Acute volume expansion attenuates hyperthermia-induced reductions in cerebral perfusion during simulated hemorrhage

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¹Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital of Dallas and the Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas; ²Department of Anesthesiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; ³Ohio Musculoskeletal and Neurological Institute, Ohio University, and Departments of Biomedical Sciences and Speciality Medicine, Ohio University Heritage College of Osteopathic Medicine, Athens, Ohio; and ⁴Copenhagen Muscle Research Center, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

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Schlader ZJ, Seifert T, Wilson TE, Bundgaard-Nielsen M, Secher NH, Crandall CG. Acute volume expansion attenuates hyperthermia-induced reductions in cerebral perfusion during simulated hemorrhage. J Appl Physiol 114: 1730–1735, 2013. First published April 11, 2013; doi:10.1152/japplphysiol.00079.2013.—Hyperthermia reduces the capacity to withstand a simulated hemorrhagic challenge, but volume loading preserves this capacity. This study tested the hypotheses that acute volume expansion during hyperthermia increases cerebral perfusion and attenuates reductions in cerebral perfusion during a simulated hemorrhagic challenge induced by lower-body negative pressure (LBNP). Eight healthy young male subjects underwent a supine baseline period (pre-LBNP), followed by 15- and 30-mmHg LBNP while normothermic, hyperthermic (increased pulmonary artery blood temperature ~1.1°C), and following acute volume infusion while hyperthermic. Primary dependent variables were mean middle cerebral artery blood velocity (MCAVmean), serving as an index of cerebral perfusion; mean arterial pressure (MAP); and cardiac output (thermodilution). During baseline, hyperthermia reduced MCAVmean (P = 0.001) by 12 ± 9% relative to normothermia. Volume infusion while hyperthermic increased cardiac output by 2.8 ± 1.4 l/min (P < 0.001), but did not alter MCAVmean (P = 0.99) or MAP (P = 0.39) compared with hyperthermia alone. Relative to hyperthermia, at 30-mmHg LBNP acute volume infusion attenuated reductions (P < 0.001) in cardiac output (by 2.5 ± 0.9 l/min; P < 0.001), MAP (by 5 ± 6 mmHg; P = 0.004), and MCAVmean (by 12 ± 13%; P = 0.002). These data indicate that acute volume expansion does not reverse hyperthermia-induced reductions in cerebral perfusion pre-LBNP, but that it does attenuate reductions in cerebral perfusion during simulated hemorrhage in hyperthermic humans.

lower-body negative pressure; heat stress; brain blood flow; volume infusion

METHODS

Eight healthy male volunteers participated in this study. The subject characteristics were (mean ± SD) age, 29 ± 5 yr; height, 180 ± 5 cm; weight, 75 ± 4 kg; body surface area, 1.5 ± 0.1 m². All subjects were nonsmokers, not taking medications and were free of any known cardiovascular, metabolic, or neurological diseases. Each subject was fully informed of the experimental procedures and possible risks before giving informed written consent. This protocol was approved by the Ethics Committee of Copenhagen (H-KF-090/004) and was registered with the Danish data protection agency and ClinicalTrials.gov under the National Library of Medicine (NCT00714766). All procedures conformed to the standards set by the Declaration of Helsinki. Subjects arrived at the laboratory euhydrated (having ingested ~1.8 liter of fluid during the prior 24 h) and having refrained from strenuous exercise, alcohol, and caffeine for a period of 24 h. These data were collected...
concurrently with those presented in a published manuscript, which tested a unique research hypothesis (3).

Instrumentation and measurements. Mean skin temperature was measured from the weighted average of six thermocouples attached to the skin (27). Body temperature was controlled via a water-perfused tube lined suit (Med-Eng, Ottawa, ON, Canada) that covered the entire body except the head, hands, one forearm, and the feet. Heart rate was continually recorded from a five-lead electrocardiogram. Mean arterial pressure (MAP) was measured via a cather placed in the brachial artery of the nondominant arm. Pulmonary artery blood temperature was measured via a flow-directed pulmonary arterial catheter (93A-831H-7.5F, Baxter Healthcare, Irvine, CA) introduced through the basilica vein of the left arm and advanced to the pulmonary artery. Central venous pressure (CVP) was measured via an alternate port on the pulmonary arterial catheter. Vascular pressures were referenced to atmospheric pressure via uniflow pressure transducers (Baxter Healthcare) that were zeroed 5 cm below the sternal notch and connected to a pressure-monitoring system (Dialogue 2000, ICB-Danica, Copenhagen, Denmark). All catheters were flushed with isotonic saline at 3 ml/h. Arterial blood samples were analyzed for changes in arterial carbon dioxide tension (PaCO2), hemoglobin, and hematocrit (Radiometer ABL700, Brønshøj, Denmark), and corrected to pulmonary artery blood temperature. Cardiac output was measured in triplicate via the thermodilution method (15). Mean middle cerebral artery blood velocity (MCAvmean) served as an index of cerebral perfusion and was measured by adjusting a 2-MHz Doppler probe (Multidop X, DWL, Sipplingen, Germany) over the temporal window (1, 29).

