

Symposium Report

Human thermoregulation and the cardiovascular system

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A key but little understood function of the cardiovascular system is to exchange heat between the internal body tissues, organs and the skin to maintain internal temperature within a narrow range in a variety of conditions that produce vast changes in external (exogenous) and/or internal (endogenous) thermal loads. Heat transfer via the flowing blood (i.e. vascular convective heat transfer) is the most important heat-exchange pathway inside the body. This pathway is particularly important when metabolic heat production increases many-fold during exercise. During exercise typical of many recreational and Olympic events, heat is transferred from the heat-producing contracting muscles to the skin surrounding the exercising limbs and to the normally less mobile body trunk and head via the circulating blood. Strikingly, a significant amount of heat produced by the contracting muscles is liberated from the skin of the exercising limbs. The local and central mechanisms regulating tissue temperature in the exercising limbs, body trunk and head are essential to avoid the deleterious consequences on human performance of either hyperthermia or hypothermia. This brief review focuses on recent literature addressing the following topics: (i) the dynamics of heat production in contracting skeletal muscle; (ii) the influence of exercise and environmental heat and cold stress on limb and systemic haemodynamics; and (iii) the impact of changes in muscle blood flow on heat exchange in human limbs. The paper highlights the need to investigate the responses and mechanisms of vascular convective heat exchange in exercising limbs to advance our understanding of local tissue temperature regulation during exercise and environmental stress.

(Received 12 September 2011; accepted after revision 3 January 2012; first published online 6 January 2012)

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Heat production in skeletal muscle

Heat is produced in all body cells from the conversion of metabolic energy into mechanical and thermal energy. This process is very inefficient and thus approximately 30–70% of the energy liberated during muscle contraction appears as thermal energy (Edwards *et al.* 1975; González-Alonso *et al.* 2000*b*; Bangsbo *et al.* 2001; Krstrup *et al.* 2001, 2003). Heat production by dynamically contracting human skeletal muscle increases abruptly and markedly at the onset of dynamic exercise, increases further at a lower rate during the early stages of exercise and eventually plateaus if exercise is of a steady-state nature. When exercise is intense, however, heat production does not level off, as illustrated in Fig. 1. A doubling in heat production is seen over 3 min of intense dynamic exercise, with half of the increase occurring during the first 38 s (González-Alonso *et al.* 2000*b*). Heat production in dynamically

contracting muscle in conditions of unrestricted flow is estimated by measuring the amount of heat accumulated in the contracting muscles, the amount of heat removed by the blood to the body trunk and the amount of heat loss from the exercising limb skin. When looking at each subdivision (in conditions in which heat exchange with the surroundings of the thigh is minimized by a thermostatically isolated system and the circulation to the lower leg is arrested), heat storage in the active quadriceps muscles accounts for the immediate elevation in heat production, whereas heat removal to the body trunk via the blood is dominant at the end of exercise (Fig. 1).

The elevation of total heat production over time in contracting skeletal muscle is tightly coupled with changes in heat liberation during metabolic ATP production early in exercise (González-Alonso *et al.* 2000; Bangsbo *et al.* 2001; Krstrup *et al.* 2001, 2003). As depicted in Fig. 2,

the contribution of anaerobic energy turnover to total energy turnover (i.e. the sum of total heat production and mechanical power output) is greatest at the onset of exercise, becoming smaller as the contribution of aerobic energy turnover increases. *In vitro* studies have shown that heat production during ATP utilization varies from 35 to 72 kJ (mol ATP)⁻¹ depending upon whether creatine phosphate (PCr), glycolysis or oxidative phosphorylation provides the energy for ATP resynthesis (Wilkie, 1968; Curtin & Woledge, 1978). Hence, both *in vitro* and *in vivo* studies show that muscle heat production can increase during high-intensity dynamic exercise by a factor of two, with a shift in ATP resynthesis from primarily PCr catabolism to primarily oxidative phosphorylation.

