Acute manipulations of plasma volume alter arterial pressure responses during Valsalva maneuvers

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Fritsch-Yelle, Janice M., Victor A. Convertino, and Todd T. Schlegel. Acute manipulations of plasma volume alter arterial pressure responses during Valsalva maneuvers. J. Appl. Physiol. 86(6): 1852–1857, 1999.—The effects of changes in blood volume on arterial pressure patterns during the Valsalva maneuver are incompletely understood. In the present study we measured beat-to-beat arterial pressure and heart rate responses to supine Valsalva maneuvers during normovolemia, hypovolemia induced with intravenous furosemide, and hypervolemia induced with ingestion of isotonic saline. Valsalva responses were analyzed according to the four phases as previously described (W. F. Hamilton, R. A. Woodbury, and H. T. Harper, Jr. JAMA 107: 853–856, 1936; W. F. Hamilton, R. A. Woodbury, and H. T. Harper, Jr. Am. J. Physiol. 141: 42–50, 1944). Phase I is the initial onset of straining, which elicits a rise in arterial pressure; phase II is the period of straining, during which venous return is impeded and pressure falls (early) and then partially recovers (late); phase III is the initial release of straining; and phase IV consists of a rapid “overshoot” of arterial pressure after the release. During hypervolemia, early phase II arterial pressure decreases were significantly less than those during hypovolemia, thus making the response more “square.” Systolic pressure hypervolemic vs. hypovolemic falls were −7.4 ± 2.1 mmHg vs. −30.7 ± 7 mmHg (P = 0.005). Diastolic pressure hypervolemic vs. hypovolemic falls were −2.4 ± 1.6 mmHg vs. −15.2 ± 2.6 mmHg (P = 0.05). A significant direct correlation was found between plasma volume and phase II systolic pressure falls, and a significant inverse correlation was found between plasma volume and phase III–IV systolic pressure overshoots. Heart rate responses to systolic pressure falls during phase II were significantly less during hypovolemia than during hypervolemia (0.7 ± 0.2 beats·min⁻¹·mmHg⁻¹ vs. 2.82 ± 0.2 beats·min⁻¹·mmHg⁻¹; P = 0.05) but were not different during phase III–IV overshoots. We conclude that acute changes in intravascular volume from hypovolemia to hypervolemia affect cardiovascular responses, particularly arterial pressure changes, to the Valsalva maneuver and should be considered in both clinical and research applications of this maneuver.

baroreflex; hypovolemia; hypervolemia

THE VALSALVA MANEUVER, first described by Valsalva in 1704 (27), entails straining against a closed glottis. The resultant constriction of the chest muscles causes a reduction in venous return, a fall in cardiac output, and a fall in arterial pressure. Cardiovascular responses to the Valsalva maneuver are complicated and have both mechanical and neural components (9, 11). The mechanical components of Valsalva responses are affected by intravascular, particularly intrathoracic, volume. The reflex components of Valsalva responses are dependent on normal autonomic function. Hamilton et al. (8) described four phases of the Valsalva maneuver, each of which has distinct arterial pressure and heart rate patterns. Phase I is the initial onset of straining, which elicits a rise in arterial pressure; phase II is the period of straining, during which venous return is impeded and pressure falls (early) and then partially recovers (late); phase III is the initial release of straining; and phase IV consists of a rapid “overshoot” of arterial pressure after the release. The four phases are illustrated in Fig. 1. A typical maneuver, performed by a normal subject, is shown in Fig. 1A.

Abnormal cardiovascular responses during Valsalva maneuvers have relevance in a clinical setting. However, some patterns associated with diseases (either larger or smaller than normal pressure changes during straining) also can be seen in healthy individuals. A “square” response, in a normal, supine subject, is shown in Fig. 1B. Changes in circulating blood volume could affect the mechanical as well as the autonomic components of the Valsalva response in both healthy and unhealthy subjects. The purpose of the present investigation was to analyze the effects of acute changes in plasma volume on patterns of Valsalva responses in six healthy men. We found the typical sinusoidal-shaped arterial pressure patterns during Valsalva maneuvers were more sinusoidal during hypovolemia and blunted (square) during hypervolemia. Phase II systolic pressure falls and phase IV pressure increases were both correlated with plasma volume. These results suggest that blood volume is an important contributor to responses during Valsalva maneuvers and should be known and considered when results are interpreted.

