



Randomized Trial of Efficacy of Crystalloid and Colloid Resuscitation on Hemodynamic Response and Lung Water Following Thermal Injury **A**

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To assess the effects of crystalloid and colloid resuscitation on hemodynamic response and on lung water following thermal injury, 79 patients were assigned randomly to receive lactated Ringer's solution or 2.5% albumin-lactated Ringer's solution. Crystalloid-treated patients required more fluid for successful resuscitation than did those receiving colloid solutions (3.81 vs. 2.98 ml/kg body weight/% body surface burn, $p < 0.01$). In study phase 1 (29 patients), cardiac index and myocardial contractility (ejection fraction and mean rate of internal fiber shortening, V_{cf}) were determined by echocardiography during the first 48 hours postburn. Cardiac index was lower in the 12- to 24-hour postburn interval in the crystalloid group, but this difference between treatment groups had disappeared by 48 hours postburn. Ejection fractions were normal throughout the entire study, while V_{cf} was supranormal ($p < 0.01$ vs. normals) and equal in the two resuscitation groups. In study phase 2 (50 patients), extravascular lung water and cardiac index were measured by a standard rebreathing technique at least daily for the first postburn week. Lung water remained unchanged in the crystalloid-treated patients ($p > 0.10$), but progressively increased in the colloid-treated patients over the seven day study ($p < 0.0001$). The measured lung water in each treatment group was significantly different from one another ($p < 0.001$). Cardiac index increased progressively and identically in both treatment groups over the study period ($p < 0.01$). These data refute the existence of myocardial depression during postburn resuscitation and document hypercontractile left ventricular performance. The addition of colloid to crystalloid resuscitation fluids produces no long lasting benefit on total body blood flow, and promotes accumulation of lung water when edema fluid is being reabsorbed from the burn wound.

THERMAL INJURY of sufficient duration and intensity causes coagulation necrosis and cell death in the

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affected tissue. Loss of capillary integrity leads to loss of isotonic fluid from the intravascular space into the tissue surrounding the injury, and in burns exceeding 25% of the total body surface, additional plasma volume may be lost into the unburned tissue.¹ Massive edema may form in the burned tissue, and its severity depends on both the extent and depth of injury and on the volume of infusate. With the loss of intravascular volume, cardiac output, blood pressure, and urinary output fall; if the intravascular volume deficits are of sufficient magnitude and are not replaced, acidosis and hypovolemic shock ensue. The loss of plasma volume is too rapid and too massive in patients with extensive burns to allow effective restoration of the intravascular volume deficit by the translocation of fluid from the interstitial and intracellular compartments.

With adequate fluid resuscitation, the fall in plasma volume and total body blood flow can be limited. Although cardiac output is restored usually to near normal levels during the latter half of the first 24 hours postburn, plasma volume is not restored to normal levels until the end of the second postburn day.² While the net plasma volume deficit is dependent upon the amount of infused resuscitation fluid, the rate of plasma volume loss into the surrounding tissue is not affected by fluid restoration during the first 18 to 24 hours following injury. Subsequently, capillary integrity returns to normal, fluid infusion effectively restores intravascular volume, and cardiac output rises to supranormal levels typical of the early postinjury hypermetabolic response.³ The rate of fluid infusion is dictated by the patient's physiologic response to resuscitation. Animal studies of organ blood flow distribution indicate that the kidney is the most poorly perfused organ following thermal injury.⁴ By implication, when renal function is adequate, other vital

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organs usually are being perfused satisfactorily, and urinary output is the most reliable and readily accessible index of effective resuscitation.

Before the realization that severe thermal injury was associated with massive loss of isotonic fluid into the injured tissues, a syndrome of "burn shock" was described, in which thermally injured patients failed to respond to the then customarily administered quantities of fluid.⁵ Subsequently, the effectiveness of massive quantities of balanced electrolyte solutions in replacing not only the intravascular volume deficit but also that of the entire functional extracellular space was demonstrated,⁶ and the use of such volume replacement has virtually eliminated renal failure and cardiovascular collapse as a cause of early postburn death. The failure of cardiac output to return rapidly to normal following infusion of fluid volumes estimated to be necessary for adequate resuscitation has been ascribed to the presence of a circulating myocardial depressant factor.^{6,7} Myocardial depression also has been postulated to explain the inability of fluid infusions to reestablish organ perfusion in certain categories of burned patients, especially those at either extreme of age.⁸ However, the existence of such a myocardial depressant factor has been proposed on the basis of decreased cardiac output, and this hemodynamic variable does not indicate directly myocardial performance. Direct measurement of left ventricular myocardial contractility during the immediate postburn period has not been reported.

The lung participates in the pathophysiologic alterations associated with large plasma volume losses and administration of large resuscitation volumes following thermal injury. In the absence of inhalation injury, successful resuscitation commonly restores systemic and pulmonary hemodynamic indices to normal, with no subsequent pulmonary complications. Inhalation injury accentuates fluid requirements during resuscitation and predisposes to the development of acute pulmonary edema during the first postburn week.⁹ Early pulmonary edema may occur also in patients with no coexisting inhalation injury or pre-existing cardiovascular disease when edema in the burn wound is being rapidly mobilized during the fourth to the eighth postburn days.

The formulas commonly used to estimate the resuscitation fluid needs of burned patients vary widely in terms of both the volume and composition of the fluids recommended. The majority of patients show a satisfactory clinical response to resuscitation no matter which formula is used to predict fluid requirements. This observation is a reflection of the physiologic tolerance of the patients treated, since the volume dosage and salt dosage of the various formulas for the first 24 hours postburn alone differ by more than twofold. Although

virtually all formulas provide for administration of colloid-containing fluids in the second 24 hours postburn, the recommended colloid-containing fluid for the initial 24 hours postburn ranges from a volume equal to that of electrolyte-containing fluid administered to no colloid-containing fluid at all. As in the case of resuscitation of other trauma patients, controversy exists over whether colloid-containing fluids are necessary, desirable, or even deleterious. Proponents of colloid-containing fluid as a part of initial postburn resuscitation have claimed that inclusion of such solutions reduces the volume of fluid required for resuscitation, maintains urinary output at a higher level than with an equal volume of crystalloid fluid, supports cardiac output, and minimizes loss of fluid into the pulmonary interstitium and other tissues. Conversely, many feel that the immediate postburn increase in capillary permeability permits leakage of blood-borne colloid, and that colloid-containing fluid is retained within the circulation to no greater extent than an equal volume of non-colloid electrolyte solution in the immediate postburn period.¹⁰ That school also considers that colloid-containing fluid has little, if any, effect on cardiac output above that of an equal volume of electrolyte-containing fluid, has no specific beneficial effect in terms of change in lung water volume, and in fact, may be deleterious when given in large amounts.¹¹

To compare the effect of resuscitation solution composition on myocardial performance and lung water following thermal injury, we studied 79 patients who were randomized to receive crystalloid or colloid-containing resuscitation solutions. Our results indicate that the addition of colloid to crystalloid solutions produces no important hemodynamic benefits and is associated with increased accumulation of lung water after the immediate resuscitation. In neither treatment group was any evidence of myocardial depression documented, and in fact, the myocardium was hypercontractile within 12 hours of injury.

