Control of the Hypermetabolic Response to Burn Injury Using Environmental Factors

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This study was performed to establish the relative efficiency of occlusive dressings and variable ambient temperature (group I) *versus* no dressings and variable ambient temperature (group II) *versus* no dressings and electromagnetic heaters (group III) for controlling the postburn hypermetabolic response. Fifteen burn patients and five normal controls (group IV) were studied when subjectively comfortable using partitional calorimetry, after which each patient was cold stressed by sequentially decreasing external energy support, and repeating calorimetry studies and serial plasma catecholamine assays. The percentage increase in heat production above predicted normal values was significantly increased for all groups when cold (C) *versus* neutral (N) (group I: [N] 24 ± 24 *versus* [C] 49 ± 25%; group II: [N] 46 ± 35 *versus* [C] 74 ± 47%; group III: [N] 21 ± 20 *versus* [C] 78 ± 25%; group IV: [N] −9 ± 12 *versus* [C] 16 ± 10%, $p < 0.05$ all comparisons). Plasma catecholamine values did not increase significantly when patients were subjectively cold. These studies do not support the role of catecholamines as the primary mediator in the cause of the postburn hypermetabolic response. Using the patients' subjective comfort status as a guide for external energy support, it is possible to greatly reduce but not to eliminate the hypermetabolic response to burn injury.

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THE CLINICAL HYPERMETABOLIC response (HMR) to burn injury, first described by Cope et al.[1] in 1953, remains a critical management problem for patients with major burn injury. Early aggressive burn wound management, whether total excision within 72 hours postburn, or sequential excision and grafting does not eliminate the HMR, and may increase the importance of any measure that can control or minimize the HMR. Our current position is that the major portion of the HMR is secondary to increased heat loss, mainly evaporative, but also by radiation when such patients are cared for without dressings.

The work of Arturson[2] and our own earlier work[3] indicate that the major portion of this response can be eliminated by external heat support from electromagnetic heaters or occlusive dressings with insulative value.

This prospective study was performed to determine heat balance for patients with burn injury to more than 30% of the body surface area. Patients were managed with three currently used forms of wound care: (1) occlusive dressings with the ambient temperature (T_A) selected by the patient for subjective comfort; (2) no dressings and a comfortable ambient temperature selected by the patient; (3) no dressings and electromagnetic (EM) heaters set for patient comfort. The goals were to: (1) establish the zone of thermal neutrality for each patient; (2) examine their responses to sequentially applied cold stress, compared with each other and the five controls; (3) determine the effect of the three treatments on plasma catecholamines (epinephrine [E], norepinephrine [NE]), with the patients at a neutral environment, and sequentially during cold stress.

Materials and Methods

The study population consisted of five normal controls and 15 children and adults (without inhalation injury), 12 of whom had burn injury to 30% or more of their body surface area, admitted to the Arkansas Childrens Hospital Burn Center. Patient demographics are summarized in Table 1. Inhalation injury was defined as deficit pulmonary function severe enough to require continual endotracheal intubation and ventilatory support after the fifth postburn day. Patients were entered into the study on a

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TABLE 1. *Patient Characteristics*

Characteristic	Group I	Group II	Group III	Group IV
No. of patients	(n = 6)	(n = 5)	(n = 4)	(n = 5)
Age	22 ± 13	36 ± 13	32 ± 12	28 ± 17
% Full-thickness burn	11 ± 16	5 ± 6	22 ± 29	
% Total burn	36 ± 13	44 ± 18	54 ± 19	

Values are expressed as means ± SD. Burn groups are not significantly different by % full thickness or % body surface area burn.

random basis, using a table of preassignment. Patients who defaulted were entered into the occlusive dressing group. This produced four experimental groups:

