Influence of increased central venous pressure on baroreflex control of sympathetic activity in humans

N. Charkoudian, E. A. Martin, F. A. Dinenno, J. H. Eisenach, N. M. Dietz, and M. J. Joyner
Department of Physiology and Biomedical Engineering, Department of Anesthesiology and General Clinical Research Center, Mayo Clinic College of Medicine, Rochester, Minnesota 55905

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Charkoudian, N., E. A. Martin, F. A. Dinenno, J. H. Eisenach, N. M. Dietz, and M. J. Joyner. Influence of increased central venous pressure on baroreflex control of sympathetic activity in humans. Am J Physiol Heart Circ Physiol 287: H1658–H1662, 2004. First published June 10, 2004; 10.1152/ajpheart.00265.2004.—Volume expansion often ameliorates symptoms of orthostatic intolerance; however, the influence of this increased volume on integrated baroreflex control of vascular sympathetic activity is unknown. We tested whether acute increases in central venous pressure (CVP) diminished subsequent responsiveness of muscle sympathetic nerve activity (MSNA) to rapid changes in arterial pressure. We studied healthy humans under three separate conditions: control, acute 10° head-down tilt (HDT), and saline infusion (SAL). In each condition, heart rate, arterial pressure, CVP, and peroneal MSNA were measured during 5 min of rest and then during rapid changes in arterial pressure induced by sequential boluses of nitroprusside and phentolamine (modified Oxford technique). Sensitivities of integrated baroreflex control of MSNA and heart rate were assessed as the slopes of the linear portions of the MSNA-diastolic blood pressure and R-R interval-systolic pressure relations, respectively. CVP increased ~2 mmHg in both SAL and HDT conditions. Resting heart rate and mean arterial pressure were not different among trials. Sensitivity of baroreflex control of MSNA was decreased in both SAL and HDT condition, respectively: −3.1 ± 0.6 and −3.3 ± 1.0 versus −5.0 ± 0.6 units·beat−1·mmHg−1 (P < 0.05 for SAL and HDT vs. control). Sensitivity of baroreflex control of the heart was not different among conditions. Our results indicate that small increases in CVP decrease the sensitivity of integrated baroreflex control of sympathetic nerve activity in healthy humans.

IMPAIRED FUNCTION of the arterial baroreflex may contribute to several forms of orthostatic intolerance in humans. In many cases, treatments that increase plasma volume ameliorate symptom development with orthostasis (14, 26, 28). Because cardiac output decreases with upright posture in humans, sympathetically mediated vasoconstrictor responses to orthostasis are more important determinants of blood pressure regulation and orthostatic tolerance than are changes in heart rate (HR) (3, 4). However, the influences of increased plasma volume and central venous pressure (CVP) on baroreflex control of vascular sympathetic activity in humans are not known.

It has been shown in humans that decreased CVP elicits sympathetically mediated vasoconstrictor responses in the periphery in the absence of changes in arterial pressure (12, 27) and that decreased CVP augments vasoconstrictor responses to carotid baroreceptor unloading (27). In animal models, it has been demonstrated that volume expansion and/or increased CVP causes reflex inhibition of sympathetic nerve activity via activation of cardiopulmonary baroreceptors (1, 11, 24). In rabbits, increased right atrial pressure was associated with attenuated arterial baroreflex control of mean arterial pressure (MAP) (21).

In this context, we questioned whether acute increases in CVP from a normal baseline, which did not alter resting HR or MAP, would inhibit integrated arterial baroreflex control of muscle sympathetic nerve activity (MSNA) in healthy humans. We evaluated the influences of acute head-down tilt (HDT) and acute volume infusion (two perturbations that caused similar increases in CVP) on HR and MSNA responses to rapid changes in arterial pressure. We measured responses to acute HDT as a second method of increasing CVP to test whether increased CVP in the absence of other changes that occur with volume infusion (e.g., decreased hematocrit) would have similar effects to those seen with volume infusion. We hypothesized that increased CVP with either volume infusion or HDT would decrease the sensitivity of arterial baroreflex control of MSNA.