Material and Methods

Patient Sample

Seventy-nine thermally injured patients were studied serially after obtaining informed consent for participation in research protocols approved by institutional review (Table 1). Control of resuscitation was obtained within four hours of injury, and all patients were admitted within 12 hours of injury. Patients were assigned by a random numbers table to receive either crystalloid or colloid resuscitation. Patients in the crystalloid arm were given lactated Ringer's solution, and those in the colloid arm were given 2.5 albumin-lactated Ringer's solution. During the first 24 hours, fluid was adminis-

TABLE 1. Patient Characteristics

	Colloid	Crystalloid
Patients	40	39
Age (years)	28 ± 7	28 ± 8
TBSB (%)	53 ± 17	48 ± 12
Resuscitation (ml/kg/% burn)	2.98 ± 1.10	3.81 ± 1.48*

Mean ± SD.

* $p < 0.01$.

TBSB—total body surface burn.

tered at a rate sufficient to stabilize vital signs and to produce a urinary output of 30 to 50 ml/hr. Resuscitation requirements for each treatment group are indicated in Table 1. Plasma volume was replaced on the second postburn day by colloid equivalent to plasma in a dosage of 0.3 to 0.5 ml/kg body weight/% body surface burn. Following the initial 24 hour resuscitation phase, 5% dextrose in water was administered at a rate which allowed each patient's weight to return to preburn levels by postburn day 7 to 10, and which maintained serum sodium and osmolal concentrations in the normal range. No patients had evidence of inhalation injury or other pulmonary disease based on clinical evaluation and on normal fiberoptic bronchoscopy, 133 xenon ventilation-perfusion lung scan, chest roentgenogram, and arterial blood gases. None of the patients demonstrated microbiologic or clinical evidence of pulmonary infection during the seven days of the studies. The patients were studied in two consecutive phases. Echocardiographic indices of myocardial performance were measured in the first 29 patients, and serial changes in lung water following resuscitation were determined in the next 50 patients.

Echocardiography Protocol

Myocardial performance was determined in three designated resuscitation time periods: initial postburn period (0–12 hours), middle postburn period (12–24 hours), and late postburn period (24–48 hours). M-mode echocardiograms were recorded by an Ekoline 20 Ultrasonoscope (Smith Kline Instruments, Sunnyvale, CA) and a 2.25-MHz focused transducer (Model C-11A). The analogue signals were recorded by a rapid response ultraviolet photographic recorder (Model 1858, Honeywell Instruments, Denver, CO). Patients were examined in the supine position, and reproducible comparisons were insured by the consistent placement of the transducer using intracardiac landmarks and assuring transducer orientation to specific cardiac structures.¹² End diastole was defined by the R-wave of the electrocardiogram QRS complex and end systole by the smallest septal-posterior wall endocardial distance. Echocardiograms were digitized on a minicomputer (Model

9830, Hewlett Packard, Inc., Palo Alto, CA), and left ventricular dimensions then were averaged over five beats and used to calculate indices of myocardial performance by standard formulas.¹³ The measurements of left ventricular size and function by M-mode echocardiography correlate very highly with those of cineangiography.¹⁴ Thermodilution cardiac output measurements, using iced 5% dextrose solution, were calculated from the mean of three consecutive measurements. Normal values for echocardiographic indices and cardiac output were obtained courtesy of the Brooke Army Medical Center Cardiac Catheterization and Noninvasive Laboratories.

Lung Water Protocol

Lung water and cardiac output were measured every twelve hours (6:00 am and 6:00 pm) for the first three postburn days and once daily (6:00 am) on postburn days five and seven. Extravascular lung water and cardiac output were determined by a standard rebreathing method, utilizing two gases of differing solubility. Lung tissue volume measured by this method has been shown to reflect with high reliability changes in lung water content in both animals and human subjects with normal and edematous lungs.^{15–19} After several minutes of quiet breathing to become accustomed to the mouthpiece and noseclip, the patient exhaled to residual volume and began breathing into a reservoir bag containing 1.5% dimethyl ether (soluble gas), 7% helium (insoluble gas), 30% oxygen, and balance nitrogen. Six to eight maximal rebreathing maneuvers were carried out for 15 to 20 seconds. The concentrations of each test gas were measured by a time of flight medical mass spectrometer (MGA 1100A, Perkin Elmer Corp., Pomona, CA). Changes in reservoir bag volume were measured with a previously calibrated data acquisition dry spirometer (Model 843, Ohio Instrument Company, Houston, TX). A fiberoptic photographic recorder (Model 1858, Honeywell, Inc.) with a frequency response of 5000 Hz recorded the electrical output of the helium, dimethyl ether, and bag volume signals. The signal tracings and calibration standards were digitized off-line from the photographic paper by a minicomputer (HP 9830), which corrected the raw data for time of passage of gases through the sampling system, for gas consumption by the mass spectrometer (60 ml/min), and for anatomic and apparatus dead space in the first end expiratory volume cycle. The disappearance of the soluble gas was plotted on semilogarithmic paper, so that its slope (pulmonary capillary blood flow) and its time zero intercept (tissue volume) could be calculated. To detect tracer gas recirculation, indicated by a decrease in the logarithmic washout slope, serial least squares lines were calculated through at least three of the first six rebreathing points

and the time zero intercept. The line yielding the best squared correlation coefficient was chosen for subsequent calculations. All measurements were made in duplicate, and intervals of at least five minutes between each study were observed to allow exhalation of any soluble gas that may have accumulated in the body. In order to compare measurements among individuals of different sizes, lung water is expressed as ml/ml alveolar volume for each patient. The normal range in this laboratory is 0.110 to 0.120 ml/ml alveolar volume. In the absence of significant pulmonary shunting, pulmonary capillary blood flow is identical to cardiac output. Thermodilution cardiac outputs were measured in conjunction with the rebreathing measurements in selected patients.

