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Review Article

THE CELLULAR, METABOLIC, AND SYSTEMIC CONSEQUENCES OF AGGRESSIVE FLUID RESUSCITATION STRATEGIES

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ABSTRACT—Increasing evidence has demonstrated that aggressive crystalloid-based resuscitation strategies are associated with cardiac and pulmonary complications, gastrointestinal dysmotility, coagulation disturbances, and immunological and inflammatory mediator dysfunction. As large volumes of fluids are administered, imbalances in intracellular and extracellular osmolarity occur. Disturbances in cell volume disrupt numerous regulatory mechanisms responsible for keeping the inflammatory cascade under control. Several authors have demonstrated the detrimental effects of large, crystalloid-based resuscitation strategies on pulmonary complications in specific surgical populations. Additionally, fluid-restrictive strategies have been associated with a decreased frequency of and shorter time to recovery from acute respiratory distress syndrome and trends toward shorter lengths of stay and lower mortality. Early resuscitation of hemorrhagic shock with predominately saline-based regimens has been associated with cardiac dysfunction and lower cardiac output, as well as higher mortality. Numerous investigators have evaluated potential risk factors for developing abdominal compartment syndrome and have universally noted the excessive use of crystalloids as the primary determinant. Resuscitation regimens that cause early increases in blood flow and pressure may result in greater hemorrhage and mortality than those regimens that yield comparable flow and pressure increases late in resuscitation. Future resuscitation research is likely to focus on improvements in fluid composition and adjuncts to administration of large volume of fluid.

KEYWORDS—Resuscitation, intravenous fluid, crystalloid, injury, complications

> "Sodium chloride…is a poison to all people when given in large doses, and occasionally very toxic in small doses to a certain class of cases."
> —Trout (1913) (1)

INTRODUCTION

Despite the overwhelming number of patients affected by postinjury fluid management strategies, consensus regarding the optimal fluid composition and volume of fluid required is lacking. Opinions on resuscitation vary from "running the patient dry" (hypovolemic) to supraphysiologic resuscitation strategies (hypervolemic). Increasing evidence has demonstrated that aggressive crystalloid-based resuscitation strategies are associated with cardiac and pulmonary complications, gastrointestinal dysmotility, coagulation disturbances, and immunological and inflammatory mediator dysfunction (Table 1) (2–10). Current recommendations for traumatic brain injury (TBI) and acute respiratory distress syndrome (ARDS) also suggest fluid therapy directed toward euvolemia (11–17). The focus of this review is on the literature supporting euvolemic resuscitation efforts as well as that condemning aggressive volume administration. However, euvolemia remains ill-defined, and opinions vary widely among clinicians. For decades, the debate has unfortunately focused on the "type" of fluid administered, not the "volume." This has been echoed in the literature, with a recent lack of randomized, controlled trials on intravenous fluid replacement therapy (18). The purpose of this review is to explain the historical events that have led to the current aggressive use of crystalloid-based strategies and to identify the deleterious effects of such an approach on cellular, metabolic, and systemic function after traumatic stress.

HISTORICAL BACKGROUND

Current fluid resuscitation strategies are based on data from the late 1950s and the 1960s which noted altered sodium and water distribution and retention after trauma and surgical stress (19, 20). Some authors concluded that the results suggested fluid restriction was needed, whereas others argued that the data supported replacement of the newly described "third space" losses. Aggressive crystalloid administration soon followed, prompting several authors of the articles to recommend "moderation" and a more judicious approach to fluid management (21). Before these studies, fluid management focused on the careful administration of saline solutions in an effort to balance input to output and to prevent weight gain. However, in the early 1980s, Shoemaker and colleagues (22–24) established the concept of "supranormal resuscitation" and the existent paradigm that surgery and trauma patients require large volumes of fluid, regardless of objective measurements, soon followed.

Shortly after the notion of supranormal resuscitation began to take hold, Stone and colleagues (25) described the potential for abbreviated laparotomy to improve survival in the patient with "lethal" coagulopathy. Over the next decade, several institutions

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TABLE 1. **Consequences of Aggressive Volume Resuscitation**

Cellular
Cytosolic acidification
Inactivation of protein kinases
Disruption of phosphorylation
Disturbances in membrane polarization
Inflammatory
Activation of phospholipase A2
Increased production and release of tumor necrosis Factor α (TNF-α)
Increased levels of IL-6, IL-8, and IL-10
Metabolic/endocrine
Altered glucose production and metabolism
Disturbance in release of insulin
Proecdysis and hypercatabolic state
Cardiac
Disruption of cardiac myocyte action potentials
Decreased cardiac output
Cardiac arrhythmias
Ventricular myocardial dysfunction
Pulmonary
Pulmonary edema
Acute lung injury/ARDS
Gastrointestinal
Increase gut permeability/bacterial translocation
Ileus
Anastomotic dehiscence
Soft tissue
Decreased tissue healing
ACS
Coagulation/hemorrhage
Dilution of coagulation factors
Increased hemorrhage volume
Decreased blood viscosity
Neurological
Disordered neurotransmitter metabolism
Disturbances in the release of catecholamines, glutamate, and acetylcholine

expounded on the basic tenants of this approach, of correcting acidosis, hypothermia, and coagulopathy before undertaking the second stage of the laparotomy. In 1993, Rotondo and colleagues (26) demonstrated that the application of "damage control" in patients with exsanguinating hemorrhage from penetrating injuries improved survival. The concept of damage control, as it applies to trauma surgery, is one of an abbreviated, resuscitative surgery, with the primary goal being the rapid control of hemorrhage and contamination. Once these objectives have been met, the patient undergoes "packing" of the abdominal cavity and temporary closure of the abdominal wall. The patient is then transported to the intensive care unit (ICU) for correction of coagulopathy, hypothermia, and acidosis.

