

New thoughts on acute volume therapy

Acute volume therapy remains a controversial issue, with many unresolved aspects.

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Modern fluid therapy requires an understanding of the underlying physiological abnormalities induced by acute illness, the nature of the fluids to be administered, the differences between the various intravenous fluid preparations, and the concepts with regard to appropriate amounts of volume to be given.

There is an array of different types of fluids available for intravenous use, including many different types of crystalloid solutions, a smaller selection of colloid preparations, and fluids derived directly, or indirectly, from blood.

Crystalloids

Crystalloid solutions expand the extracellular fluid (ECF) space and are redistributed between the intravascular and extracellular compartments in a ratio of 1:4 in proportion to the normal distribution of fluid between these two spaces. Consequently, full volume expansion after blood loss requires 3 - 4 times the volume loss to be replaced with crystalloids alone to replenish the intravascular losses. In the initial resuscitation phase, crystalloids may be deceptively effective, but once the capillary perfusion is re-established, the crystalloids will rapidly move out of the vascular space. Crystalloids will result in a reduced plasma oncotic pressure and an accumulation of fluid in the tissues.

None of the currently available crystalloid solutions completely resembles the electrolyte content of plasma. The most widely used crystalloids, 0.9% saline and balanced salt solutions such as Ringer's lactate, fall well short of the desired composition (Table 1).

(Ab)normal saline

'Normal' saline is significantly hypertonic (osmolality 308 mOsm/l) and has a very high chloride content (154 mmol/l; normal plasma range 95 - 105 mmol/l). Infusions of as little as 2 litres 0.9% saline during surgical procedures will produce a significant metabolic acidosis owing to the chloride load.¹ The clinical significance of this metabolic acidosis has not yet been established, but a number of adverse effects have been ascribed to excessive chloride administration. There is evidence that chloride loading may impair

renal function and may interfere with coagulation. However, there are no human outcome data suggesting that this may lead to decreased survival. There is a common misconception that, in patients with renal dysfunction and an elevated serum potassium, 0.9% saline is a safer intravenous fluid to use than Ringer's lactate. The acidosis associated with saline administration may cause extracellular migration of potassium from the intracellular space, leading to a paradoxical rise in plasma potassium concentrations, despite the administered fluid containing no potassium. A recent study has shown that, in patients undergoing renal transplantation, potassium concentrations were better controlled with Ringer's lactate than with saline.² There is no scientific basis for this recommendation. Hypertonic saline (usually 7.5%) has received some attention for its role in acute resuscitation, especially in field situations. There appear to be some advantages, particularly in head injuries, but no improvement in survival has been demonstrated.

Balanced salt solutions

Ringer's lactate (or acetate), like 0.9% saline, is not an ideal solution. The Cl⁻ content is substantially higher than that of plasma chloride (111 mmol/l), the Na⁺ content lower (131 mmol/l) and the osmolality of the solution is 274 mOsm/l. This may be of some relevance in critically ill patients in whom antidiuretic hormone production results in water retention in excess of sodium, and may be clinically important in patients with head injury. Several studies have demonstrated that reduced plasma osmolality is associated with increased cerebral oedema where the blood-brain barrier has been disrupted,³ but these have not been translated into clinical outcome studies.

Lactate is rapidly metabolised to CO₂ and water, resulting in a positive strong-ion difference which may lead to metabolic alkalosis. The conversion of lactate to glucose may impair glucose control in diabetics, but Ringer's lactate has been widely used without problems in these patients and there is no evidence that the lactate substantially disturbs glucose metabolism. However, it should probably be avoided in patients taking metformin where lactate metabolism may be impaired.

Table I. Approximate constituents of some common electrolyte solutions (varies among countries)

Solution	Na	K	Ca	Mg	Cl	Lac	Bic	Acet	Gluc	Osm
0.9% saline	154	154	-	-	-	-	-	-	-	308
RL	131	5	1.8	-	111	27	-	-	-	274
Plas B	131	5	1.8	1.5	111	-	29	-	-	276
Plas A	140	5	-	1.5	98	-	-	27	23	294

RL = Ringer's lactate; Plas B = plasmalyte B; Plas A = plasmalyte A; Lac = lactate; Bic = bicarbonate; Acet = acetate; Gluc = gluconate (all in mmol/l); Osm = approximate osmolarity (mOsm/l).

