

LARGE ANIMAL MODELS OF BURN HYPERMETABOLISM

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Today, there continue to exist two explanations for the rise in metabolic heat production following burn injury. One school considers the increase in heat production to be thermoregulatory adjustments to compensate for the increased rate of evaporative heat loss across the surface wound.^{1,2} The other school suggests that the metabolic response to injury is a reflection of the increased energy cost of injury.³ They argue that the basic metabolic drive is sensitive to but independent of alterations in thermoregulation.

Resolution of this controversy may depend on the development of an appropriate animal model, since the constraints of patient studies often preclude an in-depth search for basic mechanisms. If the metabolic response is purely a thermoregulatory adjustment, data collected from small fur-bearing models may be of questionable significance. Rats, for example, have a very limited metabolic response to injury, and unlike our patients, much of the extra metabolism can be eliminated by environmental heating.^{4,5} Over the last several years, we have tested the metabolic response to a 25% total body surface burn in two different large animal species.

The first animals selected were 20-40 kilogram goats. In a pilot study, oxygen consumption of these animals increased by 20-40% above control levels following injury.⁶ These results were encouraging because the metabolic response was greater than that of rats with the same size injury, but it remained less than the 50% increase observed in our patients.⁷ Another important difference was that the hypermetabolic goats were not febrile. These measurements, however, were made on partially restrained animals in a laboratory with only limited temperature control, so we wondered if a clearer picture might be obtained from resting, unrestrained animals housed in a constant thermal environment.

To achieve these conditions, we built a large open and closed respiration chamber. This is nothing more than an airtight box where the animal's metabolism is calculated from measured rates of oxygen disappearance and carbon dioxide accumulation. At the end of each run, the chamber is opened

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2 Caldwell FT Jr, Bowser BH, Crabtree JH: The effects of occlusive dressings on the energy metabolism of severely burned children. *Ann Surg* 193:579-591, 1981.

3 Aulick LH, Hander EW, Wilmore DW, Mason AD Jr, Pruitt BA Jr: The relative significance of thermal and metabolic demands on burn hypermetabolism. *J Trauma* 19:559-566, 1979.

4 Caldwell FT Jr, Osterholm JL, Sower ND, Moyer CA: Metabolic response to thermal injury of normal and thyropivic rats at three environmental temperatures. *Ann Surg* 150:976-988, 1959.

5 Farkas LG, McCain WG, Birch JR, James J: The effects of four different chamber climates on oxygen consumption and healing of severely burned rats. *J Trauma* 13:911-916, 1973.

6 Aulick LH, Baze WB, Johnson AA, Wilmore DW, Mason AD Jr: A large animal model of burn hypermetabolism. *J Surg Res* 31:281-287, 1981.

7 Wilmore DW, Long JM, Mason AD Jr, Skreen RW, Pruitt BA Jr: Catecholamines: Mediator of the hypermetabolism response to thermal injury. *Ann Surg* 180:653-669, 1974.

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and ventilated automatically, permitting a series of metabolic measurements to be conducted for as long as desired. The goat did not accept chamber confinement, however, causing us to seek a more tolerant animal.

We chose 40-80 kilogram miniature pigs. Not only had they proven to be good models of many normal and pathological conditions but had previously been used as burn models.⁹ From a thermoregulatory standpoint, they are more like man than most non-primates, since their sparse hair coat affords them no external insulation and they have no capacity for brown fat non-shivering thermogenesis like many of the smaller animals. Finally, they are reported to be resistant to invasive burn wound infection, making it possible to study the burn responses uncomplicated by systemic infection.

To date, three animals have been studied before and for three weeks after receiving a 25% TBS thermal burn. Each study consists of a series of metabolic and body temperature measurements taken on the postabsorptive animal while it rested undisturbed in the chamber overnight. Core temperature was obtained through the use of a small radiotransmitter (Model LM, Mini-mitter) located on the surface of the peritoneum deep within the abdomen. Ear pinna and back skin temperatures were recorded by a small, portable device (Solicorder, Ambulatory Monitoring) carried on the pig's back. Chamber temperature, humidity and air velocity were held constant for each study, but the temperature for any given study was varied from 3 to 35°C.

All three pigs became hypermetabolic following injury (Fig. 1). Pigs 1 and 3 had an uncomplicated postburn course, but Pig 2 became lethargic and anorexic immediately after injury. While she responded to antibiotics and eventually reached the same level of hypermetabolism as the other two animals, her initial response was blunted.

