# Propranolol Diminishes Extremity Blood Flow in Burned Patients

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**Beta adrenergic blockade diminishes the catecholamine-mediated elevations in heart rate and myocardial contractility that characterize postburn hypermetabolism. To examine how these alterations in cardiac performance affect peripheral perfusion, indirect calorimetry and leg blood flow were measured before and then after a 2-hour intravenous propranolol infusion. Five severely burned patients (55% + 7% total burn surface area), given propranolol at 8 μg/kg/minute, had a significant reduction in cardiac index and heart rate with an increased leg vascular resistance resulting in a decrease in extremity perfusion. Four healthy volunteers were given propranolol at 5 μg/kg/minute, resulting in a comparable decrease in heart rate, yet there was no change in leg vascular resistance or extremity perfusion. In both patient groups, propranolol decreased the plasma lactate concentration. This suggests that in hypermetabolic patients, beta adrenergic blockade reduces peripheral perfusion and that peripheral perfusion is not a principal determinate of plasma lactate levels. Rather adrenergic blockade appears to decrease lactate concentration as a consequence of the inhibition of lipolysis.**

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THE TREMENDOUS OUTPOURING of catecholamines after a thermal injury appears, in part, to mediate the hyperdynamic, hypermetabolic stress response.[1] In attempting to blunt this response to catecholamines, beta adrenergic antagonist has been administered with controversial efficacy. In an extensive evaluation of the relationship between catecholamines and metabolic rate in burn patients, Wilmore et al.[1] demonstrated a significant correlation between increasing urinary catecholamine excretion and an increasing metabolic rate induced by cold stress. They also identified four severely burned patients in whom cold failed to induce the catecholamine-mediated stress response and resulted in a paradoxical decrease in the metabolic rate. All four nonresponding patients later died of burn-related complications. Consequently Wilmore et al.[1] deduced that the catecholamine-mediated elevation in metabolic rate may be appropriate and integral for recovery after a major burn. Furthermore Goodall et al.,[2-4] in a series of studies, showed that the increased turnover and excretion of catecholamines after thermal injuries can deplete the adrenal medulla of catecholamines and reduce monoamine stores in sympathetic ganglia. They concluded that supplementation of adrenergic precursors may be beneficial in maintaining catecholamine synthesis and ensuring an adequate stress response and continued hypermetabolism. In contrast Herndon et al.[5] demonstrated that limited beta adrenergic blockade in burn patients may be beneficial by reducing myocardial work. In that study propranolol failed to decrease the resting energy expenditure and the overall hospital course and mortality rate were clinically unaffected. However propranolol did significantly increase urea production and may paradoxically augment protein catabolism. The purpose of this study was to assess the impact of reduced cardiac performance by beta adrenergic blockage on peripheral perfusion and lactate metabolism in severely burned hypermetabolic patients compared to normal healthy volunteers.

## Materials and Methods

### *Subjects*

Five severely burned and four healthy young men of similar size and age participated in this study as approved by the Institutional Review Board of the University of

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TABLE 1. *Patient Characteristics (Age, Size, and Severity of Burn) for Both Patient Groups*

| Characteristics | Normal Controls (n = 4) | Burn Patients (n = 5) |
|---|---|---|
| Age (yrs) | 26 ± 2 | 21 ± 3 |
| Weight (kg) | 72 ± 4 | 72 ± 9 |
| BSA ($m^2$) | 1.91 ± 0.07 | 1.88 ± 0.13 |
| Leg volume (L) | 16.2 ± 1.2 | 13.0 ± 1.9 |
| %TBSA burn | 0 | 65 ± 7 |
| %Full-thickness burn | 0 | 45 ± 11 |
| %Leg burn mean ± SEM | 0 | 65 ± 15 |

BSA, body surface area; TBSA, total body surface area; SEM, standard error of the mean.

Texas Medical Branch (OSP-89-144) (Table 1). The patients were similar in extent and severity of burn and were studied approximately 2 weeks after injury. Increases in resting energy expenditure, cardiac index, and heart rate confirmed that these patients were hypermetabolic and hyperdynamic (Table 2). Standardized treatment protocols for initial fluid resuscitation, formulated nutritional support, and manner of operative care with early burn wound excision and serial autographing allowed uniformity in patient care.[5,6] The volunteers were considered healthy by screening history, physical examination, and blood analysis. All were normal for height and weight and were not receiving any medications.