Colloids

Colloids are suspensions of particles of various sizes that aim to maintain plasma volume by maintaining the colloid osmotic pressure in plasma and thus retain the administered volume within the circulation. The archetypal colloid is albumin (with a molecular size of 69 000 daltons (69 kDa)), but it is not without problems, being a human blood product with all that entails, and also being much more expensive than other forms of intravenous fluid. Synthetic colloids include the gelatins, dextrans and hydroxyethyl starches. The gelatins are small molecules with an average size of 30 - 35 kDa and therefore a relatively short duration of action (2 - 3 h). They have minimal adverse effects on coagulation but carry the greatest risk with regard to anaphylaxis. The dextrans markedly interfere with coagulation and carry a similar risk to the gelatins in terms of anaphylaxis; they have little place in acute volume therapy, except, perhaps, from the combination of hypertonic saline/dextran in head injuries. The most widely used colloids outside the USA are the low molar substitution starches (HES 130/0.4) as these offer the best balance between good, long-lasting volume replacement and minimal adverse effects. All colloids presently available in South Africa are suspended in 0.9% saline or solutions approximating this.

The 'third space' and fluid loading

Physiological principles dictate that patients undergoing surgery retain sodium and water in the perioperative period. Although this observation initially led to the administration of minimal perioperative fluid volumes, the work of Shires *et al.*⁴ resulted in aggressive crystalloid resuscitation in an attempt to compensate for 'third-space' losses. This approach was extended by a number of studies suggesting that plasma volume expansion with colloids against a marker of cardiac performance (usually stroke volume) appeared to decrease perioperative morbidity.⁵

However, recently the third-space concept has been questioned⁶ and attention has focused on the potential adverse effects of the excess administration of crystalloid

solutions. The problem of crystalloid excess leading to diminished pulmonary function has been well recognised in thoracic surgery for many years,⁷ but it has also been shown that weight gain in the postoperative period, which equates to fluid overload, is associated with increased morbidity and mortality.⁸ Studies in trauma resuscitation suggest that targeting supranormal haemodynamic values by aggressive crystalloid resuscitation increases the risk of abdominal compartment syndrome and may increase mortality.⁹ In elective surgical procedures, particularly those involving the bowel, it has also been shown that generous crystalloid loading may lead to increased tissue-healing complications as well as adverse cardiopulmonary events.^{10,11} The problems are compounded by neither of the two widely used solutions, 0.9% saline or lactated Ringer's solution, having an ideal electrolyte composition. A more rational approach to perioperative fluid therapy would suggest that crystalloids should be given as balanced salt solutions in limited volume, and blood loss replaced largely with colloids and red blood cells.¹²

Fluid 'optimisation'

At the opposite end of the scale to the concept that crystalloid overload may be harmful is the view that appropriate expansion of plasma volume is associated with a beneficial outcome, particularly in critically ill patients. The concept presumes that there is an ideal volume expansion for each patient that will result in the least perioperative morbidity risk.¹³ Several studies have suggested that goal-directed fluid therapy may reduce the complication rate and possibly the mortality in complex surgery,¹⁴ primarily using colloid solutions. In moderate-risk surgery (cholecystectomy, hemicolectomy) crystalloid loading (up to 3 litres in the average adult, or approximately 4 ml/kg), rather than fluid restriction, has been shown to provide better outcome in terms of morbidity, although in one study it was associated with a decrease in oxygen saturation for the first 48 hours.¹⁵

Clearly, there is an optimal fluid volume that will result in the best balance between optimal tissue perfusion and minimal risk of the consequences of fluid overload. The

problem is how best to estimate optimal fluid loading in any individual patient.

Optimising fluid loading and intravascular volume

If the choice of fluid to be administered is complex, the optimal volume of fluid to be administered is even more vexing, and the most appropriate endpoints to which fluid administration should be targeted remain the subject of much debate. Recent evidence suggests that traditional methods of assessing fluid status (particularly central venous pressure (CVP)) may not only be overrated but may be completely and utterly meaningless, leading to inappropriate fluid administration.

Intravenous fluid loading is often used as first-line therapy for patients with hypotension or circulatory failure, but in only one-half of patients does cardiac output respond positively after fluid challenge.¹⁶ For the remainder of patients fluid loading may be associated with adverse consequences.

At the outset two distinct groups of patients need to be appreciated – those breathing spontaneously and those on mechanical ventilation. There are subtle differences in assessing fluid status between the two, as discussed below.

