Crystalloid vs. colloid resuscitation: Is one better?

A randomized clinical study

Richard W. Virgilio, M.D., F.A.C.S., Charles L. Rice, M.D., F.A.C.S.,
David E. Smith, M.D., F.A.C.S., David R. James, M.D., F.A.C.S.,
Christopher K. Zarins, M.D., Charles F. Hobelmann, M.D., and

The effects of hemodynamic resuscitation with protein-containing or balanced salt solution were studied prospectively in 29 patients undergoing abdominal aortic surgery. Blood loss was replaced with packed red cells and extracellular volume with either Ringer's Lactate (RL) or 5% albumin in Ringer's lactate (ALB). Fluids were given to maintain the pulmonary capillary wedge pressure (PCWP) equal to or within 5 torr above preoperative (PO) levels, the cardiac output (CO) equal to or greater than preoperative values, and the urine output at least 50 ml/hr. Serum colloid osmotic pressure (COP), CO, PCWP, the gradient between COP and PCWP (COP-PCWP), and intrapulmonary shunt (Qs/Qt) were measured PO, intraoperatively (IO), and daily for 3 days. The measured variables were similar PO in both groups. Operation time, estimated blood loss, and transfusions were similar. Total fluids received for resuscitation (day of operation) was 11.3 ± 0.8 liters (RL) and 6.2 ± 0.4 liters (ALB). Fluid balance at the end of resuscitation was 8.4 ± 0.8 liters (RL) and 3.4 ± 0.5 liters (ALB). Maximum decrease in COP was 40% (P < 0.001) in the RL group and was insignificant in the ALB group. The COP-PCWP decreased from 11 ± 1 to 2 ± 1 in RL (P < 0.001) and insignificantly in ALB. Qs/Qt increased slightly in both groups following operation but was not different between groups. Fluid balance, total fluid infused, sodium balance, total sodium infused, COP, or COP-PCWP did not significantly correlate with Qs/Qt. Two patients in the ALB group experienced pulmonary edema associated with normal COPs and elevated PCWP. There were no cases of pulmonary edema associated with low COPs and normal PCWP in the crystalloid group. These data seriously question the necessity to maintain COP by using protein-containing solutions during acute hemodynamic resuscitation. When titrated to physiological end points, even large volumes of balanced salt solutions are tolerated well.

From the Trauma Research Unit, Naval Regional Medical Center, San Diego, and the Division of Thoracic Surgery University of California, San Diego, Calif.

The primary goal of fluid resuscitation in shock and trauma is the protection of major organ function by the rapid and safe restoration of hemodynamic stability. The need for blood and the need to replenish extracellular fluid deficit with an asanguinous fluid is well established. Controversy exists, however, over what is the best asanguinous fluid in acute hemodynamic resuscitation. The two most common fluids in use today are a balanced salt solution (crystalloid) and a balanced salt solution containing albumin (colloid). The major physiological difference between the two is the addition of oncotically active albumin in the latter solution. Proponents of the use of albumin stress the importance of plasma colloid osmotic pressure in maintaining an intravascular distribution of exogenously administered fluid. Resuscitation with colloid-containing solutions maintains near-normal plasma colloid osmotic pressure and reportedly minimizes intersitial edema formation particularly in the lung. The importance of maintaining a
Table I. Associated systemic diseases

<table>
<thead>
<tr>
<th></th>
<th>Crystalloid (RL)</th>
<th>Colloid (ALB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>(angina)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

*Legend: RL, Ringer's lactate. ALB, 5% albumin in Ringer's lactate.*

Table II. Preoperative comparisons (mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Crystalloid (RL) (n = 14)</th>
<th>Colloid (ALB) (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>58 ± 2</td>
<td>58 ± 2</td>
</tr>
<tr>
<td>CI (liter/min/sq m)</td>
<td>2.9 ± 0.10</td>
<td>2.9 ± 0.11</td>
</tr>
<tr>
<td>PCWP (torr)</td>
<td>10 ± 1</td>
<td>9 ± 1</td>
</tr>
<tr>
<td>COP (torr)</td>
<td>21 ± 1</td>
<td>21 ± 1</td>
</tr>
<tr>
<td>COP-PCWP (torr)</td>
<td>11 ± 1</td>
<td>11 ± 1</td>
</tr>
<tr>
<td>Qs/Qt (%)</td>
<td>11 ± 1</td>
<td>12 ± 1</td>
</tr>
<tr>
<td>Albumin (gm/dl)</td>
<td>3.5 ± 0.1</td>
<td>3.8 ± 0.1</td>
</tr>
</tbody>
</table>

