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Comments on Point:Counterpoint: Humans do/do not demonstrate selective brain cooling during hyperthermia

HUMAN CEREBRAL PERFUSION IS REDUCED DURING PASSIVE HEAT STRESS

TO THE EDITOR: Middle cerebral artery blood velocity ($MCAV_{mean}$) is reduced up to 30% in humans following a passive increase in internal temperature of 1–1.5°C (1). If the diameter of the MCA remains unchanged during heat stress, reductions in $MCAV_{mean}$ are proportional to reductions in cerebral blood flow. In support of selective brain cooling in hyperthermic humans, White et al. (7) suggest that vasodilation of the cerebral vasculature exists, which in turn increases cranial perfusion and maintains the arterial-venous temperature difference. The authors state, "it remains to be explained how MCA velocity, and presumably cranial perfusion, is reduced in hyperthermic humans if mean arterial blood pressure is maintained and MCA caliber remains constant" (4, 7). This argument ignores the potent effects of changes in carbon dioxide partial pressures on cerebral perfusion, with hypercapnia increasing and hypocapnia decreasing cerebral blood flow, respectively (6). During moderate to pronounced passive heat stress, arterial and end-tidal carbon dioxide partial pressures decrease upward to 8 Torr (1, 2). Importantly, an 8-Torr reduction in arterial carbon dioxide partial pressure is estimated to reduce cerebral blood flow by ~24% (5) through increases in resistance of the cerebral arterioles "downstream" from the MCA (3). Thus the clear and robust reduction in $MCAV_{mean}$ during passive heat stress is likely due primarily to decreases in carbon dioxide partial pressures causing increases in vascular resistance of cerebral arterioles distal to the MCA.

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ON ZEAL FOR T_{ty}, COOLING THROUGH THE DIPSTICK HOLE, AND FOOLING THE THERMOSTAT

TO THE EDITOR: Historical perspective: I recall hearing T. H. Benzinger cautioning that T_{ty} was influenced by surface temperatures unless a large insulating muff covered the ear. Benzinger thereafter zealously promoted T_{ty}, omitting mention of this problem. My doubt that T_{ty} mirrors brain temperature solidified when McCaffery et al. (3) showed that cooling one side of the face lowered T_{ty} on that side but not on the other. For citations and critical commentary on measures of body temperature, see Ref. 1.

White et al.'s (6) illustration of cerebral veins reminds me of Falk's. Emissary veins figured in her hypothesis that SBC favored evolution of large brains. I thought that like regarding the dipstick hole in the engine block as a major route for heat transfer, ignoring the gigantic capacity of the radiator; i.e., human's capability for active dilation of the cutaneous vasculature and high evaporative heat loss. For expansion on this point, citations, and an alternative illustration, see a previous debate on SBC (2).

Quantitative points against SBC: To Nybo and Secher's (4) mention of Crezee's demonstration of minimal heat loss from large vessels, I would add Wenger's analysis of cavernous sinus heat transfer (5). Their method for estimating the A-V temperature gradient sufficient for removing brain heat production can be extended to the liver in hyperthermia, predicting nearly 1°C as blood flow falls to a minimum. How can SBC be advantageous when reducing hypothalamic temperature-driven effector responses risks sacrificing other organs? Keeping a nice cool brain while cooking your liver seems dangerous.

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KEEP YOUR HEAD ON YOUR BODY

TO THE EDITOR: Brain temperature depends on the balance between metabolic heat production and heat dissipation by blood flow, heat exchange with the ambient, and conduction to

surrounding tissues. However, the main regulators of brain temperature are the cerebral blood flow and the temperature of incoming arterial blood (6).

The rate of heat removal from the brain tissue is estimated by the product of regional cerebral blood flow and the temperature difference between brain tissue and inflowing arterial blood (4). The mean brain-body temperature gradient in normothermia varies between 0.3–0.4°C (4) and 2.3°C (1).