During this same time, several authors began describing an intra-abdominal compartment syndrome (ACS) attributable to "massive interstitial and retroperitoneal swelling" (27, 28). The initial case series from Fietsam and colleagues noted that all four reported patients had received greater than 25 L of fluid in the first 16 h of their care (27). The life-saving technique of temporarily leaving the injured abdomen open to allow correction of the coagulopathy, acidosis, and hypothermia was soon used as a means of addressing the increasingly frequent complication of supranormal resuscitation, ACS. With the open abdomen becoming seen as an increasingly acceptable option, aggressive fluid resuscitation and the subsequent development of ACS continues to the present day. Although these resuscitation strategies were initially applied to young and healthy trauma patients who were better able to tolerate such insults, this was arbitrarily applied to elective cases in older patients with cardiopulmonary disease and smaller third-space losses (23, 24).

FLUID BALANCE FOLLOWING TRAUMATIC STRESS

After trauma and surgical stress, capillary permeability increases with a resultant decrease in plasma colloid osmotic pressure and loss of intravascular fluid to the interstitial space. In response to this decrease in intravascular pressure, intravascular volume returns from the extravascular space in response to hypovolemia (18, 28). Intravascular hypovolemia results in a shift of fluid from the extravascular space in an attempt to re-expand the vascular space. Shires et al theorized that tissue injury resulted in a sequestration of fluid into the traumatized area, with a decrease in extracellular volume that should be replaced above that of "maintenance" fluid administration (20). This has been refuted by several authors who have found that postoperatively, there is a net "no change" or increase in the extracellular volume (28–31).

Acidosis decreases cardiac contractility, attenuates adrenergic receptor responsiveness to inotropic agents, and impairs perfusion of the kidneys. Along with hypothermia and coagulopathy, acidosis is part of a lethal triad that fueled the evolution of damage control surgery. Despite this, most patients after major surgery or trauma frequently receive large amounts of sodium chloride containing solutions that may worsen an already existent acidosis (32–34). In addition, when unrecognized as the source, continued attempts at correction with large and unnecessary volumes of crystalloid may occur. Although lactated Ringer (LR) solution is not associated with a metabolic acidosis, respiratory acidosis has been demonstrated in patients after its aggressive use. Several authors have noted the detrimental postoperative effects of a large lactate load in spontaneously breathing patients and the potential hazards in those patients with severe pulmonary disease (35).

CELLULAR AND INFLAMMATORY DISTURBANCES

Cellular volume seems to drive many of the basic metabolic changes responsible for protein synthesis, cell turnover, and overall cellular performance. The cellular membranes of human cells, such as those of other animals, are highly permeable to water and do not tolerate significant gradients in hydrostatic pressure. As large volumes of fluids are administered, imbalances in intracellular and extracellular osmolarity occur. Although cell volume is normally maintained within a narrow range by several regulatory mechanisms, these cellular functions can be overwhelmed by large-enough shifts in extracellular volume and osmolarity (4, 5). Cellular swelling results in cytosolic acidification, dilution of cellular protein concentration, and inactivation of important protein kinases

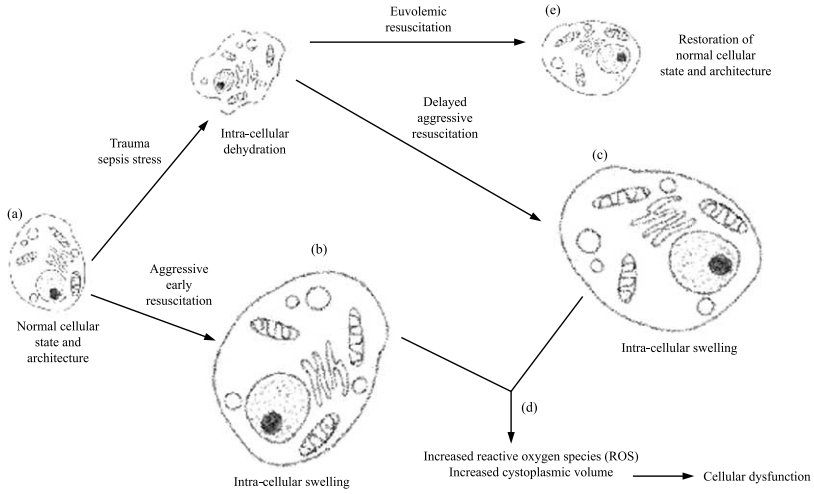

FIG. 1. **Hypothetical model of cellular dysfunction, or restoration of homeostasis, dependent on fluid resuscitation strategies.** a, Cellular volume is normally maintained within a narrow range by several regulatory mechanisms. b, Cellular function can be overwhelmed by large shifts in extracellular volume and osmolarity. c, Cellular swelling results in cystosolic acidification and disruption of intracellular signaling mechanisms. d, Disturbances in cell volume disrupt numerous regulatory mechanisms of the inflammatory cascade, resulting in activation of phospholipase A2, TNF-α, and IL-6. e, Euvolemic resuscitation maintains cellular metabolism and architecture.

with resultant disturbances in phosphorylation, all of which are vital to intracellular signaling mechanisms (Fig. 1). As a result, numerous cellular functions are disturbed, including hepatocyte, pancreatic islet cell, and cardiac myocyte activity. Hepatocyte swelling has been associated with altered glucose production and metabolism (4). As a result of cellular swelling, β islet cells acidic protease activity, normally responsible for cleaving proinsulin to insulin, is severely compromised along with the release of insulin secondary to disturbances in secretory granules. Cardiac myocyte swelling leads to depolarization of volume-sensitive chloride channels, which lead to increased membrane depolarization, enhanced membrane excitability, and shortening of the action potential duration (6).