Statistical Analyses

Data describing patient characteristics are reported as mean \pm SD, while experimentally derived data are reported as mean \pm SEM. A one-way analysis of variance was used to examine serial changes of physiologic indices within each treatment group with time. A two-way analysis of variance was used to detect treatment differences between the crystalloid and colloid groups. When physiologic indices of the treatment groups were compared to the reported values for the normal subjects, statistical difference was assessed with a one-tailed test utilizing the *t* distribution.²⁰ Statistical differences with $p < 0.05$ were accepted as significant.

Results

Echocardiographic Protocol

Echocardiographic measurements of myocardial performance were carried out in 29 patients who were randomized to two treatment arms: 15 received colloid-containing fluid and 14 received crystalloid-containing fluid. The mean age and area of total body surface burn were 27 ± 10 years and $58 \pm 20\%$ for patients in the colloid arm and 29 ± 12 years and $55 \pm 21\%$ for the patients in the crystalloid arm. The colloid-treated patients received 3.12 ± 0.93 ml/kg body weight/% body surface burn during the first 24 hours following injury, while the crystalloid-treated patients received 3.94 ± 2.24 ml/kg body weight/% burn. In contrast to the combined data for both protocols (Table 1), the difference in resuscitation requirements between these two treatment groups was not statistically significant because of the large variability of the fluid volume administered to the crystalloid group. Urinary output of the colloid-treated patients was higher than that of the crystalloid-treated patients (65 ± 30 ml/hr vs. 51 ± 22 ml/hr); however, that difference between the two treatment groups dem-

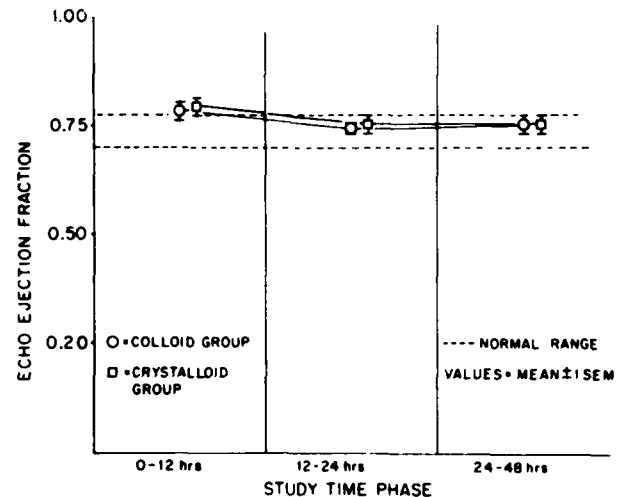


FIG. 1. Left ventricular ejection fraction during postburn fluid resuscitation.

onstrates only a trend toward statistical significance ($p = 0.08$).

Left ventricular ejection indices were measured in three consecutive time intervals. Ejection fractions were normal throughout the entire study (Fig. 1). Ejection fractions of the colloid group for each defined study interval are: 0.78 ± 0.02 , 0.74 ± 0.01 , and 0.75 ± 0.02 . Corresponding values for the crystalloid group are: 0.79 ± 0.02 , 0.75 ± 0.02 , and 0.75 ± 0.02 . The normal echocardiographic ejection fraction is 0.74 ± 0.02 . No statistical differences were evident between treatment groups, across time, or between patient groups and the normal population. The mean rate of internal circum-

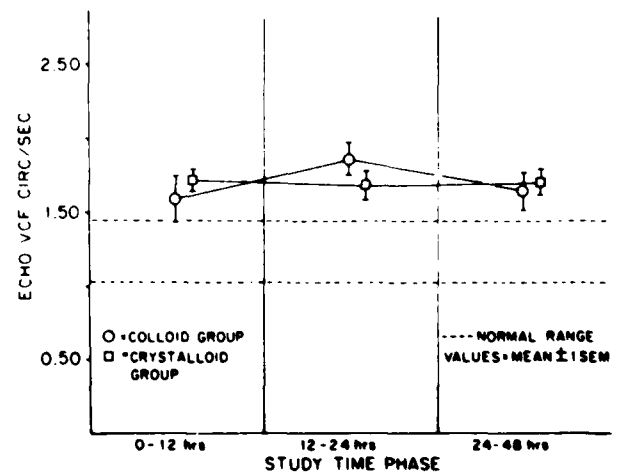


FIG. 2. Left ventricular mean rate of internal fiber shortening during postburn fluid resuscitation. The zone above the normal range reflects increased myocardial contractility, while that below reflects decreased contractility.

TABLE 2. Left Ventricular Volumes during Postburn Resuscitation

Time Period (hr)	Treatment	Thermodilution CI	ECHO CI	EDVI	SI
0-12	Colloid	3.18 ± 0.25	3.05 ± 0.43	42 ± 6	32 ± 5
	Crystalloid	2.59 ± 0.16	3.11 ± 0.21	43 ± 3	34 ± 2
12-24	Colloid	3.97 ± 0.22	4.67 ± 0.27	56 ± 3	40 ± 2
	Crystalloid	2.14 ± 0.12*	2.75 ± 0.25*	36 ± 4*	27 ± 2*
24-48	Colloid	4.17 ± 0.62	4.42 ± 0.13	52 ± 3	39 ± 2
	Crystalloid	3.74 ± 0.45	4.03 ± 0.40	51 ± 4	37 ± 3

Mean ± SEM.

* $p < 0.01$ colloid vs. crystalloid.

CI—cardiac index.

EDVI—end diastolic volume index.

SI—stroke index.

Normal: thermodilution CI = 3.60 ± 0.02 L/min/m².

ECHO CI = 3.40 ± 0.04 L/min/m².

EDVI = 60 ± 3 ml/m².

SI = 44 ± 2 ml/cycle/m².

ferential fiber shortening (V_{cf}) was in the hypercontractile range in both treatment groups (Fig. 2). In the colloid treated patients, V_{cf} was 1.59 ± 0.16 in the 0 to 12-hour interval, 1.86 ± 0.11 in the 12- to 24-hour interval, and 1.64 ± 0.14 in the 24- to 48-hour interval. V_{cf} in the crystalloid group was 1.72 ± 0.08 in the 0 to 12-hour interval, 1.68 ± 0.10 in the 12- to 24-hour interval, and 1.70 ± 0.09 in the 24- to 48-hour interval. Normal V_{cf} is 1.22 ± 0.06 circumference/second (circ/sec). V_{cf} in each treatment group at all time intervals was statistically similar. However, all values for V_{cf} in both treatment groups are increased above normal ($p < 0.05$).

