Cerebral oxygenation and hyperthermia

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Hyperthermia is associated with marked reductions in cerebral blood flow (CBF). Increased distribution of cardiac output to the periphery, increases in alveolar ventilation and resultant hypocapnia each contribute to the fall in CBF during passive hyperthermia; however, their relative contribution remains a point of contention, and probably depends on the experimental condition (e.g., posture and degree of hyperthermia). The hyperthermia-induced hyperventilatory response reduces arterial CO2 pressure (PaCO2) causing cerebral vasoconstriction and subsequent reductions in flow. During supine passive hyperthermia, the majority of recent data indicate that reductions in PaCO2 may be the primary, if not sole, culprit for reduced CBF. On the other hand, during more dynamic conditions (e.g., hemorrhage or orthostatic challenges), an inability to appropriately decrease peripheral vascular conductance presents a condition whereby adequate cerebral perfusion pressure may be compromised secondary to reductions in systemic blood pressure. Although studies have reported maintenance of pre-frontal cortex oxygenation (assessed by near-infrared spectroscopy) during exercise and severe heat stress, the influence of cutaneous blood flow is known to contaminate this measure. This review discusses the governing mechanisms associated with changes in CBF and oxygenation during moderate to severe (i.e., 1.0°C to 2.0°C increase in body core temperature) levels of hyperthermia. Future research directions are provided.

Keywords: hyperthermia, heat stress, cerebral blood flow, cerebral oxygenation, hemorrhage, syncope

INTRODUCTION

The dependence to maintain body core temperature within critically functioning limits (i.e., 37 ± 3°C) has led to seminal thermoregulatory research spanning the past 100 years (e.g., Haldane, 1905; Lindhard, 1910). From this, the capacity to effectively dissipate heat through convective and evaporative means and the concomitant cardiovascular adjustments to maintain thermoregulatory homeostasis has been topic of several extensive literature reviews (e.g., Rowell, 1974; Crandall and González-Alonso, 2010; Johnson and Proppe, 2011). Only in the last decade, however, have we begun to appropriately understand the cerebrovascular adjustments to hyperthermia. The integrative components of cerebrovascular control and ultimately oxygenation, with focus on commonly occurring levels of hyperthermia (i.e., up to +2°C core temperature) form the basis of this review. Adjustments to the three variables germane to cerebral oxygenation, fundamentally the components of the Fick equation; (1) cerebral metabolism, (2) cerebral O2 extraction, and (3) oxygen delivery (cerebral blood flow—CBF), are discussed. We further highlight the implications of cerebral heat balance and oxygenation during hyperthermic exercise, and provide methodological considerations for future work.