Disturbances in cell volume disrupt numerous regulatory mechanisms responsible for keeping the inflammatory cascade under control. Cellular swelling activates phospholipase A2, which results in an increased production of prostaglandins, lipoxygenases, leukotrienes, and epoxyeicosatrienoic acids (4–6). Acute increase in cellular volume also results in the increased production and release of tumor necrosis factor α (TNF-α) from macrophages. This multifunctional, and quite "proximal," cytokine plays one of the most prominent roles in mediating the inflammatory cascade after injury and sepsis. An increase in myocyte intracellular volume has been associated with severe injury, burns, and sepsis. These are readily worsened with large volume shifts, resulting in increased proteolysis and hypercatabolism (4, 6). Additionally, neuronal swelling causes acidification of synaptic vesicles, causing disordered metabolism, uptake, and release of neurotransmitters. As a result, global disturbances of catecholamines, glutamate, γ aminobutyric acid, and acetylcholine are observed (4, 5).

The postinjury state is associated with a number of physiological alterations that disturb the balance of proinflammatory and anti-inflammatory mediators; this can be amplified by initial aggressive resuscitation efforts. Increased levels of interleukin (IL)-6, IL-8, or IL-10 are thought to be responsible for the development of severe postoperative complications such as multiple-organ dysfunction syndrome or ARDS (35, 36). Numerous investigators have compared the effects of several nontraditional resuscitation solutions with crystalloid-based volume replacement strategies on the release of inflammatory mediators (37–42). Compared with isotonic sodium chloride solution and LR, hydroxyethyl starch (HES) and hypertonic saline are associated with significant decreases in release of proinflammatory cytokines. The serum concentrations of other endothelial-level substrates such as adhesion molecules (e.g., intercellular adhesion molecule 1) also seem to be attenuated in patients treated with HES and hypertonic saline solutions compared with standard crystalloids (37–39). This likely reflects a reduction in T helper cell proliferation and a decrease in endothelial cell damage, resulting in less production of adhesion molecules, which in turn decreases the binding and migration of neutrophils (37).

Crystalloid administration is associated with higher concentrations of proinflammatory cytokines and subsequently higher expression of adhesion molecules. Schmand et al (41) investigated the effects of an HES solution and LR on cell-mediated immunity after trauma-hemorrhagic shock and noted the HES group had improved peritoneal macrophage function and lower circulating IL-6 concentrations compared with the LR group. It is during this acute phase that the microcirculation is most vulnerable. Any potentiation of the already primed systemic capillary permeability and a loss of local control of inflammatory mediators ensue. Once this exaggerated inflammatory response has been initiated, fluid overload and edema beget further fluid replacement and worsening edema (43).

PULMONARY COMPLICATIONS

Several authors in the late 1970s noted the development of postoperative pulmonary edema in the absence of other organ pathology (44). They demonstrated that dilution of plasma by "balanced" electrolyte solutions decreases plasma colloid oncotic pressure, resulting in a transfer of water into the pulmonary interstitium. Other authors have argued that "leaky" capillaries are responsible for this edema formation (45). Although fluid shifts and balance across the pulmonary endothelium is complex, the importance of colloid oncotic pressure is certain. A decrease in colloid oncotic pressure by 50% increases the flow of fluid across the endothelium 4-fold (46). Correction of hypoalbuminemia has been shown to

decrease lung inflammation and edema formation (2). In the postoperative and postinjury patient, hypoproteinemia is common, and lung water accumulation occurs even more rapidly during crystalloid administration (47, 48).

After a series of 13 deaths from what seemed to be postoperative pulmonary edema (9 confirmed by autopsy and 4 by pulmonary artery [PA] catheterization), Arieff (2) set out to identify risk factors for mortality among these patients. He noted that during the first 36 h postoperation, volume of fluids administered and the net fluid gain was quite significant compared with historical data. Patients who sustained postoperative pulmonary edema had approximately 7000 mL/d net fluid retention. Brandstrup and colleagues (49) recently published the results of a randomized observer-blinded multicenter trial in which patients received either a "standard" resuscitation regimen or a "restricted" regimen. The restricted fluid regimen resulted in a significant reduction in postoperative cardiac, pulmonary, and tissue-healing complications. The mortality rate for the restricted group was 0% compared with an almost 5% mortality risk in the standard resuscitation group.

CARDIAC COMPLICATIONS

The Starling myocardial performance curve demonstrates that, at least until a certain point, volume expansion leads to increased cardiac output. However, beyond a designated point on a patient's curve, further increases in end-diastolic volume lead to decreases in cardiac output and worsening of cardiac performance (18). In older persons and those with cardiac and renal insufficiency, sodium and volume excess may precipitate congestive heart failure and prerenal azotemia (32). Despite this, studies demonstrating that young, healthy trauma patients could tolerate large-volume resuscitations have been applied to many, if not all, postoperative patients. The result is the impairment of pulmonary gas exchange and tissue oxygenation, exaggerated weight gains, and the development of the "classic" postoperative day 3 acute myocardial infarction as extravascular mobilization begins and overwhelms the unprepared, older heart (32). These now-standard resuscitation strategies are associated with increased mortality and an almost 3-fold increase in cardiopulmonary complications (49).

