Small-Volume Resuscitation Using Hypertonic Saline Improves Organ Perfusion in Burned Rats

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Resuscitation using small volumes (3–5 mL/kg) of 7.5% hypertonic saline (HTS) is effective for hemorrhagic shock. Whether HTS is beneficial for the initial resuscitation of burn injury is not clear. We compared the hemodynamic effects of HTS versus lactated Ringer's solution (LR) and examined organ tissue perfusion during burn resuscitation (R). Full thickness scald burn (35% of total body surface area) was induced in pentobarbital-anesthetized rats. Regional blood flows were measured using radioactive microspheres before and 30 min after burn, and after R with either HTS (4 mL/kg) or LR (at a dose required for equivalent restoration of arterial blood pressure). Data from the HTS- or LR-resuscitated groups were compared to those from a nonresuscitated group (n = 10 in each group). Mean arterial pressure decreased 30% after burn (from 120 ± 4 to 84 ± 5 mm Hg, mean ± SEM) and returned toward baseline (112 ± 7 mm Hg) at 10 min after R with HTS (4 mL/kg) or LR (22.6 ± 0.7 mL/kg), but subsequently decreased to 100 ± 7 mm Hg with HTS and 105 ± 5 mm Hg with LR at 30 min. In contrast to LR, resuscitation using HTS was associated with tachycardia. Blood flows to the skin and muscle of the normal or burn regions did not change after fluid resuscitation as compared to a nonresuscitated group. Fluid resuscitation transiently increased intestinal perfusion. Similar improvements in blood flow to the spleen were observed with HTS and LR at 10 min after R (from 128 ± 10 to 156 ± 15 and from 113 ± 10 to 145 ± 26 mL · min^{-1} · 100 g^{-1}, respectively). However, at 30 min after R, splenic perfusion in the LR group was not different from that in the nonresuscitated group. Blood flows to the brain and kidney increased 39% and 42%, respectively, with HTS. HTS was also associated with pronounced improvements in blood flows to the heart (from 346 ± 20 to 631 ± 37 mL · min^{-1} · 100 g^{-1}), liver (from 36 ± 2 to 62 ± 4 mL · min^{-1} · 100 g^{-1}), and testis (from 29 ± 2 to 43 ± 2 mL · min^{-1} · 100 g^{-1}). Resuscitation using HTS was associated with rapid improvement in organ tissue perfusion in anesthetized rats subjected to burn injury. In comparison to LR, greater increases in blood flows to the heart, kidney, liver, and testis were observed with HTS. The results suggest that significant improvement in blood flow distribution can be achieved using HTS at less than one fifth the volume of LR for the initial treatment of burn shock.

(Anesth Analg 1996;83:782–8)

Burn injury is associated with an increase in microvascular permeability leading to a loss in plasma fluid to the interstitial compartment and edema formation (1). When resuscitation is delayed, recovery can be complicated by sepsis and multiple organ failure secondary to prolonged tissue hypoxia and reperfusion injury (2). Resuscitation of burn shock should be prompt and effective in restoring normal tissue oxygenation to minimize complications and improve outcome.

Recent studies have shown that resuscitation using small volumes of 7.5% hypertonic saline (HTS) is effective for various types of shock. In the presence of endotoxic shock, HTS normalized plasma volume and augmented cardiac performance, and rapidly restored oxygen transport and regional blood flows (3,4). After hemorrhagic shock, HTS resuscitation significantly increased arterial blood pressure and cardiac output 2–5 minutes after the onset of infusion, decreased systemic vascular resistance, and augmented cardiac performance (5–8). In addition to increased perfusion pressure and vascular dilation, the ability of HTS to reverse the shock-induced endothelial swelling also contributed to the rapid restoration of organ tissue perfusion (9). Immediately after administration, the plasma volume increased by 2–4 mL for each milliliter of HTS infused because of the fluid mobilization secondary to increased osmotic pressure in the vascular compartment (10). Whether this fluid flux can counterbalance the loss of plasma volume and contribute to

Supported in part by the Davis Anesthesia Foundation.
Accepted for publication June 7, 1996.
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0003-2999/96/$5.00

the normalization of circulatory function during burn shock is not clear.