CEREBRAL METABOLISM

The metabolic demand of human cerebral tissue is such that ~20% of total body oxygen consumption is taken up by the brain, despite only occupying 2–3% of total body mass. During passive hyperthermia of 1.5°C to 2°C above resting core temperature, whole body metabolic rate increases by ~25% (Saxton, 1981). It remains unclear whether cerebral tissue significantly contributes to the rise in whole-body metabolism during passive hyperthermia. For example, the Arrhenius activation law (or Q10, temperature coefficient), which describes the relation of biological activity to changes in temperature, implies that a rise in 2°C from 37°C should yield an increase in metabolic rate of ~10%, (South, 1958). However, the change in metabolic rate associated with the Q10 effect in vitro may be more sensitive during hyperthermia, compared to hyperthermia (Sébert et al., 2003). Nonetheless, several animal preparations have demonstrated that local cerebral or whole-body passive heating yields an increase in cerebral glucose utilization (McCulloch et al., 1982; Mickley et al., 1997) and cerebral metabolic rate (CMRO2) by 5 to 10% per degree Celsius rise in core temperature (Nemoto and Frankel, 1970a,b; Carlsson et al., 1976; Busija et al., 1988). In the dog, CMRO2 was elevated by 21% at a rectal temperature (Trec) of 42.1°C compared to baseline (Trec of 37.7); however, it began to fall at 43°C (Nemoto and Frankel, 1970b). These latter data likely reflect the temperature dependence on critical cellular activity, whereby nucleotide degradation and blood brain barrier disruption (and imminent death if not treated) begins to occur at extreme core temperatures (i.e., ≥42°C in the human) (Bynum et al., 1978). The molecular mechanisms that might impact on cerebral metabolism and oxygenation beyond a rise of 3°C have not been explored in humans, and are therefore beyond the scope of this review.
In humans, positron emission tomography measurements during passive heating to roughly +2°C rectal temperature show an increased metabolic rate of glucose in the hypothalamus, thalamus, corpus callosum, cingulate gyrus, and cerebellum (Nunnleley et al., 2002). However, in the same study, significant declines in metabolic rate were observed in the caudate, putamen, insula, and posterior cingulum. To date, although regional differences are apparent, no study exists (to our knowledge) in the healthy awake human providing a measure of global cerebral metabolic rate during passive hyperthermia. In healthy humans during exercise, however, Nybo et al., (Nybo et al., 2002a) demonstrated with arterial and jugular venous sampling that cerebral metabolic rate is higher by ~7–8% when subjects are hyperthermic (see Discussion on Exercise). Whether the confounding factor of exercise precludes the conclusion that hyperthermia alone causes an increase in cerebral metabolism, remains unknown. Still, given the theoretical Q10 (temperature coefficient) considerations, in conjunction with animal studies, human positron emission tomography data and exercise studies, it is likely that hyperthermia (of up to +3°C) proffers a dose-dependent response to increase cerebral metabolic rate.

**OXYGEN EXTRACTION**

Oxygen is transported into cerebral tissue by diffusion, the speed of which is determined by the oxygen conductivity of cerebral tissue. Oxygen conductivity of cerebral tissue is fundamentally determined by the geometry of the capillaries and surrounding tissue (diffusion area and distance), and the tissue metabolism for a given oxygen gradient from the capillary to tissue (Gjedde, 2005). The speed of oxygen transport, or O2 extraction, can therefore be described as being inversely proportional to blood flow (when metabolism is held constant), and directly proportional to metabolism (when flow is held constant), and the surface area between the tissue and capillaries. As CBF, and subsequently O2 delivery is reduced, tissue extraction increases. However, because of the inverse relationship between blood flow and O2 extraction, when CBF is reduced by ~50–60%, the corresponding increase in O2 extraction is no longer sufficient to maintain a constant CMRO2 or adequate cerebral oxygenation (Lennox et al., 1935; Gjedde, 2005); i.e., a critical blood flow limit is reached. It follows that this theoretical critical flow limit is altered if metabolism changes; that is, the brain has a reduced critical CBF reserve for the maintenance of adequate cerebral oxygenation when metabolism (O2 demand) is increased. Given the above theoretical considerations, if brain metabolism increases by a liberal 10% following a 2°C increase in tissue temperature, the critical reduction in blood flow to maintain oxygenation would be ~40–50%.

**CEREBRAL BLOOD FLOW**

During passive hyperthermia, respiratory and cardiovascular adjustments disrupt the natural coupling between CMRO2 and CBF. A neurogenic mechanism, i.e., cerebral vasconstriction from increases in sympathetic nerve activity (SNA), has also been suggested to contribute to reductions in CBF during hyperthermia (e.g., Brothers et al., 2009b). Recent work in partitioning the roles of respiratory and cardiovascular mechanisms and considerations for neurogenic control of CBF during passive hyperthermia is discussed next.