METHODS

Subjects. The protocol for these studies was approved by the Institutional Review Board of the Mayo Foundation. Thirteen healthy, normotensive nonsmokers (4 women and 9 men) volunteered to participate in these studies [age: 24.5 ± 0.5 (SE) yr; height: 1.77 ± 0.02 m; weight: 72.1 ± 2.8 kg]. Subjects did not have any history of cardiovascular or other chronic disease and were not taking any medications, including over-the-counter cold or pain medications. All subjects gave written informed consent to participate in these studies. All women were studied in the early follicular phase of the menstrual cycle or in the low-hormone phase of oral contraceptives to minimize variability in autonomic control of cardiovascular function due to reproductive hormone status (2, 15).

Measurements. HR was measured from a 3-lead electrocardiogram. Arterial blood pressure (ABP) was measured on a beat-by-beat basis by finger photoplethysmography (Finapres) regularly verified by automated sphygmomanometry on the contralateral arm. CVP was measured by placement of a peripherally inserted central catheter (PICC) in an antecubital vein and advanced to the level of the superior vena cava. Placement of the PICC was estimated using external measurement of the distance from the antecubital fossa to the manubrium. The PICC was connected to a pressure transducer placed at the level of the heart.

MSNA was measured by peroneal microneurography as described by Sundlof and Wallin (22). Multiunit postganglionic MSNA was recorded from the fibular (peroneal) nerve posterior to the fibular head.
with a tungsten microelectrode. The recorded signal was amplified 80,000-fold, band-pass filtered (700–2,000 Hz), rectified, and integrated (resistance-capacitance integrator circuit, time constant 0.1 s) by a nerve traffic analyzer.

Protocol. All studies were performed in a General Clinical Research Center laboratory where ambient temperature was controlled between 22 and 24°C. Subjects reported to the laboratory between 7 and 8 AM. They were instructed not to consume any food or beverage after midnight of the evening before the study and not to exercise or drink alcohol within 24 h of the study. Subjects rested supine during placement of PICC and a regular 18-gauge intravenous catheter in the contralateral arm for nitroprusside (NTP) and phenylephrine (PE) boluses as well as placement of ECG electrodes, a Finapres cuff on the middle finger, and an automated sphygmomanometer cuff on the upper arm. Each experiment consisted of three baroreflex trials, one in each of control, HDT, and volume infusion conditions. Immediately before each trial, blood samples were collected from the intravenous catheter for measurement of hemoglobin, hematocrit, plasma osmolality, sodium, and potassium levels.

Control baroreflex trial. Subjects rested supine for a 5-min baseline period during which MSNA, ECG, and ABP were recorded continuously. ABP was verified by measuring arm cuff pressure before and after this 5-min period. This was followed by a bolus of NTP (100 μg) further by a bolus of PE (150 μg) (modified Oxford technique). Data were collected for a further 2 min, such that the total time recorded for blood pressure transients was 3 min. Subjects then rested supine for 25–30 min before the next trial.

HDT baroreflex trial. The subjects were tilted head down for 5–10 min and then continued in the head-down position throughout a baroreflex trial as described above. The goal of the tilt was to increase CVP by ~2 mmHg; therefore, the degree of tilt varied slightly among subjects, from ~8 to ~10°. Subjects were then restored to the horizontal position and rested supine 25–30 min before the next baroreflex trial.

Saline infusion baroreflex trial. Normal saline was infused (SAL) into the intravenous catheter at a volume of 10 ml/kg over 20 min. After volume infusion, a baroreflex trial was performed as above.

In the first five subjects, we performed the volume infusion with no tilt procedures to quantify the increase in CVP that occurred with this volume infusion and match this increase with the HDT procedure. In the remaining eight subjects, HDT was performed before the volume infusion protocol to allow for repeated-measures design in all subjects.

