Control of cerebral blood velocity with furosemide-induced hypovolemia and upright tilt

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Assumption of upright posture displaces blood from the upper to the lower body, decreases venous return acutely, and activates autonomic responses that defend against abrupt hypotension. Maintenance of upright posture depends critically on the continuous support of adequate venous return, arterial pressure, and, most importantly, cerebral perfusion and oxygenation (21).

Orthostatic intolerance has been associated with reductions of total body water (4, 12), but the influence of dehydration on cerebral blood flow during orthostasis has not been studied thoroughly. Utilizing transcranial Doppler ultrasound recordings from middle cerebral arteries in humans, Carter et al. (3) showed that cerebral blood velocity (CBV) decreases to a greater extent in dehydrated than euvolemic subjects during standing. Reductions of CBV with dehydration were not associated with greater reductions of arterial pressure, suggesting that dehydration may present unique challenges to the cerebral circulation during orthostasis (3).

The cerebrovasculature regulates blood flow by altering vessel caliber through autonomic (37) and myogenic and metabolic (1, 8, 25) mechanisms. Water drinking improves tolerance to central blood volume reductions in conjunction with increased cerebrovascular control, as assessed from estimates of cerebral blood pressure and flow (32), but the influence of dehydration on cerebrovascular control during orthostatic stress has not been described. The purpose of this study was to test the hypothesis that dehydration compromises the control of CBV, accounting for greater reductions of CBV during upright tilt than in the euhydrated condition.

METHODS

Subjects. Men were invited to participate in this study, which was approved by the Institutional Review Board for the Protection of Human Subjects in Research of the University of Texas at San Antonio. Written informed consent was obtained from all subjects subsequent to a verbal and written briefing of all experimental procedures. Participants were deemed healthy to participate through a standard health questionnaire (physical activity readiness questionnaire (PAR-Q)). Because of the possible influence on blood pressure and cardiovascular and cerebrovascular control mechanisms, subjects abstained from caffeine, exercise, and alcohol for 24 h before the experiment. Additionally, subjects reported for experimentation after a 12-h fast. Subjects were not tobacco users. On the basis of changes in CBV expected during head-up tilt (HUT), using a Student’s t-test-based power calculation, we estimated that a sample size of 8–10 subjects would be adequate to test our hypothesis (α = 0.05 and β = 0.8). A total of nine subjects participated [23 ± 0.5 (SE) yr old, 172 ± 2 cm stature, 87 ± 3 kg body wt].

Experimental protocol. Each subject was required to attend two separate experimental sessions. Each session was separated by 7 days and occurred on the same weekday and time as the previous session. Both experimental sessions included each of the following: 1) hydration assessment, 2) hydration protocol to maintain total body water [euvhydration (EUH)] or reduce total body water [dehydration (DEH)], and 3) HUT protocol. The order of condition assignment (EUH or DEH) was randomized and counterbalanced.

Hydration assessment. Subjects reported to the laboratory at 8 AM for determination of initial hydration status. The hydration assessment consisted of the following procedures: 1) body mass measurement, 2) urine specific gravity assessment, and 3) blood analysis for calculated estimates of relative changes (%Δ) in plasma volume (PV) and blood volume (BV). Body mass was measured using a calibrated weight scale (Body Composition Analyzer BF-350, Tanita, Tokyo, Japan). EUH in all subjects was confirmed before each protocol by assessment of urine specific gravity. Subjects provided a urine sample (~100 ml), and EUH was presumed when the specific gravity was <1.02 g/ml (31). For assessment of PV and BV, a sample of whole
blood was taken via finger lancet on the lateral side of the middle finger or through venipuncture of an antecubital vein. The blood sample was immediately transferred to a heparinized microcapillary tube; within 5 min of collection, it was centrifuged for 60 s at ~6,000 rpm at room temperature (~21°C) and then analyzed for hematocrit (HemataSTAT-II). The remaining sample of whole blood was collected into a microcuvette (HemoCue, Angelholm, Sweden) and, within 5 min of collection, placed in an automated Hb analyzer (Hb 201+. HemoCue) and analyzed for Hb concentration at room temperature. Relative changes (%) in PV and BV were estimated using alterations in hematocrit and Hb, as outlined by Dill and Costill (11).

