Post-traumatic Changes in, and Effect of Colloid Osmotic Pressure on the Distribution of Body Water

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The aim of this study was to define the post-traumatic changes in body fluid compartments and to evaluate the effect of plasma colloid osmotic pressure (COP) on the partitioning of body fluid between these compartments. Forty-two measurements of plasma volume (green dye), extracellular volume (bromine), and total body water (deuterium) were done in ten traumatized patients (mean Injury Severity Score, ISS, = 34) and 23 similar control studies were done in eight healthy volunteers who were in stable fluid balance. Interstitial volume, intracellular volume, and blood volume were calculated from measured fluid spaces and hematocrit; COP was directly measured. Studies in volunteers on consecutive days indicated good reproducibility, with coefficients of variation equal to 3.5% for COP, 6.3% for plasma volume, 4.5% for extracellular volume, and 4.9% for total body water. COP values extended over the entire range seen clinically, from 10 to 30 mmHg. Interstitial volume was increased by 55% in patients, but intracellular volume was decreased by 10%. We conclude (1) that posttraumatic peripheral edema resulting from hemodilution is located in the interstitial compartment, with no intracellular space expansion; and (2) that interstitial volume, but not intracellular volume, is closely related to plasma COP.

THE RESUSCITATION OF SURGICAL PATIENTS has been intensively studied to define the deficits sustained during and after hemorrhagic shock and to determine the optimal fluid for resuscitation. Moyers was the first to identify the survival advantage of isotonic salt solutions given in volumes two to three times as great as the blood loss sustained.[1] Shires and coworkers, in clinical[2–4] and animal[5,6] shock studies, consistently identified a decreased extracellular fluid volume prior to resuscitation, which they believed was best replaced with isotonic salt solutions. In animal studies they found an expanded intracellular volume during shock and hypothesized that the extracellular fluid deficit resulted in part from intracellular movement of water due to shock-induced dysfunction at the cell membrane.[6]

A limitation in nearly all human shock resuscitation studies in which the body water compartments are measured is the focus on elective surgical trauma, which is typically mild to moderate in degree, with minimal blood loss and hemodilution.[7–16] A further limitation is that patients are usually studied for only 24 to 48 hours after resuscitation, and the more extended time course of body water changes has not been evaluated. The perturbations in serum protein levels, oncotic pressure, and the body water spaces in elective surgery are small compared to severe trauma, and do not allow extrapolations to be made with any confidence. In contrast, patients resuscitated with isotonic salt solutions after severe trauma increase body weight by 10% to 30% and develop overt peripheral edema. We have found only one study in the literature in which all body water spaces were measured in victims of severe trauma,[16] and this study did not provide any data in regard to changes in serum proteins or colloid osmotic pressure.

The second issue we addressed was the effect of serum protein or colloid osmotic pressure levels on partitioning of water between the intravascular and interstitial spaces. In severely traumatized patients it is usual for red cell losses to be underreplaced, and hematocrit levels are maintained in the 25% to 30% range, or even lower, if patients have no cardiac problems. When isotonic salt solutions rather than protein-containing solutions are used for resuscitation, the plasma colloid osmotic pressure will be lowered in proportion to the blood loss. The use of packed cells for red cell replacement, rather than whole blood, further accentuates plasma protein dilution.

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TABLE 1. *Injurity Severity Scores and Major Diagnoses*

Patient	ISS	Diagnosis
1	34	Kidney laceration, pelvic fx, tibial fx, lumbar fx
2	48	Subdural hemorrhage, pulmonary contusion, liver laceration bladder rupture, pelvic fx, lumbar fx
3	50	Flail chest, pneumohemothorax, larynx/trachea fx, mult. fx
4	34	Flail chest, pneumohemothorax, spleen rupture
5	34	Open stomach and small bowel injuries, renal laceration, pneumothorax
6	43	Cerebral contusion, subarachnoid hemorrhage, pelvic fx, liver and splenic lacerations, gastric arterial bleed, hand fx
7	13	Mandibular fx, open wounds to palate and mouth, open wounds to forearm, hip, thigh, knee, leg, and ankle
8	13	Open wound to eyeball, facial wounds
9	N/A	Perforation of gastric ulcer, sepsis
10	N/A	Severe peripheral vascular disease, diabetes, above-knee amputation, multiple organ failure, candida sepsis

N/A, not applicable (surgical trauma).

Starling's law suggests that a decreased plasma COP should favor interstitial volume expansion if the concentration of plasma proteins filtered into the lymph is a constant fraction of the intravascular concentration.[17] Under such circumstances the transvascular oncotic gradient should decrease with plasma protein dilution. Others have shown that with hemodilution there is an increased rate of filtration of protein-poor fluid across the capillaries, an increased flow of lymph through the interstitial space, and a "wash-down" of interstitial protein levels that tends to parallel the lowering of intravascular protein levels.[18,19] This mechanism could maintain the transvascular oncotic gradient even in the face of significant hemodilution because the interstitial protein levels are about 30% to 50% of intravascular levels[18] and therefore reduce or prevent the formation of interstitial edema. These conflicting views have not yet been resolved in the literature.