*Legend: RL, Ringer's lactate. ALB, 5% albumin in Ringer's lactate. CI, cardiac index. PCWP, pulmonary capillary wedge pressure. COP, colloid osmotic pressure. COP-PCWP, the gradient between COP and PCWP. Qs/Qt, intrapulmonary shunt.*

Table III. Intraoperative comparison (mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Crystalloid (RL)</th>
<th>Colloid (ALB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation time (hr)</td>
<td>4.5 ± 0.3</td>
<td>4.6 ± 0.4</td>
</tr>
<tr>
<td>Estimated blood loss (cc)</td>
<td>3,369 ± 381</td>
<td>3,351 ± 308</td>
</tr>
<tr>
<td>Transfusion (units)</td>
<td>7.1 ± 0.6</td>
<td>6.3 ± 0.8</td>
</tr>
</tbody>
</table>

*Legend: See Table I.*

MATERIALS AND METHODS

Patients undergoing aortic reconstructive surgery were eligible for inclusion in this study. After informed consent was obtained, patients were assigned by random number to one of two groups: either colloid (ALB) or crystalloid (RL). Before operation, each patient was weighed, and arterial, central venous, and thermistor-tipped, flow-directed pulmonary artery catheters (Edwards Laboratories, Santa Ana, California) were inserted. Baseline measurements were made of arterial pressure (BP), mean arterial pressure (MAP), central venous pressure (CVP), pulmonary artery pressure (PAP), mean pulmonary artery pressure (MPAP), and pulmonary capillary wedge pressure (PCWP). Cardiac output (CO) was measured by the thermal-dilution technique. Arterial and mixed venous blood samples were taken for measurement of PaO2, PaCO2, pH on room air and again on an FiO2 of 0.45. Arterial oxygen saturations (SaO2) were calculated, and intrapulmonary shunt (Qs/Qt) was calculated from samples obtained on an FiO2 of 0.45 using the Berggren equation. Colloid osmotic pressure (COP) was measured using a membrane osmometer, as described by Weil et al. Plasma samples were obtained for determination of total protein and albumin concentrations. Urinary sodium was measured. Standard anteroposterior chest x-rays were obtained.

Following induction of anesthesia using nitrous oxide-narcotic technique, all measurements were repeated. During the operation blood loss was measured and shed red cells were replaced on a volume-for-volume basis with centrifuged packed red cells reconstituted with equal volumes of either Ringer's lactate in the RL group or 5% albumin solution in the ALB group. In addition to the reconstituted red cells, fluids were administered by the same anesthesiologist in all patients using the following criteria: (1) maintenance of cardiac output equal to or greater than baseline level; (2) maintenance of PCWP equal to or no greater than 5 torr above baseline; (3) maintenance of base excess greater than or equal to zero; (4) maintenance of hourly urinary output of 50 cc. Patients in the ALB group received reconstituted lactated Ringer's solution with 50 gm of human albumin/liter added (5% solution).

After operation all patients were transferred to the Trauma Research Unit where fluid management with the same solutions was continued using the above criteria until the following morning. Thereaf-
ter, both groups received maintenance fluids of 5% dextrose in half-normal saline to which potassium chloride was added. Following operation patients were placed on a Bennett MA-1 ventilator using the intermittent mandatory ventilation mode. Ventilator rates were set at 8/min with a tidal volume of 15 cc/kg. Weaning was begun immediately and was completed when a patient had maintained an arterial pH of greater than 7.38 on a ventilator rate of 1 for 2 hours. All measurements, including chest x-ray, were repeated that day, the following morning, and daily for 3 days. Strict fluid intake and output was recorded on each patient. Weight, serum COP, and serum albumin were measured daily for 7 days.