Previous studies on burn injury have not examined whether blood flow distribution is normalized after HTS resuscitation. We evaluated the efficacy of HTS as an initial resuscitative agent by comparing the hemodynamic effects of HTS versus lactated Ringer's solution (LR). Blood flow distribution was measured using a radioactive microsphere technique to test the hypothesis that small-volume resuscitation of burn shock using HTS can effectively restore organ tissue perfusion.

Methods

This study was approved by our institutional committee on the care and use of laboratory animals.

Male adult Sprague-Dawley rats (394–472 g, mean 427 ± 21 g) were anesthetized with sodium pentobarbital (60 mg/kg, intraperitoneally). Rectal temperature was maintained at 37.0 ± 0.5°C using a heating lamp. Body hair on the neck, back, and left groin was closely shaved. The right carotid artery was dissected and cannulated using a polyethylene catheter (PE-50). This catheter was connected to a strain gauge (23 dB; Statham Instruments, Hato Rey, Puerto Rico) for pressure monitoring. The catheter tip was advanced into the left ventricle (LV) and its position confirmed by observation of the LV pressure waveform. Additional catheters were inserted in the left femoral artery for arterial blood pressure measurement and sampling, and in the left femoral vein for infusion. Respiratory rate was obtained by observing the chest movement. All animals were given heparin 5 mg/kg. Arterial blood samples were taken for measurements of blood gas tensions, pH (Corning 170, pH-blood gas analyzer; Ciba Corning Diagnostics Corp., Medfield, MA), and hematocrit.

Regional blood flow was measured using a radioactive microsphere technique. For each measurement approximately 300,000 microspheres (DuPont, Wilmington, DE) 15 μm in diameter and labeled with ^{141}Ce, ^{85}Sr, ^{95}Nb, or ^{103}Ru, suspended in 0.2 mL of normal saline containing 0.01% Tween 80 were injected into the left ventricle. The microsphere suspension was ultrasonically and mechanically mixed to disperse aggregation prior to injection. The microspheres were injected over 20 s and the LV catheter was flushed with 0.4 mL of normal saline. A reference blood sample was withdrawn from the femoral artery catheter starting 5 s before the microsphere injection and continued for 60 s at a constant rate of 0.6 mL/min using a Harvard withdrawing pump. The order of radioisotopes was selected in a randomized fashion to eliminate systematic error on the results.

Ten minutes after catheterization, hemodynamic measurements, blood gas analyses, and blood flow determinations were obtained for baseline data. Prior to burn, anesthesia was deepened using 3% halothane in oxygen via mask for 30 s to avoid any discomfort caused by burn injury. Full thickness skin burn was induced by immersing the dorsal area in 90°C water for 15 s using a template device. This device was constructed from a piece of wood 2.5 cm in thickness with an oval, beveled cut opening that was lined with thick, soft rubber to provide a watertight seal. The device was water sealed to float on the water surface and its thickness provided excellent insulation to the nonburn area. The animal showed no evidence of distress upon immersion. The burn area was quickly dried after immersion. Hemodynamic measurements were repeated 30 min after immersion.

The rats were divided into three groups (n = 10 for each group): 1) HTS (4 mL/kg); 2) LR (at a dose that provided equal restoration of blood pressure to HTS); 3) control (no fluid resuscitation). Fluid was administered over 4 min in Groups 1 and 2. Whereas the animals in the control group were assigned randomly, the animals in the HTS group were studied prior to the LR group for the establishment of blood pressure end point. Hemodynamic measurements were obtained at 10 and 30 min after fluid resuscitation, and at equal points in time in the control group. Arterial blood was sampled before each blood flow measurement for blood gas analysis. An equal amount of normal saline was given to replace the volume loss. At the end of the experiment, the rats were killed by intravenous injections of sodium pentobarbital followed by KCl. The position of the LV catheter was verified at autopsy. The sampled organs were removed, sectioned, and weighed in counting vials. Samples were taken from the internal oblique and pectoralis muscles to represent the burn and normal muscles, respectively. Radioactivity of samples was counted using a multichannel pulse-height analyzer.

