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Progressive dry to humid hyperthermia alters exercise cerebral blood flow

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ABSTRACT

Introduction: Exercising in hot conditions may increase the risk for exertional heat-related illness due to reduction in cerebral blood flow (CBF); however, the acute effect of exercise-induced changes on CBF during compensable and uncompensable heat stress remain unclear. We tested the hypothesis that exercising in hot dry and humid conditions would have different CBF responses.

Methods: Nine healthy active males completed a 30 min baseline rest then 60 min of low intensity self-paced exercise (12 rating of perceived exertion) in a 1) control compensable neutral dry (CN; 23.7 ± 0.7 °C; 10.7 ± 0.8%R*h*) and 2) compensable hot dry (CH; 42.3 ± 0.3 °C; 10.7 ± 1.8%R*h*) that progressively increased to an uncompensable hot humid (UCH; 42.3 ± 0.3 °C; 55.2 ± 7.7%R*h*) environment in random order separated by at least 4 days.

Results: We observed that during CN environments from rest through 60 min of exercise, middle cerebral velocity ($MCAv_{mean}$) and conductance ($MCAv_{mean}$ CVC) remained unchanged. In contrast, during CH, $MCAv_{mean}$, $MCAv_{mean}$ CVC, and cardiac output (Q) increased and systemic vascular resistance (SVR) decreased. However, under UCH, $MCAv_{mean}$, $MCAv_{mean}$ CVC, and Q was reduced. No difference in mean arterial pressure or ventilation was observed during any condition. Only during UCH, end-tidal PO_2 increased and PCO_2 decreased. The redistribution of blood to the skin for thermoregulation (heart rate, skin blood flow and sweat rate) remained higher during exercise in UCH environments. **Conclusions**: Collectively, exercise cerebral blood flow is altered by an integrative physiological manner that differs in CN, CH, and UCH environments. The control of CBF may be secondary to thermoregulatory control which may provide an explanation for the cause of exertional heat illness.

1. Introduction

The acute effect of exercise-induced changes on cerebral blood flow (CBF) is unclear. Conflicting studies report an increase (Jorgensen et al., 1992), no change (Scheinberg et al., 1954), or a decrease (Querido and Sheel, 2007) in CBF. However, most report an increase in CBF and associate the changes with arterial partial pressure of carbon dioxide (PCO_2) and mean arterial pressure (MAP) see review (Querido and Sheel, 2007). Nevertheless, Ogoh and Ainslie report that global CBF remains constant and unaffected by conditions such as exercise despite changes in regional metabolism and neuronal activity (Ogoh and Ainslie, 2009). During a maximal exercise test, the progressive increase in exercise intensity of up to 60% of maximal aerobic capacity, CBF is increased but returns to baseline values above 60% due to the hyperventilatory decrease in *P*CO2 (Hellstrom et al., 1996).

Passive exposure to high ambient temperatures causes stress to the cardiovascular system, which serves two critical roles: 1) the redistribution of blood flow to the skin (for evaporative cooling) and 2) preserving aortic mean pressure (Rowell et al., 1969b) for constant cerebral blood flow (CBF) perfusion to maintain oxygen and glucose to cerebral tissue. Furthermore, exercising adds an additional stressor and when combined with heat exposures that causes a profound increase in cardiovascular strain due to the thermoregulatory adjustments that aim to defend both internal temperature and arterial blood pressure (Rowell et al., 1969b). Nybo and Nielsen (2001a, b) first reported that the increase in internal body temperature during prolonged volitional exhaustion was associated with a reduction in middle cerebral artery mean velocity ($MCAv_{mean}$) (Nybo and Nielsen, 2001b). They also reported that in both, cool and hyperthermia conditions, CBF increases initially and decreased only during hyperthymia, which accompanied an increase in ventilation and a reduction in PCO_2. This has been further supported in subsequent studies by the same group (Nybo et al., 2002).

Collectively, CBF involves an integrative process that is affected by

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pulmonary gas exchange (Ide et al., 2003; Poulin et al., 1996), cardiovascular function (Bouma and Muizelaar, 1990), and intracranial mediators of cerebral vessel resistance (Heckmann et al., 1999; Lawley et al., 2017) which ultimately affect flow (Willie et al., 2014). Exercise and environmental exposures have been reported to alter CBF and contribute to central fatigue (Nybo and Nielsen, 2001a, b; Periard and Racinais, 2015). However, the severity of heat exposure on cardiovascular strain and CBF may cause different integrative regulatory responses for maintaining CBF, arterial pressure, and thermoregulation. For example, hot dry compared to hot humid conditions affect the severity of thermal and cardiovascular strain due to compensable or uncompensable heat stress (Montain et al., 1994). Heat loss conditions that exceed the capacity of the body's heat dissipation mechanism are said to be uncompensable and internal temperatures are increased to a point of exhaustion; while compensable is defined as maintaining internal body temperature via heat dissipation. To date, the interactions of low-intensity self-selected exercise and various environmental conditions (hot dry vs hot humid) on CBF response have not been examined. We designed a study to examine the hypothesis that exercising during a progressive change from a compensable (hot dry) to an uncompensable (hot-humid) condition would have dynamic CBF responses, associated with cardiovascular and systemic vascular alterations.

2. Materials and methods

2.1. Participants

Nine healthy active males completed this study. The participant characteristics for body morphology, cardiorespiratory fitness, and physical activity are listed in Table 1. Subjects were excluded if they had any known cardiovascular, renal, neurological, metabolic diseases, or were taking medications known to affect the cardiovascular system and/or heat dissipation. A prescreening obtaining an informed written consent, health and physical activity readiness questionnaire (PAR-Q, (Pescatello and American College of Sports Medicine., 2014), body composition (Dual-energy X-ray absorptiometry, DXA, General Electric, Lunar Prodigy Primo, Madison, WI), weight (Health-o-meter 349KLX, McCook, IL, USA) and height (Stadiograph, Health-o-meter 205 HR, McCook, IL, USA) assessments. This was followed by a cardiorespiratory fitness test (VO_2max), physical activity monitor (7-day, Actigraph GT3XP-BTLE, Pensacola, FL, USA), and familiarization with all experimental procedures. All consented participants were healthy physically active, and not heat acclimated prior to testing. Testing was completed in the northern hemisphere (Lubbock, TX, USA) during the winter and spring months (average outdoor temperature, 7.0 ± 2.2 °C). This study was approved by the Texas Tech University Institutional Review Board and in agreement with the *Declaration of Helsinki*.

Table 1
Participant characteristics for body morphology, fitness, and physical activity. Results are expressed as means ± SD.