### *Study Protocol*

The study was begun in the morning following an overnight fast. In addition the burn patients had all enteral and parenteral nutrition discontinued 6 hours before initiating this study. Resting energy expenditure was assessed by indirect calorimetry using a metabolic cart (SensorMedics MMC Horizon System 4400, Anaheim, CA). Placement of femoral arterial and venous catheters allowed for pressure monitoring and serial blood sampling. Cardiac output was determined in the burn patients with a 5-mg bolus injection of indocyanine green dye *via* the central venous access and measurement of dye dilution

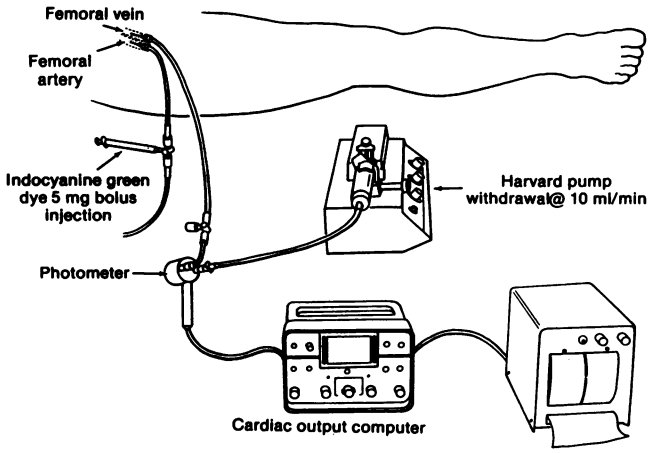


FIG. 1. Schematic diagram of bolus dye dilution method for determining leg blood flow.

from the femoral artery. Central venous access was not placed in the normal volunteers and precluded measurements of cardiac output. Leg blood flow also was determined by bolus dye dilution.[7] This entailed injection of a 5-mg bolus of indocyanine green dye into the femoral artery as blood was being aspirated from the femoral vein through a spectrophotometer (Fig. 1). The depreciation of the spectrophotometric measurement then reflected extremity perfusion as quantitated by a pediatric cardiac output computer and confirmed graphically (Lyons Medical Instruments Corp., Van Nuys, CA). The values for leg blood flow by this method were similar to results reported for age- and size-matched normals by the continuous-infusion dye dilution method[8] and for normals and patients with severely burned legs determined by plethysmograph.[9] Leg volume was assessed by the integration of several circumference measurements at 5-cm intervals with the length of the calf, thigh, and foot.

After baseline protocol measurements and blood sampling, propranolol was administered for 2 hours intravenously at 8 μg/kg/minute in the burn patients and at 5 μg/kg/minute in the healthy volunteers. These amounts

TABLE 2. *Hemodynamic Alterations for Both Patient Groups and Their Response to Propranolol*

| | Controls | | Burn Patients | |
|---|---|---|---|---|
| Hemodynamics | Basal | Propranolol | Basal | Propranolol |
| Heart rate (beats/min) | 57 ± 2 | 47 ± 1† | 134 ± 4* | 101 ± 4† |
| Mean arterial pressure (mmHg) | 103 ± 6 | 100 ± 3 | 91 ± 3 | 82 ± 2 |
| Leg blood flows (mL/min) | 3.3 ± 0.5 | 3.3 ± 0.6 | 10.9 ± 1.6* | 8.5 ± 1.3† |
| Leg vascular resistance (torr/mL/min) | 32.4 ± 4.5 | 31.7 ± 5.9 | 8.4 ± 1.1* | 9.7 ± 1.1† |
| Cardiac index (L/min/$m^2$) (normal range, 2.4–4.8) | | | 6.3 ± 0.3 | 5.0 ± 0.1† |

Mean ± SEM.
Leg measurements standardized for 100-mL leg volume.