Finally, we were interested in establishing a technique for the simultaneous measurement of the body water spaces with nonradioactive tracers because this would eliminate any hazard of radioactivity and would allow repetitive measurements in patients without any limitations due to accumulation of radiation dose.

In summary, the specific purposes of this study were: (1) to define the post-traumatic time course of changes in the body water spaces and the location and magnitude of the post-traumatic peripheral edema seen clinically; (2) to evaluate the role of plasma colloid osmotic pressure in the partitioning of extracellular body water between the intracellular and interstitial fluid spaces; and (3) to establish and validate a method using nonradioactive tracers for the simultaneous measurement of the body water spaces.

Methods

Patients

Eight severely traumatized patients (mean ISS = 34; range, 13 to 50) and two patients with surgical sepsis admitted to the Medical-Surgical Intensive Care Unit at San Francisco General Hospital between March and December 1988 were included in the study. Patients were chosen for the study because of severe trauma and large positive fluid balance. Studies were not initiated until the second or third hospital day, when patients were in stable fluid balance, without ongoing hemorrhage or other major losses. Once enrolled, they were studied on days 1, 2, 3, 5, 7, and 10, or on alternate days if unavailable on the designated day. Studies were discontinued at the time of patients' discharge from the Intensive Care Unit. Table 1 shows the individual ISS scores and major diagnoses. Four of ten patients died, two of sepsis and respiratory failure (hospital days 12 and 14), one of sepsis and cardiac failure (hospital day 12), and one of pulmonary contusion and hypoxia (hospital day 3).

Eight healthy volunteers (three female, five male) among the professional staff were recruited at San Francisco General Hospital and were studied on three consecutive days. All were in stable fluid balance and received no oral or parenteral fluid during the period of the study.

Protocol

Intravenous catheters (18 ga.) for indicator injection and blood withdrawal were placed in bilateral forearm veins if not already present. Indicators (a solution containing 0.18 mg/kg body weight indocyanine green, 13 mg/kg body weight bromine, 0.2 mL/kg body weight deuterium oxide, and 0.2 mL/kg body weight H_2O) were injected into one forearm vein at the beginning of the study and samples were aspirated from the opposite side or from an arterial line, if present. Five mL of blood were withdrawn before and 2, 4, 6, 8, and 10 minutes after indicator injection and every 20 minutes thereafter for four hours. The samples were centrifuged for ten minutes at 10,000 rpm, and plasma was separated from cells. All indicator solutions were sterilely prepared by the Parenteral Solution Laboratory at the University of California, San Francisco, and were tested for pyrogens by the limulus assay.

Measurements

Forty-two measurements of plasma volume (green dye), extracellular volume (bromine), and total body water

(deuterium), were done in patients and 23 similar control studies were done in eight healthy volunteers. Mean ideal body weight calculated from height was 70 ± 9 kg (range, 58 to 82 kg) for the volunteers and 71 ± 9 kg (range, 49 to 82 kg) for the patients.

Indocyanine green dye was used for the measurement of plasma volume.[20] Plasma samples for the measurement of the dye concentrations were recentrifuged before measurement in a spectrophotometer (DU-30 Spectrophotometer, Beckman Instruments Inc, Irvine, CA) at 805 nm calibrated with plasma samples with added known amounts of indocyanine green, yielding concentrations of 0.1 to 10 mg/L plasma.

Stable bromine in the form of sodium bromide was used for the measurement of extracellular space. The measurement of the plasma bromine concentrations were done in the Radiologic Imaging Laboratory, South San Francisco, using a fluorescent excitation technique.[21] The accuracy of the system was checked on a regular basis by analyzing vials with solutions containing added known amounts of bromine.

Deuterium oxide was used for the measurement of total body water.[22,23] We used vacuum sublimation and condensation to determine deuterium concentrations in both plasma and cell water in order to avoid artifacts due to the presence of proteins. Plasma or cell water was injected into an infrared photometer (Miran 1FF, Foxboro Co, South Norwalk, CT). The photometer was calibrated using solutions with added known amounts of deuterium oxide that had undergone the same procedure and handling as the blood samples. Concentrations in plasma water and cell water were closely correlated (r = 0.95, paired t test) and did not differ significantly. Their mean values were therefore used for the computation of total body water.

Plasma colloid osmotic pressure was measured in a membrane colloid osmometer (Model 4100, Wescor Inc., Logan, UT). The osmometer was calibrated with a water manometer (Wescor Inc., Logan, UT). Calibration and osmometer membrane function were checked before every measurement with a standard 5% human albumin solution (Albuminar 5, Armour Pharmaceutical Co., Kanakee, IL; 5 g/100 mL = 19.4 mmHg).