Data analysis. HR, ABP, CVP, and MSNA were sampled at 250 Hz using data-acquisition software (Windaq, Dataq Instruments; Akron, OH) and stored on a personal computer for offline analysis. Data were analyzed using signal processing software (CODAS, Dataq Instruments; Akron, OH).

MSNA data were analyzed using custom-designed software as previously described (6). MSNA was quantified as total integrated activity, which was defined as the summed area under the curve of the bursts of MSNA. Each MSNA recording was normalized by assigning the largest sympathetic burst under resting conditions an amplitude of 1,000. All other bursts for a particular study were calibrated against that value. The zero nerve activity level was determined from the mean voltage during a period of neural silence between sympathetic bursts. A period in which bursts were absent for >6 s was found in each tracing and used for this purpose.

Assessment of integrated baroreflex control of HR and MSNA. We used sequential boluses of NTP (100 μg) and PE (150 μg) to decrease and increase, respectively, arterial pressure. We assessed the sensitivity of baroreflex control of the heart using the relationship between R-R interval (RRI) and systolic blood pressure during these vasoactive drug boluses (7, 15). The slope of the linear portion of this relation was used as an index of baroreflex sensitivity (12–15 points per regression line). The operating point for the relation in terms of resting arterial pressure and HR was calculated as the average values over the 5-min period immediately preceding the NTP bolus. Values for RRI’s from baroreflex trials were pooled over 2-mmHg ranges for analysis to minimize variability due to nonbaroreflex influences such as respiration (7). Analysis of baroreflex sensitivity in terms of RRI gives results that are directly related to efferent vagal activity to the heart (17). However, the reciprocal relationship between HR and RRI can result in a decrease in the slope of the RRI pressure relation with changes in baseline HR due to the mathematical effect that a given change in HR results in less of a change in RRI when baseline HR is higher (16). This effect is minimized when data are expressed in terms of RR. Although there were no significant changes in resting HR in HDT or SAL trials, we analyzed the present data in terms of both RRI and HR to be comprehensive in our analysis.

An index of baroreflex control of sympathetic outflow was provided by the relationship between MSNA and diastolic blood pressure (DBP) during the drug boluses (7, 8). To perform a linear regression between MSNA and pressure, values for MSNA from baroreflex trials were first signal-averaged over 3 mmHg pressure ranges (“bins”) via custom software as described previously (6). This resulted in 8–11 points per regression line. As above, this pooling procedure reduces the statistical impact of the inherent beat-by-beat variability in nerve activity due to nonbaroreflex influences. A window of nerve activity that was 1.0 s in length and synchronized by the R wave of the electrocardiogram was signal averaged. The window was time shifted to account for the latency between R waves and sympathetic bursts. The duration of the shift was varied as needed from subject to subject, but averaged 1.3 s. Any cardiac cycle not followed by a burst was assigned a total integrated activity of zero. The operating point for the relation in terms of resting arterial pressure and nerve activity was assessed as the averaged values over the 5-min period immediately preceding the NTP bolus. DBP was used because MSNA correlates more closely with DBP than with systolic pressure (22).

Statistical analysis. Data are presented as means ± SE. One-way repeated-measures ANOVA was used to compare cardiovascular variables and MSNA at rest as well as cardiac and sympathetic baroreflex sensitivities among control, HDT, and SAL trials. When a significant effect was detected, a Bonferroni post hoc test was used to identify individual differences. ΔCVP (from baseline) was compared between volume and tilt conditions by paired t-test. P < 0.05 was accepted as statistically significant.