The use of CVP has received considerable scrutiny and has been shown to be almost meaningless in the assessment of circulating fluid volume.^{16,17} Newer means of assessing fluid status that have been critically evaluated are supported scientifically in their utility.¹⁸⁻²¹

The spontaneously breathing patient

The average normal euvoalaemic patient has a CVP very close to zero or slightly negative. This represents a state of optimal cardiac output for venous return. CVP in this situation is well suited to the detection of fluid overload or the state of congestive cardiac failure.²² Indeed, we are all skilled in the detection of a raised jugular venous pressure (JVP) for the identification of such states. The error made is not in the validity of the pressures measured but rather in the deductions made from changes in CVP. At no point can it be assumed that a greater filling pressure is associated with a greater stroke volume or cardiac output. A greater filling pressure is only indicative of the ventricle's diastolic performance on its elastance curve. Most importantly, neither CVP nor even pulmonary capillary wedge pressure (PCWP) reflects end-diastolic volume.^{16,23}

While CVP measurement or assessment of the JVP reliably identifies fluid overload, the converse is not true. CVP cannot reliably predict hypovolaemia in the spontaneously

breathing patient. (Remember – a normal CVP may be zero, or just less.) Furthermore, improvement in cardiac output does not necessarily follow the administration of fluid to increase the CVP. This has been documented in healthy volunteers in an elegant (although very invasive) study.²⁴

The mechanically ventilated patient

In these patients the traditional value of CVP assessment as a tool for fluid management has received even more emphasis. Studies in critically ill patients attest to the lack of value of such measurement.²⁵ Neither the absolute value of the CVP, nor its response to fluid administration (trend tracking), has been shown to have any scientific validity or reproducibility.²⁴

Mechanically ventilated patients have a higher mean CVP, which is more indicative of mean intrathoracic pressure than of cardiac filling or intravascular fluid status.

Some still plead for the superiority of PCWP as the ultimate tool for assessment of fluid status. Sadly, PCWP suffers the same inadequacies as CVP. As in spontaneously breathing patients, a raised PCWP is not a reliable tool for the optimisation of intravascular volume. An excessively raised PCWP is invariably associated with fluid overload, while a low PCWP may only attest to good cardiac function rather than hypovolaemia.^{23,26}

If traditional methods of assessing and optimising fluid status (the use of CVP and PCWP) are so questioned, where does the conscientious practitioner turn for better information?

Physiological means of predicting response to fluid administration

The present literature highlights two specific methods for the identification of hypovolaemia and the optimisation of intravascular fluid volume. Both have been the subject of scientific investigation and are backed by physiological insight. A distinct advantage of the methods described below is the ability to predict the response to fluid administration without first having to administer the fluid. A distinct disadvantage of the practice of trend tracking either CVP or PCWP is the need to have administered fluid before assessment of its benefit (or harm).

Passive leg raising

The old practice of leg elevation as a tool to improve circulation and cardiac output is well attested to. A positive haemodynamic response to the elevation of the lower limbs

cannot be attributed to anything other than an increase in venous return after the auto-transfusion of blood from capacitance vessels. The patient who demonstrates a positive response to passive leg raising has been reliably shown to benefit from the administration of intravenous fluid.¹⁸ This applies irrespective of whether the patient is ventilated or not.

Assessment of systolic pressure variation

There is a growing interest in the clinical value of the observed variations in blood pressure and cardiac output that result from the interactions between the heart and lungs during ventilation.²⁷ It is not uncommon to observe a rise and fall in the systolic blood pressure on an arterial line trace, or the variations detected by a plethysmograph (on a pulse oximeter), coinciding with ventilatory rhythm. This phenomenon is known as systolic pressure variation and represents a potentially powerful tool in the assessment and manipulation of fluid status.

It has recently been established that not only systolic pressure variation but also several analogous derivatives provide valuable clinical information continuously. Other derivatives studied include pulse pressure variation, pulse volume variation and pulse velocity variation.^{18,20,21} Simplistically, the observed phenomenon is the result of the continuously varying response of the left ventricle to subtle changes in end-diastolic volume, created through cardiopulmonary interaction.

The predictive value of systolic pressure variation is well attested to in ventilated patients. Patients breathing spontaneously demonstrate the same phenomenon, but critical assessment is more difficult. Inspiratory effort and swings in intrathoracic pressure vary to a greater extent with each breath. Pulsus paradoxus, well described and observed, is nothing other than a demonstration of systolic pressure variation.

In a sepsis study systolic pressure variation predicted the response of cardiac output to volume load better than either PCWP or left ventricular end-diastolic area, as determined by echocardiography.¹⁸ This is astounding evidence, bearing in mind that both variables have traditionally been regarded as clinical gold standards for the assessment of fluid status with regard to the manipulation of cardiac output.