The serial changes in cardiac indices and left ventricular volume during the first 48 postburn hours are listed in Table 2. Patients in the crystalloid-treated group had a significantly lower cardiac index in the 12- to 24-hour period when compared to the colloid treated patients ($p < 0.01$). This decrease in cardiac index was documented by both echocardiographic determinations and thermodilution techniques. However, by 48 hours postburn, this difference had disappeared, and the cardiac indices in both treatment groups had risen significantly above those determined shortly following admission ($p < 0.05$). End diastolic volume index and stroke index in both treatment groups were below normal values in the first study period ($p < 0.05$), indicating an early intravascular volume deficit. In contrast to colloid-treated patients, whose indices returned to normal, end diastolic volume index and stroke index in the crystalloid-treated patients remained significantly depressed in the 12- to 24-hour study interval ($p < 0.01$). These volume indices were obtained simultaneously with the cardiac index measurements and indicate decreased intravascular volume in this time period. However, by 48 hours, these differences between treatment groups had disappeared. Although end diastolic volume index and stroke index in both treatment groups at this time did not differ significantly from predicted normal values, they were

slightly depressed, indicating no evidence of fluid overload.

Lung Water Protocol

In the second phase of this study, 50 patients were randomized consecutively into two treatment groups of 25 patients each to receive either colloid or crystalloid fluid for resuscitation. The patients' mean age was 29 ± 8 years in the colloid group and 27 ± 9 years in the crystalloid group, while their burn sizes were $50 \pm 20\%$ and $43 \pm 12\%$ of the body surface, respectively. Neither characteristic is significantly different between treatment groups. The crystalloid-treated patients received significantly more fluid (3.74 ± 1.28 ml/kg body weight/% burn) than did the colloid-treated patients (2.89 ± 1.27 ml/kg body weight/% burn, $p < 0.01$). By the end of the seven day study, five patients in the colloid-treated group demonstrated roentgenographic evidence of pulmonary edema, as did one patient in the crystalloid-treated group. Eleven patients receiving colloid resuscitation died later during their hospital courses, while three patients treated with crystalloid resuscitation eventually died.

The serial changes in lung water and cardiac index over the seven-day study period are outlined in Table 3 (Fig. 3). Lung water in the colloid-treated patients increased significantly during the first postburn week ($p < 0.0001$). In contrast, lung water in the crystalloid-treated patients did not change significantly during the seven-day study ($p > 0.10$). Measured lung water in each treatment group was statistically different from each other ($p < 0.001$). The effect of resuscitation fluid composition is demonstrated further when lung water is evaluated as a linear function of time postburn by the regression equations $LW(\text{Coll}) = 0.116 + 0.009 \text{ PBD}$, $r^2 = 0.87$, and $LW(\text{Crys}) = 0.128 + 0.003 \text{ PBD}$, $r^2 = 0.43$ (Fig. 4).

TABLE 3. Sequential Changes in Lung Water and Cardiac Index Following Thermal Injury

Treatment	Postburn Day							
	0.5	1.0	1.5	2.0	2.5	3.0	5.0	7.0
Lung water (ml/ml)								
Colloid	0.130 ± 0.007	0.125 ± 0.005	0.120 ± 0.005	0.123 ± 0.006	0.141 ± 0.009	0.145 ± 0.009	0.167 ± 0.011	0.173 ± 0.015
Crystalloid	0.130 ± 0.005	0.123 ± 0.004	0.124 ± 0.006	0.138 ± 0.007	0.138 ± 0.008	0.140 ± 0.007	0.149 ± 0.006	0.137 ± 0.011
Cardiac index (L/min/m ²)								
Colloid	2.23 ± 0.57	2.83 ± 0.32	2.41 ± 0.29	2.48 ± 0.33	2.86 ± 0.43	3.60 ± 0.33	4.12 ± 0.33	5.59 ± 0.49
Crystalloid	2.16 ± 0.22	2.42 ± 0.14	2.29 ± 0.18	2.60 ± 0.22	2.90 ± 0.22	3.64 ± 0.28	4.41 ± 0.25	4.99 ± 0.40

Cardiac indices increased significantly during the seven-day period of study ($p < 0.01$). At no point during this study were significant differences in cardiac index found between treatment groups.

Discussion

All of the patients reported in these studies were in the young adult age group, and none had clinical evidence or a history of heart disease. Coexisting inhalation injury was excluded on the basis of diagnostic criteria having an accuracy of 96%.²¹ In both of these protocols, resuscitation fluid for the first 24 hours consisted of either lactated Ringer's solution or lactated Ringer's solution containing 2.5% albumin (2.5 gm/dl). Volume requirements were estimated as 2 ml/kg body weight/% burn and the actual infusion rate was adjusted to maintain urinary output at 30 to 50 ml/hr. The colloid-treated patients in the overall series required significantly less fluid than did the crystalloid-treated patients. This difference did not approach statistical significance in the smaller group of patients evaluated by the echocardiography protocol, partly because the patients receiving colloid-containing solutions were administered fluid at a rate which exceeded the above mentioned guidelines to resuscitation (65 ml/hr for colloid patients and 51 ml/hr for crystalloid patients).

Noninvasive M-mode echocardiographic assessment of cardiac function revealed that cardiac index in the crystalloid group was significantly lower than that of the colloid group, 2.75 L/min/m² vs. 4.6 L/min/m², in the 12 to 24-postburn-hour interval. Cardiac index in the former group was 81% of predicted normal and was not associated with any clinical evidence of inadequate vital organ function. Cardiac index in the group receiving colloid-containing fluids was 137% of predicted normal, and it is not at all certain that a supranormal cardiac output is of any physiologic benefit during postburn re-

suscitation. Thermodilution cardiac indices were systematically lower but paralleled those determined by echocardiography in all the periods. Both methods confirm that colloid-containing solutions more rapidly restore diminished cardiac output than do crystalloid-containing solutions. However, by the end of the second postburn day, when plasma deficits have been repleted, cardiac indices have returned to high normal levels in both groups.