Daily and cumulative fluid and sodium balances, intrapulmonary shunt, and COP-PCWP gradients were calculated for each patient at each observation point. For the calculation of mean wedge pressures in a given period, each patient's values were averaged, and the resultant value was used for the calculation of group means. Contrasts were sought using analysis of variance, multiple linear regression, Fisher's exact test, and Student's *t* test, where appropriate. Significance was attributed to *P* < 0.01.

**RESULTS**

Fourteen patients were assigned to the RL group and 15 patients were assigned to the ALB group. Age of the groups was 58.6 ± 2 and 58.2 ± 3 years, respectively (mean ± SEM). Both groups were well-matched for associated systemic diseases (Table I). There were three aneurysctomies and 11 aortofemoral bypasses in both groups; one patient in the ALB group underwent renal artery reconstruction only.

Preoperative measurements (Table II) and intraoperative variables (Table III) in the two groups were comparable. Fluid replacement data are summarized in Table IV. Intraoperative urinary output was 145 ± 26 ml/hr in the RL group and 139 ± 29 ml/hr in the ALB group and remained comparable until day 2 when the RL group began to diurese. Fluid replaced intraoperatively in the RL group was 5,860 ± 584 ml and 3,425 ± 465 ml in the ALB group. The amount of intraoperative transfusions in the RL group (7.1 ± 0.6 units) was slightly but not significantly higher than in the ALB group (6.3 ± 0.8 units). However, the initial hematocrit after operation was significantly higher in the RL group (43 ± 2%) than in the ALB group (35 ± 2%), but by 24 hours following operation was not different (36 ± 2% vs. 34 ± 2%). There also was no difference between groups in postoperative transfusion requirements (1 unit in each group). After operation the RL group required 315 ± 31 ml/hr and the ALB group 167 ± 16 ml/hr to maintain physiological stability. The total fluid requirement for the operative day was 11.3 ± 0.8 liters in the RL group and 6.2 ± 0.4 liters in the ALB group. The net fluid balance at the end of the operative day was 8.4 ± 0.8 liters and 3.4 ± 0.5 liters, respectively.

Although the ALB group had a higher cardiac index and a higher pulmonary capillary wedge pressure in the immediate postoperative period than did the RL group, both were within the criteria established for fluid replacement; there was no difference between the two groups by the next day.
Table V. Cardiopulmonary data (mean ± SEM)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Before operation</th>
<th>After operation</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI (liters/min/sq m)</td>
<td>Crystalloid</td>
<td>2.9 ± 0.1</td>
<td>3.1 ± 0.2</td>
<td>3.5 ± 0.2†</td>
<td>4.2 ± 0.1†</td>
<td>3.9 ± 0.5†</td>
</tr>
<tr>
<td></td>
<td>Colloid</td>
<td>2.9 ± 0.1</td>
<td>3.9 ± 0.2†</td>
<td>3.7 ± 0.2†</td>
<td>3.9 ± 0.3†</td>
<td>4.1 ± 0.3†</td>
</tr>
<tr>
<td>PCWP (torr)</td>
<td>Crystalloid</td>
<td>10 ± 1</td>
<td>11 ± 1</td>
<td>11 ± 1</td>
<td>10 ± 1</td>
<td>10 ± 4</td>
</tr>
<tr>
<td></td>
<td>Colloid</td>
<td>9 ± 1</td>
<td>14 ± 1†</td>
<td>13 ± 1†</td>
<td>11 ± 1</td>
<td>11 ± 1</td>
</tr>
<tr>
<td>Qs/Qt (%)</td>
<td>Crystalloid</td>
<td>11 ± 1</td>
<td>15 ± 1†</td>
<td>15 ± 1†</td>
<td>18 ± 1†</td>
<td>17 ± 3†</td>
</tr>
<tr>
<td></td>
<td>Colloid</td>
<td>11 ± 1</td>
<td>16 ± 1†</td>
<td>16 ± 1†</td>
<td>16 ± 1†</td>
<td>15 ± 1†</td>
</tr>
</tbody>
</table>

Legend: See Tables II and IV.
*Difference between groups (P < 0.01).
†Difference from preoperative values with group (P < 0.01).