Hydration protocol. After the hydration assessment, one of two hydration protocols (EUH or DEH) was assigned and initiated at 9 AM. DEH was induced with complete fluid restriction (for 7 h) and oral ingestion of the diuretic furosemide (40 mg). For the EUH protocol, subjects were required to drink water equating to 0.02 l/kg body mass during the 7-h protocol to maintain EUH (31). A standardized breakfast and lunch were provided during DEH and EUH conditions, except fluid intake was restricted under DEH. Subjects maintained their normal activity patterns during the 7-h EUH and DEH protocols and did not perform any additional exercise. After each 7-h hydration protocol, subjects returned to the laboratory for a posthydration protocol assessment before the HUT test.

HUT protocol. Subjects returned to the laboratory at 4 PM for the HUT protocol. Immediately after each posthydration protocol assessment, subjects were instrumented with a standard three-lead ECG (Harvard Apparatus, Holliston, MA) and a finger photoplethysmograph (Finometer, Finapres Medical Systems, Amsterdam, The Netherlands) for estimates of beat-by-beat arterial pressures. CBV was measured through the temporal window in the middle cerebral artery with a transcranial Doppler ultrasound device (MultiDop T, DWL Electronics, Sipplingen, Germany). Breath-by-breath end-tidal CO2 was monitored using a facemask covering the nose and mouth and attached to a sampling line leading to an infrared CO2 analyzer (Gambro, Enström, Sweden).

After instrumentation, subjects rested quietly for 10 min in the supine position and were then tilted head-up to 70° for 10 min on a motorized tilt table. Subjects were then returned to the supine position for a 5-min recovery period. To effectively remove contributions to low-frequency (LF) oscillations elicited by respiration (6), subjects controlled their breathing strictly by breathing in time to a metronome.

Data and statistical analysis. Data were collected at 500 Hz by computer acquisition software (DATAQ, Windaq Systems) and subsequently imported and analyzed with computerized analysis software (WinCPRS, Absolute Aliens, Turku, Finland). After R wave detection, the ECG, systolic and diastolic pressures and CBVs were identified. Cerebrovascular resistance was calculated by dividing mean arterial pressure (MAP) by mean CBV (CBV_mean). Beat-by-beat stroke volume was estimated using a modified pulse contour method (18). Data were averaged during the last 5 min of the supine period (baseline) and during the first (T1) and last (T2) 5 min of HUT.

CBVs and MAP were analyzed in the frequency domain by first resampling data at 4 Hz and interpolating nonequidistant data. Next, data were passed through a low-pass impulse response filter using a frequency cutoff of 0.4 Hz, and signal variances were expressed as a function of frequency with a Fourier transform (5). Arterial baroreflex sensitivity was calculated from cross-spectral analysis of MAP and CBV_mean within the LF range of 0.04–0.15 Hz (9). The coherence between blood pressure and cerebral perfusion was calculated using cross-spectral analysis of MAP and CBV_mean within the LF range of 0.07–0.20 Hz (36). Transfer function calculations were not performed, as most coherence values were <0.5 at baseline.

Pre- and posthydration body mass, PV, and BV changes were analyzed using a Student's t-test. Mean differences between the dependent variables of interest were compared using a 2 × 3 repeated-measures analysis of variance on hydration status (EUH vs. DEH) and position (supine vs. HUT T1 and HUT T2). Interactions were probed with Tukey’s post hoc procedure. All statistical analyses were conducted using commercially available software (SigmaPlot, Sys- tSoftWare). The probabilities of observing chance effects due to our experimental manipulations are presented as exact probability values (23).

RESULTS

Hydration results. Body mass was reduced with DEH from 86.9 ± 3 to 84.9 ± 3 kg (P < 0.001). BV and PV were reduced by 6% and 10% with the DEH protocol (P ≤ 0.008, n = 8). One subject’s data were discarded from the PV and BV analysis because of unreliable measurements resulting from technical complications. One subject developed nausea after ~7.5 min during HUT with DEH and was returned to the supine position. For this reason, comparisons are made with eight subjects during DEH T2.