RESULTS

Cardiovascular variables at rest. In control, resting SBP was 122 ± 3 mmHg, DBP was 73 ± 2 mmHg, and HR was 54 ± 3 beats/min. During HDT, resting HR (56 ± 3 beats/min) and DBP (76 ± 3 mmHg) were unchanged, although SBP showed a small nonsignificant change (127 ± 4 mmHg; P = 0.06). With SAL, there was a small, statistically significant increase in SBP (126 ± 2 mmHg; P < 0.05), although HR (55 ± 3 beats/min) and DBP (74 ± 3 mmHg) were again unchanged. MAP was not different across conditions (control, 89 ± 2; HDT, 93 ± 3; and SAL, 91 ± 2 mmHg; P > 0.05).

Muscle sympathetic nerve activity. MSNA was successfully recorded in 10 of the 13 subjects. Of these 10 subjects, 5 underwent volume infusion alone and 5 participated in both volume and tilt trials. Figure 1 shows an original recording from one subject of resting MSNA in control, HDT, and SAL trials. In this subject, as in most subjects, resting MSNA [total integrated activity in arbitrary units (AU)/min] decreased with tilt and/or volume infusion; however, two subjects demonstrated increased resting MSNA in HDT and SAL. Therefore, although mean values decreased, resting MSNA was not statistically different among trials (2,206 ± 367 AU/min for
control vs. 1.311 ± 541 AU/min for HDT vs. 1.821 ± 332 AU/min for SAL; P > 0.10).

CVP: As shown in Fig. 2A, resting CVP was 3.9 ± 0.6 mmHg at baseline and increased to 5.8 ± 0.8 mmHg after volume infusion (P < 0.05). In the subjects that underwent HDT, CVP increased from 3.5 ± 0.5 to 5.7 ± 0.6 mmHg (P < 0.05). The increase in CVP was similar for volume infusion (+1.9 ± 0.3 mmHg) and HDT (+2.2 ± 0.3 mmHg; P > 0.10 for deltas). The range of changes in CVP was 0.7–3.9 mmHg, although most subjects’ CVP increased ~2 mmHg with both maneuvers. The extent of increase in CVP did not appear to be related to baseline CVP.

Blood values. Table 1 shows values for hemoglobin, hematocrit, plasma osmolality, sodium, and potassium corresponding to each of the three baroreflex trials. HDT did not significantly alter any of these variables, whereas SAL caused small but significant decreases in hemoglobin, hematocrit, and plasma potassium.

Baroreflex trials. Changes in arterial pressure with NTP and PE injections were similar among control, HDT, and SAL conditions (P > 0.05 for AS among trials), as follows (differences in MAP from baseline): control NTP, −20 ± 3, PE, 7 ± 2; HDT NTP, −18 ± 2; PE, 12 ± 2; SAL NTP, −15 ± 4, and PE, 13 ± 4 mmHg. Regression coefficients (R²) averaged 0.67 for baroreflex relations for MSNA and 0.91 for baroreflex relations for HR/RRI.

Baroreflex control of MSNA. As shown in Fig. 2, increased CVP in both HDT and SAL trials resulted in a decrease in the sensitivity of baroreflex control of MSNA. During control, the sensitivity of arterial baroreflex control of MSNA was −5.05 ± 0.62 AU·beat⁻¹·mmHg⁻¹. Sympathetic baroreflex sensitivity was decreased during HDT (−3.32 ± 0.92 AU·beat⁻¹·mmHg⁻¹ (n = 5) and SAL (−3.08 ± 0.60 AU·beat⁻¹·mmHg⁻¹) (n = 10) (both P < 0.05 vs. baseline).

Baroreflex control of HR. The sensitivity of arterial baroreflex control of HR was not altered by HDT or SAL, as shown in Fig. 3. During control, sensitivity was 19.8 ± 2.8 ms/mmHg (RRI) and −1.02 ± 0.15 beats·min⁻¹·mmHg⁻¹ (HR) during control. This sensitivity was similar during HDT (RRI: 19.8 ± 3.8 ms/mmHg; HR: −1.14 ± 0.28 beats·min⁻¹·mmHg⁻¹) and SAL (RRI: 18.0 ± 2.4 ms/mmHg; HR: −0.93 ± 0.10 beats·min⁻¹·mmHg⁻¹) (n = 13, P > 0.05 for all comparisons).