Assuming a baseline brain-body temperature gradient of 0.5–1°C at a constant metabolic rate, then just by increasing the cerebral blood flow brain temperature might decrease with ~0.5–1°C. And what if one persists on cooling the incoming blood? In a study by Pretorius et al. (3) isolated dorsal, facial, or whole head cooling induced core cooling rates up to 0.69 ± 0.2°C/h by increased heat loss via the exposed surface while the metabolic rate remained unchanged. The effects were explained by a reflex induced centralization of circulation that increased the blood flow to the head. Brain temperature was not measured but a relatively fast and uniform lowering of brain temperature depending on the baseline gradients and cooling efficiency would be expected.

Are then the results of similar cooling methods an argument for selective brain cooling as presented by White et al. (5) or rather the consequence of ingenious thermal manipulation as showed by Nybo and Secher (2)?

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CAN THERMAL HYPERPNEA REALLY COOL THE BRAIN?

TO THE EDITOR: A disproportionate increase in ventilation clearly occurs with hyperthermia. White et al. (6, 7) appear to favor ventilation-induced brain cooling via heat exchange with the internal carotid artery; however the studies presented only address potential brain cooling during heightened ventilation via enhanced heat exchange across the nasal cavity. The interpretation of this evidence is questionable. The cooling power of a perfluorohexane nasopharyngeal spray (2) and the direct local application of ice strips and circulating 4°C water to the head and neck (3), far exceed the heat dissipation potential of human ventilation and therefore cannot be compared. Indeed, the latter study used "selective brain cooling" in the context of a targeted local hypothermia using external cooling devices. Furthermore, the reductions in intracranial temperature during 3 min of voluntary hyperventilation (18–20 breaths/min), attributed solely to ventilation-induced heat transfer across the cribriform plate (4), appear difficult to explain from a biophysical standpoint. Assuming cerebral heat balance prior to hyperventilation, and using a cerebral heat capacity of 3.64 $J \cdot g^{-1} \cdot °C^{-1}$ and brain mass of 1,500 g, an intracranial temperature decrease of 0.05 to 0.10°C/min requires an increased heat dissipation from the brain of 4.6 to 9.1 W. While the change in total inspiratory heat loss across the nasal cavity during hyperventilation (using a 1 L tidal volume) would be ~26.3 W (1), three-dimensional modeling of the nasal cavity demonstrates that even with unlimited blood perfusion of the nasal walls, a maximum heat loss of only ~1.3 W would occur at anatomical structures juxtaposed to the brain (5).

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NO EVIDENCE THAT MAMMALS WITHOUT A CAROTID RETE CAN SELECTIVELY COOL THEIR BRAINS

TO THE EDITOR: White et al. (7) argue that a carotid rete is not a prerequisite for selective brain cooling (SBC) because several mammals without a rete "clearly demonstrate SBC." They clearly have ignored the published research showing that hypothalamic temperature always exceeds arterial blood temperature in species without a rete, even during hyperthermia (for summary, see Ref. 1). While brain and arterial blood temperature have not been measured directly in healthy humans, they have been measured accurately in other mammals, including baboons, which have a similar cranial vascular anatomy to humans. Not one of more than 3,400 measurements of brain temperature per animal in baboons exposed to heat and deprived of water, with brain temperatures sometimes exceeding 40°C, was lower than the concurrent arterial blood temperature (2).

Studies cited in support of SBC in non-rete species are invalidated by temperature measurements at inappropriate sites or confounded by thermal inertia of the brain (1, 2). In horses, for example, through inertia, brain temperature fell below arterial blood temperature briefly at exercise onset when body temperatures were increasing rapidly, but otherwise always exceeded arterial blood temperature, including at maximum blood temperature (3). Similarly, the temperature of jugular venous blood draining from the head consistently exceeded arterial blood temperature in exercising hyperthermic humans, including at maximum temperature (6). The existence of SBC in humans is not "hotly debated"; there is no evidence that humans (4) or any other species without a carotid rete can implement SBC.