Calculations

The indicator kinetics were back extrapolated to the time of injection (t = 0) to eliminate indicator loss numerically. This mathematical procedure simulates instantaneous mixing of the indicator in its entire volume of distribution, before any loss. For indocyanine green the concentrations measured between the second and the tenth minute after injection were used. For bromine and deuterium oxide the indicator concentration between 60 and 240 minutes were used. These times were chosen because of a linear relationship between the logarithm of concentration *versus* time, indicating an essentially monoexponential indicator dispersion process during that period.

The linear fit of the exponential indicator dilution curves to the data points appeared visually excellent in all cases, but to assess the goodness of the fit quantitatively, a "curve coefficient of variation" (CCOV) was computed from the natural logarithm of the measured data (d(i)) and the exponential function (e(i)).[24]

$$CCOV = \{\sum_{i=1}^{n} (d(i) - f(i))^2/(n - 1)\}^{1/2}/\sum_{i=1}^{n} d(i)/n$$

For each indicator the calculated concentration at t = 0 (c_0) was used to calculate its volume of distribution $V_d = d/c_0$ (d = indicator dose). For the calculation of extracellular volume, corrections were made for Donnan equilibrium, (estimated) plasma water content (90%), and bromine distribution in erythrocytes.[21] Total body water was calculated from the mean values of the D_2O concentrations (c_0) in plasma water and cell water. Whole body hematocrit (WBH) was obtained from the peripheral hematocrit by correcting with a factor of 0.94.[25] Blood volume (BV) was calculated from plasma volume (PV) and whole body hematocrit as BV = PV / (1-WBH). Interstitial volume was calculated as the difference between extracellular volume and plasma volume. Intracellular volume was calculated as the difference between total body water and extracellular volume. Total circulating protein was calculated as the product of the measured plasma protein concentration and plasma volume. All volumes and total circulating protein were related to ideal body weight based on height.

Statistics

Measurement reproducibility in volunteers on three consecutive days was assessed by coefficients of variation (percentage of standard deviation). Comparison between means for normal volunteers and for trauma patients was done using the unpaired t test. Simple linear regression statistics were used for the analysis of relationship between different variables. Results are given as mean ± standard deviation for all volunteers or all trauma patients.

Consent

All procedures were in accord with the ethical standards of the Helsinki Declaration of 1975. An IND number 31,403 for the intravenous use of deuterium oxide and sodium bromide was obtained from the Food and Drug Administration, Department of Health and Human Services. The study was approved by the Committee on Human Research at the University of California, San Fran-

TABLE 2. *Fluid Intake and Output from Day of Admission to POD 10*

	Fluid Intake (L)			Fluid Output (L)		
Day	Salt Soln	Blood	Total	Urine	Other	Total
AD	18.1	3.7	21.8	3.5	2.5	6.0
1	3.5	1.4	4.9	2.2	0.8	3.0
2	2.6	0.5	3.1	2.6	0.9	3.5
3	2.4	0.6	3.0	2.7	0.7	3.4
4	2.7	0.5	3.2	3.7	0.5	4.2
5	4.7	1.3	6.0	2.9	2.2	5.1
6	4.1	0.6	4.7	2.8	1.6	4.4
7	3.4	0.5	3.9	2.6	1.3	3.9
8	3.3	0.6	3.9	2.7	1.5	4.2
9	3.1	0.9	4.0	4.1	1.5	5.6
10	3.1	0.3	3.4	1.6	1.0	2.6

AD, admit day; POD, postoperative day; Salt soln, isotonic salt solutions.

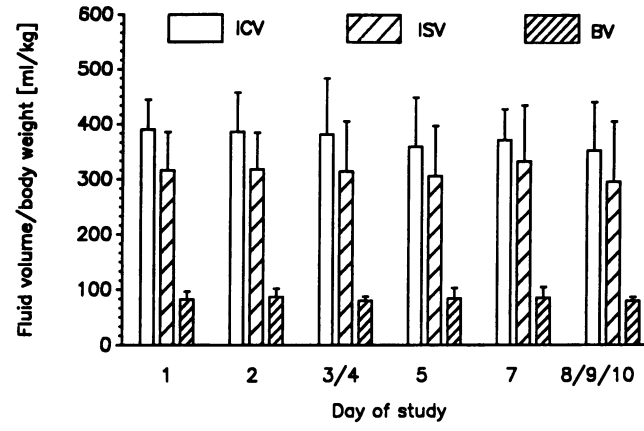


FIG. 1. Time course of body water spaces. ICV, intracellular volume; ISV, interstitial volume; BV, blood volume.

cisco. In all subjects informed written consent was obtained before initiating the study.

Results

Fluid Intake and Output

A mean of 2.5 ± 1 days elapsed from the time of the patients' arrival in the emergency room to the time of inclusion into the study. By that time the patients had received an average of 24 L of crystalloids and 5.6 L of whole blood. The fluid intake and output are tabulated in detail in Table 2, which demonstrates that the patients were in fairly stable fluid balance after the first postoperative day.

