Editorial Comment

Hyperthermia: A Hyperadrenergic State

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Several of the gentlemen present, as well as myself, went into the room without shirts . . . when the thermometer had risen much higher, almost to 260° [F], and found that we could bear that very well, . . . Perhaps no experiments hitherto made furnish more remarkable instances of the cooling effect of evaporation than these last facts; . . .

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Evaporation of 1 liter of sweat can remove 580 kcal from the body. This has enabled human subjects to withstand oven temperatures as high as 205° C while meat in the same oven became well-cooked.[1] Our well-developed sweating mechanism provides us with a unique capacity to withstand high ambient temperature. Without it, we are more susceptible than other mammals.

This editorial was stimulated by a report in this journal entitled "Arterial baroreceptor reflex modulation of sympathetic-cardiovascular adjustments to heat stress" by Kregel, Johnson, Tipton, and Seals.[2] They exposed rats, a nonsweating mammal, to an environmental temperature of 42° C before and after denervation of carotid sinus and aortic baroreceptors. Before denervation, body temperature (T_c) rose to 41° C in approximately 1.5 hours while mean arterial pressure, heart rate, estimated mesenteric and renal vascular resistance and plasma norepinephrine concentration all rose significantly. Denervation of arterial baroreceptors markedly exaggerated each of these responses, so that T_c rose to 41° C in approximately one half the time and during that time the other variables all rose faster and to much higher values. Their work indicates that hyperthermia by itself is such a powerful stimulus to sympathoadrenal activity in the rat that the cardiovascular effects of this activity must be opposed by arterial baroreceptor reflexes to prevent severe hypertension and elevated cardiac output, which in turn would lead to more rapid heat gain.

Kregel and colleagues[2] postulate that the responses of rats and those of humans may become

similar when both are placed in a situation in which heat loss is denied and T_c exceeds tolerable limits. Their study serves to emphasize the different routes taken by the two species to this "terminus." In this editorial, attention is directed to important differences as well as similarities in how human and other mammalian cardiovascular systems cope with a noncompensible thermal stress; some consequences of this stress are discussed as well.

When animals are placed in hot environments and either do not sweat or are prevented from evaporating sweat, a serious regulatory "error" is made by the cardiovascular system. The ideal response to an environment from which heat can only be gained by radiation, convection, and conduction would be the same as the response to cold, namely, reduce skin blood flow to zero by vasoconstriction and thereby increase thermal insulation of the body to minimize the rate of heat gain. Although the entire resting heat production would be retained, the consequent rate of heat gain could be far less than the rate of gain from the environment by the skin circulation.

Unfortunately, in hot environments direct local effects of heat combine with active sympathetic vasodilation to elicit maximal increases in human skin blood flow, with total flow reaching 7–8 l/min (i.e., the worst possible response for the body as a whole but one that reduces thermal injury to skin). The skin of fur-bearing mammals lacks the dense vascularity, the high blood flow capacity, and the active neurogenic vasodilator system of human skin. However, if vasoconstrictor outflow is directed to the skin in these animals, it is opposed by local vasodilator effects of heat; body skin blood flow either remains constant or increases slightly. In addition, heat is taken up from the environment by the tail, paws, ears, and other acral regions in which blood flow increases markedly[3] (see References 8 and 9 in Kregel et al[2]).

Figure 1 shows how total blood flow and its distribution changes during heat stress up to the limits of thermal tolerance in humans. Heating was achieved by holding skin temperature (T_s) of the entire body close to 40° C by direct heating with a water-perfused suit while a second water-impermeable suit prevented evaporation of sweat. Right atrial blood temperature rose rapidly and at a continuous rate (rectal temperature rose more slowly), reaching 39.1° C in less than 50 minutes. Heart rate, cardiac output, and forearm skin blood flow rose in parallel with T_c. In

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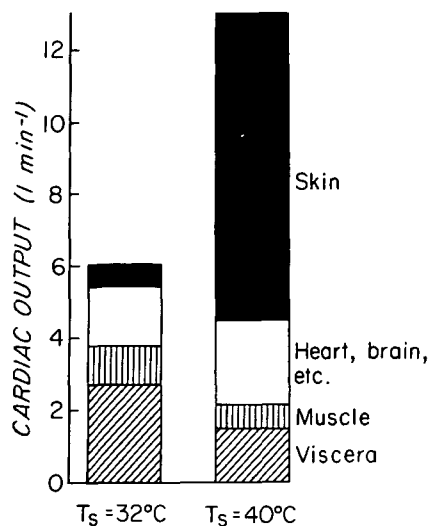
FIGURE 1. *Bar graph showing changes in cardiac output and its distribution in humans heated for 30–53 minutes by holding total body skin temperature (T_s) at 40° C (no sweat evaporation). Rise in cardiac output plus additional blood flow redistributed away from visceral organs and skeletal muscle went primarily to skin. (Adapted from References 1 and 4).*

general, cardiac output rises approximately 3 l/min for each degree increase in T_c and reaches 12–14 l/min.[1,4]