Group I, Dressings with variable ambient temperature: These patients had their burn wounds treated with Silvadene (silver sulfadiazine; Marion Laboratories, Kansas City, MO) and occlusive dressings with insulative value estimated to be equivalent to 0.75 clo.[4] Dressings were changed daily and fresh Silvadene applied after removal of any residue. Quantitative surface cultures from multiple sites were performed twice weekly and more often when indicated by the patients' clinical course. Pain control was achieved using small intravenous doses of morphine as needed. As soon as the initial debridement and dressing was completed, the patient was moved to a room with temperature and humidity control beginning at ambient conditions of 28 C temperature and 40% relative humidity (thermal neutrality for nude man). The ambient temperature then was adjusted up or down to obtain a subjective feeling of comfort by the patient, neither warm nor cold but subjectively "comfortable."

Group II, No dressings with variable ambient temperature: These patients were managed as group I except for wound management. Wounds were cleansed with normal saline and fresh Silvadene reapplied daily. Additional Silvadene was applied to the wounds as required, 24 hours a day. Starting ambient conditions were the same as for group I. Ambient temperature was then adjusted up or down to achieve patient subjective comfort.

Group III, No dressings, with electromagnetic heater: This group had their burn wounds managed as group II. However, the ambient conditions were fixed at 25 C and 40% relative humidity, and the patients were allowed to adjust the variable output from an overhead 500-W electromagnetic heater (Aragona Medical, Inc., River Vale, NJ) until they were subjectively comfortable.

Group IV, Controls: Controls were managed as burn groups I and II.

All patients were managed by staged excision and grafting of full-thickness burn wounds as soon as the patients were hemodynamically stable, with the first operative procedure usually performed within the first 10 days. Ungraftable excised burn wounds were covered with either fine mesh gauze, allograft, or Biobrane (Winthrop Pharmaceuticals, New York, NY). Split-thickness donor sites were dressed with Biobrane. Patient treatment, in other words, operative procedures, took precedence over clinical studies. The baseline metabolic tests reported in this study were all performed before the first operative procedure. Patients were not studied during periods of acute illness or sepsis. Individual burn patients had thermoregulatory heat balance studies performed weekly whenever possible, until wound healing was obtained.

Study Sequence for Group I With Dressings

Dressing changes were performed in the evening, and at 5:00 A.M. the following morning, the patient was moved to the environmentally controlled metabolic chamber (Hotpack Corp., Philadelphia, PA), which was regulated at the patients' selected ambient conditions. A heparin lock was placed the prior evening to obtain repetitive blood samples without serial venopuncture. On the morning of the metabolic study, blood was drawn for E and NE determination, after which baseline partitional calorimetry was performed. Patients then were fed breakfast, and the T_A was lowered. After a steady state was obtained at the new temperature (as determined by the oxygen consumption rate and core [T_R] and surface temperatures [T_S]), the patient was asked whether they were warm, comfortable, or cold. At this point, a 20-minute calorimetry run was performed, after which blood was drawn for E and NE assay. This sequence was repeated until the T_A at which the patient was first subjectively cold. Depending on the patient's cooperation and discomfort, sequential lowering of the T_A was continued until the patient was no longer cooperative. The study was then terminated and the patients returned to their room. The study sequence of group II without dressings was identical to that just described for group I. The study sequence for group III without dressings, T_A of 25 C, and EM heaters controlled by the patient differed in that the metabolic chamber and the patient's room were maintained at 25 C and 40% relative humidity and the EM heaters adjusted to the setting required to obtain a comfort state for the patient. The study sequence differed in that the T_A was held constant and the EM heater output lowered in 50- to 150-W decrements. The patients' first sensation of coolness was again noted and calorimetry performed at successive decrements in EM heater output, each time after a new steady state was reached. As before, blood was drawn at the end of each calorimetry period for E and

NE assay. The study sequence for group IV controls was identical to that for groups I and II.

The methodology for the partitional calorimetry studies has been previously described in detail.[3] Catecholamine assays were performed using a radio-enzymatic assay kit (Amersham Cat-A-Kit, Arlington Heights, IL).