Comparison of Volunteers and Trauma Patients

In comparing trauma patients with controls, colloid osmotic pressure was reduced by 40%, blood volume was increased by 15%, interstitial volume was increased by 55%, and the quotient of interstitial volume to blood volume was increased by 34%. The mean value of intracellular volume was slightly lower in trauma patients (10%). Results reported in Table 3 are mean values ± standard deviations on all days for controls and for patients.

TABLE 3. *Body Fluids: Normal Volunteers* Versus *Trauma Patients*

	Normals	Patients	t test
Colloid osmotic pressure [mmHg]	27.8 ± 1.6	16.8 ± 3.3	$p < 0.001$
Blood volume [ml/kg]	72 ± 7	83 ± 14	$p < 0.001$
Interstitial volume [ml/kg]	204 ± 26	317 ± 80	$p < 0.001$
Intracellular volume [ml/kg]	417 ± 78	374 ± 76	$p < 0.05$
Interstitial/blood volume [ml/ml]	2.9 ± 0.4	3.9 ± 0.9	$p < 0.001$

Time Course of the Changes in Body Water Spaces After Trauma (Fig. 1)

Sequential daily changes in the body water spaces were small (Fig. 1); there was a decreasing trend in intracellular and interstitial space volumes that did not reach statistical significance. Blood volume was constant at all times. The absence of significant changes results from the study design because measurements had to be discontinued when patients were discharged from the ICU.

Correlation Between COP and Body Water Spaces

Figures 2, 3, 4, and 5 show the individual data points for all patients and controls relating blood volume (Fig. 2), interstitial volume (Fig. 3), the quotient of interstitial volume to blood volume (Fig. 4), and intracellular volume (Fig. 5) to COP. The separation of data points into two groups is obvious, with the controls on the right having normal COPs and patients on the left having COPs between 10 and 22. Although there is a significant correlation

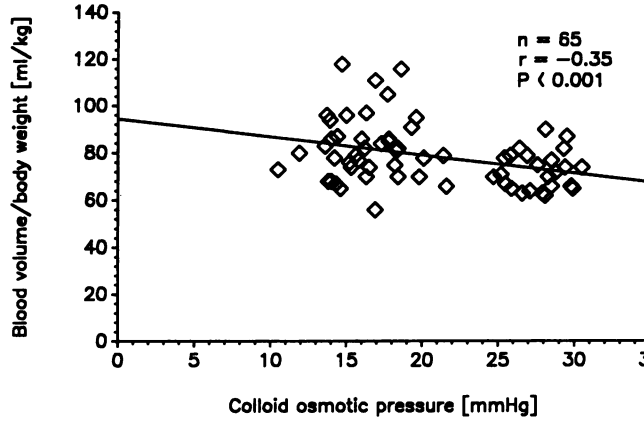


FIG. 2. Correlation between plasma colloid osmotic pressure and blood volume.

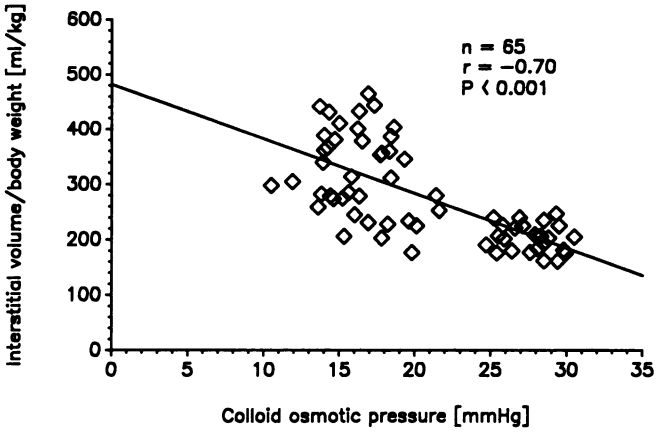


FIG. 3. Correlation between plasma colloid osmotic pressure and interstitial volume.

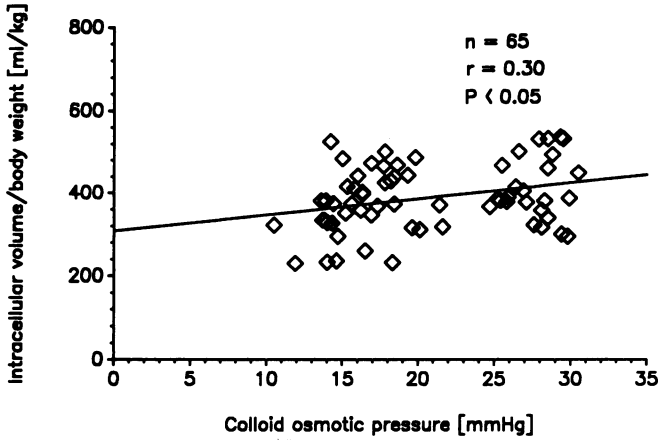


FIG. 5. Correlation between colloid osmotic pressure and intracellular volume.

for all three water spaces, the relative change in blood volume and intracellular volume with COP is slight and the regression line is near horizontal. In contrast, the dependence of interstitial space on COP, both in absolute terms (Fig. 3) and normalized with respect to blood volume (Fig. 4), appears to be large, with a mean 40% reduction in COP associated with a 55% increase in interstitial volume.