* $p < 0.05$ compared to basal controls (Student's independent t test).
† $p < 0.05$ compared to group basal (Student's paired t test).

had been determined previously to reduce heart rate by approximately 20% for each group by completion of the infusion. After 2 hours of propranolol infusion, measurements of cardiac output, leg blood flow, indirect calorimetry, and blood sampling were repeated. Blood samples were analyzed for concentrations of glucose and lactate (Beckman Instruments Auto Analyzer, Fullerton, CA). Plasma catecholamine levels were quantitated by radioimmunoassays at an independent laboratory (SmithKline Beecham Clinical Laboratories, Van Nuys, CA). In the burn patients, urine was collected from an indwelling Foley catheter. All voided urine was collected from the volunteers. Total urinary nitrogen was determined with an Erba nitrogen analyzer (Carlo Erba Instrumentation, Rodono, Italy).

### *Calculations*

Extremity vascular resistance was derived from leg blood flow and pressure measurements. Blood flow was standardized for 100-mL leg volume.

LVR = 80 (MAP—MVP) LBF

Where: LVR = leg vascular resistance (dynes sec/cm$^5$ m$^2$ 100 mL)

MAP, MVP = mean arterial, venous pressures (mmHg)

LBF = leg blood flow (L/minute 100 mL)

Net balance for lactate and glucose was also standardized for leg volume.

NB = LBF ([ART]—[VEN])

Where: NB = net balance (mmol/L/minute 100 mL)

LBF = leg blood flow (L/minute 100 mL)

[ART] [VEN] = arterial, venous concentrations (mmol/L)

A negative net balance then reflects net release of lactate or glucose from the limb.

Student's independent t test was used for statistical comparison between patient groups, while the Student's paired t test was used to assess variations within each group between basal and beta adrenergic blockade. Results were presented as mean ± SEM and $p < 0.05$ was accepted as significant.

## Results

Volunteers were well matched for size and age with the burn patients and all the subjects studied were male (Table 1). The burn injury was both extensive (65% ± 7% mean total burn surface area) and severe (45% ± 11% full-thickness burn). There was, however, a wide range in the extent of burn involving the studied leg (range of percentage of burned leg: 10% to 98%). Multiple regression analysis failed to correlate any relationship between the percentage of leg burned to the extremity blood flow or to lactate or glucose net balance. Combined early excision of the burn wound and the use of available unburned area for donor site resulted in the vast majority of the extremity studied being an open wound. This resulted in legs with open wounds of similar size and appears to have minimized any potential differences due to variations in the percentage of leg burned.[10]

The burn patients were extremely hyperdynamic, as demonstrated by basal heart rates greater than 130 and a twice-normal elevation in cardiac index. The heightened cardiac performance combined with the reduced vascular resistance of the leg produced a significant elevation in extremity perfusion (Table 2). Propranolol (8 μg/kg/minute, 2-hour intravenous infusion) lowered the heart rate by 25% ($p < 0.05$) and significantly reduced the cardiac index (Table 2). Furthermore propranolol altered extremity perfusion with an increase in leg vascular resistance and a decrease in leg blood flow. In contrast, while the propranolol infusion (5 μg/kg/minute, 2 hours) in the normal volunteers reduced the resting heart rate by 18% ($p < 0.05$), it failed to alter leg blood flow or vascular

TABLE 3. *Alterations in Lactate and Glucose Metabolism for Both Patient Groups and Their Response to Propranolol*

| Lactate/Glucose Metabolism | Controls | | Burned Patients | |
|---|---|---|---|---|
| | Basal | Propranolol | Basal | Propranolol |
| Lactate (mmol/L) | | | | |
| Arterial | 0.80 ± 0.04 | 0.69 ± 0.04† | 1.79 ± 0.28* | 1.43 ± 0.24† |
| Venous | 0.90 ± 0.04 | 0.78 ± 0.05† | 2.11 ± 0.30* | 1.78 ± 0.28† |
| Lactate net balance (mmol/min) | −0.29 ± 0.15 | −0.21 ± 0.16 | −3.92 ± 1.58* | −3.07 ± 0.80 |
| Glucose (mg/dL) | | | | |
| Arterial | 80 ± 2 | 79 ± 3 | 104 ± 6* | 97 ± 5 |
| Venous | 79 ± 1 | 78 ± 2 | 103 ± 5* | 97 ± 7 |
| Glucose net balance (mg/min) | 0.2 ± 0.4 | 1.3 ± 0.6 | 0.8 ± 1.7 | 0.1 ± 2.2 |

Mean ± SEM.
Net balance measurements standardized for 100-mL leg volume.