Experimental protocol. Following instrumentation, subjects rested quietly in the supine position while normothermic water (34°C) perfused the suit. After normothermic baseline data collection, LBNP commenced at 15 mmHg, which was immediately followed by 30 mmHg. LBNP of 30 mmHg was the highest level applied as it was expected that all subjects could tolerate this LBNP during hyperthermia for a period sufficient to obtain the desired data prior to symptoms of syncope. The duration of each LBNP stage for all thermal conditions was ~15 min, which was required to obtain the data reported in the companion paper (3). Following normothermic LBNP, the subjects underwent whole body passive heat stress by perfusing 46–48°C water through the suit. This heat stress continued until pulmonary artery blood temperature increased ~1.0°C (typically after 30–45 min), after which the water temperature was slightly reduced to attenuate further increases in body temperature during the ensuing data collection periods. The subjects were not allowed to drink at any time during the experimental procedures. Hyperthermic baseline data were then obtained, which was followed by 15- and 30-mmHg LBNP. Following a brief recovery after the cessation of LBNP and while remaining heat stressed, 500 ml of 38°C cold solution (HES 130/0.4, Voluven, Fresenius Kabi, Sweden) followed by warm saline was rapidly infused. The total infused volume was ~12 ml/kg and was typically administered in <10 min. Baseline data were collected after the completion of the infusion, which was then followed by 15- and 30-mmHg LBNP.

Data analysis. Thermal, hemodynamic, and pressure data were sampled at 50 Hz via a data acquisition system (Biopac System, Santa Barbara, CA). Data were reduced into 60-s averages during the baseline periods and following 5 min of each stage of LBNP. Stroke volume was calculated from cardiac output and heart rate, while systemic vascular resistance (SVR) was calculated as (MAP – CVP) divided by cardiac output. An index of cerebral vascular resistance (CVR) was calculated as the quotient of MAP and MCAvmean. Percentage changes in plasma volume, occurring as a result of the volume infusion, were estimated from changes in hematocrit and hemoglobin (12). Data during LBNP are presented as absolute values and as a change (Δ) from pre-LBNP baseline for each respective condition.

Statistical analysis. Data at baseline for normothermia, hyperthermia, and hyperthermia + infusion were analyzed using one-way repeated measures analysis of variance (ANOVA) (hypothesis 1), while data while during LBNP during the hyperthermia and hyperthermia + infusion conditions were analyzed using a two-way repeated measures ANOVA (2 × 3; condition × LBNP) (hypothesis 2). Data during the normothermic condition were not included in the analysis for hypothesis 2 given that the inclusion of these data was not necessary to test this hypothesis. Where appropriate, post hoc, pairwise comparisons were made incorporating a Bonferroni adjustment. Data were analyzed using SigmaPlot (v.12, Systat Software, Chicago, IL) with a priori statistical significance set at P ≤ 0.05. All data are reported as means ± SD.

RESULTS

Normothermia, hyperthermia, and hyperthermia + volume infusion baselines (hypothesis 1). Thermal and hemodynamic variables during normothermia, hyperthermia, and following the volume infusion baseline (pre-LBNP) periods are presented in Table 1. Relative to normothermia, hyperthermia was characterized by ~1.1 and ~2.8°C increases (P < 0.001) in pulmonary artery blood and mean skin temperatures, respectively, which were maintained (P = 0.084) during the infusion. The volume infusion increased plasma volume by 18 ± 5%, and augmented (P < 0.001) cardiac output, but did not affect (P = 0.999) MAP. Notably, PaCO2 was well maintained (P = 0.351) throughout these baseline periods. MCAvmean and CVR at baseline are presented in Fig. 1. Relative to normothermia, MCAvmean was reduced (P = 0.001) by 12 ± 9% during hyperthermia and was unaffected (P = 0.394) by volume infusion. CVR was similar (P = 0.471) throughout all baseline periods.