Kudsk (22) suggested that one of the reasons that "fluid overloading" has become the standard resuscitation strategy is an increased utilization of central lines and invasive monitoring. Today's surgical trainee has become not only desensitized to administration of high volumes of fluid across all patient populations but, more concerning, has likely become dependent on these invasive catheters for guiding their resuscitation efforts. Recent articles evaluating the use of PA catheters have found no improvement or worsening outcomes when these catheters are used in a high-risk patient (50, 51). Although some have indicted the dangers of the catheters themselves, the inappropriate use and misinterpretation of the PA catheter numbers has likely led to overly aggressive resuscitation strategies that have pushed these patients far off their Starling curves. This argument is supported by several articles that have found carefully interpreted catheter-directed resuscitation results in improved survival and decreased ICU resource utilization (52, 53).

Early resuscitation of hemorrhagic shock with predominately saline-based regimens has been associated with cardiac dysfunction and lower cardiac output, as well as higher mortality, compared with saline supplementation of blood product–based regimens (54, 55). Even brief delays in blood replacement in patients with hemorrhagic shock may result in higher mortality rates and worsen cardiac responsiveness to hemorrhage. Cardiac rhythm disturbances and decreased cardiac output precede the acute deterioration in patients initially treated with saline-based regimens compared with early intervention with blood products (56). When utilizing saline-based solutions, burn shock models of resuscitation have noted significant myocardial dysfunction, as demonstrated by decreased cardiac output and stroke volume. Even in the presence of otherwise adequate filling pressures, stroke volume can be reduced by 20% or more with saline regimens (55).

GASTROINTESTINAL DISTURBANCES

Among critically ill patients, several authors have noted that the development of gastrointestinal dysfunction leads to an increased risk for ventilator-associated pneumonia, longer length of ICU stay, and lower survival rates (3, 4). Increased sodium and water administration in the postoperative period results in splanchnic edema and increased intra-abdominal pressure, with a resultant decrease in tissue oxygenation, increase in gut permeability and bacterial translocation, and impaired wound healing. Clinically, these become evident as prolonged postoperative ileus with an inability to tolerate enteral nutrition and anastomotic dehiscence. The end result is the initiation of parenteral nutrition, with its associated complications, and a higher risk for sepsis, multisystem organ failure, and death (18).

In a gastrointestinal anastomosis model, use of standard resuscitation volumes of isotonic saline during surgery versus a fluid-restricted regimen was associated with a significant increase in tissue weight at the anastomotic site (57). These effects seemed to persist for more than 5 days after surgery and likely translated into impaired tissue oxygenation and anastomotic healing. Lobo and colleagues evaluated the effect of a "moderate" positive fluid balance in patients undergoing elective colon surgery (36). Patients were randomized to either a standard postoperative fluid regimen (3 L of water and 154 mmol Na per day) or a restricted group (2 L of water and 77 mmol Na per day). In addition to the 3-kg greater weight gain and longer solid- and liquid-phase gastric emptying times, time to passage of flatus and first bowel movement, length of stay, and complication rates were significantly greater in the group randomized to the standard resuscitation regimen. Similarly, Brandstrup and colleagues noted an increased risk for anastomotic leakage in their patients in the standard fluid management group versus the restricted fluid group (49).

COAGULATION DISTURBANCES AND HEMORRHAGE

There are an increasing number of studies investigating the influence of various resuscitation regimens on platelet function and coagulation (7, 8). A recent study by Barak and colleagues

noted the volume of crystalloid infusion greatly influenced coagulation (7). The authors demonstrated that patients who received less than 3 L of crystalloid intraoperatively had significantly less disturbances in their coagulation levels than those patients who received at least 3 L. This is consistent with previous investigations demonstrating the clinical significance of "dilutional" coagulopathy after excessive saline administration (7). When used in moderation, however, crystalloids have been associated with hypercoagulable states (8, 58). As with inflammation, the endothelium plays an integral role in the coagulation process. The volume of crystalloid administered, and likely the rate at which it is given, are likely to determine which factors, and how much of them, are activated at the already "primed" endothelial level (59).

The advanced trauma life support curriculum recommends resuscitation begins with 2 L of crystalloid for the hypotensive patient, followed by blood products and surgical consultation and/or intervention (60). Unfortunately, the 2-L fluid boluses are merely a starting point for the aggressive volume replacement that usually follows. This approach has been challenged by several authors based on numerous animal models of hemorrhage, demonstrating increased bleeding diathesis as a result of aggressive fluid administration (61–63). The increased arterial and venous pressures, dilution of clotting factors, and decreased blood viscosity result in increased hemorrhage volume, decreased oxygen delivery, and decreased survival rates (64, 65).

Owens and colleagues (66) evaluated the effect of three different resuscitation regimens on a group of Yorkshire pigs undergoing "controlled" hemorrhage via withdrawal of blood through peripheral catheters, followed by "uncontrolled" hemorrhage via 5-mm aortotomy hemorrhage. The animals underwent standard resuscitation to keep their cardiac index at 100% preinjury level, "low-volume" resuscitation to keep cardiac index at 80%, or no volume. Peritoneal blood loss and hemoglobin loss were significantly higher in the standard group. In addition, the oxygen delivery was lowest in the standard group and highest in the low-volume group. In several other near-fatal hemorrhage models, attempts to restore blood pressure with crystalloid-based strategies have resulted in almost uniform increases in hemorrhage volume and significantly higher mortality (67).