Regional blood flows were calculated from the ratios of radioactive counts of measured samples to those of reference blood samples and were expressed in milliliters per minute per 100 g. Heart rate (HR) was obtained from the arterial pressure tracing. The LV rate-pressure product, obtained by multiplying HR to LV systolic pressure, was used as an index of LV oxygen demand. Animals with a difference in blood flow between the left and right kidneys of greater than 10%, indicating nonuniform distribution of microspheres, were excluded from analysis. Data are expressed as mean ± SEM. Statistical analysis included analysis of variance for repeated measures followed by the Student-Newman-Keuls test for multiple comparison between groups. Difference was considered significant at probability less than 0.05.

Results

Four rats in the control group and two rats in the LR group died before completion of the study. One rat had a nonuniform distribution of microspheres between the two kidneys and was not included in the analysis. Additional rats were used for replacement to achieve equal *n* values for each group. Burn area was estimated at 35% of total body surface area. Thirty minutes after burn, all animals developed hypotension. Mean arterial blood pressure (MAP) decreased from 120 ± 4 to 84 ± 5 mm Hg without significant changes in HR. Hypertonic saline increased MAP from 84 ± 5 to 112 ± 3 mm Hg measured at 10 min after infusion. HR increased significantly at 30 min, whereas MAP decreased to 100 ± 7 mm Hg and was not statistically different from that of the nonresuscitated control group. A significantly larger volume of LR (22.6 ± 0.7 mL/kg) was required for equal restoration of MAP to HTS. At 30 min after resuscitation, MAP in the LR group remained significantly greater as compared to the control group. Respiratory rate increased significantly in all rats after burn. Resuscitation using HTS was associated with lower respiratory rate as compared to control. Left ventricular rate-pressure product decreased significantly after burn and returned toward baseline in rats resuscitated with LR. This index of LV oxygen demand increased significantly from the burn level during 30 min after HTS infusion. Rats with no resuscitation demonstrated a sustained decrease in LV oxygen demand (Figure 1).

Arterial blood gas data are shown in Table 1. In nonresuscitated rats, changes included increases in pH and Po_2, and decreases in Pco_2 and HCO^-_3. Resuscitation with either fluid prevented the increase in pH and maintained Po_2 and Pco_2 at burn level. Hemoconcentration increased after burn and returned toward baseline with HTS resuscitation. At 30 min after resuscitation, HTS was associated with lower HCO^-_3 and hematocrit as compared to LR.

Blood flows to vital organs are shown in Figure 2. Cerebral blood flow decreased approximately 30% during burn shock and remained at this level in the control group. A significant improvement in cerebral blood flow was observed at 10 min after resuscitation with either HTS or LR as compared to the control group. At 30 min, cerebral blood flow was significantly less than baseline in all groups; however, a greater cerebral perfusion was observed in the HTS group as compared to the control group. Whereas myocardial blood flow was significantly improved in the resuscitated groups, it was greater than baseline at 10 min after HTS. At 30 min myocardial blood flow returned toward baseline in HTS group, but was less than baseline values in the group resuscitated with LR. Burn shock significantly decreased renal blood flow in all groups. Hypertonic saline failed to restore