Responses during baseline and upright tilt. Hemodynamic responses to DEH and HUT are shown in Table 1. DEH reduced systolic and pulse pressures, as well as stroke volume, during the baseline, supine condition. Systolic pressure, pulse pressure, and stroke volume fell during HUT T1 under both conditions but were significantly lower (P ≤ 0.05) in the DEH condition, eliciting a greater increase in heart rate. These responses persisted at T2, except for stroke volume, which remained 18% lower in the DEH condition but was statistically

<table>
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<tr>
<th>Variable</th>
<th>Baseline</th>
<th>DEH (n = 8)</th>
<th>EUH (n = 8)</th>
<th>DEH (n = 8)</th>
<th>EUH (n = 8)</th>
<th>DEH (n = 8)</th>
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</thead>
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<tr>
<td>RRI, ms</td>
<td>985 ± 34</td>
<td>961 ± 47</td>
<td>762 ± 26*</td>
<td>692 ± 18†</td>
<td>743 ± 22*</td>
<td>693 ± 20†</td>
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<td>HR, beats/min</td>
<td>62 ± 2</td>
<td>64 ± 3</td>
<td>80 ± 3*</td>
<td>88 ± 2†</td>
<td>80 ± 3*</td>
<td>89 ± 3†</td>
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<td>SAP, mmHg</td>
<td>130 ± 3</td>
<td>121 ± 2†</td>
<td>119 ± 4*</td>
<td>109 ± 4†</td>
<td>117 ± 5*</td>
<td>108 ± 3†</td>
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<td>DAP, mmHg</td>
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<td>77 ± 3</td>
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<td>45 ± 2†</td>
<td>45 ± 2*</td>
<td>34 ± 2†</td>
<td>42 ± 3*</td>
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<td>SV, ml</td>
<td>84 ± 3</td>
<td>72 ± 4*</td>
<td>55 ± 4*</td>
<td>45 ± 3†</td>
<td>56 ± 4*</td>
<td>48 ± 4*</td>
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<tr>
<td>CVR, mmHg cm⁻¹·s⁻¹</td>
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<td>1.7 ± 0.03</td>
<td>1.8 ± 0.03*</td>
<td>2.0 ± 0.03†</td>
<td>1.8 ± 0.03*</td>
<td>1.9 ± 0.03*</td>
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<tr>
<td>End-tidal CO2, %</td>
<td>4.4 ± 0.1</td>
<td>4.1 ± 0.1</td>
<td>3.5 ± 0.1*</td>
<td>3.3 ± 0.1*</td>
<td>3.6 ± 0.1*</td>
<td>3.5 ± 0.1*</td>
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</table>

Values are means ± SE. EUH, euhydration; DEH, dehydration; T1, first 5 min of head-up tilt; T2, last 5 min of head-up tilt; RRI, heart rate; SAP, DAP, MAP, and PP, systolic, diastolic, mean, and pulse arterial pressures; SV, stroke volume; CVR, estimated cerebral vascular resistance calculated as the ratio of MAP to mean cerebral blood velocity. *P < 0.05 vs. baseline within condition. †P < 0.05 vs. EUH.

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indistinguishable from EUH ($P = 0.11$). Cerebrovascular resistance was similar between hydration conditions during baseline but was elevated at T1 during DEH ($P = 0.02$) compared with EUH. End-tidal CO$_2$ decreased for both hydration conditions during HUT ($P < 0.001$) but was similar between DEH and EUH at all time points.

Responses of CBV to DEH are shown for one representative subject in Fig. 1. Responses of CBV (systolic, diastolic, and mean) to DEH are shown for the entire subject cohort in Fig. 2. The HUT protocol reduced CBV under both hydration conditions, but DEH reduced CBV at baseline compared with EUH, and these reductions were maintained throughout the HUT protocol ($P \leq 0.02$). After normalization for changes observed at baseline following DEH, percent reductions of CBV with HUT (~15%) were consistent and not statistically distinguishable between DEH and EUH ($P > 0.5$). One subject experienced presyncopal symptoms during HUT with DEH, but no subjects experienced presyncopal symptoms during HUT with EUH.