Morphology	
Age (y)	23.4 ± 7.5
Height (cm)	173.6 ± 5.2
Weight (kg)	74.1 ± 7.6
Fat mass (kg)	20.9 ± 19.4
Fat mass (% total mass)	19.2 ± 3.2
Lean mass (kg)	57.2 ± 4.4
Lean mass (% total mass)	79.6 ± 4.7
Cardiorespiratory Fitness and Physical Activity	
VO_2max ($mLO_2 \cdot kg \cdot min^{-1}$)	52.4 ± 7.5
VO_2max ($LO_2 \cdot min^{-1}$)	4.1 ± 0.5
Peak heart rate ($beat \cdot min^{-1}$)	186 ± 9
Peak work rate (watts)	294.4 ± 32.5
Physical activity (steps·day)	8370 ± 2669
Sedentary activity (% of day)	72.4 ± 6.1
Light activity (% of day)	23.3 ± 6.4
Moderate activity (% of day)	3.8 ± 2.2
Vigorous activity (% of day)	0.3 ± 0.3

2.2. Experimental design

This study was a randomized-controlled repeated measures design. Participants were required to visit the laboratory on three occasions. The first day entailed the consent, followed by a body composition scan, then a VO_2max test, and lastly a familiarization. Participants then wore a physical activity monitor over 7 days. After 7 days, they were then randomized to two experimental conditions: 1) a compensable thermal neutral dry (control) condition dry (23.7 ± 0.7 °C; 10.7 ± 0.8% relative humidity [R*h*]) and 2) a hot condition that started compensable and progressively increased to an uncompensable environment. The hot condition started dry (~10% R*h*) during rest baseline (30 min) and during 20 min of exercise. After 20 min of exercise, humidity was ramped up over the next 40 min (up to ~55% R*h*) (See Table 2 and Fig. 1 for the ramped changes in environmental conditions). Conditions were separated by no more than 4 days. Prior to entering the climatic chamber, participants rested quietly while blood pressure, internal and skin temperatures were recorded. The participants then entered the climate-controlled chamber (Darwin Chambers Company, LLC, St. Louis, MO, USA), rested on the semi-recumbent ergometer (Corival Recumbent 929900, Lode B.V. Medical Technology, Groningen, Netherlands) while the seat was adjusted, and pedal straps were fitted. During this time, the participants rested for 30 min while instrumented for sweat capsules, laser Doppler probes, and the transcranial doppler. After 30 min, resting baseline values were obtained, participants started exercising while blinded to exercise work rate. The initial starting work was 50 W and increased by 10–20 W until the participants self-selected the exercise that represented a perceived exertion of 12 on a 20-point scale (Borg rating of perceived exertion, RPE, between light and somewhat hard) (Borg, 1982). The initial work rate was adjusted every 1 min until the rating of perceived exertion (RPE) of 12 was achieved. Oxygen uptake was measured for 5 continuous min at rest and every 10 min until 60 min of exercise was completed. Every 10 min participants were asked to rate their perceived exertion and thermal comfort, and the investigator adjusted the workload appropriately in order to maintain the RPE of 12 throughout. For the purpose of thermoregulation, matching metabolic heat production is recommended to be the best approach for controlling the confounder for group differences in mass and body surface area (Cramer and Jay, 2014; Rivas et al., 2017). Even though self-selected exercise in hot conditions allowed for participants to adjust to a lower exercise intensity (external work) as hyperthermia increased, exercise economy (see Table 2) and calculated metabolic heat production was similar between hot dry and humid conditions (hot dry 9.8 ± 2.0 w/kg vs hot humid 9.9 ± 2.2 w/kg; $P = 0.38$.). Water intake was provided ad libitum for all visits. No fan was provided under any condition; however, the circulation of air onto the participant from the conditioning unit was 1 m s^{-1} (measured with digital anemometer PROTMEX, MS6252A, Guangdong, China). Clothing was controlled for by having the participant change into 5″ 95% polyester shorts (Baleaf, Fujian, China) and 100% cotton thin sleeveless shirt (Gildan, Montréal Canada).

2.3. Peak exercise capacity test

Maximal oxygen uptake (VO_2max) was determined by a progressive, incremental graded cycle ergometer stress test to volitional exhaustion. The protocol required participants to cycle on the ergometer (Excalibur Sport Model 925900, Groningen, Netherlands) at an initial resistance of 50 W, which then increased 25 W every 1 min until volitional fatigue using automated software (Lode Ergometry Manager LEM 10, Lode B.V. Medical Technology). Participants were instructed to

Table 2
Environmental conditions, arterial blood pressure, gas exchange parameters, and work rate, during rest and exercise in neutral (open circle) and hot dry (grey circle) and humid (black circle) conditions. Results are expressed as means ± SD. † indicates statistical difference from rest; ‡ indicates statistical difference from exercise in dry condition; * indicates statistical difference from the neutral condition of same time point.