Heat storage in body tissues depends upon the interplay among heat production, heat dissipation and, to a lesser extent, energy exchanged during mechanical work. Excessive heat accumulation or liberation compromises the physiological function of cellular and organ systems, which can lead to impaired human performance (González-Alonso *et al.* 2008a; Taylor *et al.* 2008). A well-developed control system is therefore required to regulate heat exchange within the body and between the skin and the environment. The two avenues of heat

exchange inside the body are ‘intercellular conductive heat transfer’ and ‘vascular convective heat transfer’. Heat conductance through tissues in the human body is a slow process and, in limbs, is primarily dependent upon the temperature gradient between muscle and skin and the thermal conductivity of muscle. This avenue of heat exchange is particularly important in conditions of exercise in cold environments, which produces a large temperature gradient between deep muscle and neighbouring subcutaneous tissue and skin (Werner *et al.* 2008). Conversely, it plays no role when there is not a temperature gradient between muscle and surrounding skin, as during exposure to warm environments. In contrast, convective heat transfer (mass flow) from dynamically contracting limb muscles to the core of the body and to the surrounding subcutaneous limb tissues hinges upon tissue blood flow and arteriovenous blood temperature difference (according to the Fick principle; González-Alonso *et al.* 2000b). Hence, conditions that alter either limb tissue blood flow and/or arteriovenous blood temperature difference, such as exercise and/or environmental stress, are likely to induce profound changes in convective heat exchange within the exercising limbs and between the exercising limbs and the body torso. Conversely, when exercise is performed in ischaemic conditions (e.g. when limb circulation is arrested by inflation of a cuff), convective heat removal to the body

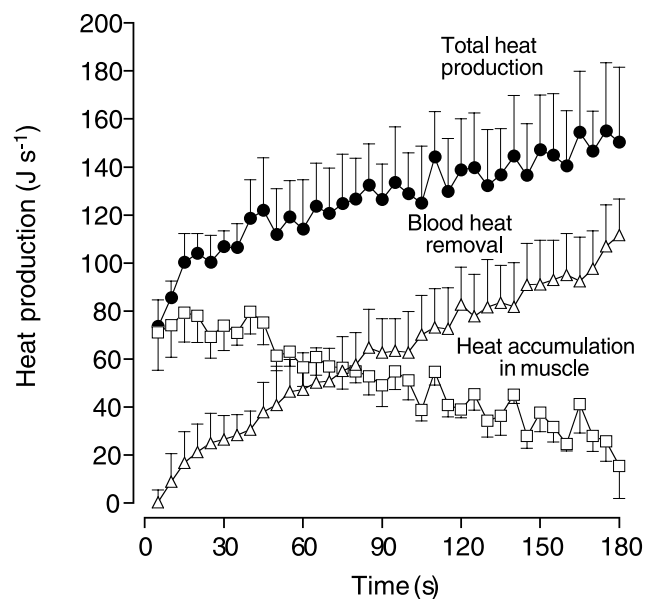


Figure 1. Heat production during intense dynamic knee-extensor exercise

Rates of total heat production and its subdivisions in terms of storage in the quadriceps muscle and removal by the blood to the body trunk are depicted for each 5 s of exercise. Note that heat storage in the quadriceps muscle accounts for the immediate increase in heat production, decreasing progressively thereafter. Conversely, heat removal by the blood is nil at the onset of exercise, increasing progressively thereafter to account for most of heat production at the end of the 180 s of exercise. (Modified from González-Alonso *et al.* 2000b.)

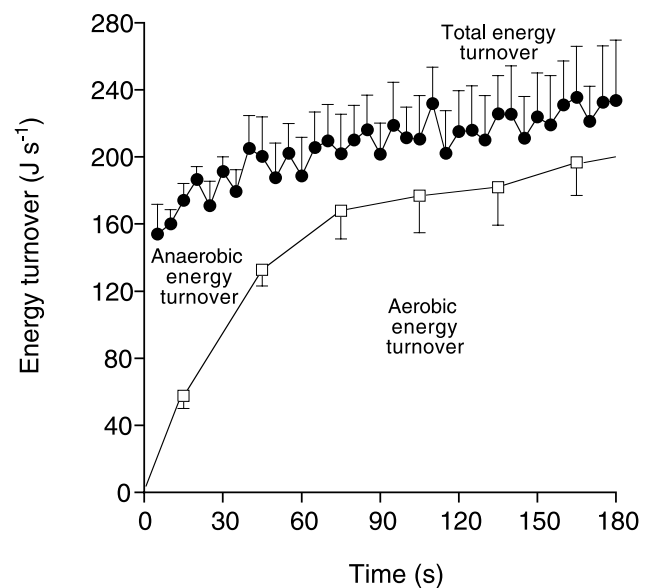


Figure 2. Total, anaerobic and aerobic energy turnover during intense dynamic knee-extensor exercise