MATERIALS AND METHODS

Subjects and protocol. Six healthy, nonsmoking normotensive men, with a mean age of 33 ± 2 yr and a mean weight of 79.6 ± 0.8 kg, gave written consent to participate in this study, which was approved by the Kennedy Space Center Human Research Review Board. During a preliminary visit to the laboratory, all subjects were familiarized with the protocols and procedures. Each subject was tested on 3 separate days, separated by at least 1 wk, in either a hypovolemic, normovolemic, or hypervolemic hydration status. The sequence of test days was randomized. All subjects abstained from exercise and caffeine for 12 h before each test period. Each subject was tested at the same time of day on each occasion. On each test day, subjects were weighed, and

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the appropriate blood volume alteration was induced. Normovolemia was defined as the subject's normal hydration state. Hypovolemia was induced with 30 mg of intravenous furosemide. Urine volume was measured continuously for at least 2 h after the injection, and testing began after urine flow had peaked. Hypervolemia was accomplished by ingestion of a flavored isotonic solution (0.9% saline) of a volume equal to 2% of lean body mass estimated by underwater weighing. The solution was consumed over 1 h in four equal portions at 15-min intervals. Testing began after the last ingestion. Immediately after each volemic treatment, subjects were instrumented for electrocardiogram, finger blood pressure (Finapres, Ohmeda, Engelwood, CO), and Valsalva expiratory pressure. Subjects rested supine for 30 min, and then Valsalva maneuvers were begun. Valsalva maneuvers were followed by a 15-min rest period, after which plasma volume was measured by using a modified Evans blue dye technique.

Valsalva maneuvers. Subjects performed five Valsalva maneuvers at an expiratory pressure of 30 mmHg. Each trial included a 30-s baseline period, a 15-s straining period, and a 2-min poststrain period. Valsalva maneuvers were begun at the end of a normal inspiration, and respiration was controlled before and after each maneuver. Valsalva responses were analyzed according to the four phases as described by Hamilton et al. (8).

Determination of plasma volume. Plasma volume was determined by a modified dye-dilution technique (7) by using sterile solutions of Evans blue dye contained in 10-ml ampules (Macarthy Medical, Romford, Essex, UK). A preinjection control blood sample was drawn followed by an intravenous injection of 11.5 mg of dye diluted with isotonic saline solution (2.5 ml), which was administered through a sterile 0.45-µm filter. One milliliter of plasma from a 10-min postinjection blood sample was passed through a wood-cellulose powder (Solka-Floc SW-40A) chromatographic column so that the dye could be absorbed. The absorbed dye was eluted from the column by using a 1:1 water-acetone solution (pH 7.0) and collected in a 10-ml volumetric flask. The postinjection solution was compared with 1-ml samples from a preinjection time (time 0) and a standard dye solution (1:50 dilution with distilled water), and all samples were read at 615 nm with a spectrophotometer. Total blood volume was calculated from the plasma volume and peripheral venous hematocrit measurements. By using these procedures in our laboratory, the test-retest correlation coefficient for blood volume was 0.969 (n = 12) and the day-to-day variation was 82 ml (1.5%; n = 17) over 4 days, 75 ml (1.5% n = 19) over 8 days, 56 ml (1.1% n = 23) over 15 days, and 71 ml (2.2%; n = 4) over 10 wk (1).

Statistics. For each Valsalva maneuver, the data were analyzed as follows: arterial pressures during the five beats preceding onset of straining were averaged to obtain baseline systolic and diastolic pressures; each of the five R-R intervals before onset of straining were converted to heart rate and averaged to obtain baseline heart rate. Valsalva responses were reduced to the following variables for statistical evaluation. For systolic and diastolic pressures, the variables were the highest single pressure during the initial phase I rise; the lowest single pressure during early phase II fall; the highest single pressure during late phase II recovery; the lowest to highest pressure during phase III-IV rise; and phase IV overshoot, which was baseline subtracted from the highest single pressure. Baroreflex sensitivity was calculated from the phase II change in heart rate/systolic pressure fall (beats·min⁻¹·mmHg⁻¹) and phase III-IV change in heart rate/systolic pressure rise (beats·min⁻¹·mmHg⁻¹). The five trials for each subject were averaged to obtain a point estimate for each subject for each volemic state. All data are presented as means ± SE.

Because data were not normally distributed (Shapiro-Wilks test of normality), a nonparametric Friedman’s ANOVA test (a nonparametric test corresponding to a repeated-measures ANOVA) was used for statistical comparisons (6). A one-factor (volemic state) randomized block (subjects) ANOVA was used to statistically evaluate volemic state differences across the primary dependent variables. When a group of primary dependent variables comprised a theoretical construct or were highly intercorrelated, a multivariate extension was applied to this basic model. Tukey’s honestly significant difference test was applied in situations where multiple comparisons were needed to evaluate volemic state means. Least squares regression analysis was used to correlate plasma volume and arterial pressure responses during phases II and III-IV.