Arterial baroreflex sensitivity and cerebrovascular control. The coherence between systolic arterial pressure and R-R interval was maintained at all times above 0.5 for all subjects [indicative of a strong relationship between the two variables (10)]. Arterial baroreflex sensitivity as expressed by the transfer function gain was not different between conditions at baseline (10.9 ± 0.5 and 8.6 ± 0.5 ms/mmHg for EUH and DEH, $P = 0.16$) and decreased for both conditions with HUT (6.5 ± 0.4 and 5.4 ± 0.5 ms/mmHg for EUH and DEH, $P \leq 0.04$). These reductions of baroreflex sensitivity with HUT were not dependent on hydration condition (interaction $P = 0.3$).

Time series and cross-spectral data for MAP and CBV$_{mean}$ are shown for one subject who did not develop symptoms of presyncope (asymptomatic) under the EUH or DEH condition during HUT and for the subject who reported nausea (symptomatic) during the DEH condition only (Fig. 3). MAP and CBV$_{mean}$ were consistently lower for the asymptomatic subject during DEH than EUH: MAP averaged 128 mmHg during EUH and 92 mmHg during DEH, and CBV$_{mean}$ averaged 53 cm/s during EUH and 40 cm/s during DEH. LF oscillations of MAP and CBV$_{mean}$ were also higher during DEH: LF MAP averaged 4.7 mmHg$^2$ during EUH and 15.3 mmHg$^2$ during DEH, and LF CBV$_{mean}$ averaged 1.4 cm/s$^2$ during EUH and 4.2 cm/s$^2$ during DEH. Coherence was substantially higher for this subject during DEH (0.87) than EUH (0.31). MAP was similar for the asymptomatic subject during EUH and DEH (93 ± 3 and 93 ± 5 mmHg), but CBV$_{mean}$ was lower during DEH (46 ± 7 vs. 61 cm/s). Consistent with the asymptomatic subject, LF MAP averaged 1.5 mmHg$^2$ during EUH and 8.3 mmHg$^2$ during DEH; LF CBV$_{mean}$ was 1.1 cm/s$^2$ during EUH and increased to 4.6 cm/s$^2$ during DEH, but coherence values were identical between hydration conditions (0.58 during EUH and 0.57 during DEH).

LF MAP and CBV$_{mean}$ oscillations derived from a Fourier transform and cross-spectral coherence analysis between MAP and CBV are shown in Fig. 4. LF MAP and LF CBV$_{mean}$ oscillations were not different between conditions at baseline but increased significantly with upright tilt ($P < 0.001$) and were significantly higher for DEH T1 than EUH T1 ($P = 0.03$ for LF MAP and $P = 0.04$ for LF CBV$_{mean}$). LF oscillations of MAP and CBV$_{mean}$ were higher than baseline at T2 ($P \leq 0.05$) but not different between hydration conditions. The coherence between MAP and CBV$_{mean}$ during baseline was similar between EUH and DEH. Coherence increased during upright tilt and was greater at T1 for DEH than EUH ($P = 0.01$) but was similar at T2 between hydration conditions. We did not calcu-
late transfer function gain between MAP and CBV mean because of the low coherence between these variables at baseline.

DISCUSSION

In this study, we document the effects of furosemide-induced hypovolemia on cardiovascular and cerebrovascular control during upright tilt. The primary novel finding of our study is that exacerbated reductions of CBV during HUT following DEH are associated with alterations in cerebrovascular control, as manifested by increased LF oscillations and coherence between arterial pressure and CBV during the first 5 min of HUT. Increased LF oscillations of CBV and MAP may represent a transient protective mechanism in response to the greater reduction in central volume (i.e., stroke volume) and CBV during DEH and orthostasis.