Assessment of myocardial contractility in the two groups revealed that ejection fraction was identical in both groups at all time periods and did not vary significantly from predicted normal. The mean rate of left ventricular internal fiber shortening (V_{cf}) showed no depression in either group at any measurement time in the first two postburn days. No decrease in V_{cf} was observed even in the group receiving only crystalloid resuscitation in the 12- to 24-hour postburn interval, when cardiac index was decreased. In fact, V_{cf} was supranor-

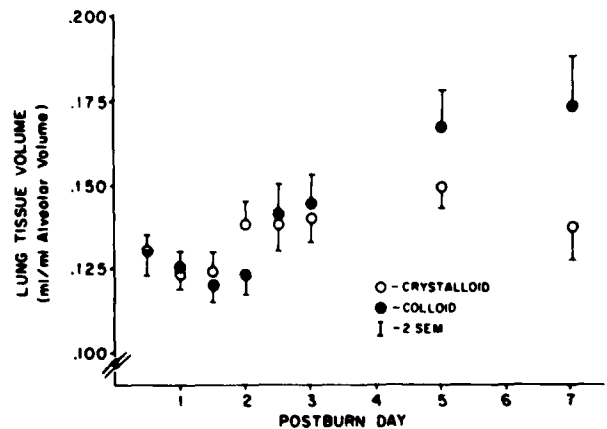


FIG. 3. Changes in lung water during the first postburn week for patients resuscitated with either crystalloid- or colloid-containing solutions.

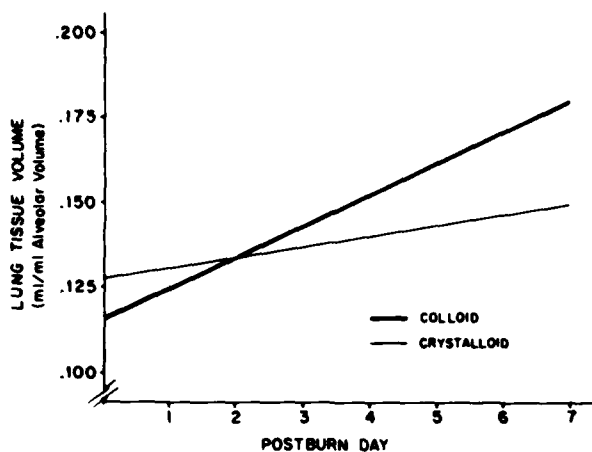


FIG. 4. Effect of resuscitation fluid composition when lung water is evaluated as a linear function of time postburn.

mal at all times in both groups, indicating a hyperdynamic, not a depressed, myocardium. Such a physiologic state might well be anticipated in light of the early postburn outpouring of catecholamines.²² Measurement of left ventricular end diastolic volume index and stroke index reveals similar depressions below predicted normal values in both groups during the first 12 postburn hours and in the crystalloid group during the 12- to 24-hour interval. These findings implicate an intravascular volume deficit as the cause of the decreased cardiac index noted in the crystalloid group and, when interpreted in conjunction with the measurements of left ventricular ejection fraction and V_{cr} , provide convincing evidence against the presence of a circulating myocardial depressant factor. During the 24- to 48-hour postburn interval, these left ventricular volume indices returned to essentially normal levels in both groups. Colloid resuscitation appears to be associated with earlier intravascular volume restitution compatible with increased intravascular retention of colloid, as compared to crystalloid, during the latter half of the first postburn day, suggesting a restoration of functional capillary integrity at this time.

In the studies of lung water, the colloid-treated and crystalloid-treated patients had burns of similar extent, but the former group required significantly less fluid to achieve clinically adequate resuscitation. Hourly urinary output was adequate in both groups. As in the earlier study group, cardiac output was higher in the colloid-treated group at both 12 and 24 hours postburn, but this difference was statistically insignificant. Cardiac output in the two groups was statistically indifferent to resuscitation fluid composition across the entire duration of

the study. The discrepancy in cardiac output between the two phases of this overall study may be explained by the larger volume of colloid administered to the patients in the echocardiographic study, which produced the supranormal cardiac outputs observed in those patients during the 12- to 24-hour postburn interval.

Using a noninvasive rebreathing technique, measured lung water was found to be influenced by composition of resuscitation solutions. While lung water content in colloid-treated patients increased significantly during the seven-day study, lung water in patients receiving only crystalloid fluids remained unchanged during that study interval. The differential effect of treatment on each group was statistically significant. Both groups displayed qualitatively similar responses in lung water following thermal injury. During the initial 36 hours following injury, lung water in both groups tended to decrease. Subsequently, lung water in the crystalloid-treated group returned to levels found immediately after injury. Patients receiving colloid-containing fluids demonstrated a progressive rise in lung water, beginning at the end of the second postburn day and continuing until the end of the study, greatly exceeding the original admission values. This phase corresponds clinically to the reabsorption of burn wound edema which occurs following resuscitation.

The validity of the rebreathing method for estimating lung water requires a brief examination. The volume in which the soluble tracer gas distributes during rebreathing measures lung tissue volume, not water volume. However, since water comprises over 80% of the lung tissue volume, the tissue volume measurements reflect primarily lung water content.²³ Moreover, the solid structures of the lung can be assumed reasonably to remain constant during the time of this study, and any change in lung tissue volume represents a change in lung water content. Since lung size is variable even in patients of the same height and weight, measured lung water was normalized by each patient's simultaneously measured alveolar volume. If anything, this approach may lead to underestimation of lung water, especially in those patients developing clinically significant pulmonary edema, since the tracer gas will not enter nonventilating portions of the edematous lung. We attempted to avoid patients likely to develop pulmonary edema during the first postburn week, but a few patients developed radiologic evidence of interstitial edema. Since this complication occurred primarily in colloid-treated patients, their progressive increase in lung water may be underestimated.

The goals of fluid resuscitation are the restoration of vital organ function and establishment of hemodynamic stability at the least physiologic cost. In thermal injury,

as in most situations of severe nonhemorrhagic fluid depletion, major deficits of the interstitial and intracellular compartments coexist with more clinically obvious intravascular volume depletion.²⁴ While colloid solutions primarily replace intravascular deficits, crystalloid solutions will rapidly and more completely replenish all compartments. Early studies of burn injury demonstrated that colloid-containing solutions administered to animal models more rapidly restored cardiac output to normal than did crystalloid solutions when administered on an equal volume basis.²⁵ However, both types of solutions produced identical effects on vital signs, pulmonary and systemic vascular resistance, arterial blood gases, plasma lactate, and lung histology. When indices of adequate intravascular fluid volume, such as venous filling pressures or urinary output, serve as guidelines for fluid administration, colloid and crystalloid solutions appear to be equally effective in restoring cardiac output and hemodynamic stability.^{26,27} To achieve comparable hemodynamic effects, larger volumes of crystalloid solution must be administered, usually 2 to 4 times the equivalent volume of colloid solutions. As a result, patients resuscitated with crystalloid solutions gain more weight, develop more peripheral edema, and have a lower plasma oncotic pressure than do similar patients resuscitated with colloid-containing solutions.