RESULTS

Baseline measurements. Average plasma volumes were 3,212 ± 109 ml at baseline, 2,862 ± 72 ml during hypovolemia (P = 0.04 from baseline), and 3,486 ± 91 ml during hypervolemia (P = 0.001 from baseline). Average supine baseline heart rate did not change with volemic state: 59 ± 3 beats/min (bpm) during baseline, 58 ± 3 bpm during hypovolemia (P = 0.85 from baseline), and 60 ± 3 bpm during hypervolemia (P = 0.84 from baseline, P = 0.69 from hypovolemia). Average systolic pressure was 117 ± 2 mmHg during baseline, 114 ± 2 mmHg during hypovolemia (P = 0.50 from baseline), and 124 ± 2 mmHg during hypervol-
emia (P = 0.37 from baseline, P = 0.73 from hypovolemia). Average diastolic pressure was 66 ± 2 mmHg during baseline, 70 ± 3 mmHg during hypovolemia (P = 0.50 from baseline), and 79 ± 4 mmHg during hypervolemia (P = 0.03 from baseline, P = 0.03 from hypovolemia).

Valsalva maneuver responses. Figure 2 depicts average systolic (A) and diastolic (B) pressure changes for all phases of the Valsalva maneuver in all three hydration states. The hypervolemic condition resulted in a significantly more square pressure profile during phase II, whereas the hypovolemic state resulted in a more sinusoidal profile. During early phase II, four of the six subjects had a greater fall in systolic pressure and five had a greater fall in diastolic pressure during hypovolemia than during normovolemia; five of six had a smaller fall in systolic pressure and all six had a smaller fall in diastolic pressure during hypervolemia than during normovolemia. Similarly, during phase III-IV, four subjects had greater systolic and diastolic overshoots during hypovolemia than during normovolemia; four had less systolic pressure and five had less diastolic pressure overshoots during hypervolemia than during normovolemia. These changes are reflected in the statistical results. During phase I, neither systolic nor diastolic pressure increases changed significantly with volemic state. However, during early phase II, both systolic and diastolic pressure reductions were significantly greater during hypovolemia than during hypervolemia. Moreover, there was a significant direct correlation between the magnitude of the early phase II systolic fall and plasma volume (Fig. 3A), as well as a direct correlation between the change in magnitude of the early phase II fall and the change in plasma volume (Fig. 3C). During late phase II, systolic pressure recovery was significantly greater during hypovolemia than during hypervolemia. Late phase II diastolic pressure recovery did not change significantly with volemic state. During phase III, systolic and diastolic pressure decreases did not differ with volemic state. Systolic and diastolic increases between phases III and IV and between phase IV and baseline did not differ with volemic state, but there was a significant inverse correlation between the magnitude of the phase III-IV systolic rise and the plasma volume (Fig. 3B) as well as the change in the magnitude of phase III-IV systolic rise and the change in plasma volume (Fig. 3D).

Figure 4 depicts the correlation between phase II systolic fall and phase III-IV systolic rise in all three volemic states. These were highly correlated (P = 0.001).

Heart rate responses to arterial pressure changes during Valsalva maneuvers were also influenced by volemic state. Average baroreflex sensitivities during early phase II systolic fall were as follows: 1.18 ± 0.41 beats·min⁻¹·mmHg⁻¹ at baseline, 0.7 ± 0.2 beats·min⁻¹·mmHg⁻¹ during hypovolemia (P = 0.49 from baseline), and 2.82 ± 0.17 beats·min⁻¹·mmHg⁻¹ during hypervolemia (P = 0.16 from baseline, P = 0.05 from hypovolemia).

During phase III-IV systolic pressure rises, baroreflex sensitivities were as follows: -0.84 ± 0.55 beats·min⁻¹·mmHg⁻¹ during hypervolemia (P = 0.72 from baseline, and -0.43 ± 0.32 beats·min⁻¹·mmHg⁻¹ during hypovolemia (P = 0.70 from baseline, P = 0.61 from hypovolemia).

**DISCUSSION**

We acutely changed plasma volume in healthy individuals and showed that, as plasma volume progresses from hypovolemia to hypervolemia, arterial pressure patterns during Valsalva maneuvers become progressively less sinusoidal and more square. Specifically, the magnitudes of phase II arterial pressure decreases and phase III-IV arterial pressure overshoots were both related to plasma volume (Fig. 3). This information underlines the importance of knowing the volume status of patients and subjects when interpreting responses to Valsalva maneuvers in both the clinical and research environments.