DEH-induced hypovolemia and responses to upright tilt. Using complete fluid restriction and furosemide ingestion, we induced a 2% reduction in body mass, a 6% reduction in BV, and a 10% reduction in PV. Studies documenting the influence of dehydration on orthostatic tolerance have reported similar reductions in body mass, BV, and PV (3, 19). Reductions of total body water challenge compensatory mechanisms that...
CBVmean (coherence) for all subjects (during EUH) despite similar end-tidal CO2, suggesting that mained significantly lower throughout the HUT protocol than condition. CBV was reduced with DEH at baseline and re-
MAP, but reductions were similar, regardless of hydration with DEH during the first 5 min of HUT. Upright tilt decreased study, upright tilt decreased stroke volume to a greater extent
perfusion during postural changes (3, 4, 7). In the current
defend against severe reductions of blood pressure and cerebral perfusion during postural changes (3, 4, 7). In the current study, upright tilt decreased stroke volume to a greater extent with DEH during the first 5 min of HUT. Upright tilt decreased MAP, but reductions were similar, regardless of hydration condition. CBV was reduced with DEH at baseline and remained significantly lower throughout the HUT protocol than during EUH (despite similar end-tidal CO2), suggesting that DEH poses unique challenges to the cerebral circulation that are not linked to downstream changes in absolute arterial pressure. Others have reported similar results and have attributed reductions of CBV during standing with DEH to increased cerebrovascular resistance (3). We also report increased cerebrovascular resistance during tilt with DEH, but such increases were statistically different from the EUH condition only during the first 5 min of HUT (Table 1) and, therefore, cannot account for the consistently lower CBV measured during T2 (Fig. 2).

Arterial baroreflex sensitivity and cerebrovascular control. It is intuitive that maintenance of stable hemodynamics during orthostasis depends on mechanisms that control dynamic changes of arterial pressure and cerebral blood flow. The sensitivity of the arterial baroreflex is reduced during tilt (34), and it has been proposed that hemodynamic collapse leading to syncope is associated with reduced cerebral autoregulatory capacity (15). Recent evidence, however, suggests that barore-
flex sensitivity and cerebral autoregulatory capacity are, in fact, related inversely in healthy humans (35). Tzeng et al. (35) propose that the two regulatory processes interact to buffer and augment cerebral blood flow to optimize cerebral perfusion with changes in arterial pressure oscillations. For example, higher arterial pressure oscillations are associated with a reduction in baroreflex sensitivity but an increase in cerebral autoregulatory capacity to protect cerebral perfusion (35). We reasoned that if DEH reduced baroreflex sensitivity during HUT, concurrent, compensatory improvements in cerebral reg-
ulation would manifest to protect against the subsequent in-
crease in arterial pressure oscillations (35). Although HUT reduced arterial baroreflex sensitivity by ∼40%, this reduction was not exacerbated with DEH and was not related to the greater increase in arterial pressure oscillations or increase in arterial pressure-CBV coherence with DEH.

Direct associations between orthostatic intolerance and the concept of reduced cerebral autoregulatory capacity have not been observed consistently, but the hypothesis that reduced cerebral autoregulatory capacity precedes presyncope, or even frank syncope, has been advanced (14–16). The relationship between DEH and cerebral blood flow is even less clear. Ogawa et al. (24) induced moderate reductions of PV (∼10%) with furosemide and documented unchanged arterial pressure and CBV. After PV reduction, coherence between CBVmean and MAP was not altered, but transfer function gain was decreased, interpreted by the authors as an improved autoreg-
ulatory capacity (24). In the current study, we confirm that PV reduction with furosemide does not alter coherence between arterial pressure and CBV, and we extend these observations to demonstrate increases in coherence in the EUH and DEH states during HUT, with significantly higher coherence values during DEH.

To our knowledge, ours is the first study to assess the influence of DEH on dynamic cerebrovascular control during upright tilt. The coherence between MAP and CBVmean was higher at T1 during DEH than EUH and remained elevated above baseline at T2 (Fig. 4). However, the initial changes of cerebral regulatory capacity at T1 during DEH stabilized at T2, while coherence continued to increase during EUH. Similar coherence between DEH and EUH at T2 indicates that chal-
lenges to the cerebral circulation during this time period reflect the orthostatic stress specifically, rather than the combined influence of HUT and DEH.