Lower-body negative pressure (hypothesis 2). Pulmonary artery temperature was ~0.2°C higher (P = 0.006) throughout LBNP following the volume infusion (38.0 ± 0.3°C), relative to during hyperthermia alone (37.8 ± 0.4°C), MCAvmean and CVR during LBNP are presented in Fig. 2. CVR remained constant (P = 0.281) as LBNP progressed, while MCAvmean decreased (P < 0.001) in both conditions. However, relative to hyperthermia, volume infusion attenuated the reduction in MCAvmean during 15 (P = 0.049) and 30 (P = 0.002) mmHg LBNP. Hemodynamic variables during LBNP are presented in Fig. 3. Cardiac output, stroke volume, MAP, and CVP all decreased (P < 0.001) as LBNP progressed, while SVR...
increased ($P < 0.001$). At both stages of LBNP, volume infusion augmented ($P < 0.001$) cardiac output and stroke volume, while it attenuated ($P = 0.004$) the reduction in MAP at 30-mmHg LBNP. During LBNP, $P_{aCO_2}$ was similar ($P = 0.559$) between hyperthermia (33 ± 5 mmHg) and volume infusion (35 ± 5 mmHg) conditions.

**DISCUSSION**

The purpose of this study was to test the hypotheses that acute plasma volume expansion during hyperthermia elevates cerebral perfusion at rest and attenuates reductions in cerebral perfusion during a subsequent simulated hemorrhagic challenge. The novel findings of this study are that acute volume expansion 1) does not reverse hyperthermia-induced reductions in cerebral perfusion at rest, but that 2) it attenuates reductions in cerebral perfusion during a subsequent simulated hemorrhage while hyperthermic. That is, an increase in pulmonary artery blood temperature of ~1.1°C (Table 1) reduced $MCA_{mean}$ by ~12% (Fig. 1), but acute volume infusion sufficient to increase cardiac output by almost 3 l/min (Table 1) did not restore $MCA_{mean}$ toward normothermic levels (Fig. 1). However, acute volume infusion during hyperthermia did attenuate LBNP-induced reductions in $MCA_{mean}$ (Fig. 2). This was likely a function of the volume infusion’s augmentation of cardiac output and stroke volume prior to LBNP (Fig. 3), which better maintained MAP at a given level of LBNP (Fig. 3), thereby forestalling LBNP-induced reductions in $MCA_{mean}$ (Fig. 2). These data indicate that cardiac output is not capable of directly (i.e., independent of arterial pressure) modulating cerebral blood flow during hyperthermia. However, the data do support that the beneficial effects of acute volume loading prior to a hyperthermic simulated hemorrhage are, at least partially, mediated via the preservation of arterial pressure and, by extension, the maintenance of cerebral perfusion.

**Acute volume expansion and cerebral perfusion during hyperthermia.** During normothermia, experimentally induced fluctuations in cardiac output directly modulate brain blood flow in humans (24). Presumably, this effect is mediated via the arterial baroreflex and subsequent changes in cerebral vascular tone occurring secondary to changes in sympathetic nerve activity (22, 23). Accordingly, we hypothesized that the same phenomenon would occur during hyperthermia, such that the augmentation of cardiac output would (at least partially) restore hyperthermia-induced reductions in cerebral perfusion. However,
this was not the case (Fig. 1). There are two potential reasons for this observation.

First, acute volume expansion during hyperthermia restores central blood volume to normothermic levels (9) and augments an already elevated skin blood flow (7). Thus increases in blood flow as a consequence of volume infusion in those vascular beds with a low vascular resistance (e.g., the cutaneous vasculature) appear likely, whereas blood flow in vascular beds with a higher vascular resistance (e.g., the cerebral vasculature) would remain constant. As evidence for this hypothesis, in the present study systemic vascular resistance further decreased during volume infusion (Table 1), while MCA\textsubscript{mean} and CVR were unchanged (Fig. 1).

Second, the effect of increasing cardiac output on the cerebral vasculature during normothermia may be mediated by the arterial baroreflex and subsequent changes in sympathetic nerve activity (22, 23). Hyperthermia impairs the responsiveness of some aspects of the baroreflex (5) and also shifts the baroreflex operating point (5, 11) to accommodate hyperthermia-induced hemodynamic changes (6). Thus the sensitivity of the cerebral vasculature to modify blood flow to a given change in cardiac output may be reduced during hyperthermia. How-
ever, this remains speculative as there is no direct evidence in support of such an arrangement. It is also notable that this hypothesis requires that the sympathetic nervous system innervate cerebral vessels and modify cerebral blood flow in humans, which remains debated (28).