Arterial pressure reductions during phase II of the Valsalva maneuver result from the drop in cardiac output secondary to the decreased venous return caused by the constriction of the chest muscles (8, 11, 27). Baroreflex-mediated increases in heart rate and sympathetic nerve activity can limit the magnitude of the
pressure reduction and effect a reversal by late phase II. Abnormally large decreases in phase II pressure are associated with inadequate reflex adrenergic activity (11, 13, 15, 18–20, 26). However, the present data show that phase II pressure reductions can be made larger simply by decreasing plasma volume and can be made smaller simply by increasing plasma volume. Hypervolemia buffers and hypovolemia exacerbates the reduction in venous return during straining. This respectively attenuates (hypervolemia) or potentiates (hypovolemia) phase II pressure falls. Because the magnitude of the phase II pressure reduction determines the magnitude of the reflex sympathetic response (4, 11, 22), which, in turn, directly affects the magnitude of the arterial pressure overshoot during phase III-IV (22), it is not surprising that when phase II is square the phase IV overshoot is smaller and when phase II is more sinusoidal the phase IV overshoot is larger. In our subjects, this same relation also was maintained in all three volemic states (Fig. 4). This finding also is consistent with previous findings that baroreflex-mediated elevations in peripheral resistance increase as plasma volume progresses from hypervolemia to hypovolemia (25).

Square arterial pressure responses during Valsalva straining are often observed in congestive heart failure patients (12, 15, 16, 21) and are thought to indicate reduced left ventricular function and/or increased filling pressure. Square responses are also seen with mitral stenosis, constrictive pericarditis, and atrial septal defects, all conditions that can maintain left ventricular filling pressure during straining (1). However, square Valsalva responses have been reported in other experimental and clinical situations. In addition to patients who have circulatory congestion and large intrathoracic volumes, responses in normal individuals can change from sinusoidal to square when intrathoracic volume is increased simply by changing from a standing to supine posture (1, 10, 13, 24). In a previous study we showed that Valsalva pressure responses in astronauts may be square before spaceflight; sinusoidal after landing, when plasma volume is reduced ~9%; and square again 3 days later, when plasma volume has recovered (5). The present study extends these observations by relating acute changes in total circulating blood volume with changes in arterial pressure patterns during Valsalva responses. Taken together, these findings support the notion that the changes we observed in this study are most probably the result of the mechanical effects of changes in circulating blood volume. Our findings in the present study that significant differences were observed only between hypovolemic and hypervolemic states but not between normovolemic and hypervolemic or between normovolemic and hypovolemic states.
volemic states (Fig. 2) are consistent with the results of Luster et al. (14), who only compared normovolemia and hypovolemia.

These data showed a significant increase in heart rate responses to phase II pressure reductions with hypervolemia. This observation does not support those of other investigators who have shown either a potentiation (2, 3, 17) or no change (23) of heart rate baroreflex responses when central volume is decreased. However, the design of the present study did not address that particular issue. Because early phase II pressure reductions were significantly different in the different volemic states, the stimulus to which the heart rate was responding was not consistent, making the baroreflex results difficult to interpret. Moreover, during phase IV overshoots, when increases in arterial pressure did not vary among the different volemic states, baroreflex responses also did not vary.

Limitations. It is likely that the changes in plasma volume induced in this study evoked small-to-moderate changes in circulating levels of hormones such as angiotensin II, vasopressin, and atrial natriuretic factor and increases in sympathetic activity, all of which act to maintain arterial pressure at baseline levels, and could possibly have confounded our measurements. If angiotensin II or vasopressin increased during hypovolemia, for example, they could increase arteriolar resistance and attenuate or prevent the arterial pressure fall during early phase II. The opposite effect would be expected during the hypervolemic state. In a similar manner, volume expansion could elicit atrial reflexes (such as the Bainbridge reflex), which could affect heart rate responses. However, we did not find any significant differences in baseline heart rates among any of the volemic states. Thus it is possible that the significant differences that we observed among the three volemic states may have been somewhat buffered by these compensatory responses, but this does not negate our conclusion that the changes we measured are most probably attributable to the mechanical effects of the changes in circulating blood volume.

In summary, we acutely manipulated circulating blood volume to determine the effects of changes in hydration status on responses to Valsalva maneuvers in healthy men. We found that arterial pressure patterns changed from sinusoidal to square as blood volume increased. We suggest that hydration status must be known and considered when Valsalva responses are evaluated either clinically or in a research environment.

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