Correlation Between Total Circulating Protein and Body Water Spaces

Blood volume correlated significantly with total circulating protein (Fig. 6). Figure 7 indicates that the partitioning of body water between the intravascular and interstitial compartment is also significantly correlated with total circulating protein. Although the total circulating protein values for the two groups overlap, there is an apparent separation of the slopes for controls and patients. At any given total circulating protein value patients had a higher blood volume (Fig. 6) and interstitial volume-blood volume ratio (Fig. 7).

Goodness of Fit of the Model and the Measured Indicator Kinetics

The goodness of fit of the data to the logarithmic monoexponential linear regression line was evaluated by the curve coefficient of variation. For the dye kinetics, the mean coefficient for all curves was 3.4%, for the bromine kinetics 4.4%, and for the deuterium kinetics 5.3%. The examples shown in Figure 8 are typical, with curve coefficients of variation of 3.1% and 1.4% for the dye, 2% and 5.8% for bromine, and 4.2% and 5.4% for deuterium.

Reproducibility in Volunteers

Studies in volunteers on three consecutive days indicated good reproducibility of the fluid space measurements. The coefficients of variation were below 7% for all directly measured variables and were only slightly higher

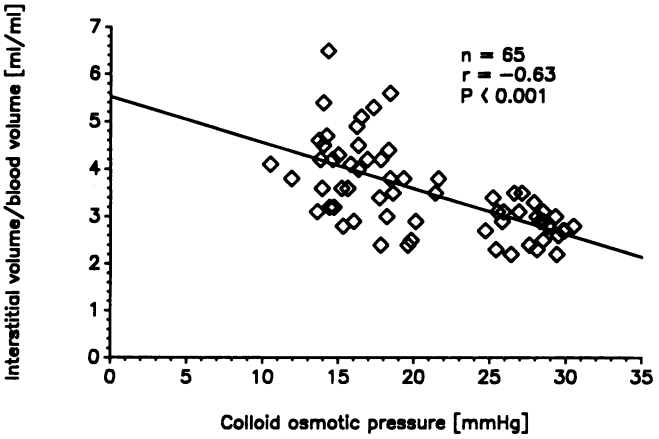


FIG. 4. Correlation between plasma colloid osmotic pressure and the quotient of interstitial volume and blood volume.

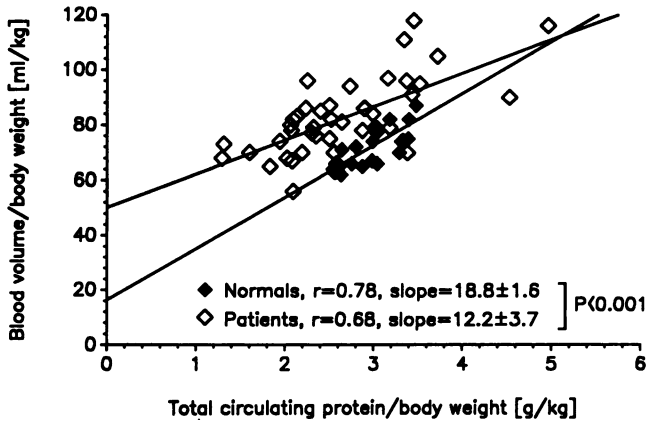


FIG. 6. Correlation between total circulating protein and blood volume.

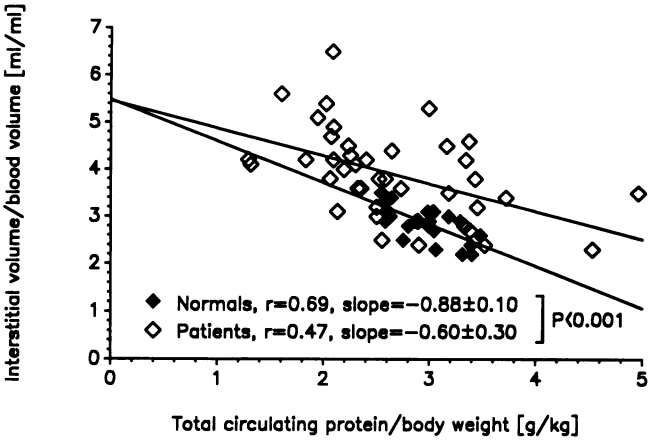


FIG. 7. Correlation between total circulating protein and the quotient of interstitial volume and blood volume.

for the derived variables (Table 4). The coefficient of variation for the interstitial volume-blood volume ratio was somewhat higher because it represents the quotient of two derived variables.