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SELECTIVE BRAIN COOLING IN HUMANS: WE DON'T FLY, BUT WE WALK JUST FINE

TO THE EDITOR: There seems to be consensus that the human brain is cooled by arterial blood; that humans possess neither a true carotid rete nor a prominent panting response; and that, during hyperthermia, emissary veins (including the angular) direct cooled blood from the head surface to internal networks (including the cavernous sini, which host the internal carotids). However, there are two debates (4, 6).

The first is about the validity of tympanic thermometry, the method used to demonstrate selective brain cooling (SBC) in humans. Although ear thermometry can be disastrous (5), properly placed tympanic thermocouple probes produce convincing data. When the angular vein is occluded with topical pressure in a hyperthermic subject, the tympanic temperature rises at a higher rate (3), and it is hard to ascribe this rise to contamination with the meatus wall temperature. Clearly, mechanisms of SBC are functional in humans.

The second is disagreement about the extent of SBC. Direct measurements are scarce and are missing completely at high (2) body temperatures; estimates of the drop in blood temperature between the aorta and the brain vary from negligible (4) to substantial (1); and the current definition's requirement that the brain must be cooler than the aorta seems overly demanding. Indeed, if arterial blood is cooled by specialized mechanisms before entering the brain, so that it removes locally produced heat while keeping brain temperatures at near-aortic levels, would this not be SBC at work? Rephrasing Nybo and Secher (4), we may not fly, but we seem to walk just fine.

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A VOICE IN SUPPORT OF COOL THINKING

TO THE EDITOR: Human SBC, due to a campaign against it, has been one of the hottest topics in thermal physiology for over 30 years. I find the campaign rather emotional than rational. Accordingly, in the opponents' papers (2, 4) there are some traces of deliberate attempts to deny the existence of human SBC. Firstly, in human experiments (4) 5 min face fanning (why not longer?!) is a priori by no means sufficient to cool the bulky human brain, secondly in the baboon model radiant heating directed toward the monkeys' heads (2) must have, obviously, resulted in selective brain heating, counteracting SBC.

Moreover, because heat exchange between cool venous blood of dural sinuses, cerebrospinal fluid, and thin-walled subarachnoid and pial arteries (1) seems to play a crucial role in human SBC, calculations showing insignificant countercurrent heat-exchange between carotid arterial and intracranial venous blood (3), even if they are correct, should not be used to refute SBC.

Concerning direct evidence of human SBC (6) I would like to add one more argument in support. I propose a reinterpretation of postoperative brain (T_{brain}) and rectal (T_r) temperature changes in a man suffering from a huge cerebral hemorrhage (5). After 2 days of a high fever, when his T_{brain} exceeded T_r, he suddenly switched to anapyrexia and his T_{brain} dropped to 33.0°C, while T_r stabilized at 36.0°C. This is an example of extreme SBC under a threat of death. Unfortunately, this adaptive response was too late and the patient died 3 days later, but his thermoregulatory system remained precise and exhibited a clear-cut circadian rhythm until the end.

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HUMAN SELECTIVE BRAIN COOLING: THE CONTROVERSY CAN BE SOLVED BY MONITORING INTRACEREBRAL TEMPERATURE

TO THE EDITOR: The current counterpoint discussion regarding human selective brain cooling during hyperthermia (6, 7) is a remarkable repetition of a discussion almost 20 years ago (1, 2). The ongoing controversy might be partly solved by mathematical modeling: calculations show that it is highly unlikely that heat removal through the skull is of significant importance (5). This view is supported by data obtained during moderate extracranial cooling in neurosurgical patients (4). Consequently, human selective brain cooling can only be achieved by direct cooling through the skull base and/or cooling of the arterial influx. Theoretically venous blood cooling the carotid arteries within the cavernous sinus might be effective. This possibility has been studied in patients, but controversy has arisen whether tympanic temperature—used in these studies—adequately represents intracerebral temperature (1, 2, 5–7). The disagreement can be solved by directly recording the intracerebral temperature. Recently it was shown that equipment designed for intranasal cooling of the skull base of pigs caused selective reduction in brain temperature (3). Similar equipment is available for human use. Thus the long-lasting controversy of human selective brain cooling can be solved by moderate cooling of the intranasal cavity and the skull base close to the cavernous sinus during simultaneous recording of intracerebral and body core temperature. The study is presently in progress.

