Perioperative Fluid Management

Donald S. Prough, MD, and Christer Svensen, MD, PhD

Although most aspects of perioperative fluid management have remained relatively constant for more than two decades, new concepts and practices are currently evolving. Until the mid-to-late 1960s, the prevailing strategy of perioperative fluid management was rigid restriction (1). After Shires et al. (2,3) convincingly demonstrated that major surgery and trauma were associated with fluid requirements that substantially exceeded usual maintenance fluid rates, perioperative volume replacement became much less restrictive. However, recent evidence suggests that excessive perioperative fluid infusion may be a frequent problem. Arieff (4) estimated, based on a 1-yr retrospective review of patients undergoing major surgery at two university medical centers in the US, an annual incidence of 8000 to 74,000 cases of postoperative pulmonary edema, including a frequency of 2.6% in patients without important comorbidities. Currently, investigators are applying kinetic analysis, using principles similar to those of pharmacokinetics, to better define responses to perioperative fluid administration, especially in situations involving pharmacologic or physiologic perturbations (5).

In the 1970s, considerable controversy revolved around the question of whether crystalloids or colloids were preferable for perioperative management. Although apparently resolved in favor of crystalloids, the controversy has arisen again as current investigators have performed meta-analyses of previous comparisons. Development of new colloid solutions, in terms of the characteristics of both the colloids and their diluents, promises to reduce problems associated with existing formulations. Research into the components of conventional crystalloid solutions may even prompt revisions in the composition of these common anesthetic tools.

This review will focus on several areas of research that are changing clinical practice, including the following:

1. The kinetics of plasma volume expansion produced by IV fluids
2. Recent developments in colloid solutions
3. Specific components of available fluids

The Kinetics of Plasma Volume Expansion Produced By IV Fluids

Principles

Conventional prediction of plasma volume expansion (PVE) after fluid infusion assumes that retained fluid (infused fluid minus excreted fluid) is distributed across body fluid spaces based on the volumes of physiologic fluid spaces (Table 1) and the Starling equilibrium, which governs the distribution of isonatremic, noncolloid fluids between PV and the ISF (the two components of ECV). The Starling equilibrium is defined as follows:

\[ Q = kA\left[(P_c - P_i) + \sigma(\pi_c - \pi_i)\right] \]

where \( Q \) = fluid filtration, \( k \) = capillary filtration coefficient (conductivity of water), \( A \) = the area of the capillary membrane, \( P_c \) = capillary hydrostatic pressure, \( P_i \) = interstitial hydrostatic pressure, \( \sigma \) = reflection coefficient for albumin, \( \Pi_c \) = interstitial colloid oncotic pressure, and \( \Pi_i \) = capillary colloid oncotic pressure. The surprisingly small proportion (<0.5%) of osmotic activity contributed by plasma proteins is essential in determining the equilibrium between IFV and PV. If serum osmolality is normal, total osmotic pressure exceeds 5400 mm Hg, only 24 mm Hg of which is colloid osmotic (oncotic) pressure.

The following equation predicts the effects at equilibrium of fluid infusion on PVE (and assumes that no fluid is excreted):

\[ \text{PVE} = \frac{V_d}{V_{\text{d}}} \times \left( \frac{V_{\text{d}}}{V_{\text{a}}} \right) \]

where \( V_{\text{d}} \) = distribution volume (Table 1). For example, an infusion of 500 mL of 5% dextrose in water, a sodium-free fluid, would equilibrate across a Vd equal to TBW (60% of total body weight). Therefore, that infusion would result in PVE = 500 mL \( \times \) (3/42) or 36 mL, if no water were excreted. Infusion of 500 mL of lactated Ringer’s solution (LRS) or 0.9% saline, for which Vd = ECV (20% of total body weight), would result in PVE = 500 mL \( \times \) (3/14) = 107 mL. Fluids containing colloids such as albumin, dextran, or HES preferentially expand PV rather than IFV or ICV. In general, isooncotic, saline-based colloid solutions will

---

**Table 1**

<table>
<thead>
<tr>
<th>Fluid Space</th>
<th>Volume (TBW)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>20%</td>
</tr>
<tr>
<td>Intracellular fluid</td>
<td>60%</td>
</tr>
<tr>
<td>Extracellular fluid</td>
<td>20%</td>
</tr>
</tbody>
</table>

---
produce PVE approximately equal to the infused volume; hyperoncotic fluids will result in greater PVE. Hyperosmotic fluids, e.g., 7.5% saline, increase venous return primarily by translocating intracellular fluid into PV (6). However, hypertonic saline infusions also transiently increase ECV through osmotic attraction of fluid from the IFV into the PV.