In an animal model, Moylan found that sodium and fluid volume doses exert independent effects on the early postburn restoration of cardiac output, with 1 mEq of sodium exerting the same hemodynamic effect as approximately 13 ml of salt-free fluid volume.¹⁰ In that study, restoration of cardiac output was influenced little by inclusion of colloid in the resuscitation regimen. In our patients, colloid solutions failed to demonstrate any clinical advantage over crystalloid solutions when resuscitation was guided by standard clinical indices, such as blood pressure, pulse rate, and hourly urinary output. Pulmonary capillary wedge pressure in our patients was characteristically below 5 mmHg during resuscitation and remained below 10 to 12 mmHg for the remainder of the postburn week. Any attempt to guide fluid infusion rate during resuscitation by elevating pulmonary capillary wedge pressure or cardiac output into the normal range, particularly with crystalloid patients, caused marked increase in urinary output and did not further improve other vital signs. Weight gain and peripheral edema did not indicate overexpansion of the intravascular volume or compromise of organ function.

Thermal injury is associated with significant alterations in pulmonary microvascular dynamics.^{28,29} In both clinical and laboratory studies, elevation of pulmonary

artery pressure and pulmonary vascular resistance have been measured within the first 12 hours postburn.³⁰ Some investigators have related these changes in patients to the effect of fluid resuscitation and have considered pulmonary systolic arterial pressure to correlate with interstitial pulmonary fluid.³¹ Others have considered the changes to reflect acute lung injury, particularly inhalation injury. In our study patients, neither resuscitation regimen was associated with elevated pulmonary artery pressure above the normal range, suggesting that neither regimen produced pulmonary edema during resuscitation and that screening for inhalation injury in these patients was effective. The measurements of lung water in the first two days postburn confirms in both treatment groups the absence of pulmonary edema.

The relationship between changes in pulmonary artery pressure and vascular resistance and changes in lung water appears to be dependent upon the primary site of flow resistance. If the increase is precapillary, as would be consistent with the measurements of cardiac output and pulmonary capillary wedge pressure in our studies and those of others, one would not anticipate an increase in lung water. If the site of the increased resistance is at the capillary or postcapillary level, as would occur with left ventricular failure or direct capillary injury, one would expect an increase in lung water. The rarity of pulmonary edema in burn patients during resuscitation suggests that the increase in pulmonary vascular resistance resides at a precapillary site. The similarity in lung water changes during the first 48 postburn hours in the two treatment groups reflects the similarity of changes of pulmonary hemodynamic indices in both groups, and speaks against a specific effect of colloid on transcapillary movement of fluid in the lung immediately following cutaneous thermal injury. Since protein sieving by the pulmonary microvasculature appears to remain normal during postburn resuscitation,²⁹ the infusion of colloid at this time appears to protect intravascular volume and to inhibit fluid loss into the pulmonary interstitium. This hypothesis is supported by the slight fall in measured lung water in both treatment groups during the first 36 hours following burn injury.

The fall of plasma oncotic pressure in burn patients following massive crystalloid resuscitation is not associated with an increase in pulmonary extravascular lung water.^{32,33} In animal models of other hypovolemic states, infusion of colloid-containing fluid has been associated with a greater increase in lung water than occurred with infusion of crystalloid fluid.^{34,35} Albumin is distributed widely throughout the body, with two-thirds located in extravascular sites. Injected albumin is distributed across the capillary membrane according to biphasic kinetics,

characterized by a fast exchange rate and by a much slower exchange rate.^{36,37} Thus albumin infused during resuscitation will equilibrate across the pulmonary capillary, even if protein sieving is unaffected by burn injury. The extracellular albumin present in the lung following resuscitation will promote subsequent fluid retention within the lung interstitium. Since this occurs at the time of rapid mobilization of burn wound edema fluid, the albumin may exert a subtraction effect on the intravascular fluid volume.¹¹ This hypothesis is supported by the significantly greater lung water measured in the colloid-treated group at seven days. Clinical observations are consistent with this concept: five of the colloid treated patients showed roentgenographic changes consistent with early pulmonary edema by the seventh postburn day, while only one crystalloid-treated patient demonstrated this complication.

We used colloid solutions containing 2.5% albumin, and the average patient in colloid treatment group received 300 to 350 g of albumin during the first 24 hours following burn injury. This colloid concentration is similar to the albumin concentration recommended in the Evans formula.³⁸ In studies assessing the effect of varying doses of colloid on resuscitation and survival following hypovolemic shock, 2 g/kg body weight of albumin produced the optimal beneficial effect.³⁹ Six per cent colloid solutions were no more effective than 3.5% solutions. Patients in our colloid group received approximately 4 g/kg body weight of albumin during resuscitation. Since this dosage was more than two times that of previously demonstrated effective levels, we did not evaluate resuscitation solutions with even higher concentrations of colloid. Based on our current findings, it is entirely possible that the use of higher concentrations of albumin may lead to even more pronounced changes in lung water. Although the numbers of patients in each treatment group are insufficient for statistical analysis at this time, the raw mortality data suggest that the addition of colloid to crystalloid resuscitation solutions may have later deleterious effects. When utilized according to the above described resuscitation guidelines, crystalloid solutions appear to be the preferred fluid for the treatment of acutely burned patients.

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DISCUSSION

DR. FRED T. CALDWELL (Little Rock, Arkansas): This work demonstrates again that the addition of albumin to resuscitative therapy during the first 24 hours post burn probably adds nothing to salt water therapy. In addition, the present work demonstrates that albumin administered during the first 24 hours post burn may be detrimental in the fluid mobilization period, by increasing lung water content and the tendency to develop acute pulmonary edema. This is fairly well accepted in patients with ARDS—adult respiratory distress syndrome—where the lung is very leaky, but the concept is rather new that in the absence of pulmonary injury colloid therapy may contribute to the development of increased lung water content.