	Neutral			Hot			Interaction	Main Effect	
	Rest	EX dry	EX dry	Rest	EX dry	EX humid	C × T	C	T
Environmental Conditions									
Temperature (^{0}C)	23.8 ± 0.5	23.5 ± 1.3	23.5 ± 1.3	42.1 ± 0.3*	42.3 ± 0.3*	42.2 ± 0.3*	*ns*	< **0.0001**	*ns*
Relative humidity (%)	11.0 ± 1.9	11.2 ± 1.5	13.0 ± 2.2	10.7 ± 0.9	13.4 ± 3.8	55.2 ± 7.7*†‡	< **0.0001**	< **0.0001**	< **0.0001**
Heat Index (^{0}C)	23.7 ± 0.4	23.6 ± 0.8	23.7 ± 0.6	39.3 ± 0.5*	40.4 ± 1.6*	68.1 ± 8.5*†‡	< **0.0001**	< **0.0001**	< **0.0001**
Arterial Blood Pressure									
Mean pressure (mmHg)	89.8 ± 9.9	93.7 ± 13.2	91.2 ± 9.1	87.9 ± 5.7	92.1 ± 10.4	92.6 ± 10.9	*ns*	*ns*	*ns*
Systolic pressure (mmHg)	122.4 ± 6.2	135.0 ± 36.0	126.6 ± 17.5	123.5 ± 8.7	149.6 ± 24.4	134.1 ± 26.3	*ns*	*ns*	*ns*
Diastolic pressure (mmHg)	73.5 ± 12.9	78.8 ± 14.3	74.0 ± 12.5	70.0 ± 7.5	65.2 ± 6.2	69.6 ± 11.9	*ns*	*ns*	*ns*
Pulse pressure (mmHg)	48.9 ± 10.8	61.9 ± 42.4	53.1 ± 24.3	53.4 ± 11.6	86.2 ± 22.7	62.4 ± 31.2	*ns*	*ns*	*ns*
Gas Exchange Parameters									
End-tidal PO_2 (Torr)	116.3 ± 2.5	106.2 ± 3.2†	105.4 ± 2.7†	116.9 ± 2.7	106.7 ± 1.9†	111.4 ± 6*†‡	< **0.01**	ns	< **0.0001**
End-tidal PCO_2 (Torr)	34.2 ± 3.4	47.1 ± 4.2†	45.1 ± 2.5†	34.5 ± 1.5	46.1 ± 2.0†	40.0 ± 5.9*†‡	< **0.02**	*ns*	< **0.0001**
VO_2 ($LO_2 \cdot min^{-1}$)	0.4 ± 0.1	2.0 ± 0.3†	2.0 ± 0.3†	0.4 ± 0.1	1.7 ± 0.2*†	1.7 ± 0.5*†‡	< **0.03**	*ns*	< **0.0001**
Breathing Frequency ($breath \cdot min^{-1}$)	17.3 ± 4.4	50.2 ± 10.1	53.8 ± 9.7	17.0 ± 3.8	48.8 ± 4.3	59.2 ± 18.2	*ns*	*ns*	< **0.0001**
Ventilation ($L \cdot min^{-1}$)	13.0 ± 3.5	47.2 ± 9.9	45.8 ± 10.3	12.4 ± 2.3	40.5 ± 5.7	45.0 ± 13.4	*ns*	*ns*	< **0.0001**
Exercise work rate									
Absolute work rate (watt)	0.0 ± 0.0	94.4 ± 17.5†	87.1 ± 18.0†	0.0 ± 0.0	81.9 ± 14.0*†	66.1 ± 26.2*†‡	< **0.04**	< **0.02**	< **0.0001**
Economy ($mLO_2 \cdot watt$)	0.0 ± 0.0	21.4 ± 2.5	23.4 ± 3.1	0.0 ± 0.0	21.4 ± 3.1	26.3 ± 6.8	*ns*	*ns*	< **0.0001**

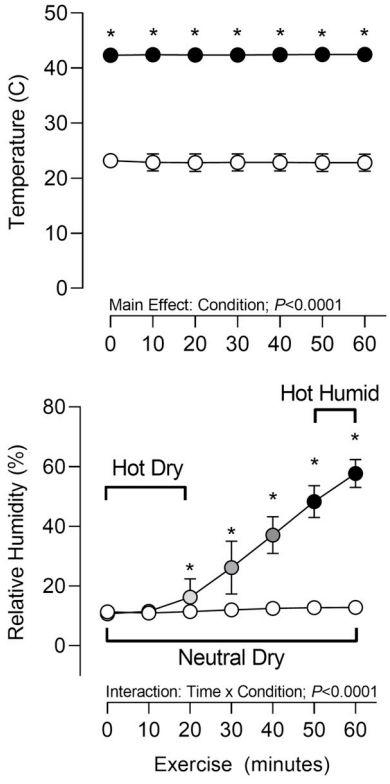

Fig. 1. Study design of ramping protocol for temperature and relative humidity. From time 0 rest, and 10–20 min was indicative of compensable heat stress (grey circles), and 50–60 min represented uncompensable heat stress (black circles). The neutral condition remained dry and cool (open circles). Results are expressed as means ± SD. * indicates statistical difference from the neutral condition of same time point.

find a cadence above 50 revolutions per minute (RPM) and maintain throughout test. Respiratory gases were analyzed using the MOXUS Modular Metabolic System (Ametek S-3A and CD-3A; AEI Technologies, Bastrop, TX, USA) after O_2 and CO_2 gas and air flow were calibrated using known gases and a 3-L syringe. RPE (Borg scale 6–20) were measured throughout the exercise test. Heart rate was monitored with a Polar chest strap (Polar Electro Inc. T31, Bethpage, NY). The test was deemed to be maximal once the participant could not maintain a consistent revolution per minute above 50 RPM (drop in 10 RPM) due to volitional fatigue. Blood capillary finger-prick lactate samples were obtained at 1 min after exhaustion (Lactate Scout+, EKF Diagnostics, Leipzig, Germany). The test was considered to be maximal if at least four of six following criteria were met: a respiratory exchange ratio (RER) of ≥1.10, a plateau in VO_2 with increasing workloads, workload volitional fatigue (a fall of 10 revolutions per minute cadence), exercise heart rate that was within 10 beats of the age-predicted maximal heart rate (207- [0.67 × age]) (Gellish et al., 2007), RPE of greater than 19, and blood lactate values greater than 8 Mm. All participants met at least 4 of the listed criteria.

2.4. Thermoregulation instrumentation and measurements

For each condition, participants were asked not to exercise, ingest alcohol or caffeine the day before or day of testing. Prior to the study, they were asked to not ingest food at least 4 h prior, ingested a telemetric pill (CorTemp Data Recorder 262K, HQ, Inc, Palmetto, FL, USA) 3 h prior to arrival, and drink 1 bottle (500 mL) of room temperature water 1 h before coming to the laboratory. Upon arrival, euhydration was confirmed (1.009 ± 0.006) via urine specific gravity (Refractometer PAL-10S, Atago Co., LTD Tokyo, Japan). Naked body weight was then obtained pre and post condition to assess whole-body fluid loss. Mean skin temperature was measured by the taping (Transpore, 3M Health Care, Neuss, Germany) of thermocouples (Omega Engineering, Stamford, CT) on the right side of the body. Mean skin temperature was calculated using weighted coefficients from six sites (chest, shoulder, lower back, abdomen, thigh, and calf) (Taylor et al., 1984). Local sweat rate was measured using a custom-built capsule (2.54 cm^2 surface area) taped to the skin of the forearm. The capsule was perfused (E20 rapid cuff inflator & AG101 air source) with dry air using drying columns (four Drierite 26800 columns with Drierite 23001 Indicating desiccant, OH, USA). The tubing prior to the capsule inlet was connected to a flow controller (Omega FMA-A2307, Stamford, CT, USA) and set to a flow rate of 500 mL min^{-1}. The outlet tubing leaving capsule was attached to capacitance hygrometry (Vaisala, Woburn, WA). Local skin blood flow perfusion was measured using a laser doppler (Moor Instruments, Devon, UK) taped to the forearm adjacent to the sweat capsule. Subjective thermal comfort (TC) and

exertion (RPE) were measured utilizing validated scales and indices (Tikuisis et al., 2002). Thermal comfort was assessed using a perception scale ranging from − 4 “Very cold” to + 4 "Extremely hot." Exercise exertion was measured using the standard Borg's RPE scale (from 6 to 20). For all scales, participants were shown the visual scales and asked to report thermal comfort, and exertion as a number that best represents their whole-body thermal sensation or exertion at that moment. One L of water was set in circulating bath (Polyscience SD07H170 7L, Polyscience Division of Preston Industries Inc., Niles, IL, USA) set at body temperature (37 °C) and provided ad libitum. Participants drank more water during hot compared to the neutral condition (546 ± 209 vs 142 ± 179 mL); however, hydration was maintained in both conditions (0.4 ± 0.4 vs 0.6 ± 0.7% change in body mass from fluid loss; $P = 0.21$).