**RESPIRATORY—ARTERIAL PCO2 (PaCO2)**

Hyperthermia in humans (among other species) is accompanied by a hyperventilatory response, and subsequently marked respiratory alkalosis. In 1905, Haldane was the first to describe, “breathing being more deeper and more frequent than usual” when hyperthermic (Haldane, 1905). The magnitude of the hyperventilatory response is highly variable between individuals, and is likely dependent upon the rate and magnitude of rise in skin and core temperature; however, the reflex hyperventilation is not usually pronounced until a threshold increase in core temperature of at least 1°C (Barltrop, 1954 and for review see White, 2006). On average, a 1.5–2.0°C increase in core temperature during passive heating yields a reduction in end tidal CO2 (PETCO2), a validated surrogate for PaCO2 (Brothers et al., 2011a) of ~5–15 mmHg (see Table 1). However, the reported decline in PaCO2 varies considerably for a given increase in core temperature, which is likely governed by whether the external heating (i.e., skin temperature) was continued or attenuated to provide a steady-state core temperature. In some studies, PaCO2 can drop below 20 mmHg, and with severe passive heating (≥2°C) pronounced hyperventilation can lead to hypocapnia-induced carpopedal spasms and tetany (Iampietro et al., 1966 and unpublished observations). The exact mechanisms responsible for the hyperventilatory response during hyperthermia in humans have not been fully delineated. It is likely that a medullar integration of skin, and deep tissue temperature, principally hypothalamic temperature (Ingram and Whittow, 1962; Boden et al., 2000), primarily determine the magnitude of hyperventilatory response to hyperthermia. Temperature reception at the carotid bodies may also play an independent role (Zapata et al., 1994). For example, perfusion of warmed blood to the isolated carotid bifurcation elicits a transient hyperventilation in dogs (Bernthal and Weeks, 1939), while bilateral dissection of the carotid nerves mitigates the ventilatory increase to whole body heating in cats (Fadic et al., 1991).

It is well established that PaCO2 is a potent modulator of CBF (Ainslie and Duffin, 2009). At rest, each mmHg change in PaCO2 above and below eupnia yields an approximate 4% increase and 2% decrease in CBF, respectively (Willie et al., 2012; and Willie et al., 2014 for review). During passive supine hyperthermia of +1–1.5°C core temperature above resting, a 10–20% reduction in cerebral blood flow is typically observed (see Figure 1 and Table 1). The role of PaCO2 in the reduction of CBF during hyperthermia remains debatable. Bain et al. (2013) recently demonstrated, using both volumetric and intra-cranial velocity measurements, that global (anterior and posterior) CBF during supine severe (+2°C esophageal temperature) hyperthermia is completely restored to normothermic values upon returning PETCO2 back to normothermic levels (Figure 2). This finding is notionally corroborated by other studies (Fan et al., 2008; Nelson et al., 2011). It should be noted, however, that although middle cerebral artery (MCAv) and posterior cerebral artery (PCAv) velocities were statistically restored to normothermic values following PETCO2 restoration during +2°C hyperthermia in Nelson et al. (2011), they were still 9 and 3% lower respectively,
MCAv = following baseline PETCO2 restoration. For example, although findings may be explained by the variability in “steady-state” CBF hyperthermia. Although difficult to reconcile, these divergent of baseline eucapnia will yield a temporary overshoot in CBF may eventually lead to an adaptive response whereby restoration absolute CO 2 reactivity appears to be maintained during hyper-

### Table 1 | Summary of human cerebral blood flow blood velocities and flow [CBF(v)] measurements during supine passive hyperthermia.

| Authors | Year | n | Hyperthermia | ∆MAP | ∆PETCO2 | ∆CBF(v) |
|---------|------|---|--------------|------|---------|---------|
| Bain et al. | 2013 | 19 | +2.0°C T_{es} +5.0°C | −1 mmHg | −7 mmHg | −20 |
| Brothers et al. | 2009a | 9 | +1.1°C T_{gi} +3.8°C | −1 mmHg | −4 mmHg | − |
| Brothers et al. | 2009b | 7 | +1.4°C T_{gi} +4.3°C | −1 mmHg | −6 mmHg | − |
| Fan et al. | 2008 | 10 | +0.5°C T_{es} +3.7°C | −14 mmHg | −3 mmHg | − |
| Low et al. | 2008 | 9 | +1.1°C T_{gi} +3.7°C | −2 mmHg | −3 mmHg | − |
| Low et al. | 2008 | 8 | +1.8°C T_{gi} +5.8°C | −2 mmHg | −15 mmHg | − |
| Wilson et al. | 2006 | 15 | +0.9°C T_{gi} +4.2°C | 0 mmHg | −2 mmHg | − |
| Ogoh et al. | 2013 | 12 | +0.3°C T_{es} +3.8°C | −1 mmHg | −2 mmHg | − |
| Stanley et al. | 2010 | 8 | +0.7°C T_{es} +4.7°C | −4 mmHg | −2 mmHg | − |
| Wilson et al. | 2006 | 15 | +0.9°C T_{gi} +4.2°C | 0 mmHg | −2 mmHg | − |