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PHYSIOLOGICAL SIGNIFICANCE OF HYPERTHERMIA-INDUCED HYPERPNEA FOR SELECTIVE BRAIN COOLING IN HUMANS

TO THE EDITOR: We would first like to address the issue of selective brain cooling (SBC). SBC is clearly defined as a lowering of the brain temperature, either "locally" or "as a whole," below the arterial blood temperature (4). Although Drs. Nybo and Secher (5) considered only SBC affecting the whole brain, thermal hyperpnea can induce local SBC in humans, affecting the frontal lobes close to the nasal passages, as Dr. White mentioned (7). We do not have enough evidence to suggest this local SBC contributes to the maintenance of physiological homeostasis, as cooling of a limited part of the frontal lobes seems not to be physiologically important. However, a future finding of SBC in a region such as the hypothalamus could support the idea that local SBC is physiologically significant. This brings us to our second point. When primates are heat stressed, those with a greater sweat response show a smaller hyperthermia-induced ventilatory response (i.e., thermal hyperpnea; Ref. 3), and humans exhibit the greatest sweat response during heat stress and the smallest thermal hyperpnea. Through evolution, thermal hyperpnea may have lost its role in maintaining thermal homeostasis (e.g., brain temperature) in humans. Indeed, the functional characteristics of thermal hyperpnea in humans are quite different from those of sweating and skin vasodilation, which occur to maintain thermal homeostasis, i.e., although skin temperature and hypohydration modulate sweating and skin vasodilation, those stimuli do not affect thermal hyperpnea, and unlike the response in panting animals, thermal hyperpnea in humans usually leads to hypocapnia and reduced cerebral blood flow (1, 2, 6).

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SELECTIVE BRAIN COOLING AS AN EVOLUTIONARY CONCEPT

TO THE EDITOR: Selective brain cooling (SBC) is an interesting concept that has raised considerable debate (6). Yet, to date there has been no convincing evidence for its existence in humans, as the vast majority of support to SBC stems from experiments using tympanic temperature (T_{ty}) to derive conclusions regarding brain temperature (5). This is crucial because the poor relationship between T_{ty} and internal temperatures has been a consistent finding during both exercise and rest in various environments (3, 4). More importantly, however, SBC goes against our fundamental notions regarding the evolutionary characteristics of mammalian thermoregulation. As suggested by White and colleagues (6) ". . .By selectively cooling the hypothalamus, humans or mammals sweat or pant less and consequently conserve body fluids." Indeed, lowering brain temperature will, ultimately, result in reduced heat loss responses (2). However, this will not help preserve the organism's thermal homeostasis, especially during exercise in the heat. Unlike other animals, evaporation of sweat is the primary physiological pathway for human heat dissipation, and risking thermal collapse by reducing sweating rate would appear to be counterintuitive, especially as one of the hallmarks of heat adaptation is an enhanced sweating response (1). The reduced heat loss responses predicted by the SBC would result in increased body heat storage with severe disruptions in thermal balance. Ultimately, to best respond to heat stress via either physiological or behavioral thermoregulation, logic would dictate that an organism requires the most accurate data on its actual thermal status, rather than the muted signal suggested by SBC.

