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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.

These were postinjury patients, two of whom were septic and two others of whom, if I read the manuscript correctly, became septic. That may modify the behavior of the capillary membrane.

My question is based on these last two issues. You used green dye to look at albumin space and albumin behavior. You have shown some fascinating data, much of which is predictable and fits what Dr. Starling told us many years ago. But you have also shown that the slopes of the relationship between protein per gram of body weight and the interstitial volume:blood volume ratio and the slopes of the relationship between protein concentration and the blood volume:body weight ratio were different in the study patients from the control patients.

I wonder if you could postulate for us the reasons for those differences. Do you think it is simply because the interstitial space is so large? Do you think, as Dr. Gann has suggested, it is because the difference in hydrostatic drive across the capillary has changed the distribution of albumin, or is it because in some of the patients the capillary membrane is altered? In analyzing your data, did you plot the slopes in the septic patients and the nonseptic patients separately? If so, were there differences in these slopes? Such differences would imply that the capillary membrane is behaving differently in the septic patients and this might be a way to analyze the behavior of the capillary membrane.

DR. PAUL R. SCHLOERB (Kansas City, Kansas): This is a complex study of eight patients with varying degrees of trauma and two with sepsis who received an average of 30 L of fluid resuscitation, consisting of 24 L of balanced electrolyte solution and about 6 L of blood.

I, too, commend their use of the stable isotope, deuterium, which parenthetically was first used in this country by Dr. Francis Moore, with whom I had the privilege of an early association. The use of stable bromide is safe and can even be used in newborn infants. We have had several years experience now with the use of both of these tracers.

The authors showed that the extracellular fluid increased by about 55% and did not change over a period of ten days. They measured body composition every day or two during this ten-day period. This presents some problems with body compositional methodology.

The patients varied considerably, from one patient with severe eye injury and facial wounds to patients with multiple fractures, pelvic fractures with presumed retroperitoneal hematomas, to patients with abdominal sepsis. It seems reasonable to suppose that the changes may have varied among these patients. They averaged all of the patient data and have presented their data as averages. Did the septic patients develop inflammatory edema with increase in extracellular fluid? Did any of the patients undergo a decline in body water in this ten-day period? With starvation and erosion of the body cell mass, one would expect intracellular fluid to decrease, yet it remained unchanged.

At the San Francisco General Hospital nutritional support would be a conspicuous part of the treatment of these patients. Was there any correlation with nutritional support and changes in body composition values? Have you any body weight data to correlate with body composition changes?

DR. BENJAMIN F. RUSH, JR. (Newark, New Jersey): I also rise to compliment the authors on the difficult project they have undertaken and also to thank them for affording the opportunity for this convention of fluid electrolyte fans at the podium.

The techniques that are being described this morning in relation to this investigation raise echoes of much of the argument, if you will, debate, in the 1960s and early 1970s over what was really happening to water and electrolytes in the shocked patient. These authors have very carefully indicated that this is a study of the chronic problem after the period of acute shock, but previously the argument was about, of course, what was happening immediately after shock.

This is an hepatocyte from a normal rat. Twenty years ago we began to distrust our measurements of fluid compartments because we were getting so many variable results. The suggestion was made that capillaries were not retaining albumin, and for that matter, that cell membranes were not properly retaining or excluding bromine or chloride or whatever else was being used to measure the interstitial compartment. This, as I said, is one of our attempts to demonstrate that you do have some degree of intracellular edema. This is a control cell. Notice that the enlargement of electromicroscopy was 3000.

This is a cell taken from an animal after shock, and the magnification is somewhat less, but I don't think there is any question that you are looking at a cell that is showing a substantial amount of edema. Finally, over a period of 24 hours, there is a significant increase in the area of such cells if you measure a couple hundred of them from an animal after shock. The most significant increase is in the period right after shock, but at two hours and 24 hours you see that there is a substantial ongoing increase in intercellular edema. Dr. Shires, ourselves, and a number of investigators went to this extreme to look at what was happening in the cell because we no longer trusted the indicators of interstitial edema.

I would like to ask the authors if they have information that indicates that in these patients, two days after shock, bromine was not entering the cell giving them an exaggerated interstial fluid space.

DR. DONALD TRUNKEY (Portland, Oregon): I have three questions. My questions relate to previous points, but I would like to have the authors be more specific in regard to these areas.

The interstitial volume remained elevated for almost the entire period of the study, and this is out of keeping with previous human data, primarily from Dr Charlie Lucas. You never really demonstrated a phase 3 component to your resuscitation and I would like to have the information on central venous pressure and weight during that four- to five-day period when you would expect phase 3 to occur. Why did you not see this phase?

I am also concerned by the variability in the injury severity score in these patients. You had two patients with an injury severity score of 13. Most of the other patients had injury severity scores greater than 30. I wonder why you couldn't show a difference, as you postulated in your manuscript, between those two patients with an injury severity score of 13 *versus* the ones that were more severely injured? This is not predictable and I have no explanation from your manuscript.