Asterisks (*) indicate values estimated from figure representation. T_{es}, T_{gi}, and T_{eg} represent rectal, esophageal, and gastrointestinal temperature respectively. n = sample size. MAP = mean arterial pressure. P_{ET}CO2 = end-tidal CO2 partial pressure. ICA = Internal carotid artery blood flow. VA = vertebral artery blood flow. MCAv = middle cerebral artery blood velocity. PCAv = posterior artery blood velocity.

FIGURE 1 | Representation of the reported percent reductions in middle cerebral artery blood velocity (MCAv) (x axis) as a function of delta core temperature (esophageal, gastrointestinal, or rectal) (y axis) during supine passive hyperthermia up to +2°C.

than baseline values. To that end, in opposition of complete CBF restoration following a return to eucapnia, Brothers et al. (2009b) reported that MCAv was only 50% restored back to normothermic values upon the restoration of P_{ET}CO2 during supine hyperthermia. Although difficult to reconcile, these divergent findings may be explained by the variability in “steady-state” CBF following baseline P_{ET}CO2 restoration. For example, although absolute CO2 reactivity appears to be maintained during hyperthermia (Low et al., 2008), the dynamics of the CBF response to eucapnic restoration will in part be determined by the magnitude of the hyperventilation response (and resultant respiratory alkalo-
sis) (Ike et al., 2003). That is, those with a larger hyperventilatory response will likely require a longer time to reach steady-state CBF values upon restoration of baseline PaCO2 due to a larger extra-cellular pH gradient. Moreover, sustained hypoventilation may eventually lead to an adaptive response whereby restoration of baseline eucapnia will yield a temporary overshoot in CBF (compared to pre-stimulus values) (Ike et al., 2003). The mechanisms of this CBF overshoot remains unclear, but may involve changes in lactate and bicarbonate (Albrecht et al., 1987; Marder et al., 1990). The transient magnitude of the CBF overshoot therefore probably depends upon the length of time and magnitude of the hypocapnia. It is clear that this can influence “steady-state eucapnic” CBF measures, and may explain the variable conclu-
sions for the role of PaCO2 in reducing CBF during hyperthermia. Nonetheless, taken the most recent data (Nelson et al., 2011; Bain et al., 2013), it is more than likely that PaCO2 explains the majority of the CBF reduction during passive hyperthermia, at least when subjects are kept in the supine position. Still, future research is warranted to better clarify this role.

In contrast to supine hyperthermia, during upright seated hyperthermia, Fujii et al. (2008) and Ross et al. (2012), found that MCAv is only partially restored back to normothermic levels upon restoration of P_{ET}CO2 with the addition of 5% CO2 to the inspired air. Furthermore, Nelson et al. (2011) found that head up tilt exacerbated the decline in MCAv and PCAv while hyperthermic, in the absence of significant further reductions in P_{ET}CO2. It is therefore evident that, during hyperther-
ia, CBF is declined by increased hydrostatic pressure associated with posture (see Cardiovascular Section), independently of PaCO2.