2.5. Cardiovascular and cerebrovascular instrumentation and measurements

Heart rate (Polar T31) was instrumented at sternum level. A blood pressure (Mobil-O-Graph 24hr PWA Monitor, ALF Distribution GmbH, Aachen, Germany) cuff was fitted (correct size according to manufacture instruction) on the left arm rested at heart level. Blood pressures were recorded and extracted from Mobil-O-Graph 24hr PWA software (HMS Client Server, version 5.1). This algorithm enabling oscillometric device with brachial cuffs has been validated with acceptable accuracy compared with intra-aortic readings (Hametner et al., 2013; Weber et al., 2011) and cardiac output and peripheral resistance (Siegfried W. et al., 2008; Weber et al., 2017) and is highly reproducible (Papaioannou et al., 2013). Mean arterial blood pressure was calculated as ((systolic + [diastolic pressure × 2]) ÷ 3). Cardiac output was obtained from Mobil-O-Graph 24hr PWA software. Systemic vascular resistance (SVR) was obtained by multiplying the MAP/CO ratio by 80, where 80 is a conversion factor to convert units to standard resistance units. Cerebral blood flow (Trans-cranial Doppler, TOC2MD, Multigon Industries, Inc., Elmsford. NY, USA) was obtained using a 2-MHz probe prepared with ultrasound gel adjusted over the temporal window to insonate the left middle cerebral artery (MCA) at a depth of 44–58 mm (Aaslid et al., 1989). The probe was held in place throughout the rest and exercise with a plastic headgear. Mean flow velocity was calculated as ((PSV + [EDV × 2]) ÷ 3) (Nicoletto and Burkman, 2009). Gosling's pulsatility index (PI) provides an estimation of downstream cerebral vascular resistance and is equal to ([PSV – EDV] ÷ MFV), whereas dilation decreases and constriction increases the PI value (Gosling and King, 1974). Notably, PI positively correlates with intracranial pressure (ICP) as a 2.4% increase is associated with a 1 mmHg change in ICP. The Pourcelot resistivity index (RI) was calculated as equal to ([PSV – EDV] ÷ PSV) with values > 0.8 indicating increased downstream resistance (White and Venkatesh, 2006). High ICPs result in high pulsatility indices (PIs) in high-resistance vascular beds, in which a formula has been derived to convert pulsatility index into ICP, with a sensitivity of 89%, and specificity of 92% (ICP = [10.93 × PI] − 1.28) (Bellner et al., 2004).

2.6. Submaximal exercise, gas exchange and work rate measurements

Oxygen uptake was obtained using a mouthpiece (Hans Rudolph, Shawnee, Kansas, USA) with the nose occluded. End-tidal O_2, and end-tidal CO_2, (expressed as a percentage of total end-tidal expiratory gas), breathing frequency, and ventilation, were measured via breath-by-breath (Moxus Metabolic System). End-tidal O_2 and CO_2 were then used to calculate end-tidal PO_2 and PCO_2 and calculated as ($PETO_2$, $PETCO_2$; percentage gas concentration ÷ 100 × ambient barometric pressure). Prior to each experimental session, the system was volume and gas calibrated as previously mentioned. Exercise work rate was continually recorded with automated software (Lode Ergometry Manager v 10, Groningen, Netherlands) and exported to Excel. Exercise economy was calculated as mLO_2 ÷ Watt.

2.7. Data and statistical analyses

Cerebral, thermal, cardiovascular variables were analyzed by a two-way repeated measures design for interactions (condition x time) and main effects with *post hoc Holm*-Sidak's multiple comparison test. Data were analyzed by GraphPad statistical software (Prism for Windows 64-bit, version 8.0.2, San Diego, CA, USA) with significance set at $P < 0.05$. Skin blood flow, sweat rate, mean skin, and intestinal temperature devices, chamber humidity and temperature were connected (analog BNC) to data acquisition and software (AD Instruments PowerLab 16/35, LabChart 8, Colorado Springs, CO, USA) analyzed as 1 min averages. Oxygen uptake was extracted from Moxus Metabolic System Software (version 4.1.12) in 1 min average and only used the last 3 min of the 5 min recording. Cerebral blood flow at systole and diastole was extracted from Multigon Industries, Inc. software (DTCD8100) and averaged from 30 pulse waveforms every 10 min. Exercise work rate was extracted from software (Lode Ergometry Manager LEM 10). Data presented as a percentage change was calculated as change from baseline ([resting value – end value] ÷ resting value). Data reported in figures and tables represents all participants that completed each condition. All data reported as mean ± SD.

3. Results

3.1. Low-intensity self-paced exercise maintained arterial blood pressure, ventilation, exercise economy, and gas exchange parameters in compensable hot and cool conditions, while end-tidal CO_2 was attenuated in uncompensable hot conditions