Rates of total and aerobic energy turnover and heat liberation for each 5 s period of intense dynamic knee-extensor exercise. Note that anaerobic heat liberation accounts for most of the total energy turnover at the onset of exercise, whereas aerobic heat liberation is dominant after some 45 s of exercise. (Modified from González-Alonso *et al.* 2000b.)

truck is nil and thus heat accumulates in the muscle (Edwards *et al.* 1975; Krstrup *et al.* 2003).

The body of literature discussing the processes involved in heat liberation from the skin to the environment is very extensive. The reader is referred to two excellent reviews on the biophysics and physiology of heat exchange between the body and the environment (Gagge & Gonzalez, 1996; Werner *et al.* 2008). On the contrary, the number of studies directly investigating the processes involved in heat exchange inside the human body, particularly in contracting limb skeletal muscle, is relatively small due partly to the complexity of performing the necessary invasive measurements of tissue blood flow and blood and tissue temperature gradients. The focus of this paper is on the latter aspect of temperature regulation.

Cardiovascular responses to exercise and environmental stress

The circulatory adjustments to exercise and environmental stress are integrative responses to a vast collection of external and internal stimuli. Based on the external stimuli, the haemodynamic responses to environmental stress and exercise are determined by the magnitude of the environmental (heat or cold) load and the duration, intensity and type of exercise. The environmental conditions and the type and intensity of exercise determine the metabolic and thermal demands for local and systemic blood flow, whereas exercise duration defines the regulatory disturbances and constraints in cardiovascular function over time (Rowell *et al.* 1996; González-Alonso *et al.* 2008a; Mortensen *et al.* 2008). Depending upon the amount of muscle mass engaged, exercise can generally be classified as small or large muscle mass exercise. Single-limb exercise, such as forearm and isolated leg exercise, are examples of small muscle mass exercise, whereas whole-body exercise, such as cycling, running and rowing, are considered large muscle mass exercise. The effects of heat and cold stress during exercise on cardiovascular function are most likely to differ during small compared with large muscle mass exercise when exercise intensity is high (Mortensen *et al.* 2008). From a mechanistic physiology viewpoint, the combination of intense whole-body exercise and heat stress poses the greatest challenge to the regulation of temperature, mean arterial pressure and oxygen delivery to the working muscles, brain and heart, because in these conditions the cardiovascular system is pushed faster to the limit of its regulatory capacity (Rowell *et al.* 1996; González-Alonso *et al.* 2008).

Prolonged whole-body exercise in the heat is associated with greater tachycardia, skin and core hyperthermia, but conflicting systemic and exercising limb blood flow responses compared with equivalent exercise in the cold (Claremont *et al.* 1975; McArdle *et al.* 1976; Nadel *et al.*

1979; Sawka *et al.* 1979; Montain & Coyle, 1992; González-Alonso *et al.* 1998, 2000a). The lack of control for subjects' hydration status, randomization of the experimental trials and familiarization of the participants with the experimental conditions might explain, at least in part, the discrepancy in the blood flow responses in the literature. In this context, people lose more body water during exercise in the heat due to higher sweat rates and thus become more dehydrated than during exercise in the cold. The question then arises as to how distinct levels of dehydration impact upon the cardiovascular responses to exercise and environmental stress. Figure 3 depicts the results from a study investigating the influence of environmental temperature and hydration status on the cardiovascular responses to moderately intense leg cycling (González-Alonso *et al.* 2000a). Subjects were randomly tested at 35 and 8°C ambient temperatures when euhydrated and dehydrated by 1.5, 3.0 and 4.5% of their body weight. When subjects were euhydrated and core temperature and oxygen uptake (\dot{V}_{O_2}) were the same during exercise in both environments, cardiac output was elevated by $\sim 1 \text{ l min}^{-1}$ in the heat, accompanied by a higher heart rate but an unchanged stroke volume. This elevated systemic blood flow might have been a response to the threefold higher skin blood flow during exercise in the heat, as the metabolic and thermal demands for exercising muscle blood flow were apparently the same.

