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Reprinted from Cardiovascular Research
Volume XVI, *No.* 3, *pages* 113–119, *March* 1982

LONDON
BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, LONDON WC1

Cardiovascular Research, 1982, **16**, 113–119

Depressed reflex vasomotor control of the burn wound

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SUMMARY Total leg blood flow was measured by venous occlusion plethysmography in five normals and 14 burned patients before and after 30 min of external heating. Leg surface temperatures were held constant, but rectal temperatures increased on the average of 0.4 to 0.5°C in all subjects following this heat load. Leg blood flow increased by 56.0% in the controls, 63.2% in five patients with essentially no leg burn (mean burn size = 1.5% leg surface), and 9.6% in nine patients with major leg injuries (mean burn size 55% leg surface). Failure of reflex vasodilatation in the burned leg was evident up to 107 days postinjury even when the wound was well-healed. All subjects sweated freely from the unburned skin. In two patients, where arm and leg blood flows were measured simultaneously, flow to the uninjured arm increased while that to the injured leg remained unchanged. This lack of reflex vasodilatation in the burned limbs suggests either that wound vessels are denervated or that they are so dilated in the basal state that further dilatation is limited. The bulk of this and other data would support the denervation concept. This physical or chemical denervation could occur at the time of injury, be localised to the area of the wound, and result in loss of both neurogenic vasoconstrictor tone and active reflex vasodilatation.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Reg 70-25 on Use of Volunteers in Research.

The acute loss in plasma volume immediately following thermal injury results in an initial fall in cardiac output.[1,2] During successful resuscitation, cardiac output begins to rise and may eventually reach levels two to three times normal in the more extensively injured patients. The hyperdynamic circulation accompanies a rise in resting metabolic rate and elevations in core and surface temperatures. Most of this extra blood flow appears to be directed to peripheral tissues, since the combined increases in visceral blood flow (splanchnic and renal) fail to keep pace with the rise in cardiac output following injury.[3,4] Normal resting skeletal muscle perfusion,[5] high surface temperatures (in the face of increased evaporative cooling of the wound) and twice normal rates of heat transfer from the core to the skin of burn patients,[6] suggest that much of the increased peripheral blood flow is directed to the body surface. More recently, we have demonstrated that most of the elevated surface blood flow is directed primarily to the burn wound,[7,8] blood flow to the uninjured legs of burned patients was essentially normal but increased in a curvilinear fashion with increasing leg injury.

This wound directed blood flow may be the result of: 1) limited vascular smooth muscle development and intrinsic tone in the rapidly growing vessels of wound granulation tissue; 2) a traumatic loss of sympathetic vasomotor innervation; and/or 3) the presence of local vasodilatory metabolites in the wound which override neurogenic or circulating vasoconstrictor influences. Vascular smooth muscle tone is evident in the granulating wound, since blood flow to the severely burned leg increases appropriately when the surface of the injured limb is heated.[7,8]

This study was designed to determine the capacity of vessels in the burned wound to dilate reflexly when the surface temperature of the injured limb is held constant and the patient's central body temperature elevated by external heating.

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Methods

Fourteen thermally injured patients, with a mean burn size of 38.5% of the total body surface, range 12 to 73%, and five normal individuals were studied (table 1). The subjects' ages ranged from 19 to 56 years. Patients selected for study were: 1) free of any pre-existing disease prior to injury; 2) normotensive and haemodynamically stable after an uneventful resuscitation; 3) in a normal state of hydration with a haematocrit greater than 33 and without abnormalities in serum electrolyte concentrations, osmolality, or pH; 4) free of systemic infection; and 5) able to participate in the study. The average size of leg burn was 36% of the leg surface – range 0 to 70%. Simultaneous arm and leg blood flow measurements were performed in two patients (patients 11 and 14) with burned legs and unburned arms.

The patients were studied from 9 to 107 days postinjury. Patients 6, 8, 9, 10, 11, 18, and 19 were studied early in their postburn course and had open leg wounds, but the other nine studies were performed on convalescent patients whose burn wounds were well healed. With the exception of patient 9, all unhealed wounds were treated by the exposure method. This involved topical application of a silver sulphadiazine cream (Silvadene® cream) or mafenide acetate cream (Sulfamylon® cream) to the injured surface. Face, trunk, and upper extremity wounds of patient 9 were covered with dressings saturated in a 5% mafenide acetate solution. While these treatments have no known direct effects on wound blood flow, they do involve considerable manipulation of the patient, often resulting in discomfort. Therefore, to insure that each subject was well rested for the study, such procedures were minimised, whenever clinically feasible, for at least 8 h prior to the study.