* $p < 0.05$ compared to basal controls (Student's independent t test).
† $p < 0.05$ compared to group basal (Student's paired t test).

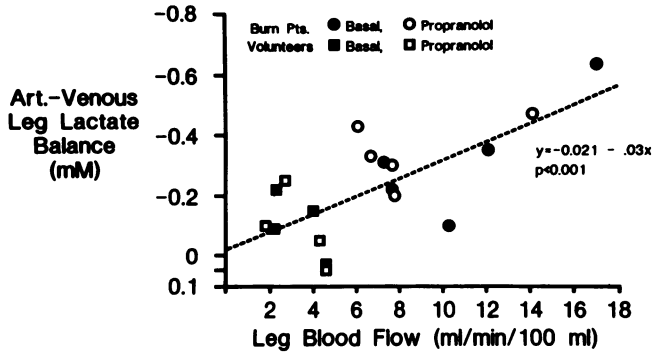


FIG. 2. Relationship of leg blood flow to lactate balance across the leg.

resistance (Table 2). The disparate dosage of propranolol between patient groups did produce similar percentage reductions in heart rate. Continuous telemetry during the propranolol infusion did not identify any cardiac arrhythmias other than sinus bradycardia in the healthy volunteers.

Both arterial and venous plasma lactate concentrations from the burn patients were elevated significantly above the lactate levels in the healthy volunteers (Table 3). Plasma samples obtained after the propranolol infusion demonstrated a significant reduction in lactate levels for both arterial and venous samples and in both groups. Also the net release of lactate from the leg was significantly greater from the burned extremities compared to the normal legs. Beta adrenergic blockade resulted in only an insignificant decrease in the negative net balance of lactate from the leg for both burned patients and controls (Table 2). Furthermore the increase in extremity blood flow correlated with an increasing arterial, venous concentration gradient for lactate across the leg ($p < 0.001$) (Fig. 2). This correlation was valid for both the burn patients and the normal controls and during basal and propranolol therapy. Common with severe burns, plasma glucose concentrations were greater in the burn patients[11]; however propranolol had no significant effect on plasma glucose concentrations or on the net balance of glucose across the leg (Table 3). This suggests that the alterations in lactate with beta adrenergic blockade are not a consequence of changes in glucose homeostasis.

The fasting burn patients were hypermetabolic when studied 2 weeks after injury, with resting energy expenditures nearly 40% greater than predicted for normals by the Harris Benedict formula ($p < 0.05$). These patients also had significantly greater urinary nitrogen loss than the controls (Table 4). Neither of these parameters in either burn patients or volunteers changed with the beta adrenergic blockade. Indirect calorimetry demonstrated higher oxygen consumption for the burn patients while the fasting respiratory quotient was similar for both the burn and control subjects. Propranolol had no effect on the oxygen consumption or the respiratory quotient (Table 4). Plasma levels of epinephrine and norepinephrine in the burn patients were more than double both the normal range and the control group ($p < 0.05$). The plasma concentration of norepinephrine was not effected by propranolol in either group. While there was an insignificant increase for the volunteers, propranolol significantly increased the epinephrine levels for the burn patients (Table 5).

## Discussion

Burn injury results in increased levels of catecholamines, which then are partially responsible for the tachycardia and increased cardiac index observed after burns.[1] This experiment demonstrated that leg blood flow also was increased after burns and is due not only to an accelerated cardiac performance but also to the diminished vascular resistance from beta adrenergic vasodilatation. Beta adrenergic blockade blunted the postburn hyperdynamics with significant reductions in cardiac index with a concomitant increase in vascular resistance.