However, kinetic analysis of PVE after fluid infusion more clearly represents probable clinical effects by accounting for total clearance of infused fluid from the circulation (7–9). Kinetic analysis of PVE replaces static assumptions with dynamic data and serves the same purposes as pharmacokinetic analysis of drug concentrations, e.g., estimating peak effects and rates of clearance. Both the effects of a bolus of fluid on PVE and the rates of infusion necessary to maintain any given level of plasma dilution can be predicted by kinetic modeling (8). Perhaps the most powerful concept of volume kinetic analysis is the mathematical demonstration of a physiologic “target volume” that intravascular volume will approach, usually quite rapidly, after a perturbation. For instance, when an isotonic crystalloid fluid or a hypertonic fluid is infused in unanesthetized volunteers, the proportion remaining in the vascular tree decreased rapidly; colloid persisted somewhat longer but still rapidly approached the original target volume (7). However, after mild hemorrhage in conscious volunteers, a greater proportion of infused isotonic crystalloid remained in the vascular tree than after fluid infusion in normovolemic volunteers (Fig. 1) (10), suggesting that more infused fluid must be retained intravascularly because hemorrhage had reduced intravascular volume below the target volume.

The effects of anesthetics and other pharmacologic interventions on volume kinetics have not been described in detail. However, the kinetics of IV saline have been compared in isoflurane-anesthetized and conscious sheep in a cross-over study (11). In conscious sheep, as in conscious humans, infusion of an isotonic crystalloid resulted in transient PVE, that rapidly resolved, primarily through urinary elimination (Fig. 2) In isoflurane-anesthetized sheep, PVE resolved equally rapidly but not as a result of urinary elimination; rather, the fluid eliminated from the intravascular volume appeared to accumulate in the IF space.

Subsequent work demonstrates that isoflurane rather than mechanical ventilation is responsible for the transfer into the IF space (12). Interactions between fluid infusion and pharmacologic interventions require continued study. Preliminary work from our laboratories, for example, suggests that various catecholamine infusions markedly influence the intravascular retention of infused fluids.

Interactions between surgical trauma and fluid kinetics also require further study. In particular, it is important to separate the influence of anesthesia from the influence of surgical procedures. Surgical trauma has long been associated with acute sequestration of IF. In otherwise healthy patients who received sodium-free fluid during open upper abdominal surgery, ECV decreased nearly 2 L and glomerular filtration rate (GFR) acutely declined by 13%; in contrast, patients who received LRS maintained ECV and increased GFR by 10% (13). During the first 10 days after resuscitation from multisystem trauma, patients demonstrated an increase in total body weight and a 55%
increase in IFV (more than 5.0 L in a 70-kg patient) (14). Accumulated fluid mobilizes and returns to the PV, most commonly on the third postoperative day. If the cardiovascular and renal systems are unable to compensate, hypervolemia and pulmonary edema may occur. However, the contributions of tissue trauma, anesthesia, and complicating infection require clarification.

Although current perioperative fluid management usually avoids hypovolemia, no tools are currently available to permit precise matching of fluid administration to fluid needs. Although this may result in inadequate fluid administration, an equally important problem is excessive perioperative fluid infusion. Arieff (4) reported 13 episodes of fatal postoperative pulmonary edema, apparently related to large volumes of perioperative fluid. He also estimated, based on a 1-yr retrospective review of patients undergoing major surgery at two university medical centers, an annual incidence of 8000 to 74,000 cases of postoperative pulmonary edema in the US (4). Most troubling was the observation that 2.6% of patients without important comorbidities developed pulmonary edema, and of these patients, 3.9% died (4).

Another troubling aspect of current fluid management is that the rapidity with which fluid is administered may influence immune function. In mice subjected to surgical trauma and shock, slower fluid resuscitation (over 120 min) was associated with more rapid restoration of normal immune function than resuscitation over 30 or 60 min (15).