Environmental conditions, arterial blood pressure, gas exchange parameters, and work rate, during rest and exercise in hot dry and humid conditions are presented in Table 2. Temperatures were maintained during rest and exercise within each condition and by design was greater in the hot (42.2 ± 0.3 °C) compared to the thermal neutral (23.6 ± 1.2 °C) condition (Main Effect: Condition, $P < 0.0001$). Relative humidity was dry (12.3 ± 4.3% R*h*) during the rest and exercise of the thermal neutral and hot dry conditions. Likewise, by design, humidity was greater during the exercise humid (55.2 ± 7.7% R*h*) condition (Interaction: Condition Time; $P < 0.0001$). The calculated heat index was lower (23.7 ± 0.4 °C) in the neutral dry than the hot dry (40.0 ± 1.2 °C) and hot humid (68.1 ± 8.5 °C) conditions (Interaction: Condition × Time; $P < 0.0001$). Mean, systolic, diastolic, and pulse pressures were not different among each condition or time point. End-tidal PO_2 was not different between conditions during rest and exercise in dry conditions; however, it increased to a greater extent during hot humid exercise (Interaction: Condition × Time; $P < 0.0001$). End-tidal PCO_2 was similar between conditions during rest and exercise in dry conditions; however, it decreased to a greater extent in the hot humid exercise condition (Interaction: Condition × Time; $P < 0.0001$). Absolute VO_2 uptake increased from rest to exercise in both the thermal neutral and hot conditions; however, it was attenuated in the hot compared to the thermal neutral conditions (Interaction: Condition × Time; $P < 0.0001$). Breathing frequency and ventilation similarly increased from rest to exercise in both conditions (Main effect: Time; $P < 0.0001$). Absolute work rate was attenuated in the hot condition compared to the neutral conditions and was further attenuated in the hot humid compared to the hot dry condition (Interaction: Condition × Time; $P \leq 0.04$). Submaximal oxygen uptake expressed as a percentage of maximal was likewise attenuated in the hot condition compared to the neutral (Interaction: Condition × Time; $P \leq 0.04$). However, exercise economy expressed as volume of oxygen per 1 W of exercise was matched between conditions and increased from rest to exercise similarly (Main Effect: Time $P < 0.0001$).

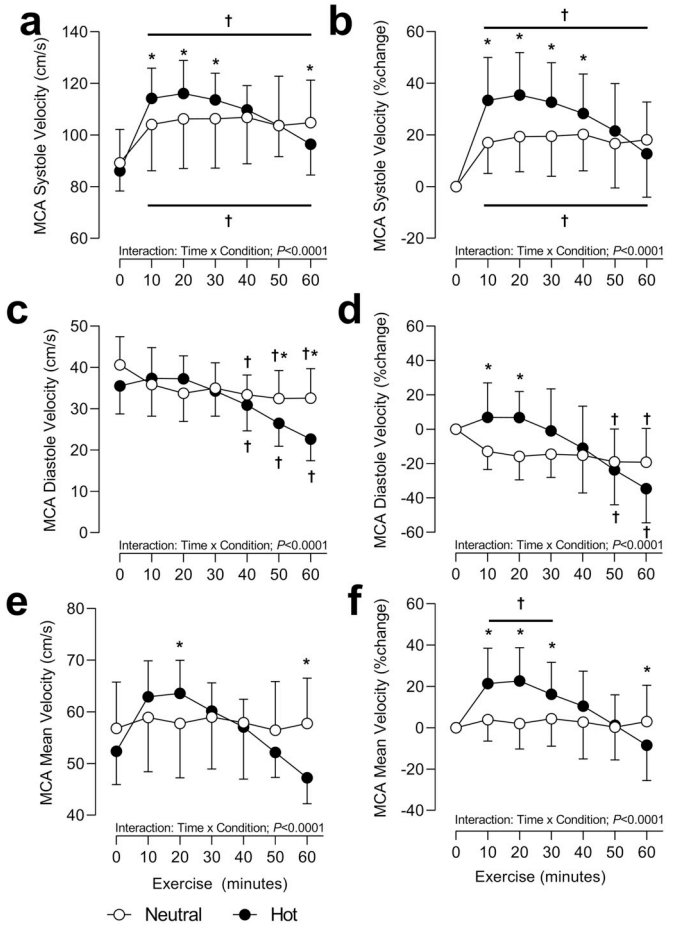

Fig. 2. Absolute and relative hemodynamic cerebral blood flow changes to during systolic (a, b) diastolic (c, d), and mean arterial pressure (e, f) while rest and exercise in neutral dry (open circle), and during the progressive hot dry to humid (black circle) conditions. Results are expressed as means ± SD. † indicates statistical difference from rest; * indicates statistical difference between conditions of same time point.

3.2. Cerebral blood flow hemodynamics differ in neutral dry, hot dry and hot humid conditions

Fig. 2 reports the absolute and relative hemodynamic CBF changes to during systole, diastole, and mean CBF from baseline rest through 60 min of exercise. The absolute systolic and relative change from rest increase to a greater extent during the initial exercise in hot dry conditions, and as humidity increased, it decreased (Interaction: Condition × Time; $P < 0.0001$). Absolute diastolic flow decreased to a greater extent in hot humid conditions (Interaction: Condition × Time; $P < 0.0001$). However, as examined as percent change, diastolic flow during neutral dry conditions is reduced compared to hot dry conditions and during hot humid conditions, both are reduced compared to resting (Interaction: Condition × Time; $P < 0.0001$). Mean CBF increases to a greater extent under hot dry conditions and reduced to a greater extent during heat humid conditions, whereas neutral dry conditions, mean cerebral blood flow is maintained (Interaction: Condition × Time; $P < 0.0001$). Absolute and relative cerebral blood flow, conductance, intracranial pressure, resistive and pulsatility indices are reported in Fig. 3. MCA $_{Vmean}$ increased from rest to exercise in the hot dry condition by 27 ± 15% ($P < 0.0001$) but decreased in the hot humid condition by −15 ± 1 4% ($P < 0.005$), whereas MCA $_{Vmean}$ did not change in the thermal neutral dry during rest to exercise conditions (Interaction: Condition × Time; $P < 0.0001$). Similarly, MCA $_{Vmean}$ conductance increased from rest to exercise in the hot dry condition by 23 ± 21% ($P < 0.003$) but decreased in the hot humid condition by −11 ± 18% to similar levels as the exercise in thermal neutral conditions (Interaction: Condition × Time; $P < 0.0001$). MCA $_{Vmean}$ conductance did not change in the thermal neutral dry rest to exercise conditions. The indices of intracranial pressure (44 ± 24%, $P \leq 0.004$), resistance (21 ± 11%, $P \leq 0.001$), pulsatility (38 ± 20%, $P \leq 0.008$) followed similar changes from rest to exercise in both environmental conditions; however during hot humid conditions pressure (94 ± 34%, $P < 0.0001$), resistance (39 ± 12%, $P < 0.0001$), and pulsatility (81 ± 33%, $P < 0.0001$), increased to a greater extent compared to the exercise in neutral and hot dry conditions (each, Interaction: Condition × Time; $P < 0.0001$).