The two pigs which had uncomplicated postburn courses (Pigs 1 and 3) were hypermetabolic on the first postburn day. Their metabolic responses peaked during the first week at about 50% above control levels. By the end of three weeks, the resting metabolic rates of all three animals were 25 to 30% above normal.

All animals were febrile during the first week, but on postburn day seven, core temperature returned to normal by the end of the overnight run. For the next two weeks, these pigs (like the goats before them) were hypermetabolic without being febrile.

The resting metabolic rate of the uninjured pig plateaued around 60 W/m² (Fig. 2). Back skin and core temperature, which began the study at about 33 and 38.5°C respectively, drifted down slowly as the animal slept. Marked fluctuations in ear temperatures were observed in all uninjured animals and reflect thermoregulatory change in skin blood flow.

Figure 3 shows the same animal on postburn day three when she was febrile and hypermetabolic. Metabolic rate has increased from 60 to between 90 and 100 W/m². Ear pinna temperature remained markedly depressed, however, suggesting that normal skin had vasoconstricted in an effort to conserve heat and raise wound and core temperature.

9. Wachtel TL, Shuck JM, Eaton RP, Schade D, Shuck LW: Glucagon, insulin, and glucose relationships in a porcine experimental burn model. *J Surg Res* 24:70-78, 1978

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During the second and third weeks post injury, when the animals were hypermetabolic and febrile, metabolic studies were conducted at different chamber temperatures. This exercise will identify any shift in the injured animal's *thermoneutral zone, lower critical temperature and thermal conductance*. The thermoneutral zone is that range of ambient temperatures where metabolic heat production is minimal. At the low end of this zone is the lower critical temperature. At this point, the animal has reached its full insulative capacity and, if placed in a cooler environment, must increase its level of heat production in order to maintain body temperature. Thermal conductance describes the rate of heat loss when the animal has achieved its insulative capacity and is exposed to environments below its thermoneutral zone. The steepness of this slope is inversely related to insulation.

Burn injury could have three possible effects. First, if the hypermetabolism is strictly the result of a cold drive, the animal will be hypermetabolic in the normal thermoneutral zone. The extra heat production can be eliminated, however, by raising ambient temperatures until the animal is no longer cold. If postburn hypermetabolism involves adaptations to two drives — cold and injury — heating the chamber will satisfy the thermal demands of the animal without affecting the energy cost of injury and this residual hypermetabolism would persist when the animal was warm and comfortable. The third possibility would develop if internally driven heat production was so great that it shifted the lower critical temperature to the left. In this case, the injured hypermetabolic animal would have an increased tolerance of cool environments.

Shifts in the lower critical temperature of the injured animals suggested that Pigs 2 and 3 became more sensitive to environmental cooling, while Pig 1 appeared to be more tolerant (Fig. 4). The most obvious difference in the three animals was the higher degree of hypermetabolism in Pig 1. The extra heat production available to this animal would mean that she would not reach full cutaneous vasoconstriction and begin to make more heat until exposed to much cooler environments. In the other two animals, where the rate of heat production was substantially lower, it was apparently not of sufficient magnitude to offset the insulative loss and the animals were left more sensitive to lower ambient temperature. In either case, the metabolic response to injury is the primary event and the animals use this extra heat for their altered thermoregulatory requirements. The temperature independence of the metabolic drive is further demonstrated by the failure to eliminate the hypermetabolism by environmental heating. Likewise, since none of the animals was febrile during these studies, their hypermetabolism cannot be explained by the Q_{10} effect.

In summary, our experience with two large animal models demonstrates: (1) they generate a greater metabolic response to a 25% TBS burn than smaller animals, but less than that seen in our patients; (2) as is the case in our patients, the metabolic response of large animals is temperature sensitive, but not temperature dependent (3) finally, the hypermetabolism in the large animal model persists after body temperatures have returned to normal.