On the basis of comparison of subjects who only participated in SAL trials with those who did both HDT and SAL trials, there did not appear to be an influence of HDT on subsequent baroreflex responses in the SAL trial. For example, the average of the decreases in baroreflex sensitivity for MSNA for those subjects who underwent SAL alone was −1.91 ± 0.66 AU·beat⁻¹·mmHg⁻¹, whereas the average decrease in subjects who underwent SAL after a HDT trial was −2.99 ± 1.59 AU·beat⁻¹·mmHg⁻¹ (P > 0.30)

**DISCUSSION**

Our goal in the present study was to test whether small increases in CVP with saline infusion or HDT alter the subsequent responsiveness of MSNA to changes in arterial pressure. Our major new findings are twofold. First, increases in CVP by ~2 mmHg from a normal baseline that did not change resting HR or MAP decreased the sensitivity of integrated baroreflex control of MSNA. Second, these changes were consistent whether the increased CVP was caused by HDT or by volume infusion.
In the present study, we report that increased CVP in the present study was not sufficient to decrease cardiac baroreflex responsiveness in our subjects.

**Total volume vs. CVP.** One of our major goals in the present study was to assess two different perturbations that increased CVP. HDT was used to assess whether it was the change in CVP itself, or some other aspect of volume infusion, that caused the reflex changes we observed. As shown in Table 1, there were small but significant decreases in hematocrit, hemoglobin, and plasma K⁺ in SAL compared with controls. There were no significant changes from baseline in any of the measured blood values during the HDT trial. Because the effects on baroreflex sensitivity we observed were consistent between HDT and SAL trials, these effects appear to be due to the increased CVP (that occurred in both trials) and not due to changes in these blood values caused by volume infusion.

**Potential limitations.** In the present study, we report that acute increases in CVP with either HDT or SAL inhibited baroreflex control of sympathetic activity in healthy humans. In the subjects who underwent both HDT and SAL, we did not rule out the possibility that acute HDT might have had prolonged effects on MSNA (we did not reassess the control level of baroreflex control of MSNA between HDT and SAL trials). However, because the subjects rested supine for 30 min between any two trials and because subjects who underwent SAL alone had similar results to those who underwent both HDT and SAL, we are confident that those SAL trials represented...
the influence of the volume infusion, and not a lingering effect of the acute HDT trial.

In the present study, we did not address the potential roles of volume-regulating hormones such as arginine vasopressin (AVP) in the altered sympathetic control mechanisms we observed. Hasser and colleagues have demonstrated that circulating AVP has an important role in the reflex sympathoinhibition seen with acute volume expansion in rabbits and rats (9, 10). It will be important in future work to examine the role of AVP in the influences of CVP we observed.

Clinical implications. In patients with orthostatic intolerance, it is likely that baroreflex dysfunction contributes to symptom development with assumption of the upright posture. In addition, peripheral vasoconstriction is a major determinant of effective responses to upright posture (3). Treatment of orthostatic intolerance often involves expansion of plasma volume, which has variable efficacy among patients (14, 26). Our observation of decreased responsiveness of baroreflex control of vascular sympathetic activity with increased plasma volume could contribute to the variable effectiveness of plasma volume expansion as a treatment for orthostatic intolerance. In this context, however, it is important to note that our studies involved acute perturbations to increase CVP. Whether the influences we observed are true for longer-term increases in volume or CVP remains unclear.

In summary, we report that increases in CVP that did not change resting HR or MAP inhibited the sensitivity of integrated baroreflex control of MSNA. This change in CVP did not have a measurable effect on baroreflex control of HR. Because peripheral sympathetic control of vascular resistance is important in successful physiological responses to orthostasis, it is important to recognize this effect of increased CVP in the context of orthostatic intolerance and changes in plasma volume in humans.

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REFERENCES