Table VI. Oncotic data (mean ± SEM)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Before operation</th>
<th>After operation</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
<th>D5</th>
<th>D6</th>
<th>D7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin mg/dl</td>
<td>Crystalloid</td>
<td>3.5 ± 0.1</td>
<td>2.5 ± 0.1†</td>
<td>2.4 ± 0.1†</td>
<td>2.4 ± 0.1†</td>
<td>2.4 ± 0.1†</td>
<td>2.7 ± 0.1†</td>
<td>3.1 ± 0.1</td>
<td>3.1 ± 0.1</td>
<td>3.1 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>Colloid</td>
<td>3.8 ± 0.1</td>
<td>4.7 ± 0.1†</td>
<td>4.5 ± 0.1†</td>
<td>4.2 ± 0.2</td>
<td>3.9 ± 0.1</td>
<td>3.9 ± 0.1</td>
<td>4.0 ± 0.3</td>
<td>3.9 ± 0.2</td>
<td>3.9 ± 0.1</td>
</tr>
<tr>
<td>COP (torr)</td>
<td>Crystalloid</td>
<td>21 ± 0.4</td>
<td>13 ± 1</td>
<td>13 ± 1</td>
<td>15 ± 0.5</td>
<td>17 ± 0.5</td>
<td>19 ± 1</td>
<td>20 ± 1</td>
<td>21 ± 1</td>
<td>22 ± 1</td>
</tr>
<tr>
<td></td>
<td>Colloid</td>
<td>21 ± 1</td>
<td>20 ± 1</td>
<td>21 ± 1</td>
<td>21 ± 1</td>
<td>22 ± 1</td>
<td>23 ± 1</td>
<td>24 ± 1</td>
<td>24 ± 1</td>
<td>24 ± 1†</td>
</tr>
<tr>
<td>COP-PCWP (torr)</td>
<td>Crystalloid</td>
<td>11 ± 1</td>
<td>2 ± 1†</td>
<td>3 ± 1†</td>
<td>5 ± 1†</td>
<td>10 ± 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Colloid</td>
<td>11 ± 2</td>
<td>6 ± 1</td>
<td>7 ± 1</td>
<td>9 ± 1</td>
<td>11 ± 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Legend: See Tables II and IV.
*Difference between groups (P < 0.01).
†Difference from preoperative values within group (P < 0.01).

The cardiopulmonary effects of this fluid replacement is shown in Table V. The Qs/Qt rose slightly in both groups but was not statistically different between the two groups.

The most striking difference between the two groups was in the protein-related variables (Table VI). There was a significant postresuscitation fall in albumin in the RL group that returned to preoperative levels on day 5. COP was decreased markedly in the RL group as compared with the ALB group and as compared with preoperative levels (40% decrease) and did not return to baseline levels until the fifth day after operation. By contrast in the ALB group, COP was maintained at the preoperative level throughout the study period. In the RL group there was an 80% decrease in COP-PCWP from the preoperative value (P < 0.01). This was secondary to decreasing COP and not to elevated PCWP. There were seven patients in whom PCWP exceeded COP. In the ALB group the decrease in COP-PCWP was secondary to an increase in PCWP and was not statistically significant. The mean time on the ventilator was 23 hours in both groups. Two patients in the ALB group developed pulmonary edema immediately after operation. These two instances occurred following infusions of 100 cc of 5% albumin solution. They were manifested by a frothy tracheal exudate, marked perihilar congestion and alveolar edema on chest x-ray, and a PCWP of 25 or greater with a stable COP. Both patients were treated with digitalis, fluid restriction, and diuretics and had prompt resolution of their pulmonary edema. With the exception of these two patients, none of the other patients in either group demonstrated any roentgenographic or clinical signs of pulmonary failure. The mean intensive care unit time for both groups was 4 days. No patients required the use of positive end-expiratory pressure.
Table VII. Sodium balance data (mean ± SEM)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>D0</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Intake (mEq)</td>
<td>Crystalloid</td>
<td>1,445 ± 120</td>
<td>*</td>
<td>473 ± 217</td>
<td>371 ± 190</td>
</tr>
<tr>
<td></td>
<td>Colloid</td>
<td>843 ± 83</td>
<td>241 ± 29</td>
<td>170 ± 10</td>
<td>150 ± 18</td>
</tr>
<tr>
<td>Sodium output (mEq)</td>
<td>Crystalloid</td>
<td>282 ± 40</td>
<td>396 ± 86</td>
<td>424 ± 75</td>
<td>290 ± 71</td>
</tr>
<tr>
<td></td>
<td>Colloid</td>
<td>205 ± 34</td>
<td>250 ± 64</td>
<td>226 ± 63</td>
<td>288 ± 88</td>
</tr>
</tbody>
</table>

Legend: See Table IV. *Difference between groups (P < 0.01).