Finally it seems to me that one of your conclusions could have been in regard to the resuscitation process itself. Your interstitial volumes are higher than those previously measured in animals and in humans. The major difference between your human model in this study is that these patients did not get whole blood, whereas previous human and animal data did get whole blood during their resuscitation.

Therefore it seems to me that one of your conclusions would be that we should return to whole blood administration to possibly minimize this large volume shift to the interstitial space in the postinjury period.

DR. FRANK R. LEWIS (Closing discussion): First, Dr. Gann, thank you for your compliments regarding the study. Indeed it is difficult to do this sort of work, and Drs. Böck and Barker deserve the primary thanks for the compulsive attention that is required to follow these patients. In regard to the hydration of the interstitial space, which occurs from the difference in solutes moving out of the cells, certainly we are aware of the work you have done in that area and believe most of that would apply during the acute shock phase. We are studying a later, more stable period, and have no reason to think solute movement plays a major role in it.

In regard to your question about methods of doing early measurements, I don't know of any way to apply this methodology for that purpose. The use of indicator dilution requires steady state kinetics, and during the acute shock phase with bleeding that would not be possible.

You asked about the long period of nondiuresis, as did Dr. Trunkey. That is partly a consequence of the way the study was done. Patients who improved during the course of the study diuresed and moved out of the intensive care unit and were dropped out of the study. By definition the patients who remained in the study for the full ten days were those who continued to have difficulty with sepsis or reoperation and therefore remained in the intensive care unit, so this study should not be taken to indicate that the antidiuretic phase does not occur in San Francisco. It is rather a manifestation of the fact that the sicker patients were the ones who remained in the study for the full period, and there were only six who did so, so that is an artifact of the way the study had to be done.

Dr. Carrico, you rightly point to increases in capillary membrane per-

meability as a possible explanation for our results. We had no method for assessing capillary membrane permeability and increases in the ratio could be caused by increases in permeability. We sought with the data we had to estimate that by simply separating the groups into those with ISS scores greater or less than 35, reasoning that the more severely injured patients might have had more capillary damage. That showed no significant difference and is not a substitute for the direct measurement of capillary permeability. Four patients in the study were clearly septic and that may have played a role, but when we looked at their data we could not show that they behaved differently from the remaining group of patients. We now have a further study underway to measure the total body permeability surface area product using albumin in order to get at that.

In regard to the accuracy of green dye: green dye binds to albumin and measures the albumin compartment in its initial decay phase, which is what we used here between two and ten minutes. If it were followed to its second logarithmic phase, one could measure a larger albumin space, but as used here the green dye method for estimating plasma volume is well accepted and is accurate.

Dr. Schloerb, all these patients were on nutritional support from the third day, and I do not think there would have been a decrease in intracellular mass based on that. In terms of your comments about possible 100% variation, I don't follow your reasoning, because we were not using differences in the intracellular mass to extrapolate to the plasma volume or the interstitial volume. In fact the coefficient of variation for each compartment was referenced to its own mean value, and I believe that the accuracies, as presented, are correct.

In terms of the use of body weights to follow patients' fluid balance—theoretically that would be excellent—but we have run into major practical difficulties in actually using it. Many of these patients are in traction and have multiple dressings that are often variably saturated. To get accurate weights one has to be absolutely certain that the sheets, blankets, pillows, dressings, traction, and so on are the same day to day. We found that very difficult to do.

With regard to diuretics, we did not use them at any time.

Dr. Rush, you questioned the use of the bromine space. There has been, as you know, controversy about bromine *versus* sulfate for the measurement of the interstitial space. Bromine typically measures a 10% to 15% larger interstitial compartment than sulfate because it penetrates poorly perfused spaces more readily, being a univalent ion. It has the advantage that it has a much longer half-time than sulfate so that the back-extrapolate to the Y axis is more accurate.

The degree of penetration of the cells in studies that have been done appear to be similar with the two indicators and I think any possible error in using one *versus* the other would be no greater than 10% or 15%, and would in no way account for the results we observed.

Dr. Trunkey, you asked about the prolonged interstitial volume augmentation. I think I have already answered that. The central venous pressure was monitored in the majority of these patients and typically was in the 10 to 14 range. Most of these patients had respiratory failure and were on ventilators.

You asked about the differences between the patients with ISS 13 and higher. There are some injuries that appeared to be coded artificially low relative to their physiologic impact. Facial injuries fall into that category, and those were the patients who had a lower ISS, including one patient who had severe pulmonary contusion.

In terms of whole blood *versus* packed cells, it is correct that the majority of these patients received packed cells. That is one of the reasons why the relative quantity of blood *versus* crystalloid is lower. The 6.5 L of blood described here is really 6.5 L of packed cells, so the equivalent is 50% to 70% greater if whole blood were used. The ratio of blood to crystalloid, therefore, appears lower than normally used.