very high correlation between baroreflex sensitivity determined by the α index and the phenylephrine methods (r = 0.96) (17) than the α index (15). Moreover, the study by Parlow and colleagues (17) compared the sequence technique to the phenylephrine method but did not assess the reliability of the α-index technique. This was done by Herpin and colleagues (10), who concluded that the reproducibility of baroreflex sensitivity measures was as satisfactory at midterm for the sequences method as for the α index.

A potential limitation may be the use of the α-index technique for a similar assessment of MSNA responses to changes in BP. However, both RR and MSNA responses were very comparable. The use of the MSNA response allowed us to exclude any direct mechanical effects of hyperventilation on the sinus node with subsequent effects on RR. Attenuation of both RR and MSNA responses supports the concept of alteration in baroreflex gain by hyperventilation. Important strengths of the study include, first, the use of a paced breathing protocol in the absence of hyperventilation to exclude any effects of central command. Second, maintenance of isocapnia during baroreflex stimulation excluded any effects of changes in CO2 on our results. Third, respiration was paced at different frequencies to eliminate possible confounding effects due to an arbitrary selection of a single respiratory frequency (5). In conclusion, increased BP during hyperventilation does not elicit any reduction in either heart rate or MSNA. Baroreflex modulation of RR and MSNA in response to hyperventilation-induced BP oscillations is attenuated. These data suggest that hyperventilation per se, in the absence of muscle exercise, joint movement, or direct baroreflex-inhibitory effects of the chemoreflex, may contribute to simultaneous increases in BP and heart rate during physiological and pathological conditions such as dynamic exercise and chemoreceptor stimulation. Baroreflex inhibition by hyperven-
tilation may thus constitute a permissive mechanism allowing simultaneous increases in BP, heart rate, and MSNA under these conditions.

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