Increased coherence signifies an increased linear relation-
ship between changes in MAP and CBVmean; this has been interpreted as representing a weakening of the cerebral auto-
regulatory capacity (13, 36, 38). However, the lack of causal relationship between increased coherence and orthostatic symptoms at T1 is highlighted by the data presented in Fig. 3. For the asymptomatic subject, coherence between MAP and CBVmean during DEH approached 0.9, representing almost complete concordance between MAP and CBV. Although MAP and CBVmean were substantially lower for this subject during DEH, LF oscillations of pressure and flow velocity were substantially higher than during EUH. In contrast, oscillations of MAP also increased during DEH for the symptomatic subject, but these increased oscillations apparently did not transfer to the cerebrovasculature, as coherence was identical for the symptomatic subject during EUH and DEH. It should be noted that presyncope for this susceptible subject mani-
fested as nausea and was associated with greater reductions in CBV during HUT. These data demonstrate that there is not a definitive association between increased coherence and symptomology (reflecting reduced cerebral perfusion). Our findings of increased oscillations and coherence for the entire subject cohort (Fig. 4) suggest that lower CBV with HUT during DEH than EUH is associated with alterations in cerebral regulatory responses that may not reflect a “weakening” of cerebral autoregulatory capacity. Indeed, with the exception of one subject, HUT during DEH was tolerated well by our subjects, suggesting that, regardless of hydration status, CBV was sufficient to prevent the onset of presyncopal symptoms. Increased oscillations of CBV have been associated with improved tolerance to central hypovolemia and, as such, may represent a normal compensatory protective mechanism to ensure adequate cerebral perfusion and the lessening of orthostatic symptoms (27–29). Rather than an impairment of traditionally interpreted cerebral autoregulation, the increase in coherence may therefore reflect simultaneous increases in MAP and CBV oscillations that are elicited to preserve cerebral perfusion under the combined stresses of orthostasis and dehydration.

It should be appreciated that functioning cerebral autoregulation does not necessarily imply unchanging flow. For example, Heistad and Kontos (17) suggested implicitly that cerebral autoregulation reflects the dynamic relationship between changes in flow and changes in pressure, rather than the observation of “unchanged” flow over a wide range of pressures, as originally outlined by Lassen (20). Recently, using infusions of nitroprusside and phenylephrine, Lucas et al. (22) demonstrated that cerebral blood flow is a linear function of blood pressure in normal, healthy subjects, supporting the concept that lack of a stable plateau region for CBV within the arterial pressure range thought to encompass cerebral autoregulatory capacity (~60 to 150 mmHg (20)) is not an abnormal response. Our results expand on this concept, suggesting that the transfer of arterial pressure oscillations to the cerebrovasculature might actually be a compensatory mechanism that allows the maintenance of cerebral perfusion in the face of hypovolemic challenge. The interpretation of an increase in coherence between arterial pressure and CBV as “ineffective” or “reduced” cerebral autoregulation should therefore be reconsidered, as an increase in coherence may in fact be beneficial, rather than detrimental, in terms of cerebral function under these conditions.

Study limitations. Measurements of CBV may not represent cerebral blood flow. The use of transcranial Doppler to assess cerebral blood flow assumes that the insonated vessel diameter remains constant. In defense of this concept, simultaneous measurement of CBV (via transcranial Doppler) and vessel diameter (via magnetic resonance imaging) during orthostatic stress indicates that the diameter of the middle cerebral artery is unaltered (33). However, because estimates of cerebrovascular resistance increased with DEH, we cannot discount the possibility that DEH and/or HUT increased sympathetic outflow to the cerebrovasculature, resulting in cerebral vasocostriction (21). Alternatively, direct influences of furosemide on vascular smooth muscle might produce constriction and, therefore, account for the increases we observed in cerebrovascular resistance. However, Pickers et al. (26) showed that furosemide has no direct effect on the caliber of arterial vascular smooth muscle in human forearm vessels. While topical application of furosemide (30 mM) increases cortical blood flow in the rat (30), its specific effect on the vasoinactivity of the middle cerebral artery in humans or animals in vivo has not been documented. It is also possible that furosemide induced changes in plasma osmolality, as well as renal blood flow (2), but the extent to which such influences might impact cerebrovascular control has not been determined.

Conclusions. DEH represents a unique challenge for cerebral regulation and subsequent maintenance of orthostatic stability. Our results support the concept that DEH alters cerebrovascular control mechanisms in association with lower CBV during the initial assumption of HUT. Increased oscillations between arterial pressure and CBV with the combination of DEH and HUT may reflect acute protective mechanisms to ensure adequate cerebral perfusion under conditions of reduced central blood volume.

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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the authors.

REFERENCES