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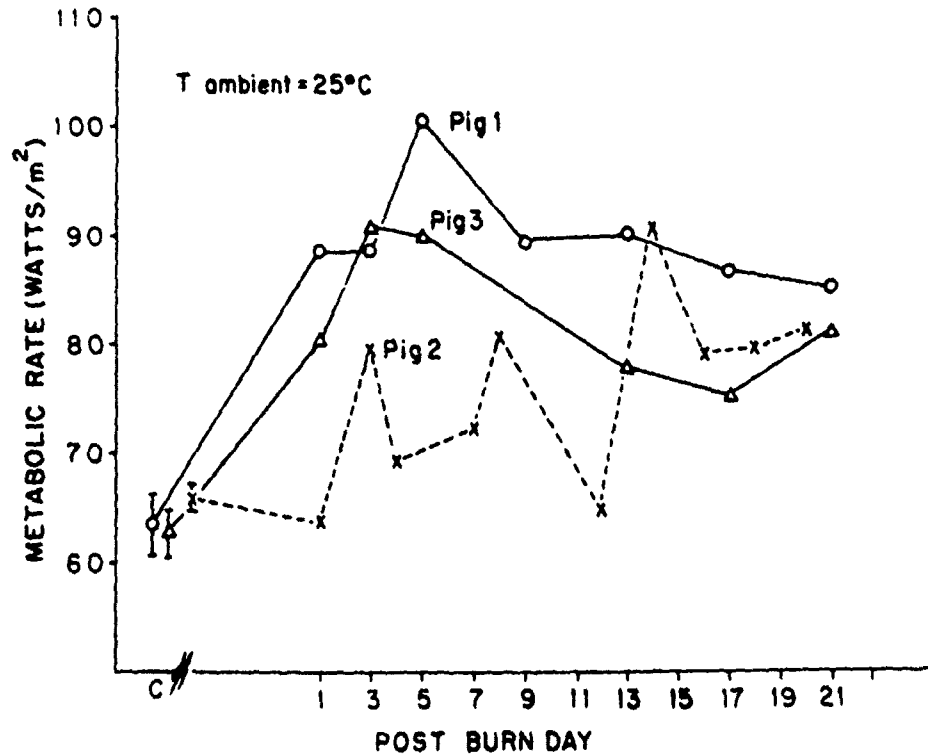


Figure 1. The increase in resting metabolic heat production of three pigs during the first three weeks post injury. Chamber temperature was 25°C, and the control values (C) represent the mean \pm SE.

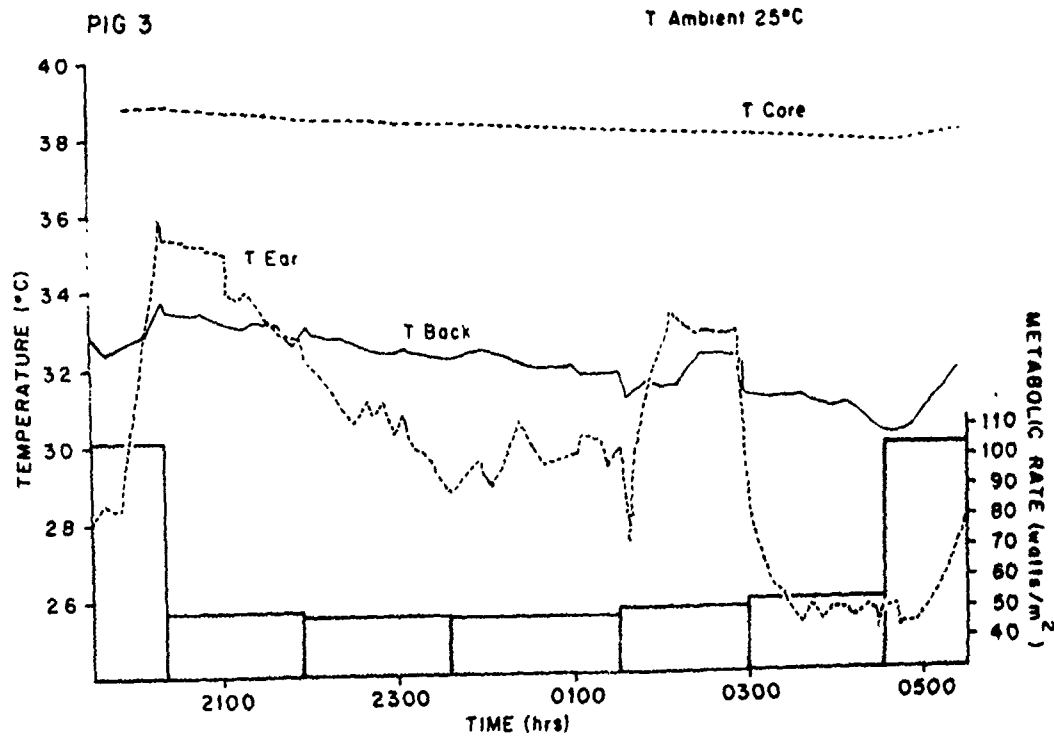


Figure 2. Variations in metabolic rate and body temperatures of the uninjured pig during a typical overnight study.