The circulatory responses to a given level of dehydration, however, vary in cold and hot environments. In contrast to the well-characterized cardiovascular strain evoked by dehydration during exercise in the heat (Sawka *et al.* 1979; Montain & Coyle, 1992; González-Alonso *et al.* 1998), graded dehydration up to 4% of body weight loss (i.e. 3 kg for a 70 kg person) does not reduce cardiac output, skin blood flow, arterial blood pressure or systemic vascular conductance during exercise in the cold. Consequently, cardiac output, and possibly active muscle blood flow (González-Alonso *et al.* 1998), is lower during moderate intensity exercise in the heat compared with exercise in the cold when dehydrated by 4%, which is the opposite response to what occurs in the euhydrated state. Hydration status can therefore explain part of the discrepancy in the cardiac output responses to environmental stress and intense whole-body exercise reported in the literature.

The literature directly comparing the effects of environmental heat and cold stress on the haemodynamic responses to small muscle mass exercise is sparse (e.g. Savard *et al.* 1988), yet evidence in resting limbs is extensive. Studies in resting limbs generally show that heat stress increases blood flow to the arms and legs, whereas cold stress reduces limb perfusion (e.g. Barcroft & Edholm, 1943). A highly controversial issue, however, is whether these differences in limb perfusion reflect changes only in skin blood flow or in both muscle and skin blood

flow. With respect to heat stress, early investigations into the partition of limb perfusion between skin and skeletal muscle in the human forearm led to conflicting results, with some studies suggesting an elevation in muscle blood flow (Barcroft & Edholm, 1946; Barcroft *et al.* 1947), but others not (e.g. Rodie *et al.* 1956; Detry *et al.* 1972; Johnson *et al.* 1976). The negative findings together with the estimate of maximal skin blood flow of 6–8 l min⁻¹, based on indirect measures of cardiac output and visceral blood flow during whole-body heat stress, promoted the idea that increases in skin blood flow with heat stress accounted fully for the rise in systemic hyperaemia and blood flow redistribution (Detry *et al.* 1972; Rowell 1974; Minson *et al.* 1998). Recent evidence in the human leg, however, challenges this widely held dogma. Using ¹³³Xe washout or positron emission tomography techniques, Keller *et al.* (2010) and Heinomen *et al.* (2011) recently showed that passive leg heating increases calf blood flow by approximately 60–65%. In parallel, we have shown significant increases in leg tissue blood flow, deep femoral venous O₂ content and muscle oxygenation and a parallel significant decline in leg arterial–deep venous O₂ differences during whole-body heat stress, both at rest and during mild knee-extensor exercise, with a small effect or no effect on aerobic metabolism (Pearson *et al.* 2011). The enhanced muscle blood flow was closely associated with increases in arterial plasma ATP concentration and muscle temperature (Pearson *et al.* 2011), which is in turn coupled to a temperature-mediated release of ATP from erythrocytes (Kalsi & González-Alonso, 2012). On the other hand, cold stress has repeatedly been shown to reduce limb blood flow in resting humans (e.g. Barcroft & Edholm, 1943; Gregson *et al.* 2011). For instance, the classic work of Barcroft & Edholm (1943) clearly showed lower forearm blood flows and deep muscle temperatures when the forearm was immersed in a water bath at 13, 20 and 25°C compared with higher water temperatures. Likewise, Gregson and co-workers recently reported a 35–40% decline in femoral artery blood flow and conductance following 10 min of cold and temperate water immersion (8 *versus* 22°C), which evoked drastic decreases in muscle and skin temperatures, but less cutaneous vasoconstriction at 8 than at 22°C water temperature, possibly reflecting a lower muscle blood flow (Gregson *et al.* 2011). Taken together, growing evidence from the human leg suggests that heat and cold stress not only alters blood flow to the skin, but also to the skeletal muscle. These circulatory adjustments might have important implications for heat transfer in resting and exercising human limbs.