These studies, combined with clinical experience, suggest the following conclusions: 1) the ability of perioperative physicians to accurately evaluate blood volume is not optimal; 2) the ability of perioperative physicians to accurately evaluate tissue perfusion is not optimal; 3) the ability of perioperative physicians to accurately identify fluid overload is not optimal; 4) the ability of perioperative physicians to accurately identify hypovolemia is not optimal; and 5) the ability of perioperative physicians to accurately define the correct rate of fluid resuscitation is not optimal.

Oxygen Delivery as a Goal of Perioperative Fluid Management

The lack of a simple, objective method of defining and achieving adequate fluid resuscitation represents an ongoing deficiency in perioperative fluid management. One promising goal is to restore a target level of systemic oxygen delivery (DO2), based on evidence that unrecognized, subclinical tissue hypoperfusion results in postoperative complications (e.g., acute renal failure, hepatic failure, and sepsis) and that these complications can be reduced by DO2 enhancement. In a single term, DO2 combines cardiac output (Q) and arterial oxygen content (CaO2), according to the equation:

\[ \text{DO2} = Q \times \text{CaO2} \times 10 \]

where the factor 10 corrects CaO2 in mL O2/dL to mL O2/L.

In high-risk surgical patients who survive, average Q and DO2 are greater than in those who succumb to critical illness (16). Survival is strongly associated with a DO2 ≥ 600 mL O2 · min⁻¹ · m⁻² (16) (equivalent to a cardiac index of 3.0 L·min⁻¹ · m⁻², a Hb concentration of 14 g/dL, and 98% oxyhemoglobin saturation). In attempting to increase DO2, several principles should be kept in mind. First, the use of crystalloid or colloid fluids to increase Q will also decrease Hb concentration; therefore, the net effect on DO2 will depend on whether the increase in Q or the decrease in Hb concentration predominates. Second, primarily increasing Hb concentration with blood transfusion will often result in a reciprocal decrease in Q; again the net effect must be measured. Third, infusion of catecholamines, often necessary to achieve targeted DO2 end points, exerts drug-dependent effects on tissue perfusion and may have different effects on outcome. Fourth, other end points, such as lactate or gut intramucosal pH (pHi), might ultimately prove to be superior to nonselectively increasing DO2, although evidence is inconclusive at this time.

Several recent trials illustrate the difficulties in resolving the question of whether targeted hemodynamic perioperative management improves outcome. Bishop et al. (17) advocated DO2 ≥ 600 mL O2 · m⁻² · min⁻¹ for resuscitation of trauma patients based on data suggesting better outcome. However, Velmaudios et al. (18), in a later study of trauma patients at the same institution, found that trauma patients randomized to receive either conventional management or maintenance of DO2 ≥ 600 mL O2 · m⁻² · min⁻¹ did not differ in outcome, although patients in the conventional management group who spontaneously achieved DO2 ≥ 600 mL O2 · m⁻² · min⁻¹ and patients in the treatment group who therapeutically achieved that level had a much better outcome than patients from either group who failed to achieve that end point (Table 2). Patients in the treatment group who failed to achieve the end point had a particularly poor outcome, perhaps suggesting some adverse effect of aggressive hemodynamic therapy in vulnerable patients.

Some clinicians are concerned that interventions used to increase DO2 to specific targets may actually be detrimental (19). Tachycardia, a known side effect of several inotropic agents, may increase the risk of myocardial ischemia, although Yu et al. (20) found no increased risk of myocardial infarction during augmentation of oxygen delivery for critically ill patients. Another concern is that therapeutic interventions may
actually disrupt individual organ function. For example, attempts to increase systemic oxygen transport with dobutamine, but not dopexamine, induced alterations in hepatic ultrastructure (21).

Of particular importance is the observation that the choice of catecholamines used to augment cardiac output may influence outcome. Wilson et al. (22) found that inotropic support with dopexamine was associated with fewer complications and shorter hospital stays than conventional treatment (control patients) or inotropic support using epinephrine, although both drugs significantly reduced the mortality rate in comparison to control patients. However, neither of two fixed doses of dopexamine lowered mortality in a randomized study of patients undergoing major abdominal surgery (23). Although dobutamine appeared to slightly worsen outcome in a randomized trial in a mixed population of critically ill patients (19), a recent randomized trial comparing conventional management to augmentation of $DO_2$ using volume expansion and dobutamine inpatients older than 60 yr of age reported better outcome in the treatment group (24).