There were two deaths, one in each group, occurring 2 and 2½ weeks after operation, both secondary to myocardial infarctions.

Body weight rose dramatically in the RL group and moderately in the ALB group in the first 3 days after operation. By the fourth day after operation, there was no difference between the groups. The mean weight gain reached its maximum on day 2 and was 8.7 kg in the RL group and 4.1 kg in the ALB group. This represented a 12% weight gain in the RL group and a 6% gain in the ALB group. Body weight in both groups had returned to baseline by the end of the first week. The RL group received a total of 1,445 ± 120 mEq of sodium, whereas the ALB group received 843 ± 83 mEq (P < 0.01) (Table VII). The positive fluid balance and weight gain was matched by positive sodium balance, and with diuresis the excretion of sodium paralleled the water excretion.

Intrapulmonary shunt, although not different between groups, did rise following operation. While this difference from baseline was statistically detectable at postoperative days 1, 2, and 3, it was clinically insignificant. To determine if COP-PCWP, COP, total sodium intake, sodium balance, total fluid infused, or fluid balance influenced Qs/Qt, linear regressions were performed of Qs/Qt on each of these variables. No linear relationships could be detected by these multiple linear regressions. A representative of these regressions is shown in Fig. 1.

DISCUSSION

The purpose of this prospective study was to compare the systemic effects of resuscitation with crystalloid or colloid solutions in a group of patients undergoing abdominal aortic surgery. These patients were selected for study because they were a high-risk group, and past experience indicated that their operations would require significant replacement of both blood and asanguinous fluid in order to maintain hemodynamic stability. Randomization resulted in two groups that were comparable in age, well-matched for associated diseases, and similar in all of their preoperative physiological measurements. All patients were treated by the same group of anesthesiologists and surgeons, resulting in similar length of operation, blood loss, transfusions, fluid replacement, and postoperative care in both groups. In this older population with serious associated diseases, the length of operation and significant blood loss (70% of estimated blood volume) constituted a significant physiological insult.

In the present study, fluids were titrated to maintain left heart filling pressures (PCWP) and cardiac output at each patient's own preoperative level. Care was taken to give only enough fluid to maintain PCWP equal to or no greater than 5 torr above the preoperative level. This method of controlling fluid infusion resulted in a cardiac output greater than the preoperative level and adequate urinary output. Formulas for fluid administration, which might lead to inadequate or excessive fluid intake resulting in hypovolemia, pulmonary edema, or heart failure, purposely were avoided. During the operation the RL group required twice as much fluid and sodium as did the ALB group to maintain PCWP and cardiac output at preoperative levels. This fluid requirement of 1,100 cc/hr in this group is almost twice that generally reported for similar operations. The use of centrifuged packed red cells rather than whole blood can account for this difference, as there is two thirds less plasma in each unit of packed cells than whole blood. In the first 12 to 16 hours after the completion of the operation, both groups of patients required infusions of additional fluid above maintenance fluid level to maintain PCWP and cardiac output. The RL group again required twice as much fluid (315 cc/hr) as did the ALB group (167 cc/hr). By 24 hours after operation,
the need for this additional fluid had ceased, and both groups of patients required only maintenance fluids of one half of the strength of normal saline solution in 5% dextrose. The net fluid balance at the end of resuscitation in the RL group was twice that of the ALB group and was associated with significant peripheral edema. This was confirmed by the 12% weight gain in the RL group as compared with the 6% gain in the ALB group. The magnitude of the positive fluid balance and weight gain for the RL group is similar to that found in baboons similarly resuscitated by Moss, et al.\textsuperscript{19} Despite the large weight gain and peripheral edema in this group, there was no physiological (Qs/Qt), radiographic (chest x-ray), or clinical (need for assisted ventilation, positive end-expiratory pressure, or supplemental oxygen) evidence of pulmonary edema.