**Do Changes in PaCO2 Alter Tolerance Time to a Simulated Hemorrhage?**

Tolerance time to a simulated hemorrhage is clearly reduced while hyperthermic compared to normothermic (Allan and Crossley, 1972; Wilson et al., 2006; Keller et al., 2009; Brothers et al., 2011b). Reductions in PaCO2 associated with hyperthermia-induced hyperventilation appear to have little influence on the reduced
that resting BP, and therefore perfusion pressure to the brain diminishively via increases in heart rate. In turn, it is now well accepted (Rowell et al., 1969; Rowell, 1986), accomplished almost exclusively, that increases in cardiac output (at times up to 13 mL·min⁻¹) (Rowell et al., 1969; Rowell, 1986), accomplished almost exclusively, via increases in heart rate. In turn, it is now well accepted that resting BP, and therefore perfusion pressure to the brain during passive, supine hyperthermia, is generally preserved, or only moderately decreased (see Crandall and González-Alonso, 2010 for a comprehensive review on the cardiovascular functioning during hyperthermia). It is interesting to note, however, that BP estimations during passive hyperthermia vary considerably (see Table 1). These variations likely reflect the difficulty in acquiring accurate BP measurements without measuring it intracranially during hyperthermia (Ganio et al., 2011). Nonetheless, in contrast to passive supine hyperthermia, it is generally accepted that adequate BP is not maintained under dynamic hyperthermic conditions, e.g., with an orthostatic challenge or hemorrhage.

Any condition that compromises CBF maintenance inherently increases the risk of syncope/reduction of cerebral oxygenation. As mentioned, tolerance to an orthostatic challenge or simulated hemorrhage is reduced when hyperthermic (Allan and Crossley, 1972; Wilson et al., 2006; Keller et al., 2009; Brothers et al., 2011b). Given that changes PACO₂ seem to play a negligible role in determining tolerance time to a simulated hemorrhage (see section Do changes in PACO₂ alter tolerance time to a simulated hemorrhage?), two key cardiovascular adjustments are likely responsible; (1) the inability to decrease systemic vascular compliance (SVC) (Wilson et al., 2002a; Ganio et al., 2012), and (2) a greater reduction in stroke volume for a given reduction in left ventricular filling pressure (i.e., a leftward shift of the operating point to a steeper portion on the Frank Starling curve) (Wilson et al., 2009). Clearly, the former dictates the latter. When normothermic, it is well established that SVC decreases during a simulated hemorrhage (Murray et al., 1968). Why SVC does not also decrease when hyperthermic, is not entirely understood. However, it is generally accepted that an inhibition of cutaneous vasoconstriction is likely at play (Crandall et al., 2010). An improvement to orthostatic tolerance following acute skin cooling while hyperthermic lends evidence to this hypothesis (Wilson et al., 2002b). The mechanisms of cutaneous vasculature control remains a complex field of study, riddled with redundant mechanistic pathways (for a review see Charkoudian, 2010). Nonetheless, it appears that human physiology places a hierarchy for heat loss during hyperthermia, potentially to the detriment of adequate central blood volume and subsequently CBF/consciousness.

Dehydration (i.e., ≥2% loss of body mass) often follows prolonged sweating, and is therefore closely tied to hyperthermia. A major cardiovascular consequence of dehydration is a dose-dependent decrease in blood volume (Kempton et al., 2009). In turn, dehydration impairs the ability to maintain adequate central blood volumes, and thus CBF during an orthostatic challenge (Harrison et al., 1986; Romero et al., 2011). Carter et al. (2006) demonstrated that the transient reductions in MCAv were larger upon standing from sitting when dehydrated (3.0% reduction in body mass), compared to euhydrated. Consistent with this finding, Moralez et al. (2012) demonstrated that dehydration (2.7% reduction in body mass) exacerbated the reductions in BP and MCAv upon standing following a 10-rep maximum leg press. It is therefore reasonable to assume that when hyperthermia is coupled with dehydration, the ability to maintain adequate CBF is further reduced during orthostatic challenges or hemorrhage.