Should end points other than $DO_2$ be chosen? Trinder et al. (25) found that a sustained low pH$_i$ (pHi $< 7.32$ for $> 1$ h) was associated with mortality but that a decreased pH$_i$ often developed many days before death. Moreover, while low pH$_i$ was an early prognostic indicator of mortality, it was not specific; the majority (70%) of patients with a low, sustained pH$_i$ recovered with conventional therapy. The prognostic value of monitoring pH$_i$ improved when used in combination with serial determinations of blood lactate (26). A recent review by Groeneveld and Kolman (27) provides a comprehensive review of the physiology, methodology, and physiologic aspects of gastrointestinal tonometry.

**Colloid Development**

The peak of the controversy between advocates of crystalloid and those of colloid occurred more than 20 yr ago, then gradually subsided. The controversy was rekindled several years ago by two systematic reviews of published, randomized trials by the Cochrane collaboration. Schierhout and Roberts (28) analyzed 26 trials, 19 of which included mortality data, in which colloid and crystalloid fluid management were compared. They found that colloid was associated with an increase in mortality of 4% (confidence interval 0%–8%) and concluded that their review did not support the continued use of colloids. Subsequent commentary argued that the analysis was flawed, in particular because of the varied nature of the original trials that were compared. The Cochrane Injuries Group Albumin Reviewers (29) then focused specifically on albumin, systematically analyzing 30 randomized clinical trials that included 1419 patients. The pooled relative risk of death was greater in hypovolemic, burned, and hypoalbuminemic patients who received albumin, averaging 1.68, with confidence intervals of 1.26 to 2.23. Again, however, the heterogeneity of the included studies caused criticism of the conclusions.

The basic arguments in favor of crystalloid and colloid fluids have changed little in the past 20 yr. Arguments in favor of crystalloids emphasize lower cost, efficacy (if enough is given), better preservation of renal function, and rapid redistribution out of the vascular tree if overinfusion occurs. Arguments against crystalloids emphasize the large volumes necessary to achieve adequate intravascular expansion, the potentially adverse effects of diffuse soft tissue edema, and the potential for precipitating pulmonary edema by diluting serum proteins. Arguments in favor of colloid fluids emphasize greater efficacy in terms of expanding intravascular volume for any given volume of infused fluid and more prolonged retention within the vascular tree. Arguments against colloids emphasize lower GFR with colloid resuscitation, interference with coagulation (especially with higher doses of hydroxyethyl starch (HES) and dextran), and more prolonged hydrostatic pulmonary edema if overinfusion occurs. Perhaps the most convincing arguments are the more prolonged expansion of intravascular volume accompanying colloid infusion in situations of major fluid loss, such as extensive surgery, and the lower cost of crystalloid fluids for most routine situations.

**Table 2. Outcomes: Patients Who Achieved and Did Not Achieve Optimal Values**

<table>
<thead>
<tr>
<th></th>
<th>With Optimal Values ($n = 42$)</th>
<th>Without Optimal Values ($n = 33$)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0% (0)</td>
<td>30% (10)</td>
<td>.0001</td>
</tr>
<tr>
<td>Organ failure</td>
<td>29% (12)</td>
<td>70% (23)</td>
<td>.0005</td>
</tr>
<tr>
<td>Sepsis</td>
<td>31% (13)</td>
<td>64% (21)</td>
<td>.006</td>
</tr>
<tr>
<td>All complications</td>
<td>60% (25)</td>
<td>76% (25)</td>
<td>.217</td>
</tr>
<tr>
<td>ICU days</td>
<td>10 ± 11</td>
<td>21 ± 24</td>
<td>.017</td>
</tr>
<tr>
<td>Hospital days</td>
<td>22 ± 11</td>
<td>31 ± 28</td>
<td>.105</td>
</tr>
</tbody>
</table>

Values are % ($n$) or mean ± SD.