3.3. Thermal and cardiovascular strain are affected greater in hot humid compared to hot dry conditions

Thermoregulation parameters and cardiovascular adjustments during rest and exercise in hot dry and humid conditions are presented in Fig. 4. Rest and after 20 min of exercise, intestinal temperatures were similar in neutral and hot dry conditions (37.4 ± 0.5 °C) but increase at the end of exercise in neutral (37.7 ± 0.6 °C, $P < 0.03$) and to a greater extent in hot humid (38.8 ± 0.8 °C, $P < 0.0007$) conditions (Interaction: Condition × Time; $P < 0.004$). Mean skin temperature was greater in the hot conditions compared to the neutral dry (32.0 ± 10.1 vs 37.1 ± 2.2 °C, $P < 0.0005$) which increased to further (38.2 ± 2.4 °C, $P < 0.0005$) in the hot humid condition (Interaction: Condition × Time; $P < 0.019$). Likewise, mean body temperature was greater at rest and during exercise in the hot compared to the neutral (35.3 ± 0.5 vs 37.1 ± 0.8 °C, $P < 0.002$), and increased further in the hot humid condition (Interaction: Condition × Time; $P < 0.008$). Thermal comfort was greater at rest (1.4 ± 0.5 vs 3.4 ± 3.9, $P < 0.0003$) and during the hot humid compared to the thermal neutral condition (Interaction: Condition × Time; $P < 0.018$). Heart rate increased to a similar degree from rest to exercise in both the neutral and hot dry conditions (rest 77 ± 13 to exercise 129 ± 17 beat·min^{-1}, $P < 0.0001$), and was higher in the hot humid (160 ± 23 $P < 0.0001$) conditions (Interaction: Condition × Time; $P < 0.002$). Skin blood flow was increased to a greater extent in the hot condition compared to the thermal neutral (Main Effect: Condition; $P < 0.0001$). Sweat rate on the forearm was greater at rest and during exercise in hot dry compared to the thermal neutral dry condition (0.06 ± 0.06 vs 0.24 ± 0.16 mg min·m^2) and increased further (0.42 ± 0.19 mg min·m^2) in the hot and humid condition (Interaction: Condition × Time; $P < 0.003$). Cardiac output increased (4.9 ± 0.4 to 6.5 ± 0.8 L min^{-1} $P < 0.0001$) during exercise in the hot dry compared to thermal neutral condition but was reduced in the hot humid condition (5.1 ± 10.7 vs 5.3 ± 1.0 L min^{-1}) as the thermal neutral condition (Interaction: Condition × Time; $P < 0.01$). Systemic vascular resistance was reduced at rest and during exercise in hot dry compared to thermal neutral condition (1527.6 ± 272.8 vs 1233.8 ± 194.1 dyn s^1·cm^5, $P \leq$ * < 0.04) but increased to thermal neutral levels thereafter in the hot humid condition (Interaction: Condition × Time; $P < 0.01$).

4. Discussion

This study tested the hypothesis that exercising under progressive changes in compensable (hot dry) to uncompensable (hot-humid) conditions would have dynamic CBF responses that are associated with cardiovascular and systemic vascular alterations. The main finding from this study was that we show the integrative process between cerebral blood flow, gas exchange, brain pressure, and peripheral resistance are coordinated differently during a progressive compensable and uncompensable heat stress protocol during exercise. Notably, the volume of blood redistribution during a progressive dry to humid heat exposure while exercising may also alter the volume of cerebral blood

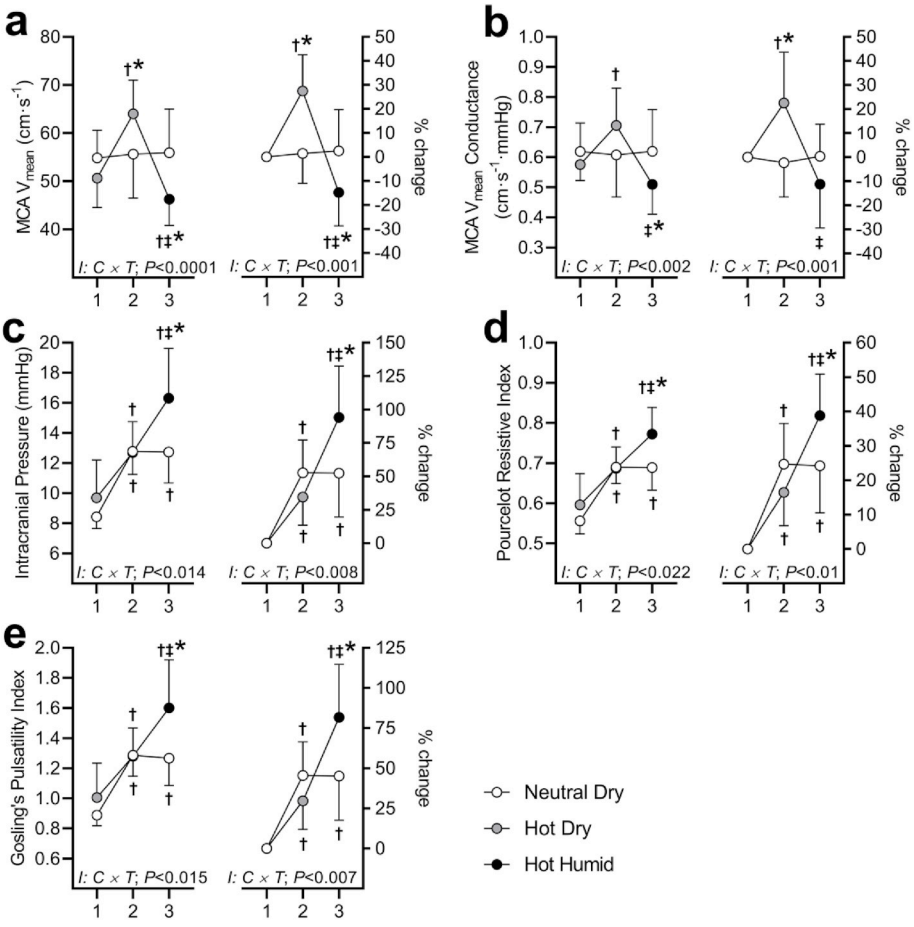

Fig. 3. Absolute and relative cerebral blood flow (a), conductance (b), intracranial pressure (c), resistive (d) and pulsatility (e) indices during rest and exercise in neutral dry (open circle), and during the progressive hot dry (grey circle) and humid (black circle) conditions. Results are expressed as means ± SD. † indicates statistical difference from rest; ‡ indicates statistical difference from exercise in dry condition; * indicates statistical difference from the neutral condition of same time point. Number 1 indicates resting in compensable dry neutral compared to dry hot conditions, number 2 indicates exercising in compensable dry neutral compared to dry hot conditions, and number 3 indicates exercising in uncompensable dry neutral compared to dry hot conditions.