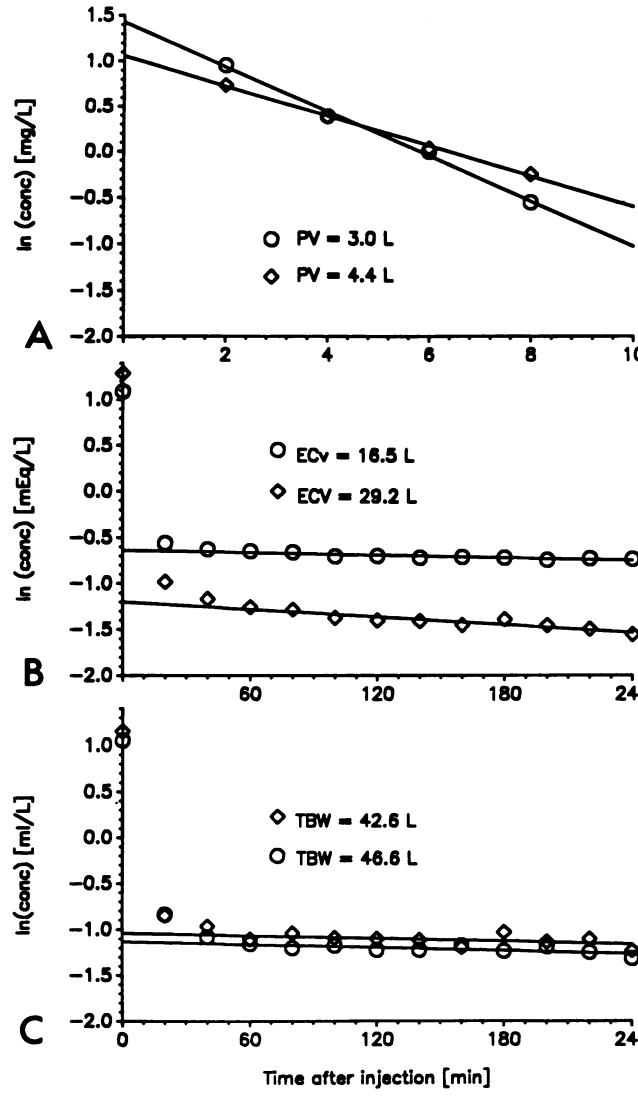
Discussion

Body Water Spaces

The principal finding in the present study was a 55% expansion of the interstitial space after isotonic salt solution resuscitation, which persisted for several days, with relatively small changes in blood volume or intracellular volume. This excess volume accumulated in the first 24 to 36 hours during acute blood loss and surgery, when whole blood was being replaced with packed cells and balanced salt solution. During the subsequent ten days of study there was a trend downward in both intracellular and interstitial spaces that did not reach statistical significance, but no marked diuresis, despite the administration of fluids at maintenance levels (see Table 2). This presumably was a result of the magnitude of the trauma sustained by these patients, as well as reoperative trauma and the secondary development of septic complications in several, which precluded spontaneous diuresis. All these patients had obvious systemic edema that was greater in dependent areas, but tended to be generalized. Because studies were discontinued in patients who were discharged from the ICU, obviously the data are not meant as a "natural history" of the body fluid spaces after trauma.

There was no evidence of an interstitial or extracellular space contraction at any time, which initially might appear to conflict with the work of Shires and coworkers but in fact is similar to his and others' findings. In a study of hemorrhagic shock in baboons that was similar to many other shock studies that they reported, Shires et al.[6] found an initial 45% contraction of muscle extracellular space at the end of the shock period. However on the first post-resuscitation day this effect was reversed, and muscle extracellular space was expanded by 32%. Doty,[16] in a clinical study of severely injured soldiers in Vietnam, found a 25% expansion of the extracellular space on the third postinjury day. Both of these results parallel the findings of the present study in which measurements were begun after resuscitation. We could not study patients during acute shock and resuscitation and therefore have no data regarding that period.

It appears that much of the controversy regarding extracellular space contraction or expansion after shock is



FIGS. 8A–C. Indicator kinetics after bolus injection of (A) indocyanine green, (B) bromine, and (C) deuterium. Note the excellent fit of the monoexponential function fitted to the data points between two and ten minutes after injection of the dye, and between 60 and 240 minutes after the injection of bromine and deuterium.

related to the time at which it is assessed and the adequacy of resuscitation. Shires et al.[6] have perhaps been misinterpreted in this regard because their own data indicate interstitial space expansion after isotonic salt solution resuscitation. The present findings are therefore in agreement with earlier work, but are of more extreme degree, probably because of the severity of trauma.

The other finding we noted is that the intracellular space is unaffected by hemodilution with isotonic solutions. This would be expected because only osmotic alterations should cause net water movement in or out of the cell mass as long as the cell membrane is intact and normally functional. In Shires'[6] work an intracellular expansion of approximately 10% was noted, but it occurred only during the shock state. Following resuscitation on day 1 and day 5 after baboon hemorrhagic shock in their studies,[6] the intracellular space was either normal or decreased in size, as was found here. Again it would appear that the widespread belief in a persistent expansion of the intracellular space after trauma is a misinterpretation of earlier findings.