TABLE 4. *Measurements of Energy Expenditure and Urinary Nitrogen for Both Patient Groups and Their Response to Propranolol*

| | Controls | | Burn Patients | |
|---|---|---|---|---|
| Metabolic Rate | Basal | Propanolol | Basal | Propranolol |
| Resting energy expendiure REE/m$^2$ | 866 ± 35 | 932 ± 28 | 1289 ± 137* | 1278 ± 95 |
| % REE/predicted REE‡ | 0.91 ± 0.04 | 1.03 ± 0.02 | 1.39 ± 0.16* | 1.38 ± 0.12 |
| Oxygen consumption (mL/kg min) | 3.32 ± 0.16 | 3.48 ± 0.28 | 4.96 ± 0.61† | 5.10 ± 0.59 |
| Respiratory quotient | 0.82 ± 0.01 | 0.81 ± 0.01 | 0.80 ± 0.01 | 0.79 ± 0.02 |
| Urinary nitrogen (g/d) | 9.5 ± 2.6 | 9.9 ± 32 | 33.1 ± 1.0* | 27.6 ± 1.7 |
| No. days study after burn | | | 15 ± 1.2 | |

Mean ± SEM
* $p < 0.05$ compared to basal controls.
† $p = 0.05$.
‡ Predicted REE calculated from Harris–Benedict equation.
REE, resting energy expenditure.

TABLE 5. *Catecholamine Levels for Both Patient Groups and Their Response to Propranolol*

| Catecholamine Levels | Controls | | Burn Patients | |
|---|---|---|---|---|
| | Basal | Propranolol | Basal | Propranolol |
| Norepinephrine (pg/mL) (normal range, 110–410) | 302 ± 21 | 280 ± 54 | 1009 ± 145* | 814 ± 152 |
| Epinephrine (pg/mL) (normal range < 50) | 61 ± 31 | 76 ± 16 | 133 ± 17* | 207 ± 4† |

Mean ± SEM.
* $p < 0.05$ compared to basal controls.
† $p < 0.05$ compared to group basal.

These alterations in hemodynamics resulted in a diminished leg blood flow, yet despite this reduction in extremity perfusion, urinary nitrogen excretion and the net balance of lactate from the leg were not affected by the beta adrenergic blockade.

By reducing extremity perfusion, beta blockade eventually may increase catabolism. While urinary nitrogen excretion was not acutely affected in this study, a prolonged reduction in peripheral perfusion with repeated administration of propranolol may explain the increase in urea production seen with chronic beta blockade reported by Herndon et al.[5] We suggest that propranolol reduces peripheral perfusion during stress physiology by a combination of reducing cardiac index and by increasing vascular resistance. This corroborates a Scandinavian study in which intra-arterial infusion of adrenaline into the femoral artery of healthy volunteers doubled extremity blood flow *via* a decrease in leg vascular resistance.[8] Beta blockade before the adrenaline infusion obviated any change in leg vascular resistance or blood flow. These studies suggest that the elevation in catecholamines observed after injury mediates peripheral vasodilatation, which augments extremity perfusion. This selective increase in epinephrine levels with beta adrenergic blockade previously was reported for healthy controls by an undetermined mechanism.[12] In contrast Aulick et al.[10] demonstrated with venous plethysmography that blood flow in the unburned leg of otherwise severely burned patients was similar to normal controls. Assuming that the systemic catecholamines were effecting equally the vascular resistance of both the burned and unburned extremities, then the presence of the wound appears to be essential for the catecholamine-mediated decrease in leg vascular resistance. Because the patients in this study had open leg wounds of similar magnitude, the importance of the wound in determining leg blood flow and the sensitivity of the vasculature to catecholamines cannot be addressed.