Conclusion

Choosing a fluid for intravascular administration is difficult. Both colloids and crystalloids have potential advantages and disadvantages. Colloids are always co-

administered in a crystalloid vehicle that may in itself warrant thought and consideration. Colloids have the distinct advantage of the need for less total volume administered for equivalent intravascular expansion.

Recent publications on the validity of CVP and PCWP are indicative of an inability to predict positive haemodynamic response to fluid administration. The overwhelming consensus is that CVP and PCWP measurement and interpretation are of little value in the assessment of fluid status and optimisation of cardiac output.

Newer dynamic means, such as systolic pressure variation, stroke volume variation, pulse pressure variation and pulse velocity variation, seem to hold much in store for clinical practice.^{18,21} Already these new derivatives appear set to displace the old stalwarts from the clinical arena. Monitoring of systolic pressure variation enables real-time prediction and determination of left ventricular response to preload enhancement. It also aids in guiding fluid therapy.²¹

Even the haemodynamic response to passive leg raising is a promising index of fluid responsiveness.¹⁸ One study has interpreted the consequences of passive leg raising within the context of systolic pressure variation.

The assessment of fluid volume status remains primarily the recognition of a syndrome complex. Peripheral perfusion, acid-base status, urine output, lactate and fluid balance remain important discriminators, but CVP and PCWP certainly not. Newer measures, including the responsiveness of flow measures to volume loading, appear useful but still require further evaluation.

References

1. Reid F, Lobo DN, Williams RN, Rowlands BJ, Allison SP. (Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study. *Clin Sci (Lond)* 2003; 104: 17-24.
2. O'Malley CM, Frumento RJ, Hardy MA, et al. A randomized, double-blind comparison of lactated Ringer's solution and 0.9% NaCl during renal transplantation. *Anesth Analg* 2005; 100: 1518-1524, table.
3. Drummond JC, Patel PM, Cole DJ, Kelly PJ. The effect of the reduction of colloid oncotic pressure, with and without reduction of osmolality, on post-traumatic cerebral edema. *Anesthesiology* 1998; 88: 993-1002.
4. Shires T, Williams J, Brown F. Acute change in extracellular fluids associated with major surgical procedures. *Ann Surg* 1961; 154: 803-810.
5. Gan TJ, Soppitt A, Maroof M, et al. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. *Anesthesiology* 2002; 97: 820-826.
6. Brandstrup B, Svendsen C, Engquist A. Hemorrhage and operation cause a contraction of the extracellular space needing replacement –