STUDY DESIGN

All experiments took place in the environmental chamber described previously.[6] Room temperature was maintained at 30°C, and relative humidity ranged between 40 to 50% during the control studies. The postabsorptive subjects, dressed in cotton shorts (controls) or appropriately draped with a light cotton towel (patients), rested supine in bed throughout the study. Nine copper-constantan thermocouples were attached to the skin at the same sites for all subjects (dorsum of foot, lateral and posterior calf, anterior and posterior thigh, dorsum of hand, forearm, abdomen and low back). In the one patient treated in dressings, thermocouples were placed on the wound under the dressings. A rectal temperature probe was inserted to a depth of 10 cm from the external anal sphincter. All tempera-

TABLE 1 *Subject characteristics*

Subject	*Age (yr)*	*Body surface area (m^2)*	*Post burn day studied*	*Burn size*	
				% Total body	*% leg*
Controls					
1	38	2.03		0	0
2	23	1.80		0	0
3	31	1.96		0	0
4	29	2.04		0	0
5	25	1.99		0	0
Mean	29	1.96		0	0
Small leg burns					
6	32	2.05	9	29.0	2.5
7	54	1.92	43*	29.5	0
8	55	2.11	11	35.5	0
9	34	2.10	27	38.0	5
10	23	1.79	13	39.0	0
Mean	40	1.99	21	34.0	1.5
Large leg burns					
11	50	1.72	25	12.0	
12	19	2.18	68*	22.5	
13	20	2.07	91*	28.0	[illegible].0
14	56	1.99	75*	29.5	65.0
15	22	1.73	70*	41.5	45.0
16	22	1.74	73*	46.0	65.0
17	20	1.72	107*	50.5	37.5
18	19	1.73	11 and 26*	67.0	65.0
19	21	1.78	15	73.0	45.0
Mean	28	1.85	56	41.0	55.0

*Wound healed, patient convalescing

tures were recorded at 5 min intervals for at least 1 h prior to the flow measurements to identify the establishment of thermal equilibrium. After the initial equilibration period, mean leg skin temperature was determined. The thermocouples were removed from that limb, and the leg was inserted into a large, pliable, water impermeable boot and then placed in a full-length plethysmograph.

Water was added to the plethysmograph at a temperature equal to the predetermined mean leg skin temperature and maintained at this temperature throughout the remainder of the study. After a 30 min equilibration period in the plethysmograph, eight to ten resting blood flow measurements were performed. A 1.5 to 2 min period separated each blood flow determination. The subject was then heated with three radiant heat lamps for 30 min. Two sets of three to four leg blood flow measurements were performed, one beginning after 10 and the other after 25 min of external heating.

In the two studies where arm blood flow was measured, mean arm skin temperature was determined by using hand and forearm thermocouples, plus two others located on the anterior and posterior surfaces of the upper arm.

BLOOD FLOW MEASUREMENTS

Leg blood flow measurements were obtained through the use of a full-length, water filled, plethysmograph described previously.[8] Briefly, this plethysmograph is a rigid rectangular box made of clear plexiglass. To facilitate its use in injured limbs, the plethysmograph can be disassembled into three sections, a thigh plate and attached boot, a trough section with a mesh sling to support the leg, and a full-length top. The subject's leg was slipped through a tailor-made opening in the thigh plate and into a loose-fitting, polyvinyl boot. The boot and thigh plate were then advanced to the proximal thigh and the leg, rested in the mesh sling of the plethysmograph. The plethysmograph was then filled with water. The water was continuously stirred by two centrifugal pumps and its temperature maintained by circulating ethylene glycol from a thermostatically controlled reservoir through copper tubing located on the floor of the plethysmograph.