**Acute volume expansion and cerebral perfusion during hyperthermic LBNP.** The ability to withstand a hemorrhagic challenge is reduced during hyperthermia, while acute volume expansion reverses this intolerance (17). The mechanisms underlying this observation are not currently known. We hypothesized that, relative to hyperthermia alone, acute volume expansion during hyperthermia would attenuate reductions in cerebral perfusion at a given level of LBNP. The present data support this hypothesis. Specifically, following volume infusion, $MCVA_{mean}$ during LBNP was higher than during hyperthermia alone (Fig. 2). These data indicate that during simulated hemorrhage cerebral perfusion is better maintained during hyperthermia following volume expansion. From the testing of our first hypothesis, the mechanism for this observation is not via the direct influence of acute volume loading, and subsequent increases in cardiac output, on cerebral perfusion prior to the simulated hemorrhagic challenge. Rather, these data support the proposal (see Refs. 3, 10) that volume expansion results in a higher cardiac output and stroke volume at a given level of LBNP (Fig. 3), which better maintains arterial pressure (Fig. 3) and in turn maintains cerebral perfusion as LBNP progressed (Fig. 2). Thus these data suggest that the preservation of simulated hemorrhagic tolerance following volume infusion during hyperthermia is, at least partially, mediated via attenuations in LBNP-induced reductions in arterial pressure and cerebral perfusion.

**Methodological considerations.** Given the invasive nature of this study, it was not feasible to randomize the three experimental conditions as this would have required three separate laboratory visits and thus arterial and right heart catheterization on three occasions. Accordingly, pulmonary artery blood temperature was slightly higher ($\sim 0.2^\circ C$) during LBNP with volume infusion relative to LBNP during hyperthermia alone. Given these slight temperature differences and that cerebral perfusion progressively decreases as internal body temperature increases, albeit at larger increments than $0.2^\circ C$ (13), these findings suggest that we likely underestimated the magnitude of the beneficial effect of acute volume expansion on changes in cerebral perfusion during LBNP.

Given that these data were collected concurrently with another study (3), coupled with the aforementioned challenges resulting in it not being feasible to perform the experimental sessions on three separate days, in the present study we did not measure LBNP tolerance. Thus these data have been carefully interpreted and the conclusions drawn only pertain to situations involving the administered levels of LBNP. Therefore, cerebral vascular responses during hyperthermia following acute volume expansion at the point of LBNP intolerance remain unknown. Nevertheless, the presented data provide insights into possible mechanisms underlying the beneficial effects of acute volume expansion on LBNP tolerance during hyperthermia.

It is also worth noting that in the present study subjects were exposed to moderate levels of LBNP three times within a relatively short time period ($\sim 90$ min). It remains unknown whether there are any physiological effects of repeated moderate LBNP over this period, and if so whether those effects would be sufficient to influence the profound changes observed during heat stress and heat stress plus volume infusion. That said, some changes do occur given that adaptation to daily LBNP exposures has been observed in as little as five consecutive days (18). Whether this influenced the conclusions drawn presently remains uncertain.

We utilized transcranial Doppler to quantify $MCVA_{mean}$, which serves as an index of cerebral perfusion given that this artery supplies $\sim 80\%$ of the blood flow received by each cerebral hemisphere (20). However, it must be acknowledged that if the diameter of the insonated artery changes, then changes in blood velocity do not always reflect proportional changes in blood flow. Yet, the diameter of the middle cerebral artery is unaffected by moderate carbon dioxide and blood pressure perturbations (16, 26). Even still, the effect of hyperthermia on middle cerebral artery diameter remains uncertain.

**Conclusions.** The present study demonstrates that acute volume expansion does not reverse hyperthermia-induced reductions in cerebral perfusion at rest, but that it does attenuate the reduction in cerebral perfusion during a subsequent simulated hemorrhage while hyperthermic. Thus cardiac output does not appear to directly (i.e., independent of arterial pressure) modulate cerebral blood flow during hyperthermia. However, acute volume loading prior to a simulated hemorrhagic event while hyperthermic attenuates the LBNP-induced reductions in arterial pressure and thereby better maintains cerebral perfusion.

**Perspectives.** Testing of these hypotheses has furthered the understanding of the mechanisms by which acute volume infusion preserves the capacity to withstand a subsequent hemorrhagic challenge during hyperthermia. The findings presented have implications for individuals at risk of a hemorrhagic injury under heat stress conditions (e.g., soldiers, firefighters, miners, etc.). The data suggest that plasma volume loading in a hyperthermic individual prior to a hemorrhagic injury will assist in the maintenance of cerebral perfusion through stabilizing arterial pressure, as opposed to a direct effect of an increase in cardiac output, independent of arterial pressure, as has been found in normothermic individuals (24).

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**


**REFERENCES**