Muscle blood flow and limb heat liberation

The flowing blood transports heat inside the body in relation to blood temperature and flow rate. Heat transfer

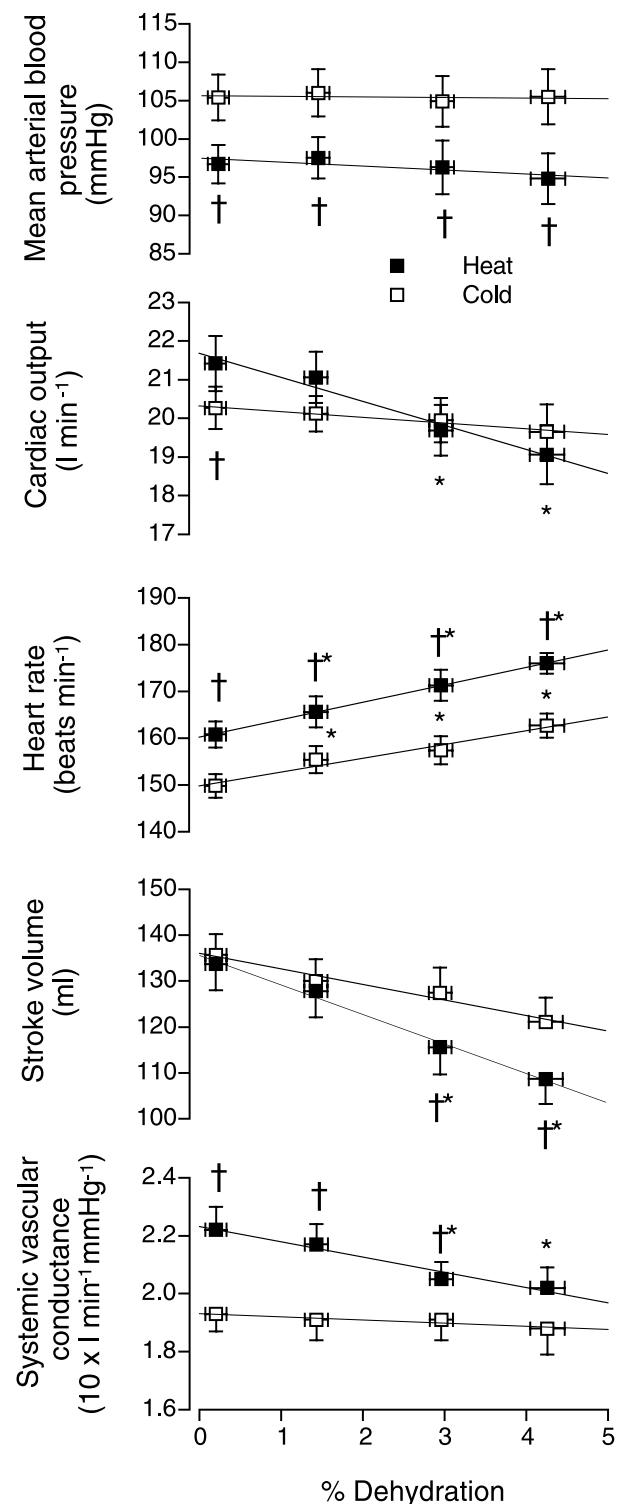


Figure 3. Cardiovascular responses to exercise and environmental stress at different levels of hydration

Note that cardiac output was elevated in the heat in normal hydration conditions, but in contrast to exercise in the cold it declined significantly with increasing levels of dehydration owing to the greater decline in stroke volume (González-Alonso *et al.* 2000a). *Significantly different from the euhydrated control condition. †Significantly different from exercise in the cold at the same hydration level

in major arteries and veins supplying and draining the limbs is bidirectional. In normal resting conditions, limb muscle and venous blood temperatures are significantly lower than arterial and core temperature (González-Alonso *et al.* 1999; He *et al.* 2002; Fig. 4). In fact, blood temperature in the limb muscle microcirculation is normally several degrees lower than core temperature due to rapid thermal equilibration between tissues and vessels (He *et al.* 2002). At the level of the major supply vessels, the resulting negative arteriovenous temperature gradient indicates that more heat is being transferred from the upper body core to the extremities than vice versa (Fig. 4). This net body core-to-limbs heat transfer helps limbs to maintain tissue temperature when their metabolic heat production is low. For instance, leg \dot{V}_{O_2} is normally about 25 ml min^{-1} in the resting state, corresponding to a total leg heat production of $\sim 0.5 \text{ kJ min}^{-1}$ based on the