It was difficult in both groups to maintain wedge pressures at precisely the preoperative level. In the RL group rapid filtration of fluid to form peripheral edema required continued supplemental infusions of 200 to 500 cc over a period of 30 minutes to maintain PCWP. When PCWP fell because infusion of RL was inadequate, tachycardia, hemoconcentration, and oliguria occurred and were reliable clinical signs of the deficit. In the ALB group PCWP tended to rise above the preoperative level with infusions of as little as 50 or 100 cc of albumin solution over 30 minutes. Two patients developed pulmonary edema after small infusions of albumin to correct a fall in PCWP. Both had preoperative evidence of compromised left ventricular function and did not tolerate small increases in PCWP resulting from the colloid infusion.
Fig. 2. There was an 80% fall in the COP-PCWP gradient following resuscitation in the crystalloid group. This fall was secondary to the 40% decrease in COP after operation and not secondary to any changes in the PCWP which was maintained at preoperative levels throughout the study.

The Starling equation defines the relation between colloid osmotic pressures and hydrostatic pressures:

\[ M = K_{hi} (P_h - P_i) - \sigma (\Pi_i - \Pi_w) \]

where \( M \) is volume of fluid filtered from blood to the interstitial space; \( K_{hi} \) is the permeability constant per unit of effective exchange area; \( \sigma \) is the reflection coefficient; \( P_h \) is capillary hydrostatic pressure; \( P_i \) is the interstitial hydrostatic pressure; \( \Pi_i \) is the plasma colloid osmotic pressure; and \( \Pi_w \) is the interstitial colloid osmotic pressure.

This equation predicts that a rise in \( P_h \) or its close equivalent, PCWP, or a fall in \( \Pi_i \) (COP), or a rise in \( \Pi_w \), would increase filtration of fluid from the vascular bed. A rise in \( P_i \), the tissue pressure would decrease fluid filtration. An increase in capillary permeability, \( K_{hi} \), also would result in an increased escape of fluid from the vascular bed. A number of investigators have studied the application of Starling’s equation to the lung, particularly the relationship between COP of plasma and pulmonary capillary wedge or left atrial pressure.\(^6\) \& \(^7\) Guyton and Lindsey\(^8\) demonstrated a relationship between fluid accumulation in the lung and the difference between capillary hydrostatic pressure and plasma colloid osmotic pressure. Levine et al.\(^9\) \& \(^10\) showed that, in addition to these capillary forces, the tissue forces \( \Pi_i \) and \( P_i \) significantly effected fluid filtration. In both studies hydrostatic pressure was elevated and COP was lowered simultaneously.

The use of only packed red blood cells for blood replacement in our patients magnified the postresuscitation oncotic differences between our two groups. This allowed us to effectively compare the influence of decreasing plasma colloid osmotic pressure and changes in gradient between colloid oncotic pressure and PCWP (COP-PCWP) on pulmonary gas exchange. The 40% decrease in COP from preoperative levels in the RL group coupled with the maintenance of PCWP resulted in a marked reduction (80%) of the COP-PCWP gradient following resuscitation (Fig. 2). In all patients in this group, the COP-PCWP gradient fell below 3 torr, and the gradient was negative in seven patients. However, none of these patients developed pulmonary edema. Pulmonary edema did develop in two patients receiving colloid who had elevated PCWP, normal COP, and slightly decreased COP-PCWP gradient (Fig. 3). This suggests that the initiating factor in the pulmonary edema was an increase in hydrostatic
pressure and not the fall in COP-PCWP gradient.

In another study from our laboratory designed to mimic the clinical situation in our RL group, baboons were subjected to repeated plasmapheresis while PCWP was maintained by Ringer's lactate infusion. No pulmonary edema could be detected in these animals by changes in Qs/Qt, compliance, or wet-to-dry lung weights, despite a drop in COP, reduction in COP-PCWP, and weight gain similar to that seen in our patients. Analysis of all of the forces active in the Starling equation in this experimental model demonstrated that the primary force preventing edema in these animals was an increased tissue pressure. It seems likely that the same explanation holds true in our RL group.