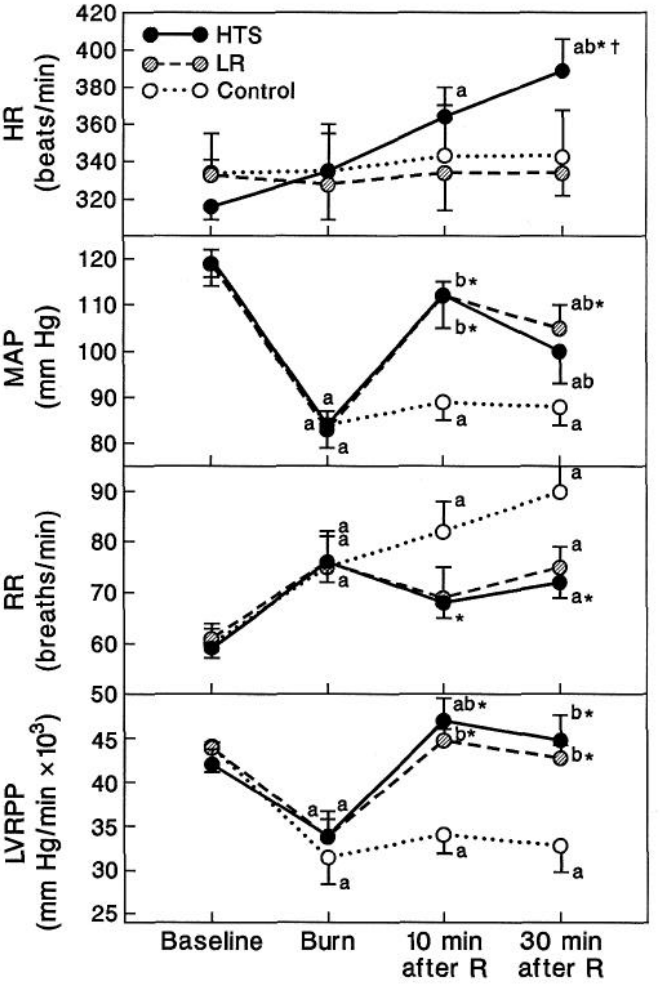

Figure 1. Effects of resuscitation (R) using either hypertonic saline (HTS) or lactated Ringer's solution (LR) on heart rate (HR), mean arterial pressure (MAP), respiratory rate (RR), and left ventricular rate-pressure product (LVRPP). R using HTS is accompanied by increases in HR and LVRPP. Values are mean ± SEM of 10 rats. [a] $P <$ 0.05 compared to baseline; [b] $P < 0.05$ compared to burn; *$P < 0.05$ compared to nonresuscitated control, †$P < 0.05$ compared to LR.

renal blood flow to baseline, but provided a transient improvement in kidney perfusion. LR had no effect on the decrease in renal blood flow secondary to burn.

As compared to LR, HTS significantly increased hepatic arterial and testicular blood flows. Arterial blood flow to the liver exceeded the baseline at 10 min and returned to baseline at 30 min after HTS. Testicular blood flow was transiently restored by HTS; it returned toward the burn level at 30 min and remained significantly greater than those measured in the control or LR group. Resuscitation failed to restore blood flow to the spleen, but greater splenic perfusion was observed with HTS as compared to the control group. Intestinal blood flow increased transiently after resuscitation with either HTS or LR (Figure 3).

Blood flow to the skin decreased 90% in the burn region, whereas it decreased 50% in the normal region.