heat equivalent of \dot{V}_{O_2} (Bangsbo *et al.* 2000). This value is only half of the $\sim 1 \text{ kJ min}^{-1}$ of heat being transferred from the body trunk to each leg when femoral venous temperature is $\sim 0.7^\circ\text{C}$ lower than femoral arterial blood temperature, resting leg blood flow is $\sim 0.4 \text{ l min}^{-1}$ and the blood specific heat is $3.61 \text{ kJ l}^{-1} \text{ }^\circ\text{C}^{-1}$ (Fig. 4). These simple estimates demonstrate that more heat is transferred into the resting leg than produced locally in resting conditions. This implies that limb tissue temperature will drop if its circulation is arrested and heat dissipation to the surroundings of the limbs is kept constant. An example of this might occur during knee or elbow surgery.

The impact of alterations in limb perfusion on heat exchange between the body core and limbs can be exemplified from the findings of He *et al.* (2002) in the rat hindlimb. To the author's knowledge, comparable limb thermodynamic data are not available for humans.

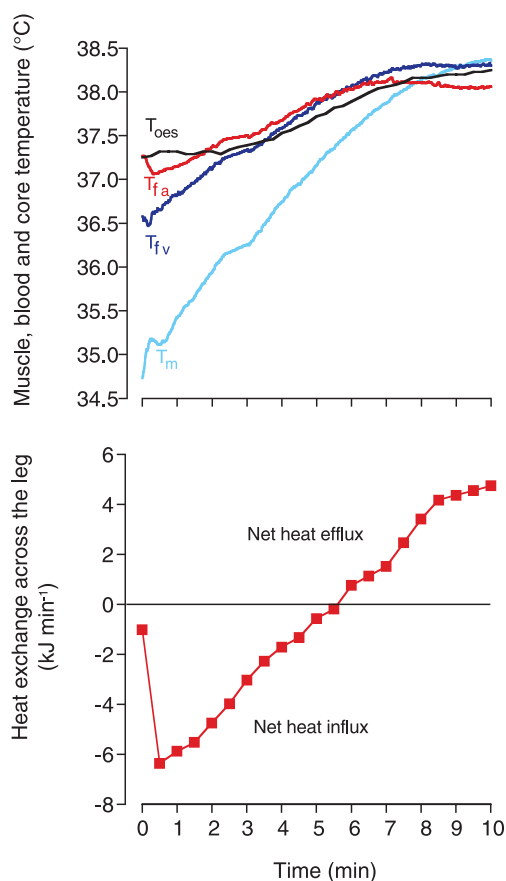


Figure 4. Temperature and heat exchange across the human leg at onset of cycling exercise

Note that muscle (T_m) and femoral venous temperatures (T_{fv}) are lower than core (T_{oes}) and femoral arterial blood temperatures (T_{fa}) at the onset of submaximal leg cycling exercise (0–3 min for T_{fa} and 0–8 min for T_m), but increase very rapidly as exercise progresses. A net heat influx in the leg is observed at rest (0 min) and during the initial 5.5 min of exercise. A net heat efflux is seen thereafter. (Modified from González-Alonso *et al.* 1999.)