Using this apparatus, limb blood flow measurements required 10 to 15 s of venous occlusion. This was accomplished by rapid inflation of a 10 cm wide tourniquet cuff placed as high on the thigh as possible. In accordance with standard technique,[9] cuff pressure was varied for each subject to obtain the highest rate of limb swelling. The increase in limb volume with venous occlusion caused water to rise in a chimney located on top of the plethysmograph. The rate of rise in column hydrostatic pressure was used to calculate arterial blood flow. Eight to ten such flow measurements were averaged to establish mean, resting leg blood flow. The plethysmograph was calibrated with the leg in place after each two to three measurements. The volume of the limb within the plethysmograph was determined by subtracting the volume of water in the plethysmograph from its known capacity. Leg blood flow values were then reported in $cm^3/100\ cm^3$ of leg volume per minute.

In two patients, simultaneous arm and leg blood flow measurements were performed before and after external heating. The plethysmograph used on the upper extremity was of the same basic design as the leg plethysmograph described previously.[8] The techniques of measurement were therefore comparable in the two limbs with no attempt made to separate foot or hand from total limb blood flow. Water temperature in the arm plethysmograph was set to the mean arm skin temperature of one subject while, in the other study, arm bath temperature was adjusted to approximate that of the leg under study. Measurements were performed every two to four min throughout the period of heating, alternating the determination between the leg and the arm.

BODY TEMPERATURE MEASUREMENT

Rectal (T_{re}) and three different mean skin temperatures (total body mean skin = T_{sk}, leg mean skin = T_{sk_l}, and arm mean skin = T_{sk_a}) were monitored in each subject. Rectal temperatures were followed at 5 min intervals throughout the study while surface temperatures were recorded *only* during the initial 1 h equilibration period. In this way, the development of steady-state T_{re} and T_{sk} identified the achievement of thermal equilibrium for each subject prior to resting blood flow measurements. In like fashion, T_{sk_a} and T_{sk_l} were utilised to set water temperature in the respective plethysmographs to levels which would approximate that of the limb surface under these resting conditions.

Total body and leg mean skin temperatures were calculated as reported previously,[8] while mean arm skin temperature was determined by averaging four surface temperatures: 1) anterior upper arm; 2) posterior upper arm; 3) forearm; and 4) dorsum of hand.

Results

Thirty min of external heating resulted in an average 0.4 to 0.5°C rise in rectal temperature in control subjects, patients with minimal leg burns, and patients with extensive leg injuries (table 2). This elevation in central body temperature increased blood flow to the control limbs from a basal level of $2.93 \pm 0.29\ cm^3/100\ cm^3 \cdot min$ (mean ± SEM) to $4.57 \pm 0.29\ cm^3/100\ cm^3 \cdot min$ after heating. This 56% increase in normal leg blood flow was comparable to a 63.2% increase in flow to the essentially uninjured legs of burned

TABLE 2 *Effects of 30 min of external heating on rectal temperature and leg blood flow*

Subject	Leg surface temperature (°C)	Rectal temperature (°C)		Leg blood flow ($cm^3/100 cm^3 \cdot min$)*	
		Before	After	Before	After
Controls					
1	34.0	36.6	37.0	2.51±0.09	4.48±0.16
2	34.0	36.7	37.0	4.06±0.18	5.42±0.12
3	33.5	36.7	36.9	2.54±0.10	3.89±0.29
4	33.8	36.7	37.1	2.64±0.16	4.33±0.09
5	33.6	37.0	37.3	2.88±0.22	4.74±0.48
Mean	33.8	36.7	37.1	2.93±0.29	4.57±0.25†
Small leg burns					
6	35.3	38.2	38.9	5.04=0.23	7.86±0.42
7	33.6	37.3	37.5	2.75±0.17	4.38±0.19
8	35.7	38.3	38.9	2.88±0.26	4.67±0.09
9	34.4	38.4	38.8	2.79±0.09	4.31±0.30
10	35.1	37.6	38.2	4.76±0.06	8.47±0.56
Mean	34.8	38.0	38.5	3.64±0.52	5.94±0.91§
Large leg burns					
11	34.2	37.3	37.4	5.21±0.27	5.57±0.09
12	34.9	37.0	37.6	4.70±0.26	6.41±0.45
13	35.5	37.3	37.6	7.12±0.16	7.18±0.16
14	35.6	37.3	37.6	7.16±0.52	7.61±0.01
15	35.8	37.0	37.3	5.09±0.18	4.88±0.62
16	34.0	37.3	37.6	7.69±0.78	6.15±0.25
17	35.1	36.7	37.5	4.81±0.08	7.69±0.30
18	35.8	37.2	38.1	12.21±0.12	12.68±0.45
18a	35.7	37.2	37.6	10.29±0.37	10.75±0.50
19	36.3	38.7	39.1	6.82±0.46	8.98±0.25
Mean	35.3	37.3	37.7	7.11±0.78	7.79±0.76