The second area in which the authors have added to our knowledge is in the etiology of the decrement in cardiac index following thermal trauma. Their paper clearly points to decreased intravascular volume, and not myocardial depression, as the primary etiology of this status. Accurate measurement of plasma and/or blood volume, immediately and sequentially following thermal trauma, may be impossible with present techniques.

I, therefore, ask Dr. Pruitt what the plasma loss curve looks like following thermal trauma, and, based on their current data, might the presently accepted early therapy following thermal trauma represent too little too late?

DR. WILLIAM MONAFO (St. Louis, Missouri): Burn shock traditionally has been accepted as a classic form of "capillary leak" shock, in which capillary sieving is impaired. Yet here the author shows clearly that fluid requirements are less in colloid-treated patients. That is a very interesting observation in a randomized controlled study, particularly since the patients did not have inhalation injury.

What is the explanation?

First, from their data, the cardiac index was the same in both groups in the 0- to 12-hour period. It was only after the 12- to 24-hour period that the colloid-treated patients had higher cardiac indices. I find that interesting because, in animals, Yoshioka, in our laboratory, and the group at Galveston found that the albumin leak into the wound is over after 6 to 12 hours.

I would, therefore, ask Dr. Goodwin if the fluid infusion volume differences persist if one separates the data into 0- to 12- and 12- to 24-hour intervals, and whether the hematocrits in those two intervals also suggest that the colloid-containing fluid was remaining within the circulation primarily within the second 12 hours.

The second point of interest is the conclusion that, despite the fact that crystalloid patients required larger water loads and larger sodium

loads, they favor its use. The addition of about 350 g of albumin appears to have deleterious effects, as they point out, not only on lung water, but, I suspect, on corporal water balance in general.

I want to ask whether they think the increased lung water is a unique phenomenon, or does it merely reflect that overall, positive water balance is greater in the colloid group at seven days?

I don't want to discuss Dr. Shires' paper out of turn, but I noticed that in his patients also, those who received colloid excreted less of their administered loads in the postoperative period.

DR. CHARLES R. BAXTER (Dallas, Texas): I think that twenty years ago, all of us could have told you what burn shock was. Today none of us can. We really do not understand in depth many of the things that we do clinically.

I would like to limit my remarks to those of the question of myocardial depressant "factor", that has been studied for some years by our group, and has been publicized as one of the causes of failure of fluid resuscitation.

First, it's important to recognize that failure of the myocardium, or a decreased contractility (however we define that term) or an inability to pump adequately is confined to a very small number of burns. It occurs in either the very massively burned individual or in those that are elderly with somewhat lesser burns. In all other burns, particularly in the normal physiologic age group, our observations exactly parallel those of Dr. Pruitt and Dr. Goodwin, that is, that there is an increase in the ejection fraction, and a smaller than normal end diastolic ventricular filling volume, regardless of what the status of the total circulating blood volume.

In the experimental hearts in which we have studied this problem, it is apparent that the heart does contract with increased force, and has a decreased ventricular volume. This seems to be a stiffness of the heart, in that it does not relax in the normal fashion, and it tends to constrict more forcibly.

So my question is: Is there any evidence that we really have in this clinical study that blood volumes, particularly plasma volumes, were normal in these individuals that showed this?

And I might say parenthetically that a study by a different technique—namely, noninvasive cardiac imaging—for the past 8 years, totally confirms the findings which you have presented.

DR. LEWIS M. FLINT, JR. (Louisville, Kentucky): It seems clear from the information presented that where lung injury is ruled out, in so far as possible, the normal lung tolerates physiologic pressures and small to moderate increases in extravascular lung water, very well.

Our interest has paralleled that of the group at San Antonio because of our involvement in the management of injured patients from blunt traumas, where the data are not quite as clear that the injured lung, or the injured brain, may tolerate edema to the same degree as do burn patients.

I would like to share with you briefly some observations that we have made in the experimental laboratory, using a different kind of colloid, that is, hydroxyethyl starch, in which our data seem clear that physiologic pressures can be tolerated by the injured lung, but that the addition of another kind of colloid—that is, hydroxyethyl starch—does increase cardiac output more efficiently than the crystalloid solution, but at the cost of increased flow through endopulmonary shunts and an increase in hypoxia at a period where oxygen delivery may be critical.

Because of our interest in these observations in experimental animals, I would like to ask two questions of the authors. One is, have they used any other forms of colloid, such as hydroxyethyl starch? And is it possible that we are beginning to see another complication of resuscitation emerge, that is, an increased incidence of sepsis in the colloid-treated patients, which might have accounted for the increased death rate in that group?

DR. LAZAR J. GREENFIELD (Richmond, Virginia): I would like to suggest one other alternative explanation for the hemodynamics observed.

Recently, we have become interested in the performance of the right ventricle shortly after resuscitation, and in looking at some of our patients who appeared to have very satisfactory ventricular filling pressures, we found that many of them demonstrated right ventricular enlargement. This enlargement produced compromise of the left ventricular function that was not reflected in contractility, which remained normal. Therefore, I wonder if the authors could tell us whether there was any evidence of right ventricular enlargement, particularly in the crystalloid-resuscitated group.

This appeared to occur in our experience, and was not reflected by filling pressures, which remained normal.

DR. WATTS R. WEBB (New Orleans, Louisiana): We have taken a little bit different tack. Instead of the urine output, we are trying to follow very much the cardiac output, the oxygen delivery, and maintaining as low as possible the pulmonary vascular pressures and the systemic resistance in the resuscitation of our burn patients.

We use hypertonic saline with albumin. We use only about 40% as much fluid to resuscitate as would have been presented here. As a result of that, we see very little in the way of pulmonary problems, and very much less in the way of peripheral edema, brain edema, gut edema, and other problems that may occur. We would feel that the amount of colloid given these patients is far more than is needed or desirable.

We have been following the lung water in our cardiac patients, as we have in the experimental situation, and found that as long as we can maintain the pulmonary microvascular pressures very low, we almost never see any pulmonary problems.

The lung is very resistant to the development of edema, much more than the periphery. Even in the presence of an experimental, very high capillary permeability, and with the utilization of albumin or other colloids, we have found that so long as one maintains low pulmonary microvascular pressures, there is very little tendency for the development of pulmonary edema.

We do like to maintain the cardiac index high. A cardiac index down in the range of 2 L/min is a degree of shock that gets close to going back to the acceptance of "laudable pus."