Central venous pressure falls in proportion to the rise in cardiac output; that is, such a high blood flow raises pressures and volumes in the compliant cutaneous vasculature so that blood volume shifts away from the body core to the body surface, further promoting the gain of heat. Despite the fall in right atrial mean pressure, stroke volume rises significantly along with a progressive rise in sympathetic nervous activity.[4] This rise in sympathetic nervous activity not only reduces splanchnic and renal blood flows (Figure 1), as occurs in the rat and some other species, but it must also increase myocardial contractile force as well. Splanchnic vasoconstriction fosters the shift in blood volume away from deep tissues to the superficial, heat-exchanging veins of skin. When splanchnic arterioles constrict, the pressures in downstream, capacious splanchnic veins (which contain 25% of total blood volume) fall as splanchnic blood flow decreases, and blood volume is passively displaced out of this region.[4] Plasma norepinephrine concentration and renin activity rise in parallel with the increase in splanchnic and renal vascular resistance.[4] The norepinephrine leaks from sympathetic neurons into the plasma and its concentration approaches values at which the transmitter begins to act as a circulating vasoconstrictor hormone (between 1 and 2 ng/ml). The norepinephrine concentrations in humans are far below those observed in rats by Kregel and colleagues[2]; in the rat the norepinephrine is derived from both the adrenal medulla and sympathetic neurons.

Thus, as soon as T_s rises in humans, the rise in T_c occurs much more rapidly than it does in small animals despite the far smaller surface-to-volume ratio in the human. Were it not for unique features of the human cutaneous circulation, such as its dense vascularization, capacious venous plexus, and active neurogenic (probably peptidergic) vasodilator system,[4] humans would gain heat much more slowly than rats. Figure 1 illustrates that the entire increase in human cardiac output plus the blood flow redistributed away from other organs goes to the skin which, with a blood flow of 7–8 l/min, makes it second only in flow capacity to active skeletal muscle. This means that the potential for heat gain is so great that denial of, or loss of, sweating in humans exposed to heat can have lethal consequences.

Baboons are nonsweating primates that are phylogenetically close to humans but they lack any significant active cutaneous vasodilator system. They illustrate what a difference this vasodilator system makes in the cardiovascular adjustments to hyperthermia. When the baboons were heated with the same intensity as the rats Kregel and colleagues studied and T_c was increased by 2–2.5° C, the fraction of cardiac output directed to the skin increased only from 3 to 14%; cardiac output did not increase. This relatively small increase in skin blood flow was achieved by redistribution of a constant cardiac output away from all visceral organs and skeletal muscle. The greatest percentage increases in skin blood flow were in the hands, feet, ears, and tail. Because of their smaller surface-to-volume ratios, the baboons gained heat more slowly than the rats (see Reference 9 in Kregel et al[2]).

Thus, the great potential for increased skin blood flow poses a special danger for humans exposed to conditions that raise T_s above T_c. When T_c reaches 40–41° C, the threat of heat stroke is present. Fur-bearing, panting mammals have heat exchange mechanisms in the head that minimize the rise in brain temperature during a time when body temperature reaches levels that would damage the brain (e.g., 41° C). These mammals possess powerful vasodilators and heat-exchange mechanisms in the tongue where blood is evaporatively cooled. In addition, other specialized vascular networks such as the carotid rete provide countercurrent exchange of heat between arteries supplying the brain and veins draining cooler tissues. Humans have no analogous heat exchange mechanisms in the head and thus cannot cool the brain without cooling the rest of the body (some recent arguments maintain that the skin circulation of the head can selectively cool the brain but to do so would require adjustments in anatomy and the physics of heat exchange [see Reference 5]).

In humans the burden of protecting the central nervous system from hyperthermia falls entirely on sweating and the cutaneous circulation, which means that brain and whole body temperature are controlled together as a single unit. This is the most serious threat to those who enjoy recreational hyper-

thermia—we have no thermal short circuit that keeps the brain, which is out of the hot bath, from experiencing the same temperatures as the rest of the body as it is heating in the hot bath.

A second potential danger involves the strain placed on the cardiovascular system. Deaths from overexposure to hot baths and saunas occur periodically. Patients with cardiovascular disease are at risk. For example, heat stress can precipitate acute circulatory collapse in patients with mild congestive heart failure. Heat injury in saunas may occur rapidly without prodromal warnings, and the risk is heightened in patients who are hypertensive or prone to coronary insufficiency.[6]

In both humans and the primates, arterial blood pressure normally declines while they are heated to their limits of tolerance[1,3,4,7]; earlier reports agree that blood pressure in rats and also dogs[7] rises when T_c reaches 41–42° C. Kregel et al[2] draw attention to the fact that after blood pressure reached its nadir midway through heating the human subjects, it rose thereafter until the end of heating.[1,4] They speculated that if T_c continued to rise toward 41° C, blood pressure might continue to increase so that a "pressor response might also be evoked in humans before the circulatory collapse accompanying heat stroke." For example, this response might be akin to the hyperadrenergic, agonal responses to asphyxia; however, hypertension appears not to be a common prodromal sign of heat stroke in humans[8] possibly because dehydration and hypovolemia are commonly

predisposing features. The maintained fall in arterial pressure in cancer patients treated by hyperthermia (T_c=41.5° C) could be attributed to their anesthesia and a rise in cardiac output that was 25% less than normal; the rise in plasma norepinephrine concentration was normal[4] (see Reference 23 in Kregel et al[2]).

The investigations of mammalian responses to hyperthermia have in common the findings that increased body temperature is a powerful stimulus to the sympathetic nervous system and great demands are placed on the cardiovascular system.

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