Differences between mean values for parameters measured or calculated for the four groups were examined for significant differences using analysis of variance. Where the value of F was significant, Duncan's multiple range test was used to detect significant differences between the individual group means. Intragroup changes in critical parameters were tested for significant differences between mean values using the paired t test. Examination was made for possible correlation between critical variables by linear regression analysis. Where positive or negative correlation was present, regressions were compared one with another using the small sample t tests for parallelism and common intercepts.[5,6] In all comparisons, the null hypothesis was rejected at the 0.05 level of probability.

These experimental protocols were approved by the Human Research Advisory Committee for the University of Arkansas for Medical Sciences, and informed consent was obtained from each patient or a guardian or spouse where appropriate.

TABLE 2. *Calorimetry When Patients Were Subjectively Neutral*

	Group			
Measurement	I (n = 6)	II (n = 5)	III (n = 4)	IV (n = 5)
H_P	58 ± 9	63 ± 15	61 ± 11	41 ± 5
% ΔH_P	24 ± 24	46 ± 35	41 ± 19	−9 ± 12
H_P-fever	52 ± 9	55 ± 12	53 ± 9	43 ± 5
E_V	32 ± 15	37 ± 11	38 ± 13	15 ± 3
Q_R	33 ± 8	36 ± 5	52 ± 5*	32 ± 2
H_O	4.0 ± 1.7	4.4 ± 0.7	2.3 ± 1.6	4.1 ± 1.0
T_B	37.4 ± 0.5	38.0 ± 0.6	37.8 ± 1.2	36.1 ± 0.2
T_S	32.9 ± 0.8	35.9 ± 1.2	35.8 ± 1.3*	33.6 ± 0.3
T_A	26.0 ± 1.6	28.6 ± 1.9	(25)	26.9 ± 0.8
T_R	38.1 ± 0.5	38.5 ± 0.5	38.3 ± 1.1	36.7 ± 0.3
ΔS	−0.2 ± 0.4	0.3 ± 3.5	−0.4 ± 0.5	0.6 ± 2.0
EMH	NA	NA	4.3 ± 4.4	NA

All heat production and heat loss measurements are expressed as W/m^2, and all temperatures as degrees Centigrade. Values are expressed as the mean ± SD.

H_P: heat production; % ΔH_P, % change in heat production when compared with predicted normal values for age and sex where the predicted normal value for group I = 48 ± 6, group II = 43 ± 3, group III = 43 ± 2, group IV = 45 ± 5[7]; H_P-fever, heat production corrected for elevation in body temperature; E_V, evaporative heat loss; Q_R, radiation heat loss; H_O, skin-to-air heat transfer coefficient; T_B, 80/20 weighted body temperature; T_S, average surface temperature; T_A, ambient temperature; T_R, rectal temperture; ΔS, stored body heat; EMH, electromagnetic heater setting, where a setting of 9 = 500 watts. (% Equation balance where heat production = heat loss: group I = 12%↑; group II = 16%↑; group IV = 15%↑.)

* Estimation of Q_R and T_S for group III is distorted by the effect of electromagnetic heaters on skin temperature.

TABLE 3. *Calorimetry When Patients Were Subjectively Cold*

	Group			
Measurement	I (n = 6)	II (n = 5)	III (n = 4)	IV (n = 5)
H_P	70 ± 7*	75 ± 19*	77 ± 12*	51 ± 6*
% ΔH_P	49 ± 26*	74 ± 47*	78 ± 25*	16 ± 10*
H_P-fever	63 ± 4*	67 ± 16	70 ± 12	53 ± 7*
E_V	35 ± 17	39 ± 18	36 ± 15	13 ± 5
Q_R	47 ± 6	50 ± 3	56 ± 9†	52 ± 1
H_O	3.5 ± 1.2	3.8 ± 1.0	3.6 ± 1.5	4.1 ± 0.5
T_B	37.3 ± 0.7	37.7 ± 1.1	37.4 ± 1.1	35.9 ± 0.5
T_S	31.8 ± 1.5	34.1 ± 2.8	33.3 ± 2.2†	31.3 ± 1.3
T_A	21.1 ± 0.8	23.9 ± 3.3	21.8 ± 3.8	21.5 ± 2.6
T_R	38.1 ± 0.8	38.6 ± 0.9	38.3 ± 0.9	36.8 ± 0.3
ΔS	−0.3 ± 2.8	0.2 ± 1.1	−1.1 ± 1.7	−2.4 ± 3.2
EMH	NA	NA	2.8 ± 3.2	NA