*Mean ± SEM; †$P<0.001$; §$P<0.01$.

patients (from 3.64±0.52 to 5.94±0.91 $cm^3/100 cm^3 \cdot min$) over identical periods of external heating. Blood flow to the extensively burned extremities, however, increased by only 9.6% (from 7.11±0.78 to 7.79±0.76 $cm^3/100 cm^3 \cdot min$). Generally, in the legs in which reflex vasodilatation occurred, this had begun by the end of 10 to 15 min of external heat when the first set of measurements were performed. Flow to these limbs continued to increase and was always higher by the end of 30 min of heat loading. There was a general, inverse relationship between size of the leg burn (%LB) and the percentage increase in leg blood flow (%BF) with external heating (fig 1). The limited capacity to vasodilate in the burned limbs was not only apparent in patients with open wounds on their legs (patients 11, 18, and 19) but was also evident in convalescent patients with well-healed leg wounds.

In the two patients where simultaneous arm and leg blood flow measurements were monitored, there was a marked increase in blood flow to the uninjured arm, while flow to the burned leg remained essentially unchanged (figs 2 and 3). This increase in flow to the arm occurred whether the water bath temperature matched that of the predetermined mean arm skin temperature or was elevated in order to approximate the temperature of the skin of the burned leg.

All subjects sweated freely during the process of external heating, but in the patients, this sweating could only be seen on the unburned skin.

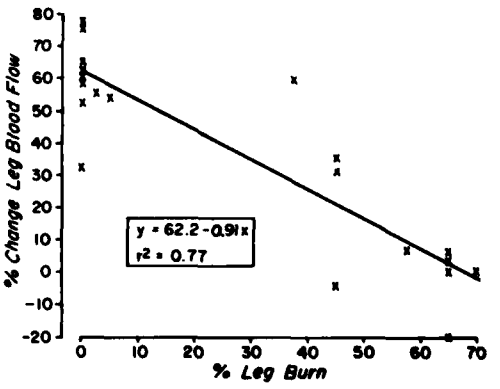

FIG 1 *The increase in leg blood flow following 30 min of reflex heating decreases with the size of injury on that particular leg.*

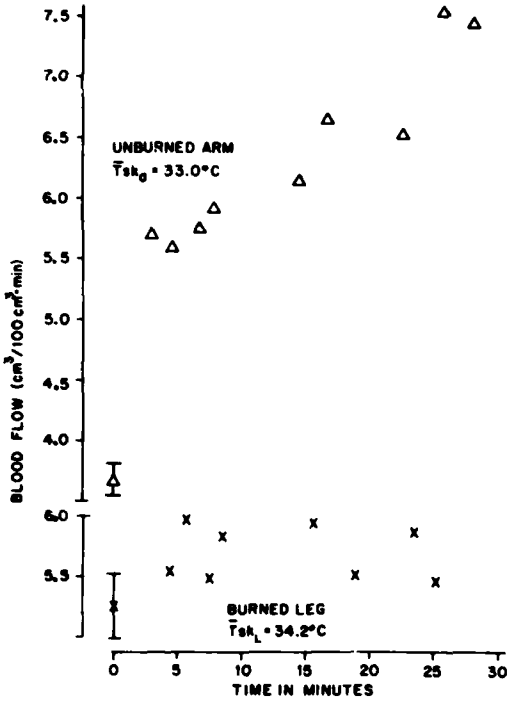

FIG 2 *Changes in blood flow to the burned leg (×) and unburned arm (△) of subject 11 during 30 min of external heating. Surface temperature of each limb was maintained at the predetermined mean skin temperature for that particular extremity. Limb blood flow at time 0 represents the mean ± SEM of four to six measurements taken just prior to heating.*

Discussion

This study clearly demonstrates impaired reflex vasodilatation in injured limbs which persists for at least 3 to 4 months post injury. The apparent loss of vasomotor control is confined to the burn wound, since this type of external or total body heating has no effect on muscle blood flow.[10-12] The general inverse relationship between size of the leg burn and the increase in leg blood flow with external heating further supports this conclusion.