Effect of Colloid Osmotic Pressure

On the basis of the Starling equation one would expect the interstitial volume to increase with decreasing colloid osmotic pressure.[17] Computer simulations have confirmed this view[26,27] and a few experimental studies[28,29] have confirmed the theoretical predictions. In one study Manning et al.[29] found a 68% decrease in plasma protein concentration over a 12-day period that decreased blood volume by 36% and plasma volume by 33%, while extracellular volume increased by 12%. An approximate calculation shows that the interstitial space would have increased by 25% to 30% under these conditions.

An alternative hypothesis is that hemodilution increases the capillary filtration rate and lymph flow, thereby lowering the interstitial colloid osmotic pressure from a "wash-down" of interstitial proteins.[18,19] This has two effects that tend to offset the plasma protein dilution and minimize the formation of interstitial edema: (1) a relocation of available protein from the interstitial to the intravascular compartment, and (2) maintenance of a relatively fixed gradient between the intravascular and interstitial oncotic pressures. Evidence in favor of this hypothesis has been presented by Aukland[18] who obtained interstitial fluid by wick catheter techniques, and observed changes over several days in rats after development of nephrosis. They showed that interstitial albumin levels were initially 50% of serum levels, but fell to near zero with a lowering of serum proteins by 50%. The intravascular to interstitial albumin gradient was relatively constant at all serum albumin levels. Zarins et al.[19] confirmed these findings, using direct lymph cannulation, but despite this apparent protective mechanism, the baboons in their study were found postmortem to have marked peripheral edema, ascites, and pleural effusions.

TABLE 4. *Reproducibility of Fluid Space Measurements on Three Consecutive Days in Volunteers in Stable Fluid Balance*

Directly Measured Variables	Percentage	Derived Variables	Percentage
Extracellular volume	4.5	Blood volume	7.0
Total body water	4.9	Interstitial volume	5.9
Plasma volume	6.3	Intracellular volume	7.3
Hematocrit	1.8	Interstitial/blood volume	11.5
Colloid osmotic pressure	3.5		

Data in patients are limited, and no correlation between interstitial compartment size and colloid osmotic pressure has been demonstrated. Ladegaard-Pedersen[11,12] could find no correlation between inulin distribution volume and colloid osmotic pressure in patients before and after major surgery. In his studies significant hemodilution was not produced, however, with the lowest COP being 23 cmH_20 and the mean 33 cmH_20. Nielsen and Engell[13–15] examined the plasma volume to extracellular volume ratio as a function of COP in major surgery patients and were unable to show any correlation. Again minimal hemodilution was seen, with the range of COP being 21 to 33 mmHg and mean 27 mmHg. In one of these studies Nielsen and Engell[15] correlated the change in interstitial fluid volume with COP in 53 major surgical patients in whom the COP range was greater, from 16 to 33 mmHg, with a mean of approximately 24 mmHg. No correlation could be shown but there was a suggestion that interstitial fluid volume was increased if COP was below 20 mmHg. Others have similarly suggested that interstitial fluid accumulates only if COP is lowered below 20 mmHg,[18,26,27] although no human data has been presented.

In the present study there was a clear increase in the interstitial volume with hemodilution, and the mean COP in the traumatized patients was 17 mmHg, with a range from 10 to 22 mmHg. It therefore seems likely that the demonstration of this correlation when it has not been shown before is due to the greater lowering of COP in our patient population *versus* the limited and more normal range observed in earlier studies.

An alternative explanation for these results is that another unidentified factor such as magnitude of tissue trauma or capillary permeability, which happens to correlate with COP, is the independent variable influencing interstitial volume. We have investigated the first possibility by separately evaluating the population of patients with ISS greater than 35 *versus* those less than 35, and the differences found appear physiologically insignificant.

Another study to evaluate the whole body permeability—surface area product as an index of permeability changes is in progress.

Permeability effects have been studied by Lucas et al.[30] in trauma patients. In their study early albumin leak was not increased. The authors concluded that the fall in plasma COP and the expansion of the interstitial fluid space were due to an alteration of the interstitial matric causing entrapment of albumin in the matrix. However the COP was not directly measured in that study, but was calculated. The use of an erroneous formula resulted in an underestimation of the plasma COP. Therefore it is not clear whether the conclusions of that paper are valid. Despite this shortcoming, the concept of the role of the interstitial matrix remains attractive and deserves further investigation.

While blood volume is only weakly correlated with COP (Fig. 2) ($r = -0.35$), both blood volume and the quotient of blood volume and interstitial volume correlate strongly with total circulating protein levels (Figs. 6 and 7). The normal controls are shown by the filled symbols and the patients are shown by open symbols. The slope of the relationship in each case between controls and patients is slightly different, and is perhaps related to the intravascular expansion by fluid administration.