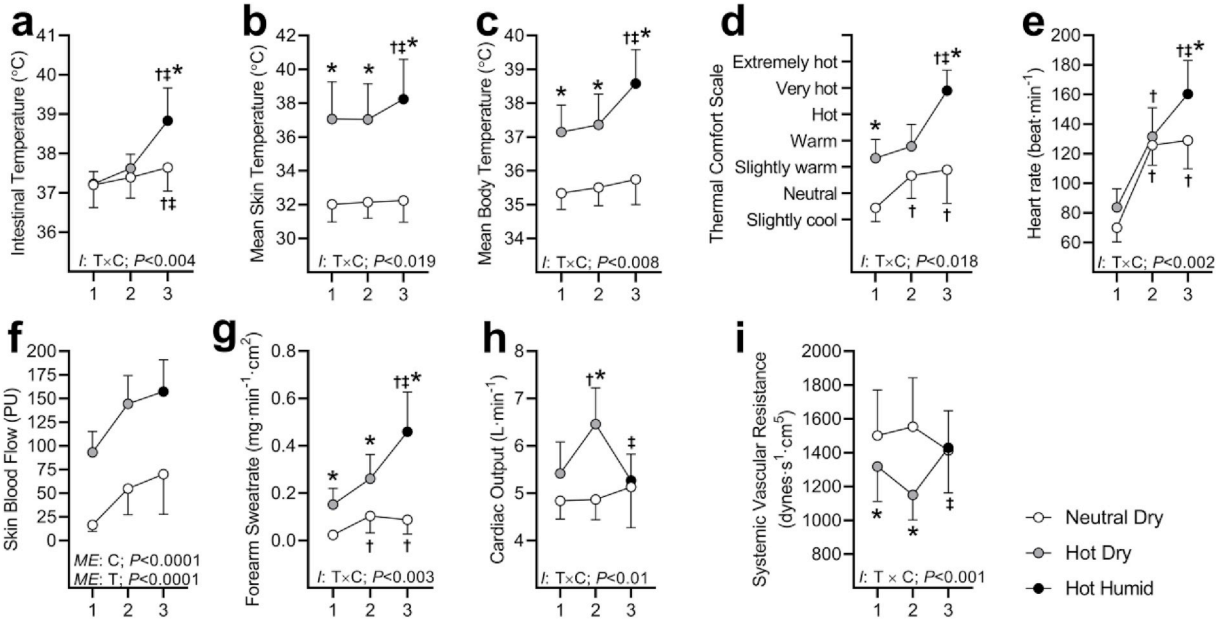

Fig. 4. Thermoregulation (intestinal temperature, a; mean skin temperature, b; mean body temperature, c; thermal comfort, d) and cardiovascular (heart rate, e; cardiac output f, skin blood flow perfusion, g; sweat rate h) adjustments during rest and exercise during the progressive hot dry and humid conditions. Results are expressed as means ± SD. † indicates statistical difference from rest; ‡ indicates statistical difference from exercise in dry condition; * indicates statistical difference between conditions of same time point. Number 1 indicates resting in compensable dry neutral compared to dry hot time, number 2 indicates exercising in compensable dry neutral compared to dry hot time, and number 3 indicates exercising in uncompensable dry neutral compared to dry hot time.

flow. Exercise heat-stress during hot dry conditions increase MCA v_{mean}, which is primarily due to a rise in blood flow velocity during systole. However, exercising in hot and high humidity attenuates MCA v_{mean}, due to reduced diastole blood flow velocity. Further, our results suggest that during low-intensity self-selected exercise, CBF hemodynamics is maintained from rest to exercise during the compensable neutral; however, during the compensable hot dry, it increases profoundly, and this occurred when there was also an increase in cardiac output, skin blood flow and sweat rate and a decrease in peripheral vascular resistance. Notably, the index of intracranial pressure and downstream cerebral resistance increased similarly under compensable dry cool and hot conditions from rest to exercise. During uncompensable hot humid, cerebral blood flow is reduced, and this may have been due to a decrease in cardiac output, and an increase in end-tidal PO_2 and decrease in end-tidal PCO_2 levels, and a further increased intracranial pressure and downstream resistance relative to the compensable dry cool and dry hot conditions. These divergent responses were not driven by ventilation. A profound peripheral vasodilation during uncompensable heat stress for thermoregulation may reduce CBF. Further, because skin blood flow perfusion and sweat rate remained unaffected, the control of CBF during uncompensable exercise heat stress may be secondary to thermoregulatory mechanisms which may provide an explanation for the cause of exertional heat illness and or heat stroke.

Others have reported that during exercise in hot conditions, CBF increased initially and decreased as a result of ventilatory-induced increase in PCO_2, and the decline in cardiac output and arterial blood pressure (Nybo et al., 2002; Nybo and Nielsen, 2001b). Our results differ slightly from these and most likely due to differences in participant fitness and study design. Nybo and Nielsen's seminal study examining CBF during exercise hyperthermia examined participants with elite aerobic capacities (i.e., 70 $mLO_2 \cdot kg \cdot min^{-1}$), in addition to the exercise being a time trial to volitional exhaustion (Nybo and Nielsen, 2001b). The participants in our study had average aerobic capacities; however, they were physically active, but they also spent a great amount of their time being sedentary (> 70% of their day). Prolonged sedentary activity has been shown to negatively affect resting cerebral blood flow (Carter et al., 2018). We found that during low-intensity self-selected exercise, ventilation was not different between hot dry and humid, or neutral conditions and mean arterial pressure was likewise maintained during exercise. Further, internal body temperature was not different between the neutral dry, and hot dry conditions supporting the concept of compensable environment. The uncompensable hot humid exercise caused hyperthermia elevations in body temperature, increase in end-tidal PO_2 and a decrease in end-tidal PCO_2 which is in agreement with others that suggest these are modifiers of CBF during rest and exercise (Ogoh and Ainslie, 2009; Querido and Sheel, 2007). Further support for PCO_2 modulating CBF has been examined by restoring the reduction in PCO_2 during high intensity exercise under heat stress, which also restored the reduction in CBF (Keiser et al., 2015). Another self-paced exercise study that examined CBF in 35 °C and 60% relative humidity environments conducted as time trial found a similar (as Nybo and Nielsen, 2001a, b) increase in ventilatory response, reductions in end-tidal PCO_2 and a reduction in mean arterial pressure (Periard and Racinais, 2015). Thus, the self-paced high intensity time trial exercise reduction in CBF may involve many factors associated with high intensity exercise. Other mediators of CBF during exercise include muscle mechanoreceptors, chemoreceptors, glucose, lactate, catecholamines and temperature (Ainslie and Duffin, 2009; Prodel et al., 2016; Willie et al., 2014); all of which can confound interpretation the with high-intensity exercise. A strength in our design is that we utilized low-intensity exercise in addition to isolating CBF response from hot dry and hot humid conditions.