Table 1. Arterial Blood Gas Values in Resuscitated and Nonresuscitated Rats

	Baseline	Burn	10 min after R	30 min after R
pH				
HTS	7.36 ± 0.01	7.40 ± 0.01	7.37 ± 0.01*	7.33 ± 0.04*
LR	7.37 ± 0.02	7.40 ± 0.02	7.37 ± 0.01*	7.39 ± 0.01*
Control	7.38 ± 0.01	7.42 ± 0.02	7.44 ± 0.02†	7.45 ± 0.01†
Po_2 (mm Hg)				
HTS	79.6 ± 2.2	93.7 ± 7.8	103.2 ± 7.8†	97.4 ± 8.4†
LR	78.1 ± 2.7	94.1 ± 4.0†	93.1 ± 3.9†	95.3 ± 2.7†
Control	78.7 ± 3.9	90.1 ± 6.3	99.0 ± 2.5†	97.5 ± 7.4†
Pco_2 (mm Hg)				
HTS	47.0 ± 2.3	38.0 ± 2.0†	37.5 ± 1.8†	35.1 ± 1.2*†
LR	47.0 ± 1.3	36.0 ± 1.5†	39.5 ± 2.2*†	37.8 ± 1.4*†
Control	45.4 ± 1.4	35.9 ± 2.6†	32.8 ± 2.2†	28.5 ± 2.3†‡
HCO^-_3 (mEq/L)				
HTS	26.5 ± 0.8	23.3 ± 0.8†	21.6 ± 0.7†	19.6 ± 1.2†§
LR	27.0 ± 0.5	22.5 ± 0.6†	22.4 ± 0.6†	22.5 ± 0.4*†
Control	26.7 ± 0.6	22.6 ± 1.0†	21.5 ± 0.9†	19.7 ± 1.6†
Hct (%)				
HTS	43 ± 1	46 ± 2†	43 ± 2*‡	43 ± 2‡§
LR	44 ± 1	49 ± 1†	44 ± 1*‡	47 ± 1†
Control	45 ± 1	48 ± 1†	49 ± 2†	46 ± 1

Values represent the mean ± SEM of 10 rats.
R = resuscitation; HTS = hypertonic saline; LR = lactated Ringer's solution; Hct = hematocrit.
* $P < 0.05$ compared to control; † $P < 0.05$ compared to baseline; ‡ $P < 0.05$ compared to burn; § $P < 0.05$ compared to LR.

Resuscitation with either HTS or LR had little effect on skin perfusion. Burn shock decreased muscle blood flow in the normal region by 28%, but muscle blood flow remained unchanged in the burn region. HTS or LR transiently improved muscle blood flow in the burn region as compared to the control group, but this was not observed in blood flow to normal muscle.

Discussion

Severe burn injury is associated with a plasma volume deficit secondary to increased microvascular permeability. The primary goal of resuscitation for burn injury is to promptly normalize tissue oxygenation by ensuring adequate ventilation and circulating blood volume. Recent reports indicate that small-volume resuscitation using HTS is effective for rapid restoration of organ perfusion in hypovolemic or endotoxic shock (7,11,12); however, the effects of HTS on regional blood flow during burn injury have not been studied. In this investigation, we examined the changes in hemodynamics and blood flow distribution after HTS resuscitation of burned rats.

Significant improvements in perfusion were observed in most measured regions after resuscitation with either fluid, but greater increases in blood flows to the heart, kidney, liver, and testis were observed with HTS, suggesting that a substantial reduction in vascular resistance in these vascular beds was induced by HTS. In hypotensive or normotensive dogs, HTS infusion caused a sudden and sustained increase in coronary blood flow (7,8). The augmented myocardial blood flow associated with HTS infusion was also observed in dogs with β-adrenergic blockade, suggesting that coronary vasodilation was not totally due to increased myocardial metabolic demand. In addition, when HTS was infused directly into canine hearts with HR held constant and at a dose small enough to avoid systemic pressure changes, blood flow measured from a distal coronary vessel increased significantly and returned to baseline after termination of the infusion (unpublished data). These findings confirmed that the increase in myocardial perfusion was due to a direct vasodilator effect of HTS. Recently, Crystal et al. (13) reported a potent direct vasodilation when a 7.5% saline solution was infused directly into the coronary vessel. Similar vasodilator effects after infusion of hypertonic solutions of urea or dextrose were reported by Marshall and Shepherd (14), suggesting that vasodilation was caused by hypertonicity rather than through a specific action of the sodium ion. In addition to vasodilation, plasma volume expansion appeared to be an important contribution to the increase in cardiac output and restoration of organ tissue perfusion. Wolf (10) demonstrated a rapid volume expansion which occurred immediately after hypertonic saline infusion. In animals subjected to hemorrhagic shock, it was estimated that plasma volume increased by 2–4 mL for each milliliter of HTS (15,16). More recently, Mazzoni et al. (9) reported that HTS reduced endothelial swelling and normalized capillary lumenal diameter in hemorrhagic rabbits. The