ABDOMINAL COMPARTMENT SYNDROME

Perhaps the most impressive and obvious indictment of large-volume crystalloid resuscitation is the development of the now-"accepted" complication of ACS. Numerous investigators have evaluated potential risk factors for developing ACS and have universally noted the excessive use of crystalloids as the primary determinant (16, 17, 68, 69). Balogh and colleagues (68) demonstrated that the supranormal resuscitation approach to trauma patients was associated with significantly more crystalloid administration and an increased incidence of ACS, multiple-organ failure, and death. Although the development of ACS in the severely injured abdomen (primary ACS) is well described, more concerning is the development of ACS in patients without any underlying abdominal injury (secondary ACS), occurring most likely from current resuscitation strategies. In a recent study evaluating complications arising from 344 patients with open abdomens, an alarming one third of the patients were the result of secondary ACS (70).

Secondary ACS usually develops in younger trauma patients with severe chest, pelvic, or long-bone injuries often managed with liberal amounts of crystalloids. The mortality in these patients, typically as a result of acute lung injury and multiple system organ failure, uniformly exceeds 50%, despite early decompression of the abdominal hypertension (16, 17, 68, 69). Investigators from Houston noted both emergency department and pre-ICU crystalloid administration were predictive of both primary and secondary ACS. The administration of 3 L or more of crystalloid in the emergency department (which is standard in some trauma centers) was associated with significant risk for developing both primary and secondary ACS. Even when confronted with the end result of an overly aggressive resuscitation (in the form of secondary ACS), several institutions have reported the development of "recurrent" ACS after a decompressive laparotomy (71). In light of this, a paradigm shift toward "alternative" resuscitation strategies, using hypertonic saline, colloids, and earlier utilization of vasopressor agents, seems warranted (68, 69).

PREHOSPITAL

Despite a lack of evidence demonstrating a benefit to prehospital fluid resuscitation in trauma patients, the practice is now the standard of care. More concerning, the type of fluid, the appropriate rate of administration, and the resuscitations themselves remain unguided and unsupervised (72, 73). Recently, the largest prehospital organization in the United Kingdom issued a consensus statement calling for more "restrained" and "cautious" use of crystalloids in prehospital setting (74). In fact, improved survival has been demonstrated in patients with traumatic amputations by reducing prehospital fluid administration (66). Several prehospital hemorrhage models have demonstrated that limiting the initial resuscitation volume, before definitive care, leads to a reduction in hemorrhage volume and the subsequent crystalloid and blood requirements (72, 73). Resuscitation regimens that cause early increases in blood flow and pressure may result in greater hemorrhage and mortality than those regimens that yield comparable flow and pressure increases late in resuscitation (75, 76).

Although numerous laboratory investigations have noted an increase in the rate of hemorrhage and mortality when "normotension" is the therapeutic end point, clinical extrapolation of deliberate hypotension has, for the most part, been confined to a single prospective trial by Bickell and colleagues in the early 1990s (76). Hypotensive patients with penetrating torso injuries were randomized in the field to receive either standard intravenous fluid resuscitation or no fluids. This regimen was continued throughout transport, during emergency department evaluation and management, and until arrival in the operating room. Despite the lack of prehospital fluid resuscitation, the mean blood pressure between the groups was similar, and the intraoperative blood loss was significantly

less in the delayed resuscitation group. Additionally, the length of stay was shorter, and the mortality rate was lower in the delayed resuscitation group. This clinical study helped lend further support to animal models demonstrating worse outcomes when a normotensive state is aggressively pursued (61–63).

SUMMARY

In 1967, amid conflicting data regarding fluid resuscitation requirements, Moore and Shires (21) made a plea in the *Annals of Surgery* for "moderation." The editorial by these surgeon-scientists, who had authored the studies investigating postoperative fluid management, was prompted by the excessive use of crystalloids that seemed to follow publication of their articles. To this day, however, their pleas have been, for the most part, ignored. Despite growing data demonstrating the deleterious effects of aggressive crystalloid-based resuscitation strategies, large-volume resuscitations continue to be the standard of care in many, if not most, surgical and trauma ICUs. Cardiac and pulmonary complications, gastrointestinal dysmotility, coagulation disturbances, and immunological and inflammatory mediator dysfunction have been identified as consequences of such an approach in resuscitation volumes. In addition, the development of the complication of ACS (especially in the absence of abdominal injury) has been attributed to current resuscitation strategies (68, 69).

Future resuscitation research is likely to focus on improvements in fluid composition and adjuncts to the administration of a large volume of fluid. Several recent studies have actually noted that a euvolemic state is associated with better outcomes in the postoperative period, in ARDS, and in TBI (12–15, 39). This article has focused on such by promoting neither extreme of the resuscitation strategies proposed by several authors, but rather a "middle ground" of moderation as supported by the present literature. As a result of the evolving literature, renewed interest in the early use of vasopressor agents to support hemodynamics (versus continued administration of crystalloids) has appeared. Most recently, vasopressin has been identified as a potential answer to vasodilatory states and distributive shock after injury and exaggerated inflammatory responses (77, 78). In fact, vasopressin has been associated with improved survival (compared with aggressive crystalloid regimens) in liver trauma, uncontrolled hemorrhage, TBI, and chest trauma (79–81). Perhaps, with further clinical studies to support early utilization of "physiological" doses of vasopressin and improvements in resuscitation fluid composition, a 30-year-old plea for moderation will finally be heard and practiced.