All heat production and heat loss measurements are expressed as W/m^2, and all temperatures as degrees Centigrade. Values are expressed as the mean ± SD

H_P, heat production; % ΔH_P, % change in heat production when compared with predicted normal values for age and sex where the predicted normal value for group I = 48 ± 6, group II = 43 ± 3, group III = 43 ± 2, group IV = 45 ± 5[7]; H_P-fever, heat production corrected for elevation in body temperature; E_V, evaporative heat loss; Q_R, radiation heat loss; H_O, skin-to-air heat transfer coefficient; T_B, 80/20 weighted body temperature; T_S, average surface temperature; T_A, ambient temperature; T_R, rectal temperature; ΔS, stored body heat, EMH, electromagnetic heater setting, where a setting of 9 = 500 watts. (% Equation balance where heat production = heat loss: group I = 17%↑; group II = 17%↑; group IV = 27%↑.)

* Values are significantly greater for these patients when cold as compared with neutral (See Table 2), by paired t test.

† Estimation of Q_R and T_S for group III is distorted by the effect of electromagnetic heaters on skin temperature.

Results

Calorimetry and Heat Balance

The data for neutral studies for all groups are summarized in Table 2, and for cold studies in Table 3. Estimated heat loss exceeded heat production (Hp) for groups I, II, and IV under both neutral and cold conditions by an average of 16%. This probably reflects the inability to accurately measure average surface (T_S) and body temperature (T_B) with these experimental circumstances. The use of EM heaters for group III precludes estimation of radiational heat loss.

Heat production correlates with percent body surface area burn only for neutral studies for group II (no dressings and variable ambient temperatures [T_A]) alone and combined with neutral data for group III (without dressings with EM heaters) ($r = 0.71$, $p < 0.05$; Fig. 1).

Percent body surface area burn is positively correlated with rectal temperature (T_R) for group II both for neutral and cold measurements, and groups I, II, and III for pooled neutral measurements ($p < 0.05$ for all three regressions; Table 4 and Fig. 2).

All groups, including the controls, demonstrated a significant percent increase in the rate of Hp between mea-

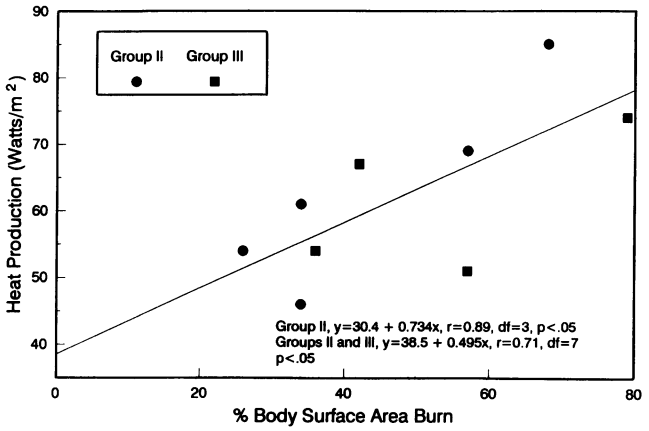

FIG. 1. Linear regression analysis of percentage of body surface area burn and heat production when the patients were subjectively neutral (groups II and III).