It is conceivable that the total circulating protein is held constant by the interstitial protein wash-down mechanism already mentioned. This mechanism therefore fulfills a double purpose. First, the interstitial—intravascular COP difference is held constant, and second, total circulating protein is maintained. The first mechanism helps to keep the interstitial space as dry as possible, while the second mechanism maintains blood volume at adequate levels.

Methodology

The indicator dilution methodology employed in the present study is well established and we did not employ any novel methods of analysis. What is different here is the combination of nonradioactive indicators for all water spaces, which has the advantage that the measurements can be repeated as often as desired without concern about radioactive hazards to patients or investigators, or accumulation of dose with multiple studies.[20–23] The estimates of extracellular volume in volunteers are within the limits previously reported[11,25,31,32] and the increases in interstitial volume in patients correlated with the clinical impression (positive fluid balance, pitting edema). There has been some controversy in the literature over the use of bromine *versus* sulfate for measurement of the extracellular space. Bromine, which is a smaller univalent ion, is believed to penetrate poorly perfused compartments more readily, and to penetrate the intracellular compartment to a greater extent. Thus it might tend to overmeasure the interstitial space. Sulfate would not have this property, but conversely would not penetrate interstitial spaces with a low perfusion-to-volume ratio. The decay of the sulfate radioactivity curve is several times faster than bromine, and potentially leads to greater uncertainty regarding the back extrapolate to the Y-axis in determining initial indicator concentrations.

Actual data suggests that both of these indicators work effectively to estimate the extracellular space, and that differences in measured volumes are no more than 10% to 15%.[25,31,32] The changes defined in the present study are therefore not attributable to differences in the behavior of bromine *versus* sulfate.

An increase in the cellular permeability for bromine during the study period would lead to an overestimation of the extracellular compartment and an underestimation of the intracellular compartment. While we have no evidence that a change in the cellular permeability has not occurred in our patients, there is no evidence in the literature for such permeability changes.

Conclusions

(1) Post-traumatic peripheral edema resulting from hemodilution is located in the interstitial compartment, with no intracellular space expansion. (2) The expansion of the interstitial space, both in absolute terms and normalized with respect to blood volume, is inversely related to plasma colloid osmotic pressure. (3) The nonradioactive assessment of total body water, extracellular volume, and plasma volume can be routinely used in a clinical environment. Reproducibility of all fluid space measurements assessed in volunteers on three consecutive days was good and the results are consistent with those published in the literature.

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Discussion

DR. DONALD S. GANN (Baltimore, Maryland): I think we should note that, despite the fact that Dr. Böck said that all these methods were common, this is the first time that nonradioactive tracers have been combined successfully in the study of traumatized patients for the simultaneous measurement of all three body fluid compartments. I am sure that is difficult to carry out.

The finding that plasma oncotic pressure was maintained successfully despite massive noncolloid fluid administration is an interesting one, although it seems that the authors have overlooked one mechanism that may be very important in these patients. As noted first by Skillman and Moore and subsequently in our own laboratory, the administration of noncolloid fluids hydrates the interstitium and converts the colloid phase of the interstitium from a gel phase to a sol phase. This hydration permits access to the large capillary finestrae and renders the capillary permeable to albumin. As a result, extracellular fluid expansion will move protein from the interstitial compartment into the plasma. The driving force for this initially is an increase in interstitial pressure, as described by Arthur Gayton, but subsequently volume decreases without further increase in pressure and edema forms, as these workers have noted.

It seems to me then that all of the phenomena observed in this study occur clearly in the preshock state, as the authors are careful to note, and that the really interesting shifts of fluid can't be measured at the present time with these techniques. These involve the movement of fluid out of the cells in response to trauma, which does not induce shock, as first described by Stewart and Rourke in the mid 1930s. Again we have studied that, and the shift seems to be driven primarily by solute that is mobilized by the hormonal response to injury.

I would like to ask the authors if they visualize any method by which these initial shifts could be measured. Note also, that as shock develops, fluid moves into the cells as Dr. Shires and his coworkers described, thus offsetting the normal physiologic compensatory mechanism and removing the driving force for volume restitution.

The other question that I have is that these patients were studied for a very long period of time, as Dr. Böck pointed out, without significant changes in their interstitial volume. When did these patients finally diurese? They seem to have gone a whole week without doing so. I presume that they got well.

DR. C. JAMES CARRICO (Seattle, Washington): This was a difficult study that used nonradioactive (stable) tracers to evaluate body fluid distribution 48 hours after injury in patients who had received a remarkable amount of crystalloid (about 24 L).

Three points are worth considering in trying to understand the findings. They are timing, the nature of the tracers, and patient selection. Timing has already been alluded to by Dr. Gann. These patients were past the point of acute cellular changes and it is not surprising that they had significant interstitial edema. The second of the three points is the tracers and what they do. Indocyanine green dye was used to measure plasma volume. This tracer attaches to albumin, so we were looking at the albumin space and at the behavior of the albumin in these patients. I will come back to that issue in a moment. The third issue is patient selection.