Published in final edited form as:
Acta Physiol (Oxf). 2010 August ; 199(4): 407–423. doi:10.1111/j.1748-1716.2010.02119.x.

Cardiovascular function in the heat-stressed human

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Abstract

Heat stress, whether passive (i.e. exposure to elevated environmental temperatures) or via exercise, results in pronounced cardiovascular adjustments that are necessary for adequate temperature regulation as well as perfusion of the exercising muscle, heart and brain. The available data suggest that generally during passive heat stress baroreflex control of heart rate and sympathetic nerve activity are unchanged, while baroreflex control of systemic vascular resistance may be impaired perhaps due to attenuated vasoconstrictor responsiveness of the cutaneous circulation. Heat stress improves left ventricular systolic function, evidenced by increased cardiac contractility, thereby maintaining stroke volume despite large reductions in ventricular filling pressures. Heat stress-induced reductions in cerebral perfusion likely contribute to the recognized effect of this thermal condition in reducing orthostatic tolerance, although the mechanism(s) by which this occurs is not completely understood. The combination of intense whole-body exercise and environmental heat stress or dehydration-induced hyperthermia results in significant cardiovascular strain prior to exhaustion, which is characterized by reductions in cardiac output, stroke volume, arterial pressure and blood flow to the brain, skin and exercising muscle. These alterations in cardiovascular function and regulation late in heat stress/dehydration exercise might involve the interplay of both local and central reflexes, the contribution of which is presently unresolved.

Keywords

baroreflexes; cerebral perfusion; dehydration; exercise; hyperthermia

Humans have the capability to withstand large variations in environmental temperatures, while relatively small increases in internal temperature (i.e. as little of ~3 °C) can lead to injury and even death. Elevations in skin blood flow and sweating are the primary heat exchange mechanisms in humans that protect against a heat-related injury. The importance of these mechanisms is exemplified in the calculation that if heat was not liberated from skin, internal temperature would reach the upper ‘safe’ limit within 10 min of moderate

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Conflict of interest
There is no conflict of interest.

exercise (Kenney & Johnson 1992). These heat-dissipating responses are accompanied by important, even critical, cardiovascular adjustments, which, if they were not present, would compromise thermal regulation during exercise and/or exposure to elevated environmental temperatures. There is little doubt that Johannes Lindhard understood these important concepts. In fact, in 1910 he published an article titled 'Investigations into the conditions governing the temperature of the body' in which the relationship between rectal temperature and 'heat-producing processes of the body' was investigated (Lindhard 1910). Later he reported on the temperature of human muscles at rest and during exercise (Buchthal *et al.* 1944). A student who studied under Lindhard's and Krogh's guidance, Marius Nielsen, continued to investigate human temperature regulation (Nielsen 1938, Christensen *et al.* 1942, Asmussen & Nielsen 1947, Nielsen & Nielsen 1962, 1965a,b).

The objective of this article is to present findings pertaining to cardiovascular responses associated with human temperature regulation. The review is divided into two parts with part one focusing on cardiovascular responses to passive (i.e. non-exercising) heat stress, while the second part focuses on cardiovascular responses associated with exercise heat stress. Given numerous outstanding review articles on these topics (Rowell 1974, 1983, 1986a,b,c, Johnson 1992, Johnson & Proppe 1996, González-Alonso *et al.* 2008), this review will focus primarily on relatively new findings (i.e. within the prior ~15 years), while salient work done prior to this period will be only briefly addressed.

Key cardiovascular responses to passive heat stress

Clearly the primary stimulus by which internal temperature is elevated in humans is through exercise. However, heat-related injuries and deaths can occur in non-exercising humans, especially those with prior medical conditions such as cardiovascular disease (Semenza *et al.* 1996, 1999). Particularly prevalent was the large number of 'excess' deaths during the 1995 Chicago heat wave of individuals with a prior 'heart condition' (Semenza *et al.* 1996). Investigations into cardiovascular responses to passive heat stress are valuable towards the identification of potential mechanisms responsible for heat-induced injuries and deaths in patient populations. Moreover, cardiovascular responses to passive heat stress provide a benchmark from which the effects of combined exercise and heat stress can be compared.

Studies investigating thermal and cardiovascular responses to passive heat stress typically heat the subject via water-perfused suits, in which hot water is perfused through a tube-lined suit worn by each subject; by water immersion of the entire body or just limbs (such as the legs) in warm water; or by exposure of the individual to warm environmental conditions using a climatic chamber. In all cases an elevation in skin temperature is the primary mode by which internal temperature is elevated; although depending on the approach the magnitude of the increase in skin temperature can greatly differ. A limitation of the interpretation of these studies is the lack of consistency of the magnitude of the heat stress, primarily defined by the magnitude of the increase in internal temperature; with some studies reporting heat stress being as little as a 0.5 °C increase in internal temperature whereas other studies report increasing internal temperature upwards to 2 °C.

During pronounced passive heat stress, skin blood flow of humans is estimated to increase from ~300 mL min^{-1} upwards to 7500 mL min^{-1} (Rowell *et al.* 1969a, Rowell 1986c). In order to prevent large decreases in arterial blood pressure due to pronounced increases in total vascular conductance associated with cutaneous vasodilation, cardiac output must increase along with decreases in vascular conductance of non-cutaneous beds. The combination of these responses results in either no change, or only minimal reductions in arterial blood pressure. Rowell *et al.* (1969a) and Rowell (1986c) showed that during a pronounced passive heat stress, cardiac output can be as high as 13 L min^{-1}, with ~50% of

that value estimated to be directed towards skin. This elevation in cardiac output is primarily mediated through increases in heart rate as stroke volume either does not change or is marginally increased in young healthy heat-stressed subjects (Damato *et al.* 1968, Rowell *et al.* 1969a, Minson *et al.* 1998). Redistribution of blood flow from non-cutaneous tissues is evident from passive heat stress studies showing that post-ganglionic muscle sympathetic nerve activity increases (Niimi *et al.* 1997, Crandall *et al.* 1999a, 2003, Cui *et al.* 2002b,c, 2004a, Keller *et al.* 2006) while vascular conductance in other beds (i.e. splanchnic and renal) decreases (Rowell *et al.* 1971, Rowell 1986c, Minson *et al.* 1998). Thus, pronounced heat stress in humans has been termed a 'hyperadrenergic state' as it is accompanied with the aforementioned responses (Rowell 1990). These primary cardiovascular responses to passive heat stress are depicted in Figure 1. Recent studies provide further insight into the effects of heat stress on cardiovascular responses, specifically the effects of heat stress on baroreflex responsiveness, central blood volume, cardiac function, and control of the cerebral vasculature. These areas are the primary focus of the first part of this review.

Heat stress and baroreflex responsiveness

The mechanisms responsible for reduced orthostatic tolerance in heat-stressed humans have not been fully elucidated, although Lind *et al.* (1968) showed this response was not due to enhanced pooling of blood in the leg during the orthostatic challenge. The central components governing thermoregulation are located in the hypothalamus (Strom 1960), and electrical stimulation of the hypothalamus modifies the baroreceptor reflex (Reis & Cuénod 1965, Gebber & Snyder 1970). Thus it seemed feasible that heat stress may impair baroreflex function, which could compromise blood pressure control while individuals are in this thermal condition.