In contrast to the apparent reduction in CBF with an orthostatic challenge when dehydrated, Fan et al. (Fan et al., 2008)
demonstrated that when subjects were supine, dehydration (1.5% reduction in body mass) increased resting MCAv by ~11%. When subjects were made hyperthermic, however, dehydration appeared to have little or no effect on the reduction in MCAv. It is difficult to reconcile why MCAv was increased with normothermic dehydration compared to euhydration. Increases in CBF during passive supine dehydration may be related to the increased osmolality of extracellular fluid via cerebral cellular shrinkage [i.e., increased concentrations of solutes in the extracellular fluid cause an intra-to extra cellular fluid shift (Kempton et al., 2009)]. In turn, CBF during supine dehydration may be increased to maintain an appropriate ionic milieu for neuronal function. Nonetheless, during passive supine hyperthermia, the marked reductions in MCAv associated with the reduced PaCO2 seem to shadow any effect of dehydration (Fan et al., 2008).

**NEUROGENIC CONTROL**

Sympathetic nerve activity in the muscle and skin vasculature is significantly elevated during hyperthermia (Bini et al., 1980; Niimi et al., 1997; Cui et al., 2004; Keller et al., 2006). Hyperthermia decreases vascular conductance of the splanchnic and renal tissue, presumably also via increased SNA (Rowell, 1983). Indeed, it is commonly accepted that the primary mechanism of blood flow redistribution to the cutaneous tissue during hyperthermia is driven by SNA (Rowell, 1990). Whether increased SNA during hyperthermia affects the cerebral vasculature, however, remains speculative. It is well recognized that perivascular adrenergic nerves richly innervate the cerebral arteries, (Edvinsson and Hamel, 2002), while the smooth muscle cells of the arterioles possess both alpha- and beta-adrenergic receptors (Edvinsson, 1982). This suggests that the cerebral vascular has the potential to be mediated by neurogenic factors. In animal models, CBF is reduced with stimulation of the superior cervical ganglion (Heistad et al., 1978; Cassaglia et al., 2008). In humans, unilateral trigeminal ganglion stimulation decreases CBF (Visocchi et al., 1996), while stellate ganglionic blockade increases CBF (Umeyama et al., 1995; Ide et al., 2000). The above animal and human studies support a tonic neurogenic control of CBF. Therefore, several authors have speculated that reductions in CBF during hyperthermia may, in part, be due to increases in cerebral SNA (see Crandall and González-Alonso, 2010 and related references). However, this notion is based primarily by deduction when PaCO2 and MAP cannot explain the full reduction in CBF (see Discussion on the Role of Arterial PCO2). Although an attractive hypothesis, several caveats persist to accept that SNA decreases CBF during hyperthermia. First, redundant mechanisms (e.g., dilator agents such as nitric oxide, prostanoids, and histamine) may act to counteract a noradrenaline-induced vasoconstriction of the cerebral vasculature. Specifically, when brain metabolism is elevated (see Discussion on Metabolism and Hyperthermia), a “functional sympatholysis” or “metabolic restraint” might mitigate the influence of SNA (Gross et al., 1983; Busija and Leffler, 1987). This is in agreement with animal studies that report a global increase in CBF to passive hyperthermia (Carlsson et al., 1976; Busija et al., 1988) that cannot be entirely explained by changes in PaCO2. Second, the density of alpha- and beta-adrenergic receptors on the cerebral arterioles vary depending on vessel size (Edvinsson, 1982), suggesting that a heterogeneous response, potentially modified by hyperthermia, may exists for a given increase in SNA. Third, the relative influence of SNA on the cerebral vascular seems to be dependent upon levels of blood pressure. That is, sympathetic activation has a larger influence during hypertension, compared to normotension (Bill and Linder, 1976; Edvinsson et al., 1976; and reviewed in Willie et al., 2014). Lastly, the cerebral vasculature has been shown to exhibit a “vasomotor escape” following prolonged maximal SNA stimulation of over 5 ± 7 min (Sercobe et al., 1979), suggesting that the influence of SNA on the cerebral vasculature may be dependent on the duration of the stimulation. That CBF has recently been shown to fully recover to normothermic values when PaCO2 is returned to eucapnia (Bain et al., 2013) supports the notion that increases in SNA during hyperthermia proffer a negligible effect on global CBF. Nonetheless, future studies are required to better understand this potential mechanism. Administration of a centrally acting α2-adrenoreceptor agonist (provided no changes in MAP), cervical ganglion block, or measurements of cerebral noradrenaline spillover (Mitchell et al., 2009) during hyperthermia with concomitant measures of global CBF and maintenance of eupnia, is likely warranted.