surements made while the subjects were subjectively comfortable as compared with when the patients were subjectively cold ($p < 0.05$ all comparisons using paired t test, see Tables 2 and 3). For burn patients with occlusive dressings (group I) while comfortable, the average increment in the rate of Hp above predicted age-matched normals from the literature[7] was 24%. When corrected for the effect of increases in T_R, the average percent increase was 10.5%. When these same patients were cold, the increments were 49% and 35%, respectively ($p < 0.002$ for values uncorrected for T_R). For patients in group II (treated without dressings and variable T_A) when comfortable, these values are 46% increase in Hp and 27% when corrected for T_R, compared with 74% and 54% when cold ($p < 0.04$). For group III (patients managed with EM heaters), when comfortable these values are 41% and 21%, compared with 78% and 61% when cold ($p < 0.05$). These data show that by using external energy support or occlusive dressings, it is possible to decrease but not eliminate the HMR to burn injury. Occlusive dressings appear to be the most efficient method for controlling the HMR, with EM heaters intermediate, and variable T_A is the least effective.

Zone of Thermal Neutrality

The mean value for preferred T_A for group I was 25.6 ± 0.9; for group II, 28.8 ± 2.1; and for group IV (controls), 27.1 ± 0.7. These data suggest that the zone of thermal neutrality after major burn injury is shifted upward when the patients are treated without dressings. The only significant difference between these groups, however, was between groups I and II ($p < 0.05$).

Plasma and Urinary Catecholamines

These data are summarized in Table 5. There were no significant intragroup differences in mean plasma E and NE concentrations comparing neutral *versus* cold values. Mean plasma E values for the two exposed burn groups were significantly higher than values for the control group for both neutral and cold conditions. Plasma E values for burn group I (with dressings) were not significantly different from values for controls when neutral or cold. Plasma E concentrations demonstrate positive correlation with Hp only for burn group II when cold. There were no significant intergroup differences in the urinary excretion rate of E, calculated for 72-hour urine collections. Mean plasma NE concentrations for exposed burn group II when neutral and cold, and exposed burn group III when cold, were significantly higher than values for controls both neutral and cold. Urinary NE excretion rates for the exposed burn groups were not different from one another, but were significantly higher than rates for the burn group with dressings and the control group. The urinary NE excretion rate for the burn group I with dressings did not differ significantly from values for the control group.

Discussion

These data support the concept that the major drive for postburn hypermetabolism is a thermoregulatory response to an increased rate of heat loss, mainly evaporative, but also radiational when patients are treated without dressings.

This portion of the HMR can most easily be controlled with insulative occlusive dressings, but also with EM heaters when patients are treated without dressings.

These data do not support catecholamines as the primary mediators of the HMR,[8] although some plasma level of at least E seems required for a maximal HMR. Changes in catecholamine metabolism after burn injury resemble

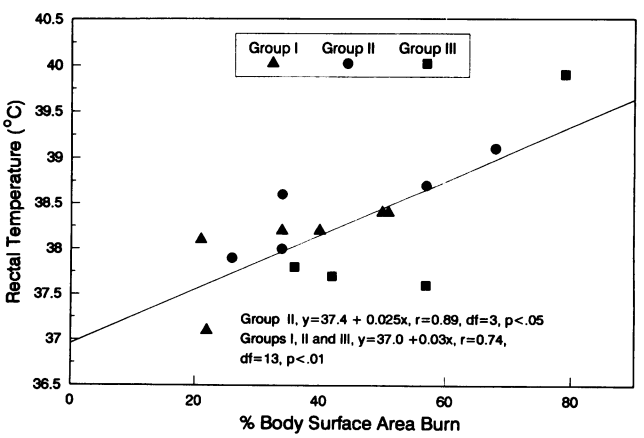

FIG. 2. Linear regression analysis of percentage of body surface area burn and rectal temperature when the patients were subjectively neutral (groups I, II, and III).