This experiment also addresses the effects of the postburn hyperdynamic hypermetabolism on lactate kinetics. If it is assumed that increases in lactate production are related to the acceleration of anaerobic glycolysis after thermal injury, then a decrease in peripheral perfusion will increase lactate production. Because this study demonstrated the opposite, *i.e.*, that increased extremity blood flow is related to an increased net release of lactate from the leg, the supposition that lactate production is related inversely to the availability of oxygen for continued aerobic glycolysis appears unlikely. Also, while beta blockade significantly reduced cardiac index and plasma lactate in this study, whole-body oxygen consumption remained unchanged. This correlates with the findings of Wilmore et al.,[9] who observed that leg blood flow and lactate production correlated with the extent of the leg wound but was not associated with any changes in limb oxygen consumption. It is plausible, though, that a stimulated rate of glycolysis results in excess pyruvate production (as shown by Wolfe, et al.[13]) in quantities greater than can be consumed by the pyruvate dehydrogenase (PDH) enzyme complex. As a consequence excess pyruvate is shunted to lactate resulting in higher plasma lactate concentrations. Elevations in the rate of glycolysis after burns have been well documented with the result that pyruvate production is accelerated.[14,15] Furthermore recent animal studies have identified alterations in the PDH enzyme complex during bacteremia resulting in a decrease in pyruvate oxidation.[16,17] If the efficiency of this enzyme complex also is decreased after burns, additional shunting of pyruvate to lactate would occur.

In this study beta blockade significantly lowered the plasma lactate concentrations both in healthy men and in postburn patients. Wolfe et al.[15] demonstrated that the glycolytic-gluconeogenic cycling was not altered by propranolol in burn patients and implied that beta blockade does not lower lactate levels by decreasing the production of pyruvate. However that same study did show that the accelerated rate of lipolysis after thermal injury was reduced significantly by propranolol. Kaiser et al.[18] suggested that accelerated fat oxidation results in increased production of acetyl CoA and citrate. Accumulation of acetyl CoA then may retard pyruvate oxidation by inhibiting PDH. Propranolol thus appears to decrease the percentage of acetyl CoA formed by fat oxidation and results in increased pyruvate oxidation. Therefore beta blockade may diminish lactate production by inhibiting lipolysis.

This experiment, however, did not identify a significant increase in the respiratory quotient with propranolol administration coincident with the decrease in lactate. This lack of effect on respiratory quotient, despite the inhibition of lipolysis, can be explained by noting that the increased triglyceride, fatty acid cycling in burn patients results in a great excess of lipolysis relative to the concentration of fatty acids required for oxidation. Even in healthy volunteers, 70% of the free fatty acids generated by lipolysis are re-esterified.[19] As a consequence lipolysis can be significantly reduced without greatly affecting the respiratory quotient and reiterates that glucose availability, and not the availability of fatty acid, is the predominant determinant of the respiratory quotient.

The clinical significance of this study demonstrates that propranolol can blunt the cardiac and peripheral vascular response associated with postburn hypermetabolism. These reductions in cardiac performance and peripheral perfusion correlated with reduced lactate production and lower blood lactate concentrations. If these effects can be sustained without adverse consequences on energy expenditure or protein metabolism, beta adrenergic blockade may indeed warrant a clinical application in treating severely burned patients.

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### Discussions

Dr. Gil Ward (Miami, Florida): I rise to ask the heretical philosophical question: Why do you want to change the metabolic response? Are you sure an increased cardiac output, a decreased peripheral resistance, and an increased lactate production are bad?

The metabolic rate is unquestionably elevated, and to date we only know its consequence, not its absolute cause. I have always been uncomfortable attempting to blunt a physiologic response until I am certain the response is detrimental to the patient. And herein lies the conundrum. What is normal for an abnormal circumstance?

I am not suggesting we should avoid putting out physiologic fires. But in similar sense, we should not avoid allowing a physiologic break fire.

I have three questions, the first regarding technique and model. Why do the authors think an excised burn wound or an open donor site are equivalent to nonexcised burn wounds?

My experience is that patients with clean, open, excised wounds and donor sites are better and on the road to recovery, acting well when compared to patients with wounds partially unexcised at a 2-week post-injury period.

Second at 2 weeks after injury, a 65% total body surface area burn is well into a period of septic complications and influences. What was the condition of these burn patients regarding sepsis at the time of study?

And, third, if the amount of lactate production is truly dependent on the burn wound size, in artificially reducing its production by pharmacologic manipulation, might you be shutting off the only metabolic means by which the injured tissue can survive?

Dr. Basil Pruitt (San Antonio, Texas): I would like to compliment Dr. Gore and his colleagues on this study, which extends their earlier observations on the hemodynamic and metabolic response of burn patients to beta adrenergic blockade.

Although the authors found that propanolol infusion exerted no statistically significant effect on net glucose balance in the limbs studied, it