Based upon numerous studies evaluating the effects of heat stress on baroreflex responses, four key observations can be summarized. (1) Generally, heat stress does not alter baroreflex control of heart rate (Crandall 2000, Yamazaki & Sone 2000, Wilson *et al.* 2001, Yamazaki *et al.* 2001, Cui *et al.* 2002b). The exceptions are from a few studies in which the change in heart rate during relatively small spontaneous oscillations in blood pressure is attenuated during heat stress (Crandall *et al.* 2000, Lee *et al.* 2003). It is possible that these latter observations are due to reduced cardiac vagal activity associated with heating (Crandall *et al.* 2000) given that when greater changes in baroreceptor loading were caused either mechanically (Crandall 2000, Yamazaki & Sone 2000) or pharmacologically (Wilson *et al.* 2001, Cui *et al.* 2002b), the baroreflex gain of the blood pressure to heart rate relationship was unchanged due to whole-body heating. (2) Baroreflex control of muscle sympathetic nerve activity is typically not attenuated by heat stress, but rather is unchanged or even elevated (Cui *et al.* 2002b, 2004a, Keller *et al.* 2006). The exception is a study showing attenuated changes in muscle sympathetic nerve activity relative to blood pressure changes induced by the valsalva manoeuvre in heat-stressed subjects (Yamazaki *et al.* 2003). Apart from the acute nature of the blood pressure change during the valsalva manoeuvre (i.e. typically less than 10 cardiac cycles), relative to the longer duration of the hypotensive challenge to systemic nitric oxide administration and lower body negative pressure, reasoning for these differing responses is not forthcoming. (3) Cutaneous vasoconstrictor responses are attenuated by local and whole-body heat stress (Wilson *et al.* 2002a), whereas muscle vasoconstrictor responses are not impaired when muscle temperature is elevated ~4 °C (Keller *et al.* 2007). Attenuated cutaneous adrenergic vasoconstrictor responsiveness (Wilson *et al.* 2002a), coupled with upwards to 50% of cardiac output being directed towards the skin in the heat-stressed subject, may be the mechanism responsible for attenuated blood pressure changes upon changing carotid sinus transmural pressure (Crandall 2000), as well as during systemic phenylephrine administration (Cui *et al.* 2002c). (4) Despite somewhat varied baroreflex responses to heat stress, this exposure consistently

shifts the baroreflex curve to the prevailing heart rate, muscle sympathetic nerve activity and blood pressure (Crandall 2000, Yamazaki *et al.* 2001, 2003, Cui *et al.* 2002b, Crandall *et al.* 2003, Keller *et al.* 2006). In summary, the bulk of the data do not support the hypothesis that heat stress attenuates baroreceptor control of heart rate or muscle sympathetic nerve activity to relatively pronounced changes in arterial blood pressure. However, heat-induced alterations in post-synaptic cutaneous vasoconstrictor responsiveness may attenuate baroreflex control modulation of systemic vascular conductance.

Heat stress and blood volume distribution

Passive heat stress causes pronounced reductions in central venous pressure which, depending on the magnitude of the heat stress, can approach 0 mmHg (Rowell *et al.* 1969a, Johnson & Proppe 1996, Minson *et al.* 1998, Crandall *et al.* 1999b, Peters *et al.* 2000, Wilson *et al.* 2007, Keller *et al.* 2009). The mechanism responsible for this reduction in central venous pressure has been proposed to be due to a redistribution of blood from the central circulation to cutaneous vascular beds (Johnson & Proppe 1996). Despite heat stress-induced reductions in central blood volume being hypothesized (Müller 1905, Glaser *et al.* 1950, Eisalo 1956, Koroxenidis *et al.* 1961, Frayser *et al.* 1966), Rowell *et al.* (1969a) reported a slight increase in central blood volume during whole-body heat stress when indexed from mean transit time of a dye injected into the right atrium and sampled at the aortic arch (see Fig. 1). Such a finding is perplexing given the discord between reductions in central venous pressure and Rowell's observation of a slight increase in central blood volume.

To clarify this question, Crandall *et al.* (2008) evaluated changes in regional blood volume during passive heat stress using technetium-99m labelled autologous red blood cells, coupled with gamma camera imaging. Although with this approach absolute measures of central blood volume were not obtained, relative changes in regional blood volumes were quantified. The heat stress caused typical haemodynamic responses, similar to that outlined in Figure 1, including a reduction in central venous pressure from 5.5 ± 0.7 to 0.2 ± 0.6 mmHg ($P < 0.001$). Accompanying this central venous pressure response were greater reductions in thoracic blood volume (14 ± 2%), heart blood volume (18 ± 2%) and the volumes of the heart plus the central vascular structures (17 ± 2%), relative to responses in subjects who were not heat stressed but were supine for a similar duration following technetium-99m administration as the heat-stressed subjects (Fig. 2). In addition, heat stress decreased liver (23 ± 2%) and spleen (27 ± 2%) blood volume, which is consistent with previously reported reductions in splanchnic blood flow by heat stress (Rowell *et al.* 1969a, 1971, Minson *et al.* 1998). These data provide clear evidence that heat stress decreases central blood volume, which is likely due to a redistribution of blood from the central to the cutaneous vascular beds, coupled with increases in cardiac output (Johnson & Proppe 1996).

Heat stress and cardiac function

Consistent with a reduction in central venous pressure, passive heat stress results in parallel decreases in left ventricular filling pressure as indexed from pulmonary capillary wedge pressure (Wilson *et al.* 2007, 2009). Reduced central blood volume and ventricular filling pressures, accompanied with preserved or slightly elevated stroke volumes has led to the suggestion that heat stress increases the inotropic state of the heart (Rowell 1986c, Johnson & Proppe 1996). Consistent with that hypothesis, Crandall *et al.* (2008) showed that whole-body heat stress increases ejection fraction. However, these findings must be interpreted with the recognition of the indirect nature of this measurement and the load dependency of ejection fraction, resulting in an imprecise measure of systolic function, particularly given changes in ventricular loading status during a heat stress. For this reason, Brothers *et al.*

(2009a) identified the effects of heat stress on echocardiographic indices of cardiac systolic and diastolic function. The primary observations from that study were: (1) Heat stress has no effect on indices of diastolic function as indicated by an unchanged left ventricular filling velocity, an unchanged early diastolic mitral annular velocity and an unchanged ratio of blood velocity/mitral annular velocity during the early phase of diastole. However, the preservation of these indices of diastolic function, despite heat stress-induced decreases in ventricular filling pressures (Rowell *et al.* 1969a, Minson *et al.* 1998, Crandall *et al.* 1999b, Wilson *et al.* 2007, 2009) and central blood volume (Crandall *et al.* 2008), leaves room for speculation that diastolic function is perhaps improved during heat stress. (2) Heat stress increased left ventricular systolic function as evidenced by an increase in peak septal and lateral mitral annular systolic velocities and isovolumic acceleration (Fig. 3). (3) Heat stress significantly increased left atrial systolic function as evidenced by an increased velocity of blood during the atrial contraction phase of left ventricular diastolic filling and an increased velocity of the septal and lateral mitral annulus during the late phase of diastolic relaxation relative to normothermia.

Increases in left ventricular end-diastolic cross-sectional diameter, often indicated by its filling pressure, increase the ability of the left ventricle to produce force and thereby stroke volume (Sarnoff & Mitchell 1961, Katz 2006). This concept, termed Frank–Starling mechanism (Frank 1895, Patterson & Starling 1914, Patterson *et al.* 1914), is represented *in vivo* by a series of hyperbolic curves relating changes in pulmonary capillary wedge pressure (as an index of left ventricular end-diastolic volume) relative to stroke volume. Given the hyperbolic shape of these curves, the magnitude of change in stroke volume for a given change in filling pressure is largely affected by the shape of the curve and the location of the operating point on that curve. A reduction in left ventricular filling pressure caused by passive heat stress, coupled with an absence of a reduction in stroke volume, suggests heat stress causes a leftward shift of the Frank–Starling curve. Wilson *et al.* (2009) experimentally validated this hypothesis upon examining the relationship between pulmonary capillary wedge pressure and stroke volume during 15 and 30 mmHg lower body negative pressure while subjects were normothermic and heat stressed (Fig. 4). Heat stress shifted the operating point to a steeper portion of the Frank–Starling curve such that for a given reduction in ventricular filling pressure there was a greater reduction in stroke volume. This larger reduction in stroke volume was not compensated for by a proportionally greater increase in heart rate, resulting in a larger reduction in cardiac output for a given reduction in left ventricular filling pressure or level of lower body negative pressure when the individual was heat stressed (Wilson *et al.* 2009), which likely is a primary mechanism for heat stress-induced reductions in orthostatic tolerance (Keller *et al.* 2009).