REFERENCES

1. Trout HM: Proctoclysis—an experimental study. *Surg Gynecol Obstet* 16: 560–562, 1913.
2. Arieff AI: Fatal postoperative pulmonary edema: pathogenesis and literature review. *Chest* 115:1371–1377, 1999.
3. Kaneki T, Koizumi T, Yamamoto H, Fujimoto K, Kubo K, Shibamoto T: Effects of resuscitation with hydroxyethyl starch (HES) on pulmonary hemodynamics and lung lymph balance in hemorrhagic sheep; comparative study of low and high molecular HES. *Resuscitation* 52:101–108, 2002.
4. Lang F, Busch GL, Ritter M, Volkl H, Waldegger S, Gulbins E, Haussinger D: Functional significance of cell volume regulatory mechanisms. *Physiol Rev* 78:248–273, 1998.
5. Christensen O: Mediation of cell volume regulation by calcium influx through stretch-activated channels. *Nature* 330:66–68, 1987.
6. Haussinger D, Schliess F, Warskulat U, vom Dahl S: Liver cell hydration. *Cell Biol Toxicol* 13:275–287, 1997.
7. Barak M, Rudin M, Vofsi O, Droyan A, Katz Y: Fluid administration during abdominal surgery influences on coagulation in the postoperative period. *Curr Surg* 61:459–462, 2004.
8. Ng KF, Lam CK, Chan LC: In vivo effect of hemodilution with saline on coagulation: a randomized controlled trial. *Br J Anaesth* 88:475–480, 2002.
9. Turkan H, Ural AU, Beyan C, Yalcin A: Effects of hydroxyethyl starch on blood coagulation profile. *Eur J Anaesthesiol* 16:156–159, 1999.
10. Watters JM, Jackson T, Muller PJ, Malinoski D, Todd SR, Schreiber MA: Fluid resuscitation increases inflammatory response to traumatic injury. *J Trauma* 57:1378, 2004. Oral presentation at the Eighteenth Annual Scientific Meeting of the Eastern Association for the Surgery of Trauma; January 10 – 15, 2005; Ft Lauderdale, FL.
11. Eberhard LW, Morabito DJ, Matthay MA, Mackersie RC, Campbell AR, Marks JD, Alonso JA, Pittet JF: Initial severity of metabolic acidosis predicts development of acute lung injury in severely traumatized patients. *Crit Care Med* 28:125–131, 2000.
12. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome: the ARDS Network. *N Engl J Med* 342:1301–1308, 2000.
13. Mitchell JP, Schuller D, Calandrino FS, Schuster DP: Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization. *Am Rev Respir Dis* 145:990–998, 1992.
14. McCunn RP: Traumatic brain injury. *Curr Opin Crit Care* 9:503–509, 2003.
15. Bishop MA, Jorgens J, Shoemaker WC, Appel PL, Fleming A, Williams D, Jackson G, Wo CJ, Babb L, Manning T: The relationship between ARDS, pulmonary infiltration, fluid balance and hemodynamics in critically ill surgical patients. *Am Surg* 57:785–792, 1991.
16. Raeburn CD, Moore EE, Biffl WL, Meldrum DR, Offner PJ, Franciose RJ, Burch JM: The abdominal compartment syndrome is a morbid complication of post injury damage control surgery. *Am J Surg* 182:542–546, 2001.
17. Biffl WL, Moore EE, Burch JM, Offner PJ, Franciose RJ, Johnson JL: Secondary abdominal compartment syndrome is a highly lethal event. *Am J Surg* 182:645–648, 2001.
18. Holte K, Sharrock NE, Kehlet H: Pathophysiology and clinical implications of preoperative fluid excess. *Br J Anaesth* 89:622–632, 2002.
19. Moore FD: *Metabolic Care of the Surgical Patient*. Philadelphia: WB Saunders, 1959.
20. Shires T, Williams J, Brown F: Acute changes in extracellular fluids associated with major surgical procedures. *Ann Surg* 154:803–810, 1961.
21. Moore FD, Shires G: Moderation. *Ann Surg* 166:300–301, 1967.
22. Kudsk KA: Evidence for conservative fluid administration following elective surgery. *Ann Surg* 238:649–650, 2003.
23. Shoemaker WC, Appel P, Bland R: Use of physiologic monitoring to predict outcome and to assist in clinical decisions in critically ill postoperative patients. *Am J Surg* 146:43–50, 1983.
24. Shippy CR, Shoemaker WC: Hemodynamic and colloid osmotic pressure alterations in the surgical patient. *Crit Care Med* 11:191–195, 1983.
25. Stone HH, Strom PR, Mullins RJ: Management of major coagulopathy with onset during laparotomy. *Ann Surg* 197:532–535, 1983.
26. Rotondo MF, Schwab CW, McGonigal MD: "Damage control:" an approach for improved survival in exsanguinating penetrating abdominal injury. *J Trauma* 35:375–383, 1993.
27. Fietsam R Jr, Villalba M, Glovers JL, Clark K: Intra-abdominal compartment syndrome as a complication of ruptured abdominal aortic aneurysm repair. *Am Surg* 55:396–402, 1989.
28. Gutelius JR, Shizgal HM, Lopez G: The effect of trauma on extracellular water volume. *Arch Surg* 97:206–214, 1968.
29. Nielsen OM, Engell HC: Extracellular fluid volume and distribution in relation to changes in plasma colloid osmotic pressure after major surgery. A randomized study. *Acta Chir Scand* 151:221–225, 1985.
30. Virtue RW, LeVine DS, Aikawa JK: Fluid shifts during the surgical period: RISA and S35 determinations following glucose, saline or lactate infusion. *Ann Surg* 63:523–528, 1966.
31. Nielsen OM, Engell HC: The importance of plasma colloid osmotic pressure for interstitial fluid volume and fluid balance after elective abdominal vascular surgery. *Ann Surg* 203:25–29, 1986.
32. Lobo DN: Fluid, electrolytes, and nutrition: physiological and clinical aspects. *Proc Nutr Soc* 63:453–466, 2004.
33. Scheingraber S, Rehm M, Sehmisch C, Finsterer U: Rapid saline infusion