Notably, the time rested prior to exercise exposure in hot environments may increase the magnitude of CBF response. Others rested for 5–10 min prior to the exercise (Nybo and Nielsen, 2001b; Periard and Racinais, 2015) whereas we used a 30 min resting baseline to allow for cardiovascular adjustments prior to exercise. This phenomenon is described as the after-drop and after-rise of heat moving through a mass of tissue that may affect the core-shell regulatory signal (Webb, 1986, 1992). In addition to redistribution of blood from the core to the skin, an afferent signal via muscle metaboreflex may increase cerebral blood flow regulation (Prodel et al., 2016). Mild passive heat stress has been reported to increases cutaneous blood flow via metaboreflex stimulation (Kondo et al., 2003), and heat exposure prior to exercise may have contributed to the increase in CBF via metaboreflex stimulation during exercise; however, this is speculation and has not been investigated in hot conditions. We show for the first time, that the hemodynamics of altered CBF for the hot compensable conditions is driven by elevations in systolic flow (likely from the contractile force of the heart), and during uncompensable heat stress, the reduction in CBF is due to reductions in flow during diastole (Fig. 2).

Others have reported that self-paced exercise is affected by high skin temperature (Schlader et al., 2011). We found similar, that self-paced exercise at absolute and relative maximal work rates was lower in the hot dry condition compared to the thermal neutral. However, when we examined the exercise economy, no difference was found between conditions. The adjustments of self-paced exercise may be due to maintaining perceived exertion and metabolic demand as economy may become worse in hot compared to cool environments at a fixed external work rate (Rivas et al., 2017). Further, as Rowell et al (1969a, b) first reported, the high skin temperatures result in cardiac output adjustments, peripheral venous tone, and cutaneous skin blood flow perfusion during rest and exercise (Rowell et al., 1969a, 1969b). Our results are in agreement, as we showed high skin blood flow perfusion, an increase in sweat rate, with elevated cardiac output and a reduction in peripheral vascular resistance during rest and exercise in hot dry conditions and these may have affected the absolute selection of self-paced exercise.

The severity of cardiovascular and thermal strain is affected during compensable and uncompensable heat stress (Montain et al., 1994). As exercise hyperthermia develops, cardiovascular drift occurs as cardiac output is reduced that may be due to the increase in heart rate (Chou et al., 2018; Coyle and Gonzalez-Alonso, 2001). Our results are in agreement as we showed when hyperthermic levels of body temperature occurred during the hot humid uncompensable, heart rate was greater with no further increase in skin blood flow perfusion. We add to this literature showing that the increase in heart rate, decrease in cardiac output, coupled with end-tidal PO_2 and PCO_2 changes influence the reduction in CBF during exercise in uncompensable heat stress. However, these responses were not influenced by differences in ventilation or mean arterial pressure. Notably it is unclear if the heart rate and cardiac output changes are causing the changes in end-tidal PO_2 and PCO_2 and the further increase in intracranial pressure and downstream resistance. It seems likely that body temperature is altering heart rate, end-tidal PO_2 and PCO_2 levels, and peripheral resistance. We found that skin blood flow and sweat rate remained higher and unaffected during the hot uncompensable and compensable conditions, thus the control of CBF may be secondary to thermoregulation. Exercising in uncompensable environments increases the risk for exertional heat-related illness such as heat exhaustion and heat stroke that may be due to the reduction in CBF. In rats, cerebral blood flow ischemia is reported in response to heatstroke due to dopamine release (Kao et al., 1994; Lin, 1997). Notably, the reduction of CBF will also increase extraction of O_2 for the maintenance of cerebral oxygen uptake (Bain et al., 2014). We report in our study that low intensity exercise at self-paced exercise in uncompensable environments reduces cerebral blood flow to a greater extent than compensable hot dry and neutral environments. Notably, the participants in this study reported reductions in CBF before reaching thermal comfort levels of feeling “extremely hot.” The majority had a feeling of “very hot” when CBF was reduced.

There are several limitations that require critical evaluation. The direct gold standard for measurement of global CBF based on the Fick

principal and invasive measures (Young et al., 1989). In this study, we used the index of global CBF via transcranial Doppler ultrasound to measure the middle cerebral artery velocity due the majority (~80%) of blood volume delivered to the middle cerebral artery (Lindegaard et al., 1987) and is a reliable and valid index of CBF (Ainslie and Duffin, 2009). All measures were made in the seated upright posture on non-weight bearing exercise. Thus, our results may differ from supine conditions and weight bearing activity. The increased sympathetic activity and decreased venous return may have an increased response on cerebral autoregulation compared to supine rest. Given that sympathetic activity has an important role in cerebral regulation, we cannot determine how upright sympathetic activity during rest or exercise had on our results. However, given that both neutral and hot conditions were similarly upright we can at least determine the comparison between conditions was controlled for. Our study design examined directional changes in CBF and thermoregulatory parameters during a progressive hot dry to humid protocol and therefore cannot precisely determine the underlying causes of reductions in CBF. Further work should utilize supplementing CO_2 or O_2 to answer this question and isolate the cool vs hot dry vs hot humid conditions independently, rather than a progressive change as we did in this study to confirm or refute our results. Additionally, because we examine a progressive compensable dry to uncompensable humid heat exposure in one condition, there may have been an order effect of these outcomes. Lastly, we utilized algorithm enabling oscillometric device that has been validated with acceptable accuracy and reproducibility compared with intra-aortic readings (Hametner et al., 2013; Papaioannou et al., 2013; Siegfried W. et al., 2008; Weber et al., 2011; Weber et al., 2017) but not during exercise heat stress.

5. Conclusions

Our findings indicated that under neutral compared to a progressive hot compensable to hot uncompensable protocol, CBF is dynamically changed, possibly by an integrative physiological response that differs in neutral dry, hot dry, and hot humid environments. Further, the CBF adjustments maybe secondary to peripheral thermoregulatory control such as cardiac output, heart rate, peripheral vascular resistance, skin blood flow perfusion, and sweat rates. Clinically, exercising in uncompensable environments increases the risk for exertional heat-related illness that may be due to the reduction in CBF.

Author contributions

E.R. contributed to the conception and design of the experiment. E.R., P.S., K.A. collected and analyzed the data and drafted the manuscript. All authors contributed to the interpretation of the data and revised the final manuscript for important intellectual content. All authors have approved the final version of the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtherbio.2019.07.036.

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