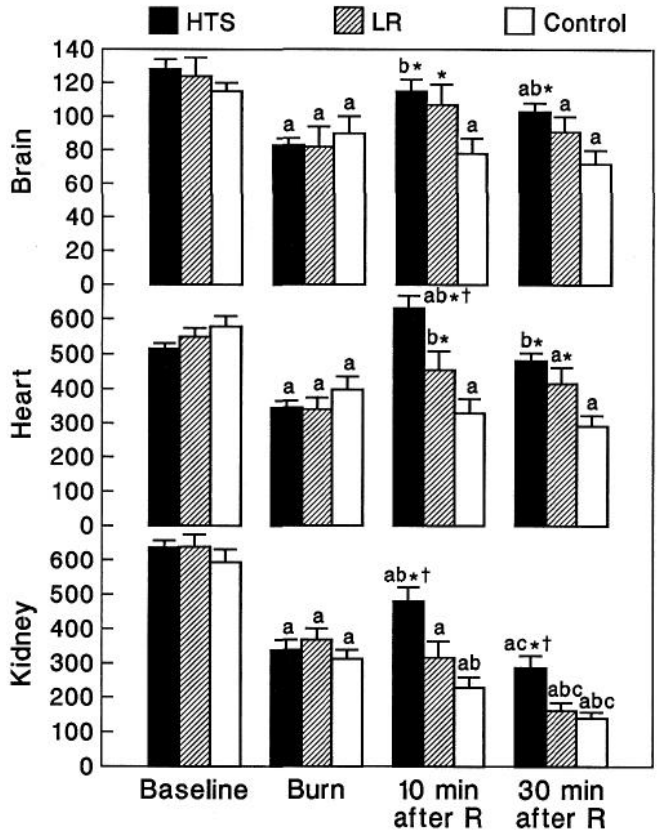

Figure 2. Bar graphs showing blood flows to vital organs after resuscitation (R) with either hypertonic saline (HTS) or lactated Ringer's solution (LR) as compared to nonresuscitated control. Greater improvements in myocardial and renal blood flows are observed after HTS as compared to LR. Values (mL · min^{-1} · 100 g^{-1}) are mean ± SEM of 10 rats. [a] $P < 0.05$ compared to baseline; [b] $P < 0.05$ compared to burn; [c] $P < 0.05$ compared to 10 min after R; * $P < 0.05$ compared to nonresuscitated control; † $P < 0.05$ compared to LR.