produces hyperchloremic acidosis in patients undergoing gynecologic surgery. *Anesthesiology* 90:1265–1270, 1999.
34. Williams EL, Hildebrand KL, McCormick SA, Bedel MJ: The effect of intravenous lactated Ringer's solution versus 0.9% sodium chloride solution on serum osmolality in human volunteers. *Anesth Analg* 88:999–1003, 1999.
35. Takil A, Eti Z, Irmak P, Yilmaz Gogus F: Early postoperative respiratory acidosis after large intravascular volume infusion of lactated Ringer's solution during major spine surgery. *Anesth Analg* 95:294–298, 2002.
36. Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP: Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomized control trial. *Lancet* 359:1812–1818, 2002.
37. Lang K, Suttner S, Boldt J, Kumle B, Nagel D: Volume replacement with HES 130/0.4 may reduce the inflammatory response in patients undergoing major abdominal surgery. *Can J Anesth* 50:1009–1016, 2003.
38. Felfernig M, Franz A, Braunlich P, Fohringer C, Kozek-Langenecker SA: The effects of hydroxyethyl starch solutions on thromboelastography in preoperative male patients. *Acta Anaesthesiol Scand* 47:70–73, 2003.
39. Attuwaybi B, Kozar RA, Gates KS, Moore-Olufemi S, Sato N, Weisbrodt NW, Moore FA: Hypertonic saline prevents inflammation, injury, and impaired intestinal transit after gut ischemia/reperfusion by inducing heme oxygenase 1 enzyme. *J Trauma* 56:749–759, 2004.
40. Pascual JL, Khwaja KA, Ferri LE, Lorenzo E, Giannias B, Evans DC, Razek T, Michel RP, Christou NV: Hypertonic saline resuscitation attenuates neutrophil lung sequestration and transmigration by diminishing leukocyte-endothelial interactions in a two-hit model of hemorrhagic shock and infection. *J Trauma* 54:121–132, 2003.
41. Schmand JF, Ayala A, Morrison MH, Chaudry IH: Effects of hydroxyethyl starch after trauma-hemorrhagic shock: restoration of macrophage integrity and prevention of increased circulating interleukin-6 levels. *Crit Care Med* 23:806–814, 1995.
42. Lang K, Boldt J, Suttner S, Haisch G: Colloids versus crystalloids and tissue oxygen tension in patients undergoing major abdominal surgery. *Anesth Analg* 93:405–409, 2001.
43. Powers KA, Zurawska J, Szaszi K, Khadaroo RG, Kapus A, Rotstein OD: Hypertonic resuscitation of hemorrhagic shock prevents alveolar macrophage activation by preventing systemic oxidative stress due to gut ischemia/reperfusion. *Surgery* 137:66–74, 2005.
44. Arieff AI, Llach F, Massry SG: Neurological manifestations and morbidity of hyponatremia: correlation with brain water and electrolytes. *Medicine* 55:121–129, 1976.
45. Shoemaker WC, Hauser CJ: Critique of crystalloid versus colloid therapy in shock and shock lung. *Crit Care Med* 7:117–124, 1979.
46. Powers KA, Kapus A, Khadaroo RG, He R, Marshall JC, Lindsay TF, Rotstein OD: Twenty-five percent albumin prevents lung injury following shock/resuscitation. *Crit Care Med* 31:2355–2363, 2003.
47. Layon J, Duncan D, Gallagher TJ, Banner MJ: Hypertonic saline as a resuscitation solution in hemorrhagic shock: effects on extra vascular lung water and cardiopulmonary function. *Anesth Analg* 66:154–158, 1987.
48. Rackow EC, Weil MH, Macneil AR, Makabali CG, Michaels S: Effects of crystalloid and colloid fluids on extra vascular lung water in hypoproteinemic dogs. *J Appl Physiol* 62:2421–2425, 1987.
49. Brandstrup B, Tonnesen H, Beier-Holgersen R, Hjortso E, Ording H, Lindorff-Larsen K, Rasmussen MS, Lanng C, Wallin L, Iversen LH, et al,: Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Ann Surg* 238:641–648, 2003.
50. Richard C, Warszawski J, Anguel N, Deye N, Combes A, Barnoud D, Boulain T, Lefort Y, Fartoukh M, Baud F, et al,: Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 290:2713–2720, 2003.
51. Sandham JD, Hull RD, Brant RF, Knox L, Pineo GF, Doig CF, Laporta DP, Viner S, Passerini L, Devitt H, et al,: A randomized, controlled trial of the use of pulmonary artery catheters in high-risk surgical patients. *N Engl J Med* 348:5–14, 2003.
52. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 345:1368–1377, 2001.
53. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM et al,: Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 32:858–873, 2004.
54. Gibson JB, Maxwell RA, Schweitzer JB, Fabian TC, Proctor KG: Resuscitation from severe hemorrhagic shock after traumatic brain injury using saline, shed blood, or a blood substitute. *Shock* 17:234–244, 2002.
55. Maxwell RA, Gibson JB, Fabian TC, Proctor KG: Effects of a novel antioxidant during resuscitation from severe blunt chest trauma. *Shock* 14:646–651, 2000.
56. Conahan ST, Dupre A, Giaimo ME, Fowler CA, Torres CS, Miller HI: Resuscitation fluid composition and myocardial performance during burn shock. *Circ Shock* 23:37–49, 1987.
