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 (Tc) 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 Tc 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 sympathetic-adrenal 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 colleagues2 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 Tc 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 non-compensable 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 vaso-dilation 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 markedly3 (see References 8 and 9 in Kregel et alP).

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,) 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 Tc. In
general, cardiac output rises approximately 3 l/min for each degree increase in $T_c$ and reaches 12−14 l/min.\(^4\)

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\(^9\)).

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 $T_s$ 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 experi-
encing 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 period-
ically. Patients with cardiovascular disease are at risk.
For example, heat stress can precipitate acute circu-
latory collapse in patients with mild congestive heart
failure. Heat injury in saunas may occur rapidly
without prodromal warnings, and the risk is height-
ened 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 tolerance1,3,4,7; earlier reports agree
that blood pressure in rats and also dogs7 rises when
Tc reaches 41–42°C. Kregel et al2 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 specu-
lated that if Tc continued to rise toward 41°C, blood
pressure might continue to increase so that a "pres-
sor response might also be evoked in humans before
the circulatory collapse accompanying heat stroke."7
For example, this response might be akin to the
hyperadrenergic, agonal responses to asphyxia; how-
ever, hypertension appears not to be a common
prodromal sign of heat stroke in humans8 possibly
because dehydration and hypovolemia are commonly
predisposing features. The maintained fall in arterial
pressure in cancer patients treated by hyperthermia
(Tc=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 concentra-
tion was normal4 (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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