Heat stress and the cerebral vasculature

Whole-body heat stress decreases cerebral perfusion in the supine resting human (Wilson *et al.* 2002b, 2006, Fan *et al.* 2008, Fujii *et al.* 2008, Low *et al.* 2008, 2009, Brothers *et al.* 2009b), which is not entirely accounted for by concurrent reductions in arterial carbon dioxide tension (Wilson *et al.* 2006, Brothers *et al.* 2009b). The latter point was recently confirmed given that cerebral perfusion and cerebral vascular conductance remained well below pre-heat stress levels after end-tidal carbon dioxide partial pressures, which can be reduced by 15+ mmHg during heating (Wilson *et al.* 2006, Crandall *et al.* 2008, Fan *et al.* 2008, Fujii *et al.* 2008, Brothers *et al.* 2009b), were returned to pre-heat stress levels (Brothers *et al.* 2009b) (Fig. 5). The mechanism by which heat stress decreases cerebral vascular conductance and perfusion independent of reduced arterial carbon dioxide partial pressures is not clear. One possibility could be increased cerebral sympathetic activity. Sympathetic nerve activity increases by approximately 90% to the muscle vasculature and 300–600% to the skin vasculature during passive heat stress (Bini *et al.* 1980, Niimi *et al.*

1997, Cui *et al.* 2002a, 2004b,c, Keller *et al.* 2006). Furthermore, blood flow to the renal and splanchnic regions is reduced presumably as a result of increased sympathetically mediated vasoconstriction (Rowell *et al.* 1970, 1971, Johnson & Proppe 1996, Minson *et al.* 1998). While the role of sympathetic control of the cerebral vasculature remains controversial (van Lieshout & Secher 2008, Strandgaard & Sigurdsson 2008), animal studies have shown that the cerebral arteries are richly innervated with sympathetic nerve fibres (Nelson & Rennels 1970, Edvinsson 1975). Evidence for cerebral sympathetic activity has also been demonstrated in human studies that have identified a reduction in cerebral perfusion during unilateral trigeminal ganglion stimulation (Visocchi *et al.* 1996) and an increase in cerebral perfusion after stellate ganglionic blockade (Umeyama *et al.* 1995, Ide *et al.* 2000). Furthermore, cerebral autoregulation is impaired following removal of autonomic neural activity with trimethaphan (Zhang *et al.* 2002) and systemic blockade of α_1-adrenergic receptors with prazosin (Ogoh *et al.* 2008). Therefore, it is plausible to speculate that heat stress-induced increases in cerebral sympathetic activity may contribute to reductions in cerebral perfusion in the heat-stressed human.

From the aforementioned findings, it is clear that even prior to the onset of an orthostatic event cerebral perfusion is compromised by whole-body heat stress. Reduced cerebral perfusion in the heat-stressed human will attenuate the reserve by which cerebral blood flow can further decrease prior to the onset of syncope. Thus, heat-stress induced decreases in cerebral perfusion likely contribute to reductions in orthostatic tolerance.

Maintenance of cerebral perfusion over a wide range of systemic blood pressures (e.g. from ~60 to ~150 mmHg) is carried out by a variety of mechanisms including cerebral autoregulation which acts to offset changes in perfusion pressure by adjusting the resistance of the cerebral vasculature (Heistad & Kontos 1983, Paulson *et al.* 1990). Should heat stress attenuate cerebral autoregulation, this would result in a greater reduction in cerebral perfusion for a given reduction in perfusion pressure, ultimately leading to reduced orthostatic tolerance. Consistent with this hypothesis, Wilson *et al.* (2006) identified that for a given level of orthostatic stress (via lower body negative pressure) when subjects were heat stressed the reduction in cerebral vascular conductance and perfusion was significantly greater, relative to when subjects were normothermic. Doering *et al.* (1999) were the first to seek whether heat stress alters cerebral autoregulation. Counter to an expected reduction, in mildly heat-stressed subjects (~0.4 °C increase in internal temperature) they reported an increase in an index of cerebral autoregulation. Given the relatively minor heat stress in that study, Brothers *et al.* (2009c) and Low *et al.* (2009) further investigated this question, using varied techniques in more profoundly heat-stressed subjects relative to the level of heating in the Doering *et al.* study. Regardless of whether the blood pressure oscillations were relatively small (Low *et al.* 2009) or quite large (Brothers *et al.* 2009c), cerebral autoregulation was not compromised by heat stress. In contrast, and depending on the frequency of blood pressure oscillation analysed, these investigators found either no change or enhanced cerebral autoregulation by heat stress; the latter being consistent with the original findings of Doering *et al.* (1999). Taken together, whole-body heat stress either does not change or perhaps improves cerebral vascular autoregulation.

Cardiovascular responses to combined exercise and heat stress

The combination of exercise and heat stress can pose one of the most severe challenges to the regulation of the cardiovascular system in humans. The interplay between the magnitude of thermal stress, the intensity and duration of exercise and the individual training, heat acclimatization and hydration status will dictate the extent of the cardiovascular challenge. These factors should therefore be thoroughly considered in predicting whether heat stress will promote compensatory adjustments or severe circulatory strain that could lead to

accelerated fatigue or collapse in exercising people. Conceivably, the greatest cardiovascular strain and alterations in cardiovascular regulation are expected to occur in untrained, unacclimated and hypohydrated subjects who perform intense, prolonged exercise in a hot and humid environment. World-class, heat-acclimated and euhydrated athletes might be on the other end of a continuum and show minimal alterations in cardiovascular function under comparable extreme exercise and environmental conditions. This second component of the review will primarily discuss evidence and ideas concerning the responses and regulation of the human cardiovascular system when confronted with the combined stresses of exercise and environmental heat stress or dehydration-induced hyperthermia. The impact of alterations in limb blood flow on convective heat transfer and internal temperature regulation will also be briefly discussed in the context of the classic observations of Nielsen (1938).

Over the past 45 years our understanding of human cardiovascular function during thermal stress and exercise has been influenced very profoundly by the work of Loring Rowell and colleagues at the University of Washington. In a landmark study, they (Rowell *et al.* 1966) were the first to demonstrate in a group of untrained individuals performing graded exercise in a hot and a thermoneutral environment that severe thermal stress readily perturbs cardiovascular function when the intensity of exercise is moderate to intense. The key features indicative of cardiovascular strain during exercise were the significantly lower stroke volume, central blood volume, aortic pressure and cardiac output and the markedly elevated heart rate reaching near-maximal values. The decreased central blood volume with heat stress across all four submaximal exercise intensities examined supported the idea that a lowering in venous return and filling of the heart might be an important factor involved in the depressed stroke volume and ultimately cardiac output with combined heat stress and exercise. In line with this view, they showed in a subsequent study using a water-perfused suit that the marked alterations in central blood volume, central venous pressure, stroke volume, heart rate and cardiac output evoked by superimposing severe heat stress upon light and high intensity cycling were almost restored to normothermic control values by perfusing the suit with cold water (Rowell *et al.* 1969b). During walking in a very hot environment, however, cardiac output increased over time due solely to increases in heart rate (Rowell *et al.* 1967). Thus this pioneer research demonstrated that the repercussions of combined heat stress and exercise on cardiovascular function are dependent upon the intensity of exercise and implied that cardiac output and perfusion pressure are compromised in untrained subjects when both the metabolic and thermoregulatory demands are high.

Limb muscle and skin perfusion during combined exercise and heat stress

These early observations of a compromised cardiovascular function during heat stress exercise and the latter finding that forearm blood flow (index of skin blood flow in the resting forearm) increases progressively during leg exercise (Johnson & Rowell 1975) form the basis for the most influential hypothesis in this field postulating that the combination of heat stress and exercise results in a competition between the exercising skeletal muscles and the skin compartments for the available cardiac output such that blood flow to the active muscles would be reduced at the expense of an elevated skin circulation (Rowell 1974, 1983). According to this hypothesis, the pumping capacity of the heart cannot meet the joint demands for blood flow of the exercising muscle and the skin during exercise and heat stress. Experimental evidence in animals and humans, however, shows that blood flow to active limb muscles and tissues is either maintained or increased when heat stress is superimposed upon light to moderate intensity prolonged exercise (Laughlin & Armstrong 1983, Armstrong *et al.* 1987, Savard *et al.* 1988, McKirnan *et al.* 1989, Nielsen *et al.* 1990, 1993, 1997). In the human studies, the cardiovascular system appeared to respond adequately to the additional thermoregulatory demand for an elevated skin perfusion by

increasing cardiac output (Savard *et al.* 1988, Nielsen *et al.* 1990, 1993, 1997) and possibly reducing visceral blood flow beyond the control exercise levels (Rowell *et al.* 1965, Ho *et al.* 1997). To understand this response, it is important to bear in mind that cutaneous vasodilatation is noticeably restrained during combined heat stress and exercise compared with the levels observed during resting hyperthermic conditions (Johnson 1992, Kenney & Johnson 1992). During upright exercise, skin perfusion in the resting forearm reaches a plateau at a core temperature of ~38 °C despite further increases in skin and internal temperature (Brengelmann *et al.* 1977, González-Alonso *et al.* 1999c). Although knowledge of the skin perfusion across all body segments including the exercising limbs is very limited, the magnitude of the cardiac output increase and the reduction in visceral blood flow during heat stress exercise indirectly suggest that whole-body skin blood flow might be elevated by 1–2 L min^{-1} above control exercise (Nielsen *et al.* 1993, 1997, Ho *et al.* 1997, González-Alonso *et al.* 2000a). This estimate is based on the still unresolved concept that hyperthermia-induced muscle vasodilatation does not contribute to heat stress-mediated hyperaemia. Regardless of this possibility, evidence from submaximal exercise studies does not seem to support the hypothesis of a regulatory priority of the skin circulation over the skeletal muscle circulation whereby flow from active muscles is redistributed to the skin.