57. Chan ST, Kapadia CR, Johnson AW, Radcliffe AG, Dudley HA: Extracellular fluid volume expansion and third space sequestration at the site of small bowel anastomoses. *Br J Surg* 70:36–39, 1983.
58. Ruttman TG, Jams MF, Finlayson J: Effects on coagulation of intravenous crystalloid or colloid in patients undergoing peripheral vascular surgery. *Br J Anaesth* 89:226–230, 2002.
59. Boldt J, Heesen M, Welters I, Padberg W, Martin K, Hempelmann G: Does the type of volume therapy influence endothelial-related coagulation in the critically-ill? *Br J Anaesth* 75:740–746, 1995.
60. American College of Surgeons. *Advanced Trauma Life Support for Doctors*. Chicago, IL: American College of Surgeons, 1997.
61. Kowalenko T, Stern S, Dronen S, Wang X: Improved outcome with hypotensive resuscitation of uncontrolled hemorrhagic shock in a swine model. *J Trauma* 33:349–353, 1992.
62. Bickell WH, Bruttig SP, Millnamow GA, O'Benar J, Wade CE: The detrimental effects of intravenous crystalloid after aortotomy in swine. *Surgery* 110:529–536, 1991.
63. Riddez L, Johnson L, Hahn RG: Central and regional hemodynamics during crystalloid fluid therapy after uncontrolled intra-abdominal bleeding. *J Trauma* 44:433–439, 1998.
64. Capone A, Safar P, Radovsky A, Wang YF, Peitzman A, Tisherman SA: Complete recovery after normothermic hemorrhagic shock and profound hypothermic circulatory arrest of 60 minutes in dogs. *J Trauma* 40:388–395, 1996.
65. Smail N, Wang P, Cioffi WG, Bland KI, Chaudry IH: Resuscitation after uncontrolled venous hemorrhage: does increased resuscitation volume improve regional perfusion? *J Trauma* 44:701–708, 1998.
66. Owens TM, Watson WC, Prough DS, Uchida T, Kramer GC: Limiting initial resuscitation of uncontrolled hemorrhage reduces internal bleeding and subsequent volume requirements. *J Trauma* 39:200–207, 1995.
67. Stern SA, Dronen SC, Wang X: Multiple resuscitation regimens in a near fatal porcine aortic injury hemorrhage model. *Acad Emerg Med* 2:81–82, 1995.
68. Balogh Z, McKinley B, Cocanour CS, Kozar RA, Valdivia A, Sailors MR, Moore FA: Supra-normal trauma resuscitation causes more cases of abdominal compartment syndrome. *Arch Surg* 138:637–643, 2003.
69. Maxwell RA, Fabian TC, Croce MA, Davis KA: Secondary abdominal compartment syndrome: an underappreciated manifestation of severe hemorrhagic shock. *J Trauma* 47:995–999, 1999.
70. Miller RS, Morris JA Jr, Diaz JJ Jr, May AK, Herring MB: Complications after 344 damage control open celiotomies. *J Trauma* 57:436, 2004.
71. Gracias VH, Braslow B, Johnson J, Pryor J, Gupta R, Reilly P, Schwab CW: Abdominal compartment syndrome in the open abdomen. *Arch Surg* 137: 1298–1300, 2002.
72. Dutton RP, Mackenzie CF, Scalea TM: Hypotensive resuscitation during active hemorrhage: impact on in-hospital mortality. *J Trauma* 52:1141–1146, 2002.
73. Dretzke J, Sandercock J, Bayliss S, Burls A: Clinical effectiveness and cost-effectiveness of pre-hospital intravenous fluids in trauma patients. *Health Technol Assess* 8:1–118, 2004.
74. National Institute for Clinical Excellence: Appraisal consultation document on pre-hospital initiation of fluid replacement therapy in trauma. Available at: http://www.nice.org.uk/page.aspx?o=85337. Accessed October 24, 2005.
75. Stern SA, Kowalenko T, Younger J, Wang X, Dronen SC: Comparison of the effects of bolus vs. slow infusion of 7.5% NaCl/6% dextran-70 in a model of near-lethal uncontrolled hemorrhage. *Shock* 14:616–622, 2000.
76. Bickell WH, Wall MJ Jr, Pepe PE, Martin RR, Ginger VF, Allen MK, Mattox KL: Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *New Engl J Med* 331:1105–1109, 1994.
77. Landry DW, Levin HR, Gallant EM, Ashton RC Jr, Seo S, D'Alessadro D, Oz MC, Oliver JA: Vasopressin deficiency contributes to the vasodilation of septic shock. *Circulation* 95:1122–1125, 1997.
78. Raedler C, Voelckel WG, Wenzel V, Krismer AC, Schmittinger CA, Herff H, Mayr VD, Stadlbauer KH, Lindner KH, Konigsrainer A: Treatment of uncontrolled hemorrhagic shock after liver trauma: fatal effects of fluid resuscitation versus improved outcome after vasopressin. *Anesth Analg* 98:1759–1766, 2004.
79. Sanui M, Cohn SM, Feinstein AJ, Patel MB, Majetschak M, Proctor KG: Vasopressin during resuscitation from traumatic brain injury. *Anesthesiology* 101:A414, 2004. Presented at American Society of Anesthesiologists 2004 Annual Meeting; October 23, 2004; Las Vegas, NV.
80. Feinstein AJ, Cohn SM, Sanui M, King DR, Proctor KG: Vasopressin reduces mortality after pulmonary contusion. *J Trauma* 59:876–883, 2005.
81. Feinstein AJ, Patel MB, Sanui M, Cohn SM, Majetschak M, Proctor KG: Resuscitation with pressors after traumatic brain injury. *J Am Coll Surg* 201:536–545, 2005.