The fact that there is not a generalized capillary permeability outside of the burned area has been very beautifully demonstrated by the work of Robert Demling, who showed that there was a lot of leakage in the area of the burn, very minimal in the lung, and almost no increase in the areas outside of the actual burned area.

It would be very interesting to know the cause of death in these patients. It seemed to be much higher in those who received colloid, but if the deaths occurred at a later date, it would be, perhaps, unrelated.

We have found that urinary output, as an index of resuscitation of the patient, is actually a very inadequate indicator, because urine output is so dependent on many other factors and because of the marked stimulation of aldosterone, the renin-angiotensin system, ADH, and other things, it very poorly reflects the amount of volume on board. We have seen patients who may have 8, 10, 20 L of salt water on board, and have almost no urine output, because of the massive endocrine stimulation.

DR. CLEON W. GOODWIN (Closing discussion): In answer to Dr. Caldwell's question, previous investigators at our Institute have found that the time course of plasma volume alterations has two definite phases. During the first 24 hours, plasma loss rate was quite high; subsequently, this obligatory plasma loss ceased, and there was a net gain of plasma volume during the following postburn days. Whether or not this implies a repair of leaky capillary membranes remains to be demonstrated especially in the lung. Demling has shown very nicely that protein filtration by the lung—an uninjured lung—remains intact over at least the first two or three days following cutaneous thermal injury.

In answer to Dr. Monafó's question on the capillary leak, again I can only refer to Dr. Demling's data. We cannot from our clinical experience say that there is a leak which has repaired itself. I must admit, however, that it is highly suggestive that such occurs. Both fluid composition regimens used in our study were capable of restoring intravascular volume in the first 12 hours as indicated by our echocardiographic indices. In the subsequent 12 hours, colloid was more effective, and this suggests repair of a capillary leak of protein. We have not separated the fluid requirements into 12-hour intervals and looked at this specifically at this time, but we plan to do so.

Dr. Monafó asked if this increase in lung water in the colloid-treated patients is a special phenomenon of that organ or part of general organ dysfunction. I think the latter possibility is the correct one. Dr. Shires' previous paper pointed out that his colloid-treated patients had lower urine outputs in the postoperative period. Our patients demonstrated the same thing. Using our guidelines for adequacy of resuscitation, the colloid-treated patients had much more difficulty with urine output in the 2 or 3 postburn days following resuscitation. The long-term effects of general organ dysfunction is suggested by the higher mortality data for the entire colloid group.

Dr. Baxter proposed a myocardial depressant factor in burn patients several years ago, and pointed out that this occurred most commonly in two very restricted groups of patients. In patients with coronary artery disease, one does not have to postulate a circulating myocardial depressant factor for these patients to explain inadequate cardiac output and poor tissue perfusion. The other group of patients are those with very large burns, exceeding 90% of the body surface. Such patients occasionally demonstrate a low output syndrome, especially if resuscitation is delayed. These patients fail to respond to volume resuscitation even when pushed to the point of pulmonary edema. Whether or not there is a circulating myocardial depressant in these patients, however, is not settled. We have data which indicate that the myocardium is hypercontractile, even in these patients, and so we are left with having to look for another lesion to explain this. Possibly Dr. Greenfield's explanation will be the correct one.

Dr. Flint has pointed out his experience with hydroxyethyl starch. We have used no plasma volume expanders other than albumin. Hydroxyethyl starch in particular, if you read the package insert, is limited to 1000 to 1500 ml per day, and in these patients who receive 10 to 20 L of fluid in the first 24 hours, we would very rapidly exceed what the FDA has said is allowable.

Whether or not colloid is the direct cause of increased lung water or is a dangerous drug which leads to increased mortality cannot be answered by this paper. I would like to point out that we have presented

raw mortality data, and not statistically analyzed data, with just 50 patients. The sample of patients is too small to allow statistical evaluation with probability models at this time. We have since studied 50 additional patients, which may allow an adequate analysis of this problem.

Dr. Greenfield has studied right ventricular function for quite some time. Previous studies by Dr. Martyn and Dr. Burke have indicated that right ventricular dysfunction does occur in burn patients. However, they have divided their data into two groups. One group—the majority of their patients—actually had normal right ventricular function indices postburn, did not demonstrate any lung disease, and are very similar to our patients. This group had low pulmonary artery pressures and very moderate pulmonary hypertension, and this description corresponds nicely to our patients who we think are normal in this study. As such, the pulmonary artery pressures in our patients were only very moderately elevated, and correspond to the normal group of patients in whom Martyn and Burke documented normal right ventricular function.

Martyn's group was composed of an older population which had sustained much larger burns, had severe inhalation injuries, and required mechanical ventilation. These people had demonstrable right ventricular dysfunction.

Many investigators have pointed out that right ventricular dysfunction will cause left ventricular dysfunction. Echocardiography is not a very good way to study right ventricular dysfunction, and we have not used the thermal indicator techniques to look at the washout curves which are used to evaluate right ventricular end diastolic index and ejection fraction.

Lastly, Dr. Webb's experience is totally unique, compared to ours. We did not use hypertonic saline as a routine and cannot make any valid comparisons of our data with his. We agree that the lung is quite resistant to edema. Any fluid that does leak into a noninjured lung is very rapidly removed by the lymphatic circulation. We agree with Dr. Webb on maintaining low pulmonary microvascular pressures. During resuscitation, the wedge pressure in most of our patients is quite low, almost uniformly below 5 mmHg, and any attempt to guide fluid resuscitation by raising pulmonary capillary wedge pressures to higher levels, or to raise cardiac index to higher levels, as he suggests, results in urinary outputs which may range between 200 to 400 cc per hour.

The correct guideline for assessing postburn resuscitation is subject to some debate. Over the years, we have elected to use urinary output, blood pressure, and pulse rate as our guides. We do not routinely use intravascular monitoring cannulas in patients because of the risk of infection and the reliability of these simple physiologic indices. If we were to follow his advice and push cardiac indices into the normal range, we would get very high urinary outputs and increased edema, and we think this may be more dangerous in burned patients receiving hypertonic resuscitation. Again, I cannot correlate this to potential advantages or disadvantages of hypertonic resuscitation.

We really have not examined closely the cause of death directly. The deaths in our patients occurred after the first postburn week—often many weeks later, and it may not be possible to ascribe their deaths to the infusion of colloid. However, I think the possibility remains that early organ compromise may lead to delayed complications and death later on.