It is universally accepted that severe heat stress suppresses $\dot{V}O_{2max}$ and work capacity during exhaustive incremental exercise (Rowell 1974, Hales *et al.* 1996, Sawka & Coyle 1999). The question then arises as to whether blood flow to active muscles is indeed reduced at the expense of an elevated skin perfusion when heat stress is superimposed upon exercise requiring maximal cardiovascular function and aerobic capacity. Surprisingly, direct data are still lacking on the blood flow responses of the active limb muscles and skin and the systemic circulation during incremental whole-body exercise in heat-stressed individuals. Notwithstanding, an integrative view of the exercising limb and systemic circulatory responses to maximal exercise was recently reported in trained individuals performing constant load cycling under heat stress and normal conditions (González-Alonso & Calbet 2003, González-Alonso *et al.* 2004). An advantage of this exercise model is that it allows investigation of the functional and regulatory capacity of the cardiovascular system in conditions where workload-related changes in metabolic demand and active muscle mass are minimal in comparison with that occurring during exhaustive incremental exercise or self-selective pacing trials. The potentially confounding influence of altered workload-related metabolic and mechanical reflexes on cardiovascular control is therefore minimized. In using this model, González-Alonso& Calbet (2003) showed that blood flow to the exercising legs increases similarly with and without heat stress during the first minute of maximal cycling but thereafter is attenuated and drops faster with heat stress accompanying a quicker decline in cardiac output and arterial blood pressure (Fig. 6). Strikingly, vascular conductance in the active legs and systemic circulation do not decline despite the concomitant increases in circulating catecholamines indicative of enhanced sympathetic vasoconstrictor activity. Importantly, systemic blood flow and arterial pressure responses are elevated or unchanged with heat stress compared with control conditions during the early stages of constant maximal exercise (González-Alonso & Calbet 2003). This contrasts with the diminished cardiac output and arterial pressure seen during moderate and intense exercise in untrained individuals (Rowell *et al.* 1966). It therefore seems that during the early stages of maximal heat stress exercise in trained individuals the higher thermoregulatory demand for skin blood flow is met at least in part by a 1–2 L min^{-1} higher cardiac output. However, hyperthermia more quickly pushes the cardiovascular system to its regulatory limit, where cardiac output and blood flow to exercising limb muscles and skin cannot be maintained for a longer duration.

The mechanisms underlying the restrictions in locomotor limb blood flow during maximal exercise have not been systematically investigated, but they plausibly involve the interplay

of local and central reflexes signalling alterations in thermal, metabolic, mechanical, barosensitive and vascular events in different regions of the body including the skeletal muscle, brain and heart (Rowell 2004, Mortensen *et al.* 2008). The reductions in locomotor limb blood flow and cardiac output during constant maximal exercise and the levelling off in these variables during incremental maximal exercise are temporally related (González-Alonso & Calbet 2003, Mortensen *et al.* 2005, 2008, Calbet *et al.* 2007, Vogiatzis *et al.* 2009). During constant load maximal exercise with and without heat stress, arterial and central venous pressures decline such that the vascular conductance of the active legs and systemic circulation remain unchanged. This suggests that active limb blood flow is reduced secondary to the decline in perfusion pressure, rather than an actual vasoconstriction of the vasculature perfusing the active muscle and skin. In this construct, the reduction in cardiac output might be indirectly involved in this process via its effect on perfusion pressure. Locally, the unaltered leg vascular conductance takes place in the presence of an everincreasing plasma noradrenaline concentration suggesting that neurally mediated vasoconstriction does not occur in the vessels perfusing the exercising limb muscles and skin, even though muscle and skin sympathetic vasoconstrictor activity are likely to be augmented (Ray & Gracey 1997, Ichinose *et al.* 2008). An enhanced metabolic vasodilatation evoked by accumulation of vasodilator substances in the blood (including ATP and other adenine nucleotides) and the muscle interstitium might offset the increased sympathetic vasoconstrictor drive at least in skeletal muscle thereby maintaining limb muscle vascular conductance (Vanhoutte *et al.* 1981). This phenomenon resembles the functional sympatholysis occurring in the skeletal muscle vasculature in conditions of increased sympathetic nerve drive during exercise and hypoxia (Remensnyder *et al.* 1962, Hanada *et al.* 2003, Rosenmeier *et al.* 2004), which underlies the maintenance of resting limb perfusion and the increase in exercising limb blood flow during hypoxic exercise.

Cardiac function during combined exercise and heat stress

Our knowledge and understanding of cardiac function during intense exercise and of the mechanisms underpinning the fall in stroke volume prior to exhaustion are still inadequate. From a cardiac perspective, the fall in stroke volume and cardiac output during constant maximal exercise with and without exogenous heat stress might be the result of a number of factors that negatively affect cardiac pre-load, ventricular afterload and/or myocardial contractility (Rowell 1974, Poliner *et al.* 1980, Higginbotham *et al.* 1986). Neither blood pooling in the compliant cutaneous vasculature (which could potentially diminish venous return) nor augmented ventricular afterload appear likely possibilities as stroke volume, central venous pressure and arterial pressure fall similarly during heat stress and control conditions (González-Alonso *et al.* 2000a, González-Alonso & Calbet 2003). The decline in central venous pressure could be interpreted to mean that a reduction in venous return contributes to the fall in stroke volume (Rowell *et al.* 1966, Rowell 1974). However, a reduced venous return and a concomitant diminution in left ventricular pre-load do not seem to exert an independent effect because stroke volume only declines during the last minute of exercise, but right atrial pressure declines from the start of exercise. This suggests that several factors interact to transiently depress diastolic and/or systolic cardiac function during maximal exercise.

Seeing the declines in cardiac output, exercising limb blood flow and brain circulation, it seems possible that the coronary circulation and left ventricular function are transiently suppressed during maximal exercise, thereby contributing to the reduction in stroke volume. A small attenuation in the myocardial perfusion-to-work relationship could lead to myocardial dysfunction, as oxygen (extraction) reserve is very small to compensate for a significant blunting in oxygen supply. Severe tachycardia might be another factor. Studies in humans and dogs manipulating heart rate by pacing the heart demonstrate that severe

tachycardia leads to disproportional reductions in diastolic filling time and left ventricular enddiastolic volume which compromise stroke volume and cardiac output (Templeton *et al.* 1972, Parker & Case 1979). Human studies demonstrate that hyperthermiainduced tachycardia reduces stroke volume during exercise (González-Alonso *et al.* 1997, Fritzsche *et al.* 1999) and that blunting the increase in internal temperature and heart rate restores most of the fall in $\dot{V}O_{2max}$ evoked by marked hyperthermia and dehydration (Nybo *et al.* 2001). Taken together, the decline in stroke volume during maximal exercise with and without exogenous heat stress is associated with reduced venous return, severe tachycardia and possibly a blunting in myocardial oxygen supply in relation to actual cardiac work.

Cerebral perfusion during combined exercise and heat stress

The active limb muscles are not the only tissues that might experience a reduction in perfusion during exercise and heat stress. The human brain circulation might also be compromised (Nybo & Nielsen 2001, Nybo *et al.* 2002, González-Alonso *et al.* 2004). In this regard, middle cerebral blood velocity declines significantly during prolonged exercise in the heat while it is kept constant during exercise in a thermoneutral environment (Nybo & Nielsen 2001, Nybo *et al.* 2002). During constant maximal exercise, however, cerebral perfusion declines after ~90 s, regardless of the presence or absence of heat stress, as indicated by a progressive drop in both middle cerebral artery mean blood velocity and frontal cortex tissue oxygenation and the concomitant increases in brain oxygen extraction (González-Alonso *et al.* 2004) (Fig. 7). These responses are in sharp contrast to that happening during the first ~90 s of exercise where middle cerebral artery mean blood velocity increases and cerebral oxygen extraction and frontal cortex tissue oxygenation remain stable. This suggests that global brain aerobic metabolism increases early in exercise possibly in response to enhanced neural activation in regions of the brain related to locomotion, the maintenance of equilibrium, vision and cardiovascular control (Delp *et al.* 2001). The large increases in oxygen extraction that occur after ~90 s of maximal exercise are accompanied by smaller reductions in cerebral perfusion, signifying that global brain metabolism and neural drive is further enhanced when approaching exhaustion. Therefore, the physiological repercussions of reductions in perfusion to the brain are apparently less severe than in contracting skeletal and cardiac muscle because, in contrast to the muscles' exhausted oxygen reserve, the human brain maintains a large oxygen reverse on exhaustion, which appears to protect this vital organ against the small declines in oxygen delivery occurring during exercise.