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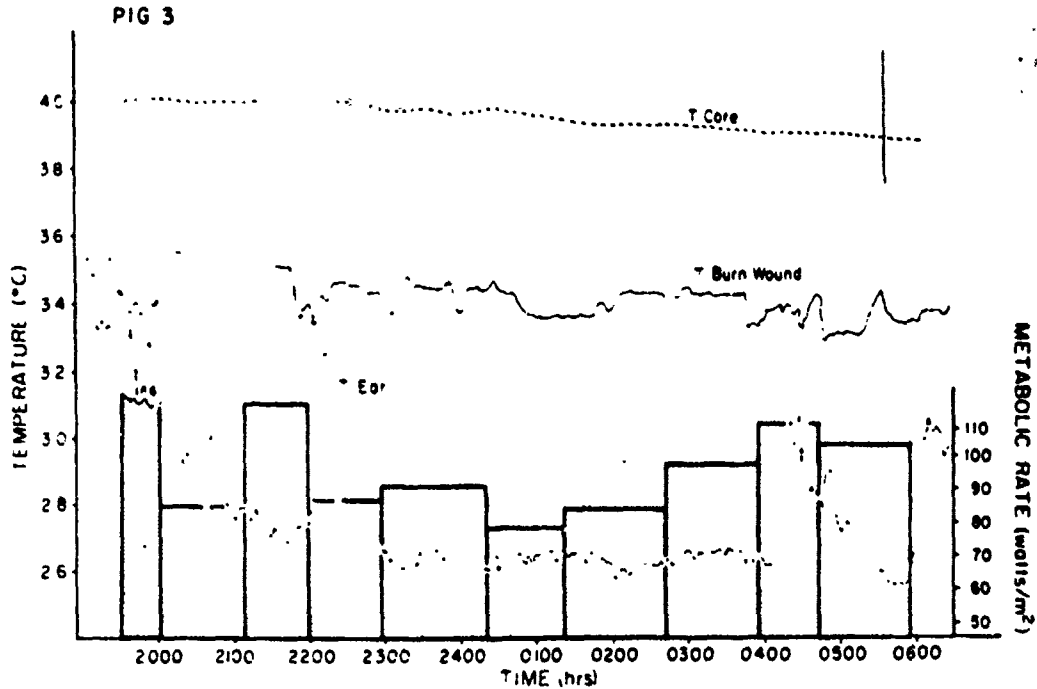


Figure 3. Variations in metabolic rate and body temperatures of a hypermetabolic, febrile pig on the third day post injury. Chamber temperature was 25°C.

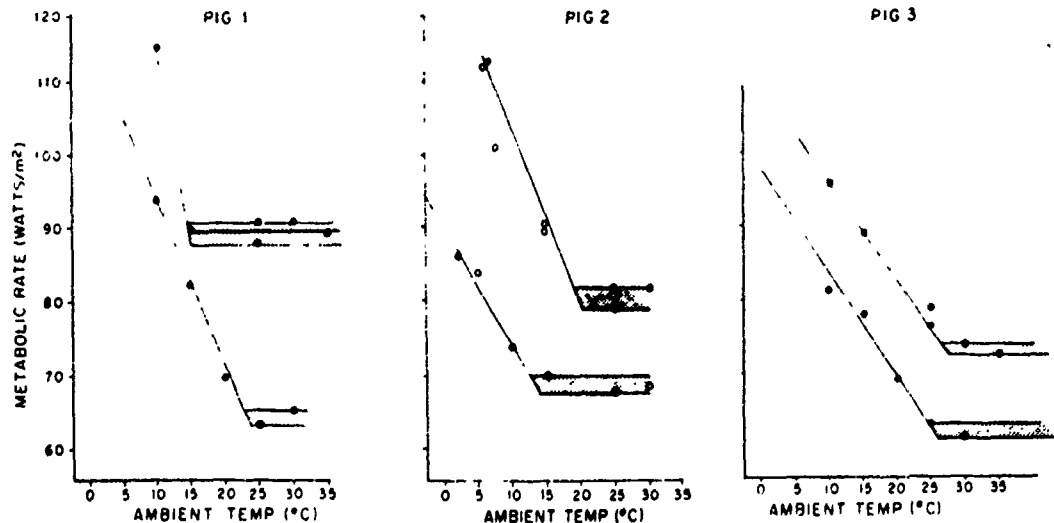


Figure 4. The effects of burn injury on the thermoneutral zone, lower critical temperature and thermal conductance of three pigs.