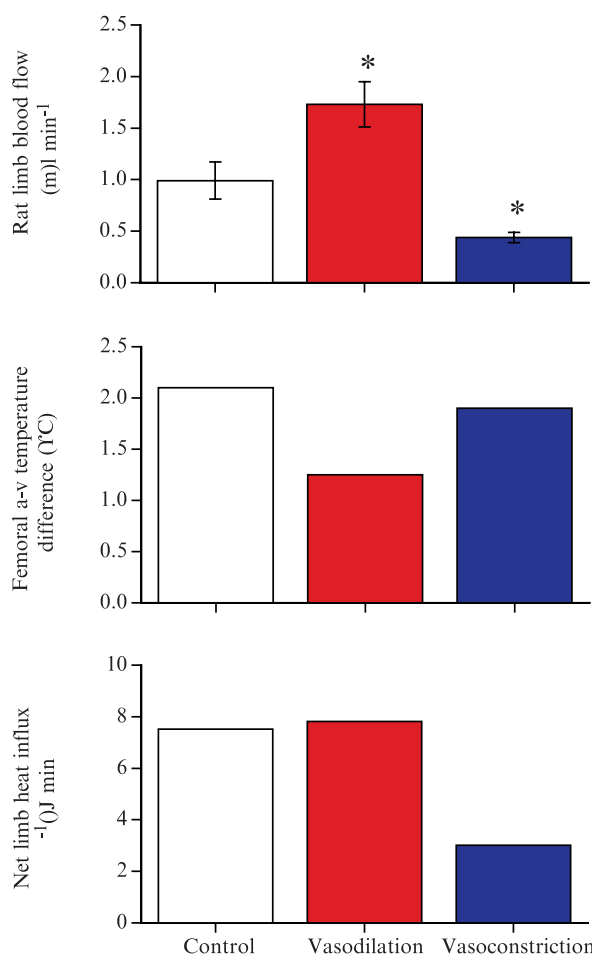


Figure 5. Influence of limb blood flow on blood temperature and heat exchange across the resting rat hindlimb

Note that increases in blood flow in the resting hindlimb do not change the net limb heat influx, because of compensatory changes in femoral arteriovenous (a-v) temperature differences (drawn from data reported by He *et al.* 2002). *Significantly different from control.

Femoral artery and vein blood flow was increased by infusion of the nitric oxide donor sodium nitroprusside (vasodilatation), normal (control) or reduced by infusion of noradrenaline (vasoconstriction; Fig. 5). Increases in blood flow were accompanied by parallel reductions in femoral arteriovenous temperature difference, thus net limb heat influx was the same. In contrast, when femoral artery blood flow was reduced, heat influx into the hindlimb was reduced, accompanying an essentially unchanged arteriovenous temperature gradient. Therefore, the findings of He and co-workers (2002) indicate that increasing limb blood flow in resting limbs does not necessarily increase the net amount of heat being transferred from the body trunk to the limbs because of compensatory tissue-to-blood thermal exchange adjustments within the leg tissues. However, reducing blood flow might have an impact on limb heat transfer. In the resting human leg, femoral venous blood temperature has been shown to decrease by up to 0.5°C with progressive increases in blood flow from 0.4 to 8 l min⁻¹ evoked by intrafemoral artery infusion of ATP (González-Alonso *et al.* 2008b). Whether similar thermal adjustments to those described in the rat hindlimb occur in the human leg warrants detailed investigation.

Exercise illustrates a different scenario, in which not only limb tissue perfusion and convective heat exchange, but also heat production increase. During the initial stages of leg exercise, the temperatures of the contracting muscle and the outflowing femoral venous blood increase at a faster rate than the temperatures of the inflowing femoral arterial blood and the upper body core (González-Alonso *et al.* 1999), yet a negative femoral arteriovenous blood temperature gradient prevails during the early stages of exercise, signifying that more heat is still transferred from the upper body core to the exercising limbs in normal environmental conditions (Fig. 4). After a few minutes of exercise (duration will depend on the initial temperatures and the rate of heat production or exercise intensity), muscle and venous blood temperature becomes higher than arterial blood and upper body core temperature. At this point in time, heat transferred from the exercising limbs to the body torso becomes positive, increasing thereafter to reach a plateau when exercise is of light-to-moderate intensity. To date, data on heat exchange in human limbs in different environmental and exercise conditions are very limited, thus the ideas discussed above require thorough scrutiny.

Summary and future directions

Our knowledge and understanding of human thermo-regulation and its interaction with cardiovascular regulation during exercise is largely based upon data from resting limbs. The observation that a significant amount of heat produced by the exercising

muscles is liberated directly from the skin of the exercising limbs (González-Alonso *et al.* 1999) highlights the need to investigate the responses and mechanisms of vascular heat exchange in resting and exercising limbs. Quantification of heat production and convective heat exchange in human limbs is likely to shed new light onto the role of muscle blood flow in the control of tissue temperature during environmental stress and exercise.

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Acknowledgements

The author apologises to all the authors whose work has not been cited due to space restrictions and thanks all the collaborators who made possible the completion of the work reviewed here. Recent author’s work has been supported by the Gatorade Sports Science Institute and PepsiCo.