TABLE 4. *Linear Regression Analysis*

Group	Subjective Status	X Variable	Y Variable	Regression	df	r	p
I	C	T_R	H_P	Y = −195.09 + 6.96 X	4	0.82	0.04
II	N	E_VHL	H_P	Y = 17.38 + 1.22 X	3	0.92	0.02
II	N	T_S	H_P	Y = −385.43 + 12.49 X	3	0.98	0.003
II	N	T_R	H_P	Y = −1004.91 + 27.77 X	3	0.93	0.02
II	C	E_VHL	H_P	Y = 36.89 + 0.98 X	3	0.89	0.04
II	C	PE	H_P	Y = 49.88 + 0.23 X	3	0.92	0.03
II	C	%BSA	E_VHL	Y = −1.85 + 0.94 X	3	0.95	0.01
II	C	%BSA	PE	Y = −55.24 + 3.74 X	3	0.88	0.05
II	C	%BSA	T_R	Y = 36.6 + 0.05 X	3	0.94	0.02
II	N	%BSA	H_P	Y = 29.93 + 0.76 X	3	0.90	0.04
II	N	%BSA	E_VHL	Y = 11.25 + 0.60 X	3	0.94	0.02
II	N	%BSA	T_B	Y = 36.58 + 0.03 X	3	0.93	0.02
II	N	%BSA	T_S	Y = 33.19 + 0.06 X	3	0.94	0.02
II	N	%BSA	T_R	Y = 37.4 + 0.025X	3	0.89	0.05
III	C	%BSA	T_B	Y = 35.29 + 0.06 X	3	0.90	0.04

N, neutral; C, cold; %BSA, % body surface area burned; H_P, heat production; E_VHL, evaporative heat loss; Q_R, radiation heat loss; T_R, rectal temperature; T_S, average surface temperature; T_B, average body temperature (80%/20%); PE, plasma epinephrine.

a secondary general response to stress. The HMR is present in rats with burn injury after adrenal medullectomy.[9,10] Plasma values for E, the calorigenic amine, do not correlate consistently with any element of the heat balance equation. In two clinical studies, beta-adrenergic blockade produced an average reduction in the rate of Hp of 20% in one study and none in the second study.[11,12] In a third clinical study employing alpha and beta block, 64% of the original increase in Hp was still present.[8]

Elevation in T_R after burn injury is a very consistent finding, and in the current studies is directly proportional to percent body surface area burn in nonseptic burn patients (group II) both when subjectively neutral and when cold (See Fig. 2 for the neutral regression. The neutral and cold slopes of these regressions are not significantly different for patients in group II.).

Clinical studies have demonstrated increased plasma concentrations of endotoxin in burn patients for at least 1 week after burn, and during episodes of sepsis.[13,14] Interleukin-6 may remain elevated for as long as 6 weeks after burn injury and correlates well with increased T_R.[15–17]

A major portion of the increase in T_R after burn injury may represent expression of an exaggerated, prolonged acute phase response.[18,19] The role of the cytokines interleukin-1 and interleukin-6 and tumor necrosis factor in the pathogenesis of increased T_R after burn injury is only now beginning to be investigated. The frequency and importance of endotoxin, originating in the gut or burn wound, in activating fixed and circulating macrophages as well as in other cell lines to produce these cytokines, which act as internal pyrogens, continues to be studied.[20]

Thus far there is little or no evidence that these cytokines are the primary mediators of the HMR, but they may produce an additive effect to the thermoregulatory increment in Hp driven by increased heat loss, to the extent that they shift the hypothalamic thermoregulatory set point temperature upward, inducing increased T_B. By the Q_{10} effect, these cytokines further increase the rate of