The reduced circulatory response to reflex heating could be explained on a physical basis if 1) the wound is fully dilated prior to the addition of external heat, or 2) high resting cardiac outputs in these patients with leg burns have exhausted the cardiovascular reserve needed to support the added heat stress. While both factors may modify the vasodilator capacity of the burned limb, leg blood flow measurements performed on one patient (patient 15), at three different times in his hospital course, demonstrated that circulation to the injured leg increased significantly when leg surface temperature was raised 5°C for 30 min (table 3). This occurred even when the patient was febrile and had high resting heart rates. However, blood flow to this same leg did not change when the surface temperature was held constant and the patient's rectal temperature increased 0.3°C by external heating (table 2). Additional evidence that the general cardiovascular reserve of these patients was not exceeded by external heating was:

1) blood flow to the uninjured arms increased while that to the burned leg did not (figs 2 and 3);

2) maximum pulse rates at the end of heating commonly ranged from 120 to 130 and never exceeded 144.

Since these physical limitations do not explain the failure to vasodilate the burn wound, one must examine the integrity of the vasomotor reflex arc. Appropriate circulatory and sweating responses in the

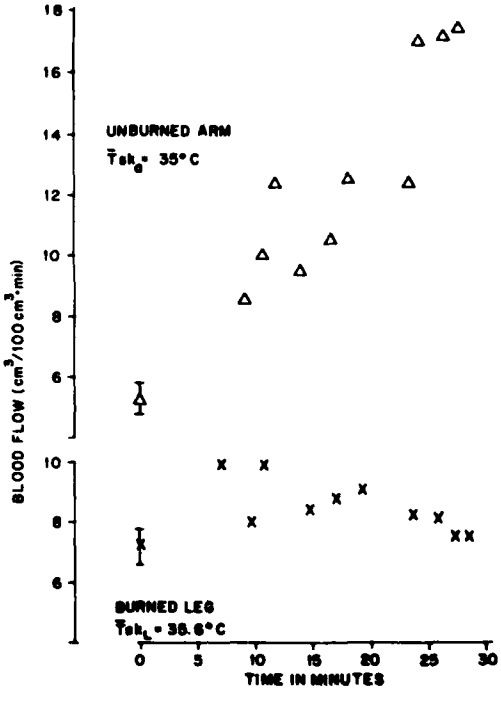

FIG 3 *Changes in blood flow to the burned leg (×) and unburned arm (△) of subject 14 during 30 min of external heating. Surface temperature for both limbs was maintained at a level comparable to that of the burned leg. Leg blood flow at time 0 represents the mean ± SEM of four to six measurements taken just prior to heating.*

TABLE 3 *Changes in rectal temperature, leg blood flow and heart rate with a 5°C increase in leg surface temperature for 30 min*

	Rectal temperature (°C)		*Leg blood flow* (cm³·100 cm⁻¹·min)*		*Heart rate*	
Postburn day	*Before*	*After*	*Before*	*After*	*Before*	*After*
7	38.8	38.8	5.88±0.20	7.90±0.24	110	134
14	37.5	37.8	6.24±0.16	9.32±0.27	110	120
50	37.1	37.4	4.65±0.33	7.91±0.38	84	98

*Mean ± SEM

uninjured skin indicate that stimulus strength, function of the afferent limb, and central integration of this reflex were adequate. The site of reflex failure must, therefore, reside somewhere in the efferent limb. This study and an earlier one[8] have ruled out any basic failure of the effector organ, since burn wound vasculature exhibits a degree of basal tone which can be manipulated by direct changes in temperature (table 3). Consequently, the loss of reflex vasomotor control must indicate that the wound is "functionally" denervated. This could result from: 1) an actual physical disruption of sympathetic nerves at the time of injury and/or; 2) changes in the local chemical environment which affect wound neuromuscular transmission of the innervated vessels.