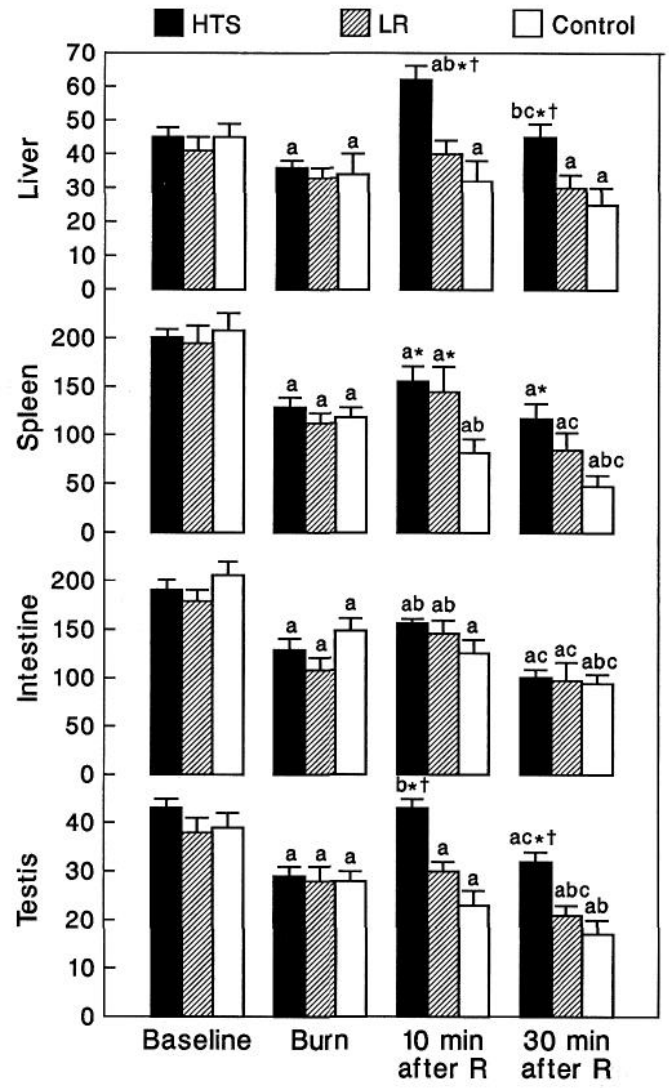

Figure 3. Bar graphs showing organ blood flows measured before and after burn injury and following resuscitation (R) with either hypertonic saline (HTS) or lactated Ringer's solution (LR). A remarkable improvement is observed in blood flow to the liver and testis following HTS. Resuscitation transiently improves blood flow to the intestine. Values (mL · min^{-1} · 100 g^{-1}) are mean ± SEM of 10 rats. [a] $P < 0.05$ compared to baseline; [b] $P < 0.05$ compared to burn; [c] $P < 0.05$ compared to 10 minutes after R; * $P < 0.05$ compared to nonresuscitated control; [+] $P < 0.05$ compared to LR.

results of their study support the postulate that hypertonicity may have a specific ability to restore capillary flow in addition to its benefit on systemic circulation.

Resuscitation with either fluid provided a small and transient improvement in blood flow to the intestine but did not improve peripheral musculocutaneous flow. Our data of blood flows to skin and muscle supported the concept that blood flow was redistributed to the visceral organs at the expense of the muscular and cutaneous beds. Rocha e Silva et al. (17) proposed that HTS caused a selective vasoconstriction in the peripheral bed to shunt blood flow to more vital organs. Although the presence of such vasoconstriction remains to be confirmed, the fact that peripheral perfusion did not improve after resuscitation with either HTS or LR suggests that redistribution of blood flow may not be directly related to HTS. Blood flow measurement using radioactive microspheres may be inaccurate when assessing low-flow regions such as skin and muscle. In the present study, such inaccuracy was limited by injecting a large number of microspheres (300,000) and by sampling large pieces of skin and muscle for radioactive counting to assure that each tissue sample contained at least 400 spheres. Blood flow data in our study were consistent with those reported previously in rats under comparable experimental conditions (18).

Resuscitation using HTS produced a rapid and remarkable recovery of cardiovascular function (5–7); however, the cardiovascular improvement was temporary. In the rats, the effects of hypertonic saline tended to wane by 30 minutes. We limited our observation to this time period during which the differences