TABLE 5. *Plasma and Urinary Catecholamines*

Group	Subjective Status	n	Plasma E (pg/mL)	Plasma NE (pg/mL)	Urine E ($\mu g/m^2 \cdot hr$)	Urine NE ($\mu g/m^2 \cdot hr$)
I, Bandaged, variable T_A	N	6	96 ± 62	663 ± 514	1.5 ± 0.7	2.3 ± 1.9
	C	6	76 ± 56	622 ± 595		
II, Exposed, variable T_A	N	5	87 ± 62	1000 ± 528	2.1 ± 1.4	5.2 ± 0.6
	C	5	108 ± 75	1274 ± 502		
III, Exposed, EMH	N	4	74 ± 25	829 ± 438	2.6 ± 1.8	7.1 ± 3.2
	C	4	130 ± 72	1135 ± 242		
IV, Controls	N	5	19 ± 11	314 ± 174	1.5 ± 0.7	1.0 ± 0.3
	C	5	18 ± 9	342 ± 158		

Values are expressed as mean ± SD.

N, neutral; C, cold; E, epinephrine; NE, norepinephrine; T_A, ambient temperature; EMH, electromagnetic heater. Urinary catecholamines were estimated on individual 72-hr urine collections made with the patients in a neutral environment.

Hp. In support of this idea, ibuprofen, which blocks the final effector limb for internal pyrogens, lowers T_B of burn patients, with an associated decrement in Hp approximately equivalent to the Q_{10} effect of lowering T_B.[21,22]

Conclusions

(1) The major drive for the postburn HMR is increased evaporative and radiational heat loss.
(2) That portion of the HMR driven by increased heat loss can be reduced to a manageable level or eliminated by using insulative dressings and ambient temperature control or no dressings with EM heaters. In both forms of management, using the individual patient's subjective perception of comfort (warmth or cold) as a guide for external energy support, it is possible to greatly reduce but not eliminate the HMR to burn injury.
(3) Catecholamines are not the primary mediators of the HMR, although some level of these amines is required for a maximal HMR.

HYPOTHESIS

A separate portion of the postburn HMR in nonseptic patients is secondary to the Q_{10} effect of a chronic increase in body temperature directly proportional to burn wound size, in response to a shift in set point temperature in the pre-optic anterior hypothalamus. This shift is mediated by the cytokines interleukin-1 or interleukin-6 by the arachidonic acid cascade and prostaglandin E.[19] Theoretically, it should be possible to manage this component of the HMR separately from that component driven by increased heat loss.

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Discussion

DR. J. WESLEY ALEXANDER (Cincinnati, Ohio): Thank you, Dr. Bland, Dr. Jones, Members and Guests. I am most pleased that Dr. Caldwell has asked me to discuss this paper, because we have differed considerably in our opinions as to what causes the hypermetabolic response after a burn injury. In previous studies, Dr. Caldwell has claimed that the heat loss is the primary driving force, and in contrast, our laboratory has shown that the hypermetabolic response can be reduced by approximately 80% by feeding immediately after burn injury, at least in burned animals, and to a lesser extent, perhaps, in humans. Early feeding is associated with a marked reduction in the translocation of bacteria and endotoxin from the gut, which activates macrophages and triggers the hypermetabolic response by the release of cytokines and eicosanoids. This suggests a primary endogenous mechanism.

In the current paper, Dr. Caldwell and his associates now provide clear evidence in the comparison of three small and not necessarily comparable but very well-studied groups of burn patients that the major drive for the postburn hypermetabolic response in patients who are not at thermal neutrality and not treated with occlusive dressings is increased evaporative loss and radiational heat loss. They also suggest that if you do control thermal neutrality in a closed environment with dressings, these factors are not that important. It is indeed not surprising that increased heat production occurs in patients and even in controls who have muscle tenseness or even shivering from being cold.

They also showed that heat production correlated with the size of burn and rectal temperature. Furthermore, there was increased heat production in group 1 patients even when corrected for rectal temperature. It thus seems that the two divergent views are both correct. Increased heat production occurs in patients who are cold or have large evaporative water losses. And hypermetabolism also occurs because of increased cytokine production, in part triggered by translocation of bacteria and endotoxin from the gut.

I have two questions. From the large standard errors of and the means