Tissue inflammation, whether it be a result of injury or the invasion of microorganisms, is characterised by a local increase in blood flow to the affected site and a secondary spread of this vasodilatation, referred to as the arterial flair. These changes in the microcirculation are mediated both by local chemical factors released during injury (*ie*, prostaglandins (PGE), histamine, serotonin) and various humoral factors introduced via the blood stream — the principle vasoactive agents in this category being the kinins. Many such chemical factors have been identified in the burn wound.[13–15] The effects of these inflammatory products on local nervous activity was described by Zweifach,[16] who reported that during inflammation precapillary sphincters became refractory to vasoconstrictor stimuli. He suggested that this refractoriness may be related to the ability PGE to suppress adrenergic transmission, as demonstrated earlier by Horton.[17] (Since prostaglandins also have direct effects on cutaneous vascular smooth muscle,[18 19] the exact mechanisms by which they affect neurogenic control of small blood vessels in inflammatory tissue is still unclear.) Alternately, local wound chemistry could cause the chronic release of neurotransmitter from vasodilator nerves and thereby limit the capacity of these nerves to respond to additional extrinsic stimulii. In addition to these various inflammatory products, vessels in the burn wounds may be dilated in areas of low oxygen tension[20] or by the enhanced lactate production[21] and elevated temperatures of the local environment.[8] This combination of inflammatory and metabolic factors creates a local chemical environment which could readily reduce the influence of any sympathetic vasomotor nerves in granulation tissue.

In any form of tissue injury, actual physical disruption of sympathetic efferent nerves would also contribute to a reduction in reflex control of wound blood flow. This physical denervation would not only explain the inability to actively vasodilate the burn wound but may also increase basal flow by releasing the microvasculature from tonic neurogenic vasoconstriction.

The prolonged duration of faulty reflex vasomotor control in the burned limbs is consistent with the concept of actual physical denervation, since several studies have demonstrated that nerve regeneration and vascular reinnervation of granulation tissue involves a considerable period of time.[22 23] A basic timetable for such reinnervation was provided by one animal study,[22] where the utilisation of transparent chambers permitted direct visualisation of granulation tissue. In that particular model, recognisable nerve fibres and active arteriolar contractions were observed on the fringes of the wound as early as 3 to 4 weeks postinjury. The rate of nerve growth decreased with time, however, and in some instances, ceased before many newly formed vessels were innervated. In some animals, arterioles were 3.5 to 7.5 months old before definite active contractions were observed. Others, who have studied the general sensory innervation of skin grafts,[23] have commented on the slowness of cutaneous nerve regeneration. They concluded that the degree of reinnervation depended on the availability of neurolemmal pathways for the ingrowing nerves. Such pathways were least accessible in split-thickness grafts, which resulted in greater scarring. In the current study, five patients with leg burns (patients 12, 13, 14, 18, and 19) had this type of graft on the leg under study. Freund *et al*[24] found that a well-healed full-thickness burn wound dilated with direct application of heat but failed to reflexly vasoconstrict or vasodilate. Healed partial-thickness injuries, on the other hand, possessed good local and reflex vasomotor

control. While no such distinction could be made in the current study, all such work suggests that reflex control of wound blood flow depends both on the extent of actual trauma and the degree of wound repair. For example, inflammatory and altered metabolic vasoactive influences should gradually subside as the wound heals and assumes a character more like that of normal skin. Likewise, nerve regeneration develops slowly and reaches a level of vascular reinnervation ultimately determined by the developing scar.

The loss of neurogenic or reflex control of the burn wound has recently been confirmed in a large animal model.[25] Basically those studies extended our understanding of the control of blood flow in the granulation tissue of a surface wound by demonstrating that new wound vessels possess vascular smooth muscle with functioning α- not β-adrenergic receptors. In that particular model (injured goat hindlimb), wound vascular tone was unaffected by changes in either oxygen delivery or glucose metabolism. Likewise, while the local chemical environment may contribute to the observed lack of neurogenic vasomotor tone, a series of cross-perfusion studies failed to demonstrate the presence of any circulating vasoactive agent in the effluent from the injured leg.

These studies of the effect of body heating on limb blood flow support the concept that burn wound neovasculature is "functionally" denervated. Depending on the extent of trauma and degree of repair, this denervation may result from an actual physical disruption of vasomotor efferent nerves and/or chemical alterations of neuromuscular transmission in those vessels which retain their innervation. Regardless of the precise mechanism involved, such denervation would: 1) elevate basal wound blood flow by releasing the neovasculature from tonic neurogenic vasoconstriction; and 2) prevent active vasodilatation in the wound in response to an additional heat stress. This loss of neural control allows local environmental factors to exert a great influence on wound blood flow. Consequently, the control of wound circulation becomes less like that of normal skin and more like that of other critical tissues (heart, brain, working skeletal muscle), where blood flow varies as a function of local metabolic conditions rather than as part of integrated total body thermoregulatory or baroreceptor reflexes.

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