The suppression of brain blood flow early in upright exercise is related to factors other than cardiac output because middle cerebral blood velocity declines when cardiac output is increasing during exercise (Nybo *et al.* 2002, González-Alonso *et al.* 2004). The blunted perfusion pressure is a more likely factor because the decreases in left and right middle cerebral artery blood velocity are temporally associated with reductions in arterial and central venous pressures (González-Alonso *et al.* 2004). A role of perfusion pressure on brain circulation is demonstrated during an orthostatic challenge where middle cerebral artery blood velocity declines drastically when arterial and central venous pressures are compromised (Van Lieshout *et al.* 2003). The decline in P_aCO_2 associated with hyperthermia-induced hyperventilation may also be a factor accounting for a portion of the decline in cerebral blood flow during hyperthermic exercise (Rasmussen *et al.* 2006). Another all-encompassing possibility is that local factors reducing the vasodilator and/or increasing the vasoconstrictor activities suppress brain perfusion. In this regard, the plasma concentration of the potent vasodilator adenosine triphosphate is elevated in the jugular vein (accompanying decreases in venous oxygen saturation), while the brain is apparently taking up large amounts of catecholamines on exhaustion in both conditions and the arterial and jugular venous carbon dioxide partial pressure is declining, suggesting that both vasodilator

and vasoconstrictor activities are elevated. Clearly the elucidation of the local mechanisms involved in the decline in cerebral perfusion during prolonged and maximal heat stress exercise warrants further studies quantifying the contribution of the vasodilator and vasoconstrictor systems.

Cardiovascular strain during exercise with dehydration and hyperthermia

Cardiovascular responses to exercise in the heat with and without dehydration have been extensively studied (Saltin & Stenberg 1964, Sawka *et al.* 1979, Nadel *et al.* 1980, Montain & Coyle 1992a,b, González-Alonso *et al.* 1995, 1997, 1998, 1999c, 2000a). Different experimental approaches that reduce body water either prior to exercise (e.g. diuretics, sauna, exercise, water restriction) or during exercise (fluid restriction) have been used to investigate the effects of reduced body fluids on cardiovascular function. The cardiovascular strain produced by different methods of body water deficits is essentially similar (Sawka & Coyle 1999). However, factors such as environmental conditions, intensity, position and type of exercise all influence the extent of the dehydration-mediated cardiovascular alterations (Montain *et al.* 1998, González-Alonso *et al.* 1999c, 2000a). The cardiovascular strain inflicted by environmental heat stress and that evoked by dehydration bear several similarities probably because internal body hyperthermia and reduced body fluids are common elements accompanying both stresses. A major difference, however, is that skin temperature in the exercise-induced dehydration studies (usually performed in compensable hot environments with fan cooling) is normally maintained at ~34–35 °C (Montain & Coyle 1992b, González-Alonso *et al.* 1999a), while in the heat stress studies using a water-perfused suit or no fan cooling it might gradually increase up to ~38–39 °C (Rowell *et al.* 1969b, González-Alonso *et al.* 1999c).

The progressive dehydration incurred during prolonged moderate intensity cycling in compensable heat conditions is associated with gradual reductions in perfusion pressure and blood flow to the skin and locomotor limb tissues accompanying increases in plasma noradrenaline levels and core temperature (Sawka *et al.* 1979, Montain & Coyle 1992a,b, González-Alonso *et al.* 1995, 1998, 2000a) (Fig. 8). Cardiac output also declines with marked dehydration and hyperthermia because the larger declines in stroke volume compared with the parallel increases in heart rate (Sawka *et al.* 1979, Montain & Coyle 1992a,b, González-Alonso *et al.* 1997). Brain and visceral perfusion are likely to also decline as the lowering in exercising leg blood flow and skin blood flow account for two-thirds of the decline in cardiac output (González-Alonso *et al.* 1998) and similar levels of hyperthermia and global cardiovascular instability have been associated with reductions in the middle cerebral artery blood velocity and renal and splanchnic blood flow (Rowell *et al.* 1965, Nybo & Nielsen 2001). Remarkably, these alterations in cardiovascular function are completely prevented when people fully maintain hydration status by fluid ingestion during exercise in the heat (González-Alonso *et al.* 1995, 1998) or when dehydrated subjects exercise in the cold and intravascular fluid losses are restored with a plasma volume expander (González-Alonso *et al.* 1997). The diminished intravascular fluids (or related haematological changes) and hyperthermia are therefore important factors underpinning the cardiovascular strain produced by dehydration during exercise in the heat.

The reduction in stroke volume underlies the fall in cardiac output with dehydration and hyperthermia (Montain & Coyle 1992a, González-Alonso *et al.* 1997, 1999b, 2000a). Interestingly, when thermoregulatory demands of exercise are minimized in a cold environment and the rise in core temperature is blunted, the decline in stroke volume and the increase in heart rate are significantly attenuated. In these conditions the significant drop in cardiac output normally observed with dehydration and hyperthermia in the heat is prevented (González-Alonso *et al.* 2000a). Plasma volume expansion in dehydrated and

normothermic subjects completely reverses the otherwise small reduction in stroke volume during exercise in the cold, despite the persistent 3–4 L extravascular dehydration (González-Alonso *et al.* 1997). Similarly, hyperthermia without dehydration induces a small decline in stroke volume during exercise in the heat, which is associated with an increased heart rate; whereas preventing dehydration and hyperthermia via fluid ingestion fully ameliorates these alterations in both stroke volume and heart rate (González-Alonso *et al.* 1995, 1997, 1998). Hence the reductions in cardiac stroke volume underlying the decline in cardiac output in dehydrated and hyperthermic individuals might be largely related to diminished intravascular volume and the hyperthermia-induced tachycardia.

In 1938, Marius Nielsen (who worked closely with Lindhard and Krogh in The Zoophysiological Laboratory at the University of Copenhagen) demonstrated that core temperature during prolonged moderate exercise was similar across a wide range of ambient temperatures (i.e. 5–35 °C) (Nielsen 1938). Because heat exchange pathways are very different in cold and hot environments, Nielsen's seminal observation provided the foundations for the idea that core temperature and thus the underlying heat fluxes between the exercising limb muscles and the environment surrounding the limbs, the exercising limbs and the body core, and the body core and the environment surrounding the trunk are well-regulated responses. In this context, the aforementioned dehydration-induced reductions in exercising limb blood flow might impair convective heat transport from active muscle to the surrounding environment and the body core and thus contribute to hyperthermia, independently of the influences of concurrent reductions in sweating rate and skin blood flow (Nadel *et al.* 1980, Montain&Coyle 1992a). This idea was put to test by quantifying the convective heat transfer from the exercising leg to the body core (i.e. leg blood flow × arterial–venous (a–v) temperature difference, according to the Fick principle) and total heat production from the heat equivalent of leg $\dot{V}O_2$ (González-Alonso *et al.* 1999a, 2000b). The results suggested that dehydration impairs heat transfer from the leg to core. More strikingly, they indicated that more than onehalf of the metabolic heat liberated in the contracting leg muscles is dissipated directly to the environment surrounding the leg. These findings highlight the importance of investigating heat-dissipating mechanisms in the exercising limbs and how the stresses of dehydration and heat stress impact upon thermoregulatory function.

Conclusions and future directions

Passive heat stress has the capacity of causing pronounced strain on the cardiovascular system, evidenced by large increases in sympathetic neural activity, heart rate and left ventricular contractility, coupled with reductions in central blood volume, left ventricular filling pressures and cerebral perfusion. The mechanisms resulting in compromised blood pressure control that accompanies such exposure are not entirely clear, although the prevailing data do not support the hypothesis of heat stress-induced impairment in baroreflex responsiveness.