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ANOTHER VOICE IN SUPPORT OF COOL THINKING

TO THE EDITOR: The mathematical equations governing the general cooling process in a body resemble those of vibrations. As such, cooling could be free and forced just like free vibrations and forced vibrations. The free cooling depends on the anatomy especially the surface area, and forced cooling depends on the physiology. A spherical body has the least surface area-to-volume ratio. In fact, for a solid sphere this ratio is 4.83, whereas it is 7.21 for a tetrahedron. Thus for a round human head, possible free cooling is minimal and for a rather pyramidal head of some animals, it is maximal. For thermoregulation during hyperthermia, the head then has to perform some degree of forced cooling, i.e., selective brain cooling (SBC).

This is done through blood circulation and sweating via convection and evaporation, respectively (6). Compared to the rest of the body the density of sweat glands is high in the forehead (5). This arrangement is meant for evaporative cooling of the head. Among the Inuit, sweat glands are functional predominantly in the face as a token of adaptation (4). Emissary veins, nasal cavity, tympanic cavity, and cerebrospinal fluid in humans with a larger brain are an ontological basis for SBC (1). It is argued (3) that carotid rete is essential for SBC; but the horse serves as a counterexample (2). Additionally, some anatomical variations in population living in hot climates for an effective SBC include thick everted lips, broader nasal cavity, and bigger paranasal sinuses that provide more evaporating surfaces (1).

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A RELIABLE AND VALID TOOL TO NONINVASIVELY MEASURE BRAIN TEMPERATURE: THE MISSING LINK

TO THE EDITOR: The crux of the controversy whether selective brain cooling in humans is "physiological" (4, 6), is the fact that noninvasive means to measure cerebral temperatures have yet to be established. MR imaging-based methods exist and appear promising (2, 3). However, validity and reliability of those methods remain unsolved issues in humans.

Studies on patients with acute brain injury revealed increased brain temperatures compared to body temperatures; 0.3°C difference in 20 acute brain injury patients measured with invasive methods (vs. central venous temperature; Ref. 5) and >1°C difference in 40 acute ischemic stroke patients based on MR-spectroscopic methods (vs. tympanic temperature; Ref. 3).

Similar MR-based methods were applied on healthy individuals who underwent surface cooling of the head, which, by the way, did not reveal significant changes of brain temperatures (2). This study, however, suggested that deep brain temperature (thalamus) tended to be cooler than axillary temperature (36.6 ± 0.4 vs. 37.1 ± 0.3°C).

From a thermodynamic standpoint, the brain is unique in that heat dissipation is limited due to the surrounding skull. Thus brain temperature is mainly defined by brain metabolism, arterial input, and cerebral blood flow (CBF). It is well-accepted that brain cooling is associated with a decrease in CBF, possibly via coupling with decrease in metabolism (1). Now, would this then imply that an increase in arterial input temperature (hyperthermia) and subsequent increase in brain temperature leads to an increase in CBF that would lead to increased heat removal? For healthy subjects this remains only theory unless reliable and valid means are provided to noninvasively measure brain temperature.

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SELECTIVE BRAIN COOLING IN HUMANS DURING EXERCISE

TO THE EDITOR: Numerical modeling using the newly developed and validated Generic Bioheat Transfer Model (3) shows that the rectal and blood temperature change was ~0.1°C higher than the deep brain temperature change as a result of a 2-h-long exercise doubling metabolic heat generation and producing 1 l/h of sweating. Therefore, by the definition of the selective brain cooling (SBC), the SBC was achieved (2, 4). However, given the standard deviation of the current temperature probes on the order of 0.1–0.2°C the simulation result suggests that the SBC may be undetectable in humans during exercise (2). Direct invasive brain and body thermometry will need to be performed to verify the result and conclude the debate. The numerical simulation was performed by approximating humans as a two cylinder model with the total surface area of 1.07 square meter and the average body weight of ~80 kg (head = 4.77 kg, trunk = 75.45 kg). Deep brain temperatures can be statistically significantly varied from the rectal temperature by changing head-surface boundary conditions (e.g., cooling pads, etc) and/or carotid artery inlet flow temperatures (1, 4).

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