ICU = intensive care unit

From Velmahos et al. (18), with permission of the publisher.
Regardless of the controversy, development of newer colloid fluids continues, often emphasizing alterations in the composition or diluent of HES formulations. To understand these developments, review of the terminology used to describe HES solutions is useful. HES is a highly branched derivative of amylpectin, obtained from cornstarch. Because amylpectin is rapidly degraded by α-amylase, metabolic degradation in the commercial products is reduced by substituting hydroxyethyl groups for anhydroglucose residues at three positions (C2, C3, and C6). HES solutions are characterized by three numerical factors: average molecular weight, degree of substitution, and substitution site. For example, an HES solution designated 200,000/0.5/4.6 would have an average molecular weight of 200,000 (although the mixture will contain a variety of sizes of molecules), a substitution ratio of 0.5 (half of the anhydroglucose sites will have hydroxyethyl groups), and 4.6 times as many C2 as C6 sites will be substituted.

Potentially important clinical differences associated with differing constituents of HES solutions include changes in coagulation and excretion. For example, HES 130,000/0.4/11.2 was associated with fewer in vitro clotting changes than HES 70,000/0.5/3.2 or HES 200,000/0.5/4.6 (30).

The choice of diluents also may exert clinically important effects. The HES solution commonly used in the United States is dissolved in 0.9% saline and, when infused in large doses, is associated with hyperchloremic metabolic acidosis. Hextend®, an HES solution dissolved in a balanced electrolyte solution including lactate, should theoretically be less prone to this complication and may exert less effect on coagulation, perhaps because of the inclusion of a modest amount of calcium in the diluent (31). It is interesting that the composition of HES solutions should now be receiving so much attention, given the long and generally safe record of earlier formulations. Further research is necessary to define the clinical value and cost-effectiveness of the newer products.

Specific Components of IV Crystalloid Fluids

Crystalloid fluids have many components that vary among specific formulations, but three components—sodium, lactate, and chloride—have received considerable attention recently. The importance of sodium concentration is based on the effects of changing serum osmolality on brain water as well as a variety of other effects of hypertonic resuscitation fluids. Lactate, originally added to lactated Ringer’s solution as a precursor for bicarbonate, now appears to exert pharmacologic effects that may be disadvantageous. Chloride, in the higher-than-physiologic concentrations present in 0.9% saline, has now been associated clearly with hyperchloremic metabolic acidosis that is dose-dependent.

Because the normal blood-brain barrier is highly impermeable to sodium, small changes in serum sodium exert greater osmotic pressure gradients across the cerebral capillary bed than do relatively large changes in serum protein concentrations (32). For instance, an increase of 5 mEq/L in serum sodium would increase osmolality by 10 mOsm/kg, or 186 mm Hg of osmotic pressure. In contrast, the osmotic pressure exerted by a normal serum protein concentration across the blood-brain barrier would be only approximately 23 mm Hg (Table 3).

The effects of changes in colloid osmotic pressure and serum sodium on brain water or ICP have been extensively studied in animals with normal brains, in experimental models of brain injury, and in humans. In anesthetized rabbits, plasmapheresis that reduced plasma [Na+] sufficiently to reduce plasma osmolality by 13 mOsm/kg (baseline value = 295 mOsm/kg) increased cortical water content and ICP; in contrast, reducing protein to reduce oncotic pressure from 20 to 7 mm Hg produced no significant change in either variable (32). Reduced colloid osmotic pressure also did not increase brain water after experimental cryogenic injury (33). Because the blood-brain barrier enhances the influence on brain water of changes in serum sodium (32), hypotonic solutions (including lactated Ringer’s solution) are more likely to increase brain water content than 0.9% saline or colloids dissolved in 0.9% saline. However, after traumatic brain injury (TBI), Drummond et al. (34) demonstrated that colloid osmotic pressure could influence brain water accumulation, perhaps because TBI, especially if accompanied by secondary hypoxic injury, damages the blood-brain barrier (35).