A key issue in all human studies such as ours is the criteria used for determining the presence of pulmonary edema. The most accurate measure of increase in lung water or pulmonary edema is to weigh the lungs, as was done in our baboon studies. In clinical studies isotope dilution techniques for measuring pulmonary extravascular water, chest roentgenograms, lung compliance, and intrapulmonary shunt have been utilized to quantitate pulmonary edema. We chose determination of intrapulmonary shunt as the most clinically useful index of significant pulmonary edema.

Skillman, Restall, and Salzman studied the difference between resuscitation with colloid and electrolyte in a group of patients similar to ours. Whole blood was used to replace blood loss, and fluid was given by formula and not based on measurements of hemodynamic function. Moreover, their electrolyte group received 31 gm of albumin after operation (on the day of operation), and, because of “ethical considerations,” received an additional 69 gm on the first day after operation. As a result, the postoperative albumin levels in the electrolyte group were not significantly changed from preoperative values. This is in contrast to the marked fall in albumin and COP in our RL group. In this study alveolar-arterial oxygen gradient on 100% oxygen (A-aPAO2) was used to diagnose pulmonary edema. The higher postoperative A-aPAO2 in the electrolyte group was interpreted as demonstrating increased pulmonary extravascular water. Sodium intake correlated linearly with A-aPAO2 in these patients. Our RL patients received more sodium.
Fig. 4. After operation the A-aDO₂ was significantly higher in the crystalloid group at a time when the intrapulmonary shunts were similar in both groups. This difference in A-aDO₂ reflects the difference demonstrated in cardiac outputs after operation and does not represent differences in pulmonary gas exchange properties. Therefore, A-aDO₂ should not be used as a measurement of pulmonary dysfunction. By day 1, when the cardiac outputs between the two groups were comparable, so were the A-aDO₂ measurements.

(1,400 vs. 500 mEq), had a higher positive fluid balance (9 vs. 4 liters), gained more weight (8 vs. 3 kg), had lower COPs (13 vs. 22 torr), yet we found no differences in postoperative pulmonary function between the electrolyte and colloid groups. In our patients there was no correlation between sodium intake or balance, fluid intake or balance, plasma COP, or COP-PCWP and intrapulmonary shunt.

The difference between our findings and Skillman et al.’s may be attributed to his use of A-aDO₂ measured during 100% oxygen breathing as an index of pulmonary edema. The A-aDO₂ can be influenced as much by changes in cardiac output as by changes in pulmonary gas exchange. Several authors have shown that 100% oxygen breathed for even short periods of time can change low ventilation-perfusion units into true shunt units. Therefore, accurate determination of changes in pulmonary gas exchange requires measurement of intrapulmonary shunt using mixed venous oxygen samples on a fraction inspired oxygen level which is low enough to prevent absorptive atelectasis but high enough to eliminate desaturation of blood due to moderately low ventilation units. This was accomplished in our study by using mixed venous oxygen samples on a FIO₂ of 0.45.

Skillman et al. did not measure cardiac output or mixed venous oxygen level, but did report a lower plasma volume in the electrolyte group. This lower plasma volume would be likely to result in a lower cardiac output, and thus in a lower mixed venous oxygen content. If the mixed venous oxygen content was lower in the electrolyte group, a large A-aDO₂ would result without a change in Qs/Qt. In fact, when we calculated the A-aDO₂ in our patients, the immediate postoperative A-aDO₂ levels were higher in the RL group than in the ALB group, yet Qs/Qt was identical. At this time, cardiac output was
significantly lower in the RL group (Fig. 4). With additional fluid infusion in the RL group, cardiac output and A-$\text{a}O_2$ became comparable with those of the ALB group. The only three patients in Skillman et al.'s series who went into clinical pulmonary edema received excess Ringer's lactate. The excess amount of fluid in these patients may have elevated PCWP and caused left ventricular failure.