Compelling evidence indicates that the combination of intense whole-body exercise and environmental heat stress or dehydration induced-hyperthermia results in significant cardiovascular strain prior to exhaustion, which is characterized by reductions in cardiac output, stroke volume, arterial pressure and blood flow to the brain, skin and exercising muscle. The local and central mechanisms underpinning these responses remain unresolved. Reductions in skeletal muscle blood flow might not only affect muscle metabolism during exercise but also convective heat transfer to the environment surrounding the exercising limbs and the body core. The study of the muscle and skin circulations in the exercising and non-exercising limbs and the heat fluxes within the body could provide novel insight into how core temperature and its effector responses are regulated in exercising humans.

Acknowledgments

This work was supported by the National Institutes of Health HL61388 and HL84072 (C.G.C.), Marie Curie Training program, Gatorade Sports Science Institute, Team Denmark, Novo Nordisk and the Danish National Research Foundation (J.G.-A.).

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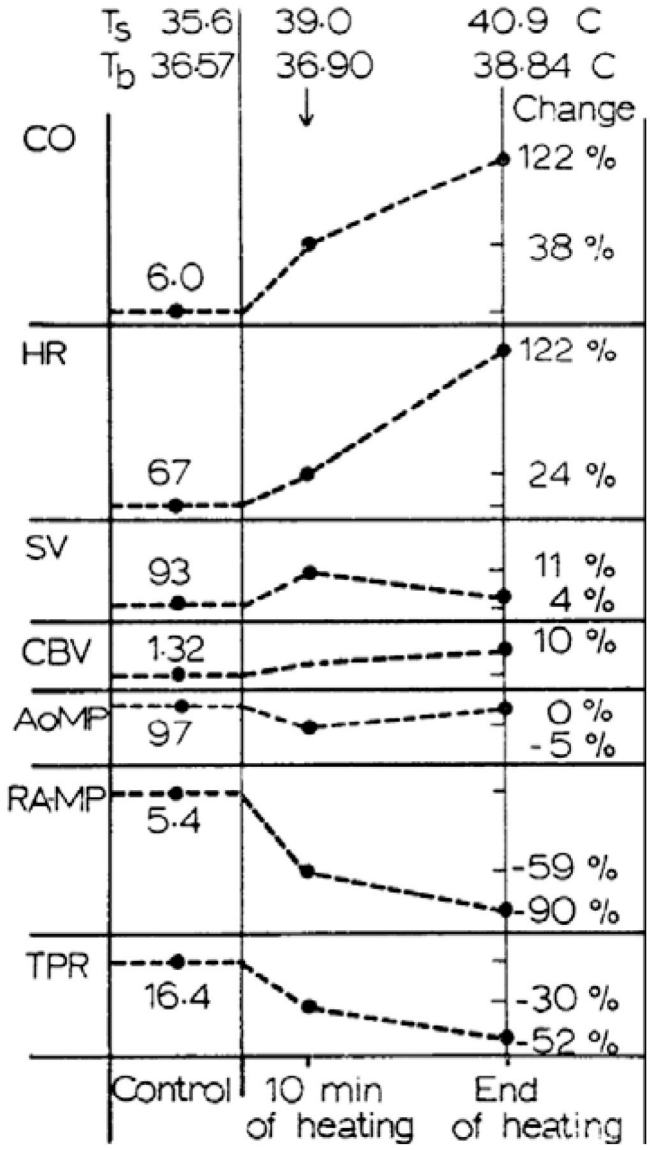

Figure 1.

Classic cardiovascular responses to increases in skin temperature (T_s) resulting in a large increases in body temperature (T_b) reported as a per cent change in the indicated value relative to pre-heat stress baseline. CO, cardiac output; HR, heart rate; SV, stroke volume; CBV, central blood volume; AoMP, aortic mean arterial blood pressure; RAMP, right atrial mean blood pressure; TPR, total peripheral resistance. Note that the effects of heat stress on central blood volume have recently been shown to decrease as opposed to slight increases observed by these investigators (see Fig. 2). Figure from Rowell *et al.* (1969a); republished with permission from The American Physiological Society.

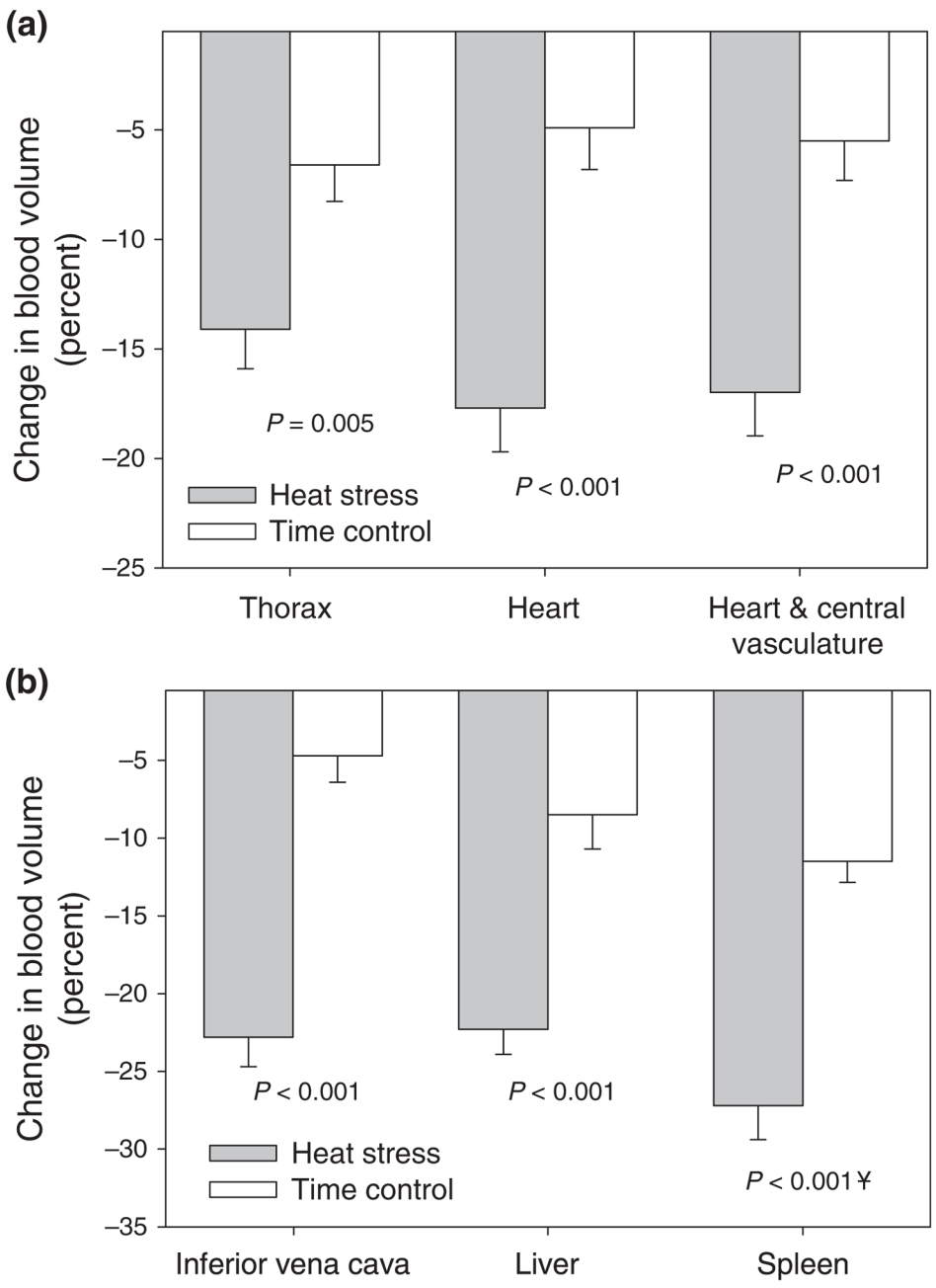

Figure 2.

Percent change in blood volume from the indicated regions between experimental (i.e. heat stressed) and time control subjects. In each of the indicated regions heat stress significantly reduced blood volume relative to the time control trials. Figure from Crandall *et al.* (2008); republished with permission from Wiley-Blackwell.