Hypertonic sodium solutions acutely reduce brain water and therefore tend to reduce ICP. In a double-blinded, cross-over study in head-injured children, 3.0% saline decreased ICP significantly, whereas 0.9% saline had no effect (36). It is reasonable to speculate that the effects on ICP represent a combination of interstitial and cellular dehydration. Isolated brain cells rapidly restore intracellular volume after hypertonic dehydration (37). In animals with cryogenic brain injury, hypertonic solutions reduced ICP and decreased brain water in normal brain tissue (38). In animals with intracranial mass lesions and hemorrhagic shock, resuscitation with hypertonic saline also improved regional CBF and cerebral oxygen delivery (39). In dogs with intracranial hypertension, acute, bolus fluid resuscitation from hemorrhagic shock was associated with progressive intracranial hypertension. Supplemental fluid infusion, given as necessary to maintain cardiac output, further exacerbated intracranial hypertension (40). Data in anesthetized cats subjected to fluid percussion injury and mild hemorrhage...
failed to show any improvement in ICP or CBF when the resuscitation fluid was 3.0% saline (41). In fact, although postresuscitation ICP was variable, many animals resuscitated with hypertonic saline demonstrated a delayed rise in ICP, suggesting rebound intracranial hypertension. Other experimental data also suggest the possibility of rebound intracranial hypertension after hypertonic resuscitation from shock and intracranial hypertension (42).

It is important to consider the comparability of experimental models to the clinical situation. Models that examine the acute effects of rapid administration of fluids of varying tonicity usually demonstrate differences in brain water; those that look at slower, “maintenance” rates of administration usually find negligible differences. Shapira et al. (43) compared the effects on brain water of a variety of fluids administered to head-injured rats for 18 h after injury. No differences in brain edema were evident between groups that were fluid restricted and those infused with 25% glucose, 5% dextrose in 0.45% saline, or an isotonic gelatin-based plasma expander.

Clinical trials have evaluated hypertonic solutions for prehospital resuscitation. Vassar et al. (44) compared 250 mL LRS with 7.5% saline in 6.0% dextan 70 for prehospital resuscitation of trauma patients in whom systolic blood pressure was ≤100 mm Hg. Although there was no overall difference in mortality, in the subset of patients with severe head injury (53 of 186 patients), 32% of those who received HSD survived, compared with only 16% of those who received LRS (P = 0.04). In a subsequent randomized multicenter study, Vassar et al. (Table 4) evaluated the effects of 250 mL sodium chloride with and without 6% and 12% dextran 70 for the prehospital resuscitation of hypotensive trauma patients (45). A small subgroup of patients with Glasgow Coma Scale scores <8 but without severe anatomic injury seemed to benefit most from resuscitation with 7.5% saline (45).

Less hypertonic solutions have been used for in-hospital resuscitation of patients with head injury. Shackford et al. (46) used hypertonic lactated saline (Na concentration 250 mEq/L) or LRS to treat systolic blood pressures <90 mm Hg or urinary output <0.5 mL · kg⁻¹ · h⁻¹ during the first five days of intensive care. Although the hypertonic group required more interventions to reduce ICP, the baseline ICP was higher in that group and the overall trend in ICP was more favorable. Simma et al. (47) randomized severely head-injured children to receive either hypertonic saline (Na concentration 268 mEq/L) or LRS for the first 3 days after injury. The children receiving hypertonic saline required fewer interventions to maintain ICP <15 mm Hg and had fewer overall complications, although survival and duration of hospital stay were similar. Other investigators also have reported extensive experience with the use of hypertonic saline solutions for maintenance therapy in neurologic patients (47–49).

Other effects of hypertonicity also have received increasing attention. Among reported physiologic changes associated with hypertonic fluids include alterations in the cytotoxicity of polymorphonuclear leukocytes (50), sequestration of neutrophils in the lung (51), priming of neutrophils (52), and endotoxin-induced vascular permeability (53). Initial concerns regarding the adverse neurologic sequelae of hypertonic resuscitation appear to have been premature. Patients tolerate acute increases in serum sodium to 155–160 mEq/L without apparent harm (44,54). Third, central pontine myelinolysis, which occasionally follows rapid correction of severe hyponatremia, appears to be most likely after correction of chronic hyponatremia (55) and has not been observed in clinical trials of hypertonic resuscitation.