**CEREBRAL HEAT BALANCE, OXYGENATION, AND EXERCISE**

Human cerebral tissue uses oxygen at a metabolic rate of between 3 to 3.5 mL O2·100 g cerebral tissue−1·min−1 (Lassen, 1985), producing approximately 0.6 j g−1·min−1 heat, which must then be removed via cerebral circulation (reviewed in: Nybo and Secher, 2004). During hyperthermia, cerebral heat balance is compromised from reductions in CBF (Nybo et al., 2002b) and therefore reductions in convective heat loss (arguably the only avenue for cerebral heat loss). An increased cerebral temperature can impair blood-brain barrier integrity (Watson et al., 2005), particularly when combined with dehydration (Watson et al., 2006). The exact interaction between temperature, blood brain barrier opening and cerebral oxygenation remains obscure.

During hyperthermia exercise capacity is reduced (e.g., Rowell et al., 1966, and for reviews of the potential mechanisms involved see Nybo, 2007 and Cheuvront et al., 2010). Reductions in exercise capacity and a faster onset of fatigue likely stem from interactions of both central and peripheral factors (Nybo and Secher, 2004), including observed alterations in EEG α/β arousal levels with greater perceived exertion and decreased motor unit activation (Nybo and Nielsen, 2001; Morrison et al., 2004; Todd et al., 2005; Périard et al., 2011). Decreases in voluntary activation tend to correlate to reductions in MCAv (measured via Doppler ultrasound), but these reductions can be partially restored when breathing a hypercapnic gas mixture to offset changes in ventilation and PETCO2 levels from heat-induced hyperventilation (Ross et al., 2012). However, although preventing hypocapnia during normothermic exhaustive cycling exercise can exhibit increases in MCAv, performance is unchanged (Subudhi et al., 2011). As such, it is likely that a direct effect of increased temperature on CNS and neuromuscular functioning, rather than detriments to cerebral oxygenation, is the primary factor governing decreased exercise capacity while hyperthermic.
Recent data have collectively provided a salient understanding of cerebral oxygenation during varying degrees of whole-body hyperthermia, however several avenues of experimentation remain. First, it is evident that direct measurements of arterial and cerebral venous blood in humans are required to experimentally verify changes in cerebral metabolism and oxygenation with separate levels of CBF during hyperthermia. Second, albeit inherently difficult to execute, a conclusive study on the role of SNA on separate levels of CBF during hyperthermia. Third, the importance of extra-cranial contamination on NIRS-derived oxygenation values has been highlighted during changes in skin blood flow (Davis et al., 2006) and also where scalp ischemia induced by inflation of a circumferential cranial tourniquet impacted NIRS readings (Davie and Grocott, 2012). Although newer clinically available NIRS monitors use algorithms to subtract light absorption from superficial tissue (e.g., scalp, skin, bone, pia matter) from deeper tissue (Zheng et al., 2013), the utility during hyperthermia and/or exercise remains to be established. Lastly, the interactive role of dehydration, heat acclimatization and certain pathologies (e.g., heart failure, diabetes, autonomic disorders, etc.) on cerebral oxygenation during heat stress should be focus for future work.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 09 January 2014; accepted: 18 February 2014; published online: 04 March 2014

Citation: Bain AR, Morrison SA and Ainslie PN (2014) Cerebral oxygenation and hyperthermia. Front. Physiol. 5:92. doi: 10.3389/fphys.2014.00092

This article was submitted to Integrative Physiology, a section of the journal Frontiers in Physiology.

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