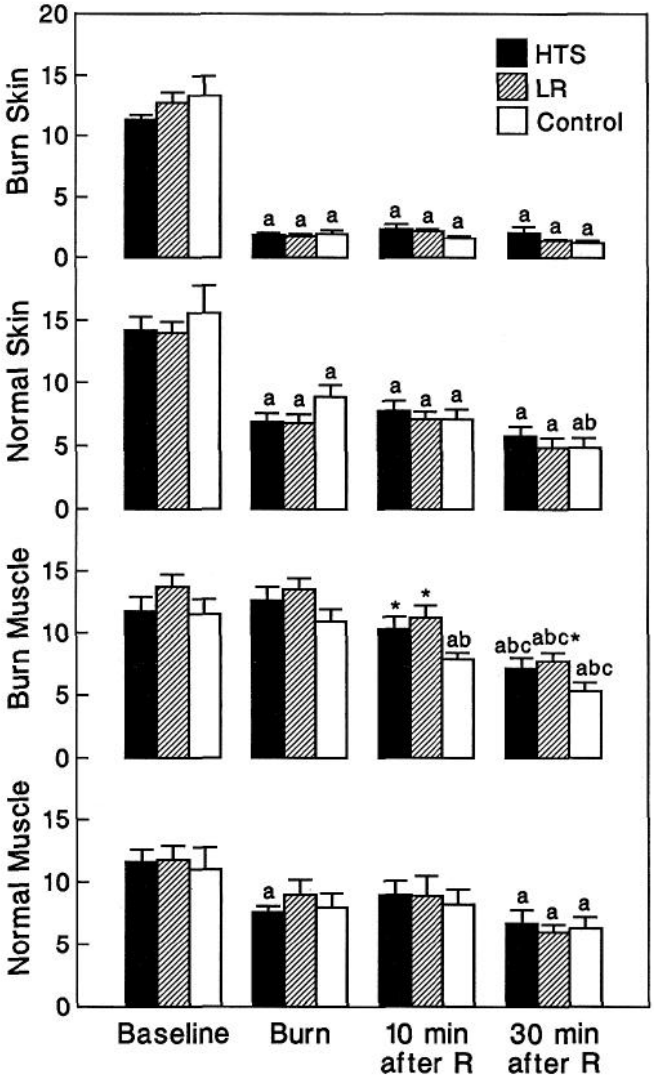

Figure 4. Bar graphs showing blood flows to skin and muscle in the burn or normal region. Except for a small improvement in blood flow to burn muscle, resuscitation (R) using either fluid has no effect on blood flow to these regions. Values (mL · min^{-1} · 100 g^{-1}) are mean ± SEM of 10 rats. [a] $P < 0.05$ compared to baseline; [b] $P < 0.05$ compared to burn; [c] $P < 0.05$ compared to 10 min after R; * $P < 0.05$ compared to nonresuscitated control.

between the two groups occurred. Rats were chosen for this study to limit the enormous cost for radioactive microspheres and disposal of radioactive materials. The small body size and blood volume of this animal species did not permit simultaneous measurement of blood volume and/or assessment of organ function. Additional studies are required to address these issues.

Whether HTS is the fluid of choice for burn resuscitation remains controversial. When infused at a smaller dose and a slower rate, HTS did not restore hemodynamic function in burned rats under experimental conditions similar to ours (19). In burned patients with free water excess during the early postburn period, HTS at low concentration (approximately 1.5%) had no advantage over the conventional resuscitation with LR (20). In contrast, hypertonic solutions have been shown to provide a temporary improvement in cardiovascular function in burned sheep (21), to improve microcirculation and reduce postburn injury in pigs (22), and to enhance cardiac contractile function in burned guinea pigs (23). Hypertonic saline was also reported safe and effective for resuscitation of severely burned children and adults (24,25). Our data suggest that organ perfusion can be temporarily restored after the initial resuscitation of burn using small volumes of HTS. The present study focuses on the immediate effects of HTS; further investigations are necessary to examine the efficacy of additional resuscitative effort after the initial resuscitation using HTS.

In summary, the results of this study indicate that the initial resuscitation of burn shock using HTS provides a rapid and temporary restoration of blood pressure and perfusion of vital organs. This circulatory improvement can be achieved with HTS at less than one fifth the volume of the conventional LR. Small-volume resuscitation using HTS may be particularly beneficial for prehospital management of burns and avoidance of possible complications associated with large-volume resuscitation.

The authors are grateful for the technical assistance of Renae Wurschmidt, Karrie Berg, Scott Lee, and Sherry Loveland in preparing this manuscript.

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