Weil and his associates have been interested in the relationship between the COP-PCWP gradient and the development of pulmonary edema. They concluded that when the COP-PCWP gradient declines below 9 torr, there is a substantial risk of pulmonary edema, especially when the decreasing gradient is secondary to decreases in colloid osmotic pressure. They studied patients with acute myocardial infarctions with and without pulmonary edema. They found that all the patients who developed pulmonary edema had a COP-PCWP gradient below 3 torr. Pulmonary edema was diagnosed radiographically using a modification of Turner's scale of assessing edema on portable supine anteroposterior chest x-rays. Even though the $\text{Fi}_O_2$ measurements were variable, there was no statistical difference between the $P_aO_2$ measurements in patients with or without pulmonary edema, as defined radiographically. Therefore, one has to question the clinical significance of the radiographic diagnosis of pulmonary edema when there appeared to be no difference in gas exchange between the groups with or without pulmonary edema.

In our studies we used the oncometer developed by Weil et al. to measure COP. Our preoperative COPs were nearly identical to the resting COP found in their patients. All patients in our RL group had a COP-PCWP gradient of less than 3 torr, and seven patients had a negative gradient, and yet there was no physiological, radiographic, or clinical evidence of pulmonary edema.

Stein, Weil, et al. studied the effect of infusion of either crystalloid or colloid in hypovolemic patients. The fluid was infused in aliquots of 50 to 200 cc over 10 minutes. Sixteen patients developed pulmonary edema, seven received only colloid, and seven received only Ringer's lactate. Two additional patients received both Ringer's lactate and colloid. Once again, radiographic criteria were used to diagnose pulmonary edema and no mention was made of arterial blood gas data.

Review of the data shows that patients who were resuscitated with colloid and who developed pulmonary edema had a normal colloid osmotic pressure and significant elevation (11 to 19 torr) of the left ventricular filling pressure (LVFP). The decrease in the COP-PCWP gradient (+6 to 0 torr) was secondary to an increase in the hydrostatic pressure. These gradients were significantly lower than those in the crystalloid group who developed pulmonary edema. The gradients in patients who developed pulmonary edema with LVFP below 18 torr were not significantly different from the gradients in patients who did not develop pulmonary edema. This would suggest that decreasing gradients are important in the development of pulmonary edema only when that decrease is secondary to increases in hydrostatic pressure with or without concomitant decreases in COP. In our RL group, as long as we did not allow the pulmonary vascular pressure (PCWP) to increase, the level of COP was of little clinical significance. Patients with clinical pulmonary edema in both Weil et al.'s and our study who responded successfully to treatment (diuretics, digitalis) demonstrated dramatic decreases in hydrostatic pressure with little change in COP.

Resuscitation with albumin-containing fluid is based on two major concerns: hypoalbuminemia favors the accumulation of fluid in the interstitium of the lung, and use of a colloid solution is necessary to adequately replace and maintain plasma volume. Since we did not measure pulmonary extravascular water, one may question the assumption that the lack of physiological, radiographic, or clinical evidence of pulmonary edema is proof that there was no associated increase in pulmonary extravascular water in the RL group. However, if there was, we could not demonstrate any resultant morbidity. Since we could find no detrimental effects from even marked reductions in serum oncotic pressure, it is difficult to accept the hypothesis that the use of albumin-containing solutions is essential during hemodynamic resuscitation.

Our ability to maintain pulmonary capillary wedge pressure, cardiac output, and urinary output without the benefit of significant colloid replacement, again, is indirect evidence that plasma volume was replaced adequately in the RL patients. To do so, however, requires approximately twice the volume as when a colloid solution is used. Unless one is titrating fluid administration to physiological parameters such as left heart filling pressures and cardiac outputs, the tendency is to underresuscitate when using an electrolyte solution. This is especially true because of the redistribution of this noncolloid solution into the interstitial space. Also one must
guard against interpreting weight gain and peripheral edema as overexpansion of intravascular volume. This interpretation will lead to inadequate volume replacement with its cardiovascular sequelae.

If definite physiological end points are used for fluid administration, restoration of normal physiology and normal organ function can be accomplished with or without the use of colloid. Since the cost of albumin can be 50 times as great as that of crystalloid solutions, the rational decision must favor the use of a crystalloid solution with packed cells for resuscitation following trauma, major surgery, or shock.

REFERENCES