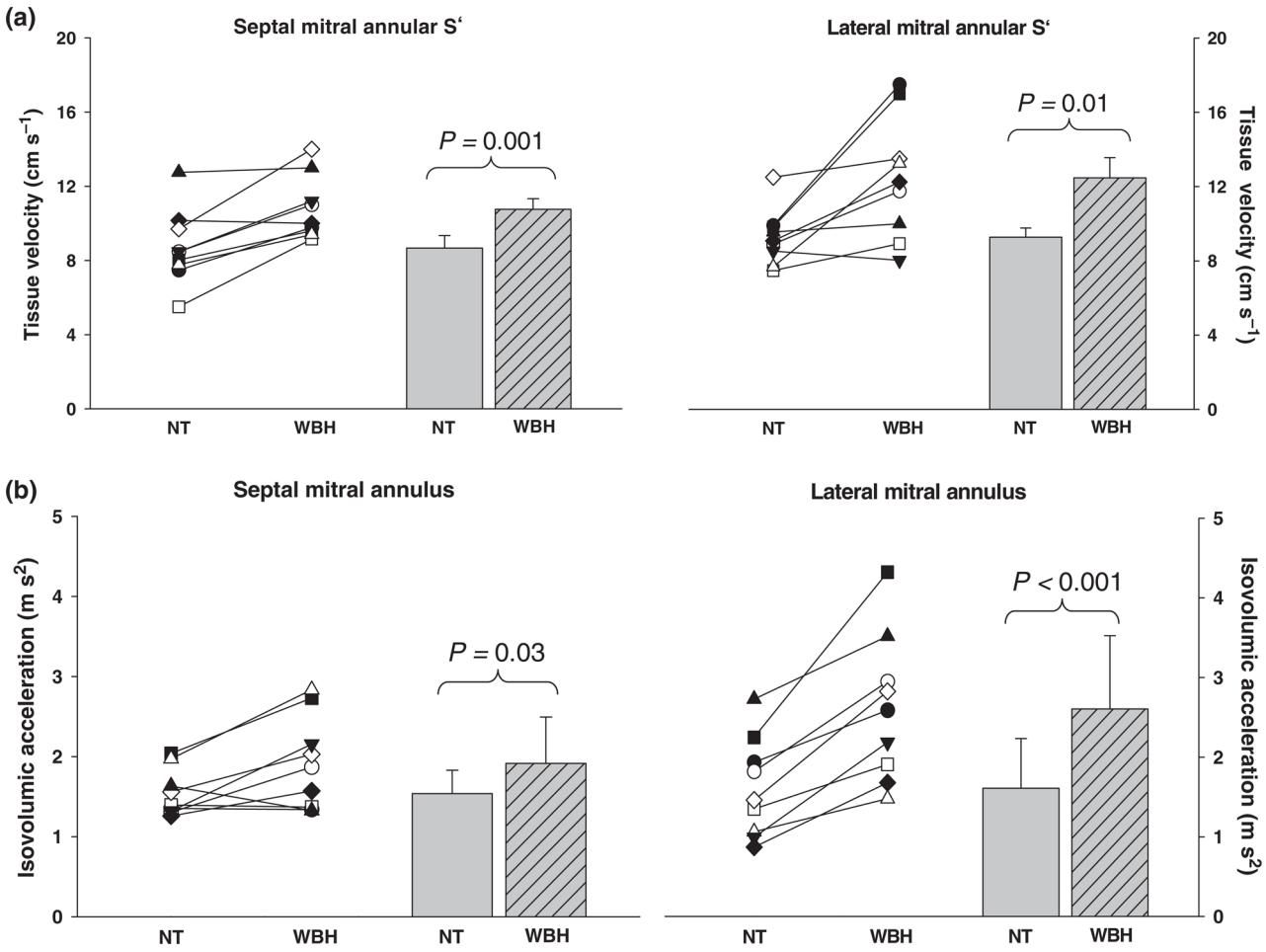

Figure 3.

Peak septal and lateral mitral annular systolic velocities (S′; panel a) and isovolumic acceleration of the septal and lateral mitral annulus (panel b). Individual (left-hand side of each panel) and group averaged (right-hand side of each panel) echocardiographic measurements of the indicated data during normothermic (NT) and whole-body heat-stress (WBH) conditions. Increases in the indicated parameters by heat stress are indicative of an increase in cardiac systolic function. Figure from Brothers *et al.* (2009a); used with permission from The American Physiological Society.

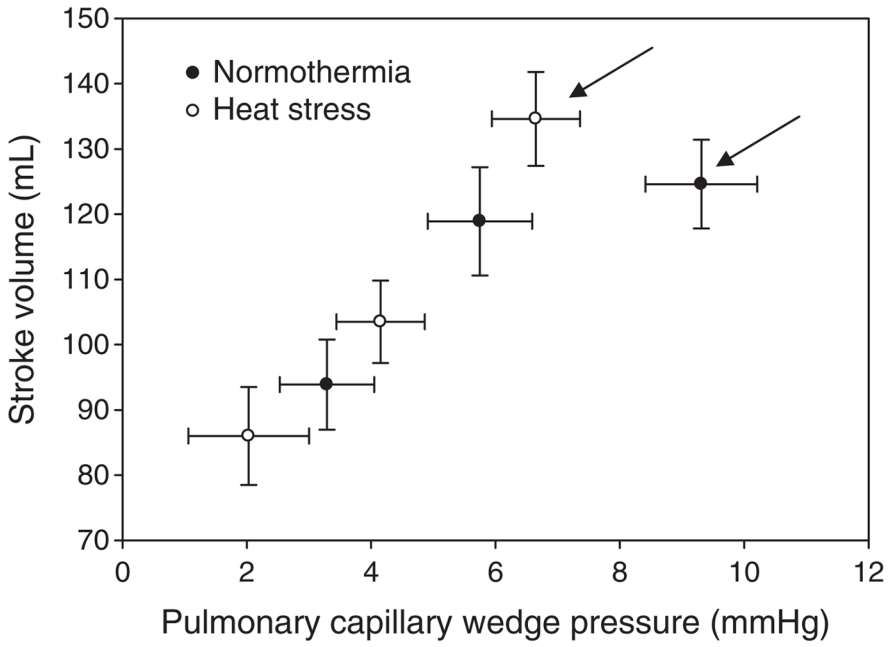

Figure 4.
Effect of thermal stress on the Frank–Starling relation via plotting the relation between pulmonary capillary wedge pressure and stroke volume. Data points were generated via lower body negative pressures (LBNP) of 0, 15 and 30 mmHg. The arrows indicate the operating point for the respective thermal conditions. The operating point is defined as the prevailing pulmonary capillary wedge pressure and stroke volume prior to the onset of LBNP. Figure from Wilson, Brothers, Tollund, Dawson, Nissen, Yoshiga, Jons, Secher and Crandall. *J Physiol* **587**, 3383–3392, 2009; republished with permission from Wiley-Blackwell.

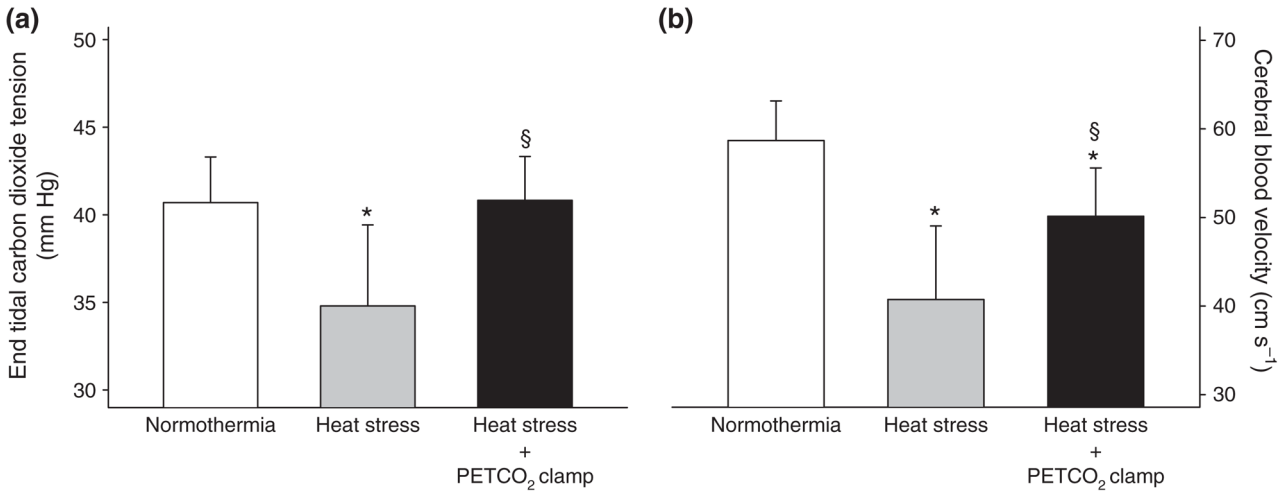

Figure 5.