- evidence and implications? A systematic review. *Surgery* 2006; 139: 431-432.
7. Arieff AI. Fatal postoperative pulmonary edema: pathogenesis and literature review. *Chest* 1999; 115: 1371-1377.
 8. Lowell JA, Schifferdecker C, Driscoll DF, Benotti PN, Bistrian BR. Postoperative fluid overload: not a benign problem. *Crit Care Med* 1990; 18: 728-733.
 9. Balogh Z, McKinley BA, Cocanour CS, *et al.* Supranormal trauma resuscitation causes more cases of abdominal compartment syndrome. *Arch Surg* 2003; 138: 637-642.
 10. Brandstrup B, Tonnesen H, Beier-Holgersen R, *et al.* Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Ann Surg* 2003; 238: 641-648.
 11. Nisanevich V, Felsenstein I, Almog G, Weissman C, Einav S, Matot I. Effect of intraoperative fluid management on outcome after intraabdominal surgery. *Anesthesiology* 2005; 103: 25-32.
 12. Joshi GP. Intraoperative fluid restriction improves outcome after major elective gastrointestinal surgery. *Anesth Analg* 2005; 101: 601-605.
 13. Bellamy MC. Wet, dry or something else? *Br J Anaesth* 2006; 97: 755-757.
 14. Grocott MP, Mythen MG, Gan TJ. Perioperative fluid management and clinical outcomes in adults. *Anesth Analg* 2005; 100: 1093-1106.
 15. Holte K, Foss NB, Andersen J, *et al.* Liberal or restrictive fluid administration in fast-track colonic surgery: a randomized, double-blind study. *Br J Anaesth* 2007; 99: 500-508.
 16. Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients. A critical analysis of the evidence. *Chest* 2002; 121: 2000-2008.
 17. Bendjelid K, Romand JA. Fluid responsiveness in mechanically ventilated patients: a review of indices used in intensive care. *Intensive Care Med* 2003; 29: 352-360.
 18. Boulain T, Achard JM, Teboul JL, Richard C, Perrotin D, Ginies G. Changes in BP induced by passive leg raising predict response to fluid loading in critically ill patients. *Chest* 2002; 121: 1245-1252.
 19. Parry-Jones AJ, Pittman JA. Arterial pressure and stroke volume variability as measurements for cardiovascular optimisation. *International Journal of Intensive Care* 2003; Summer: 1 - 5.
 20. Reuter DA, Felbinger TW, Kilger E, Schmidt C, Lamm P, Goetz AE. Optimizing fluid therapy in mechanically ventilated patients after cardiac surgery by on-line monitoring of left ventricular stroke volume variations. Comparison with aortic systolic pressure variations. *Br J Anaesth* 2002; 88: 124-126.
 21. Tavernier B, Makhotne O, Lebuffe G, Dupont J, Scherpereel P. Systolic pressure variation as a guide to fluid therapy in patients with sepsis-induced hypotension. *Anesthesiology* 1998; 89: 1313-1321.
 22. Starling EH. The Arris and Gale lectures. Some points in the pathology of heart disease. *Lancet* 1897; 1: 652-655.
 23. Calvin JE, Driedger AA. The hemodynamic effect of rapid fluid infusion in critically ill patients. *Surgery* 1981; 90: 61-76.
 24. Kumar A, Anel R, Bunnell E, *et al.* Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. *Crit Care Med* 2004; 32: 691-699.
 25. Lichtwarck-Aschoff M, Zeravik J, Pfeiffer UJ. Intrathoracic blood volume accurately reflects circulatory volume status in critically ill patients with mechanical ventilation. *Intensive Care Med* 1992; 18: 142-147.
 26. Ellis RJ, Mangano DT, VanDyke DC. Relationship of wedge pressure to end-diastolic volume in patients undergoing myocardial revascularization. *J Thorac Cardiovasc Surg* 1979; 78: 605-613.
 27. Preisman S, Pfeiffer U, Lieberman N, Perel A. New monitors of intravascular volume: a comparison of arterial pressure waveform analysis and the intrathoracic blood volume. *Intensive Care Med* 1997; 23: 651-657.

In a nutshell

- Modern fluid therapy requires an understanding of the underlying physiological abnormalities induced by acute illness, the nature of the fluids to be administered, the differences between the various intravenous fluid preparations and concepts regarding appropriate amounts of volume to be given.
- Crystalloid solutions expand the extracellular fluid (ECF) space and are redistributed between the intravascular and extracellular compartments in a ratio of 1:4 in proportion to the normal distribution of fluid between these two spaces.
- The most widely used crystalloids, 0.9% saline and balanced salt solutions such as Ringer's lactate, fall well short of the desired composition.
- 'Normal' saline is significantly hypertonic (osmolality 308 mOsm/l) and has a very high chloride content (154 mmol/l; normal plasma range 95 - 105 mmol/l).
- Infusions of as little as 2 litre 0.9% saline during surgical procedures will produce a significant, metabolic acidosis owing to the chloride load.
- Ringer's lactate (or acetate), like 0.9% saline, is not an ideal solution. The Cl⁻ content is substantially higher than plasma chloride (111 mmol/l), the Na⁺ content lower (131 mmol/l) and the osmolality of the solution is 274 mOsm/l.
- Colloids are suspensions of particles of various sizes that aim to maintain plasma volume by maintaining the colloid osmotic pressure in plasma, thus retaining the administered volume within the circulation.
- Recently the 'third space' concept has been questioned and attention has focused on the potential adverse effects of excess administration of crystalloid solutions.
- Intravenous fluid loading is often used as first-line therapy for patients with hypotension or circulatory failure, but in only half of patients does cardiac output respond positively after fluid challenge. For the remainder of patients fluid loading may be associated with adverse consequences.
- Mechanically ventilated patients have a higher mean CVP, more indicative of mean intrathoracic pressure than of cardiac filling or intravascular fluid status.
- The patient who demonstrates a positive response to passive leg raising has been reliably shown to benefit from the administration of intravenous fluid.
- It has recently been established that not only systolic pressure variation but also several analogous derivatives provide valuable clinical information on a continuous basis.
- The predictive value of systolic pressure variation is well attested to in ventilated patients. Patients breathing spontaneously demonstrate the same phenomenon, but critical assessment is more difficult.