### Table 3. Acute Effects of Changing Osmotic Pressure in the Cerebral Capillaries

<table>
<thead>
<tr>
<th>Osmoles</th>
<th>Osmolality (mOsm/kg)</th>
<th>Osmotic Pressure (mm Hg)</th>
<th>Osmotic Pressure Difference (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plasma</td>
<td>IF</td>
<td>Plasma</td>
</tr>
<tr>
<td>[Na⁺], protein, nonprotein</td>
<td>282.6</td>
<td>282.6</td>
<td>5454</td>
</tr>
<tr>
<td>[Na⁺] acutely ↑ 5.0 mEq/L</td>
<td>292.6</td>
<td>282.6</td>
<td>5640</td>
</tr>
<tr>
<td>Protein</td>
<td>1.2</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>Protein ↑ × 2</td>
<td>2.4</td>
<td>0</td>
<td>46</td>
</tr>
</tbody>
</table>

IF = interstitial fluid

### Table 4. Predicted vs. Actual Survival

<table>
<thead>
<tr>
<th></th>
<th>LR</th>
<th>HS</th>
<th>HSD-6%</th>
<th>HSD-12%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire cohort</td>
<td>45</td>
<td>50</td>
<td>50</td>
<td>49</td>
</tr>
<tr>
<td>Predicted (%)</td>
<td>47</td>
<td>48</td>
<td>52</td>
<td>40</td>
</tr>
<tr>
<td>Actual (%)</td>
<td>49</td>
<td>60</td>
<td>56</td>
<td>45</td>
</tr>
<tr>
<td>GCS ≤ 8 (n)</td>
<td>25</td>
<td>29</td>
<td>26</td>
<td>30</td>
</tr>
<tr>
<td>Predicted (%)</td>
<td>14</td>
<td>13</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Actual (%)</td>
<td>12</td>
<td>34</td>
<td>27</td>
<td>30</td>
</tr>
</tbody>
</table>

Trauma patients with hemorrhagic shock; randomized to immediate resuscitation with 250 mL of lactated Ringer’s solution or 250 mL of 7.5% saline (HS), 7.5% saline with 6% dextan 70 (HSD-6%), or 7.5% saline with 12% dextan 70 (HSD-12%). Predicted survival from TRISS scores.

GCS = Glasgow Coma Scale score.

Modified from Vassar et al. (45), with permission of the publisher.
Lactate, long considered to have no pharmacologic effects other than serving as substrate for production of bicarbonate, appears to exert important effects on cellular function, at least in experimental animals. In rats resuscitated from hemorrhagic shock, lactate infusion is associated with increased apoptosis in both the gastrointestinal tract and liver (56). Also in rats, LRS was associated with rate-dependent immune suppression (15). However, LRS improved survival compared with 0.9% saline in rats with massive hemorrhage (57). Clearly, further work is necessary to define appropriate constituents and rates of delivery of various crystalloid fluids.

Perhaps one of the more surprising sets of observations regarding fluid therapy in the last decade has been the recognition that 0.9% saline, long a mainstay of fluid management, produces dose-dependent hyperchloremic metabolic acidosis. Taken as a group, several recent articles (58–60) suggest that metabolic acidosis is a direct consequence of rapid replacement or expansion of extracellular volume with fluid containing no bicarbonate (61,62). If the fluid contains bicarbonate substrate (e.g., lactate), the acidosis is more quickly resolved than if the fluid contains chloride in concentrations that exceed normal (5).

Summary
Fluid management has progressed rapidly in the last three decades. Current regimens are sufficient to restore systemic perfusion in the majority of patients undergoing surgery. However, important questions remain to be answered regarding the frequency of complications of current fluid therapy and the comparative advantages of different fluid formulations in a variety of clinical circumstances.

References
7. Deleted in proof.


43. Shapira Y, Artru AA, Cotet S, et al. Brain edema and neurologic status following head trauma in the rat: no effect from large volumes of isotonic or hypertonic intravenous fluids, with or without glucose. Anesthesiology 1992;77:79–85.


53. de Carvalho H, Matos JA, Bouskela E, Svensjö E. Vascular permeability increase and plasma volume loss induced by endotoxin was attenuated by hypertonic saline with or without dextran. Shock 1999;12:75–80.


61. Prough DS, Bidani A. Hyperchloremic metabolic acidosis is a predictable consequence of intraoperative infusion of 0.9% saline. Anesthesiology 1999;90:1247–9.