End-tidal carbon dioxide tension and middle cerebral artery blood velocity (MCA V_{mean}) during normothermia, heat stress, and heat stress after end-tidal carbon dioxide ($PETCO_2$) concentration was returned to pre-heat stress levels. The reduction in $PETCO_2$ concentration during heat stress was completely abolished by the $PETCO_2$ clamping procedure (panel a). Heat stress reduced MCA V_{mean} relative to normothermia. Restoration of $PETCO_2$ to the normothermic level while subjects were heat stressed (heat stress + clamp) attenuated the decrease in MCA V_{mean} relative to control heat stress without the clamp; however MCA V_{mean} remained reduced when compared with normothermia (panel b). These data indicate that mechanisms other than reduced $PETCO_2$ contribute to the reduced cerebral perfusion that occurs in heat-stressed individuals. *Significantly different relative to normothermia; §significantly different relative to control heat stress. Figure from Brothers *et al.* (2009b); republished with permission from Wiley-Blackwell.

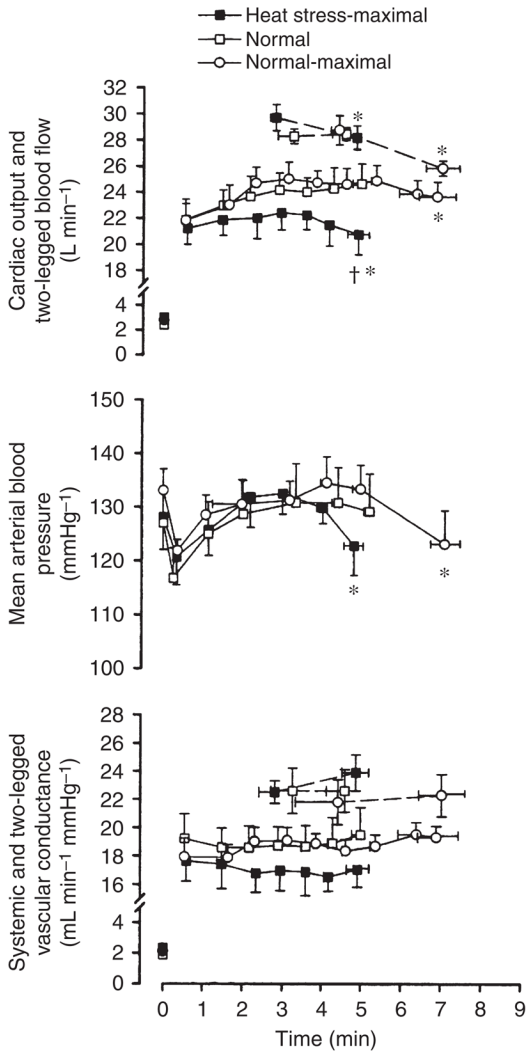

Figure 6.

Haemodynamics during maximal whole-body exercise in heat-stressed humans. Systemic and exercising limb blood flow and vascular conductance during constant maximal exercise with heat stress and control conditions. Note the significant reductions in cardiac output and leg blood flow and arterial blood pressure leading to unchanged vascular conductance. *Significantly lower than corresponding peak exercise values, $P < 0.05$. †Significantly lower than control (normal) trials, $P < 0.05$. Figure from González-Alonso & Calbet (2003); republished with permission from the American Heart Association.

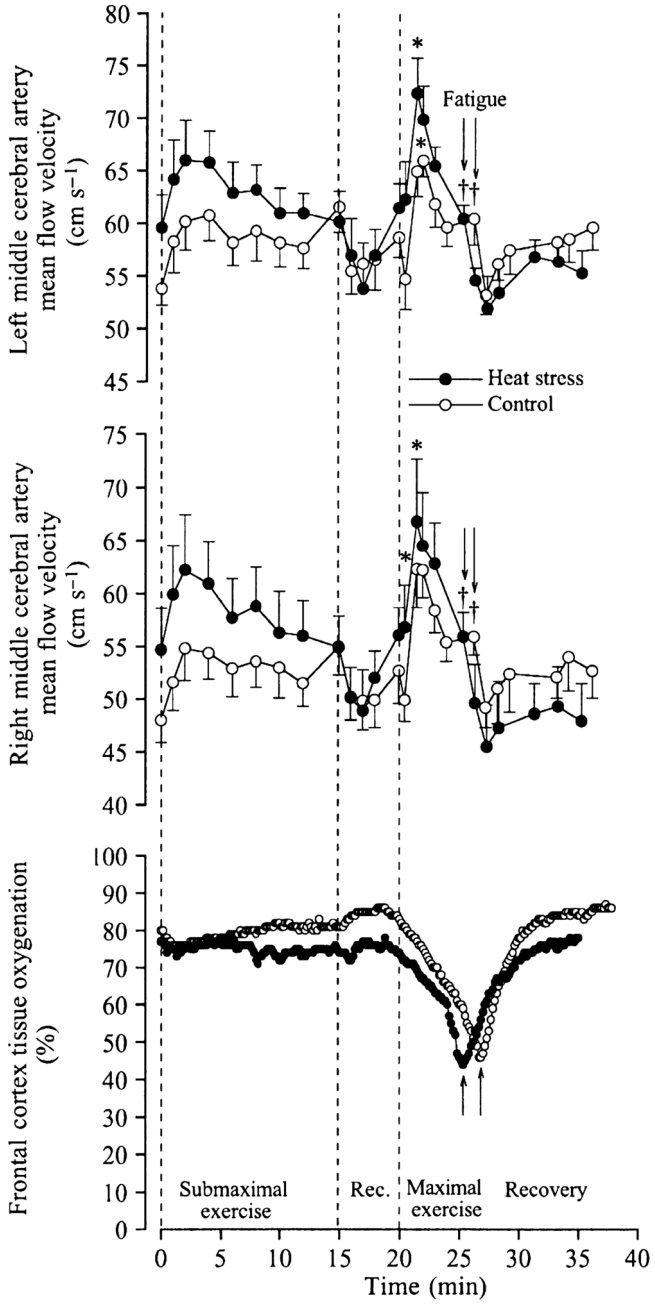

Figure 7.

Cerebral circulation and oxygenation during maximal whole-body exercise in heat-stressed humans. Left and right middle cerebral artery blood velocity and near-infrared spectroscopy-determined cerebral tissue oxygenation at rest, during submaximal and maximal cycling and during 10 min of recovery in heat stress and control conditions. Note the marked reductions in blood velocity accompanying the declines in tissue oxygenation. *Higher than value at start of exercise, $P < 0.05$. †Lower than peak value during maximal exercise, $P < 0.05$. From González-Alonso *et al.* (2004); republished with permission from Wiley-Blackwell.

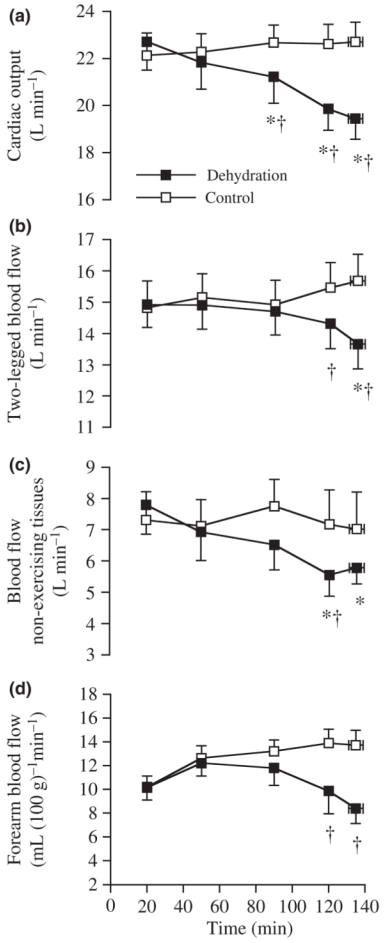

Figure 8.

Haemodynamics with dehydration during prolonged exercise in the heat. Systemic and peripheral blood flow during prolonged cycling in the heat with and without dehydration and hyperthermia. Note that the declines in cardiac output are accompanied by reductions in blood flow to the exercising legs, the skin and possible visceral blood flow. *Significantly lower than 20 min value, $P < 0.05$. †Significantly lower than control, $P < 0.05$. From González-Alonso *et al.* (1998); republished with permission from Wiley-Blackwell.