

Sodium reduction during cardiopulmonary bypass: Plasma-Lyte 148 versus trial fluid as pump primes

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At the start of a cardiopulmonary bypass (CPB) procedure there is a rapid haemodilution with the fluids used to prime the circuit. Data collected before and after CPB begins can be used to investigate the properties of these priming fluids; for example, their acid–base effects.^{1–4} The same methodology can reveal their immediate impact on plasma sodium concentrations^{3–5} and associated tonicity.

It has been asserted that, as with chloride, the sodium concentration in 0.9% sodium chloride (154 mmol/L) is “supra-physiological”.⁶ However, it is important to remember that the appropriate comparative physiological norm is the sodium concentration in the plasma water, which makes up 93% of the normal total plasma volume, the remainder being non-aqueous protein and lipid material.⁷ As a result, a normal sodium concentration of 140 mmol/L, as measured in healthy plasma, corresponds to a plasma water sodium concentration of 150.5 mmol/L.

By this criterion, a crystalloid solution with a sodium concentration of 140 mmol/L is mildly hypotonic unless it contains a large coincident potassium concentration (at least 10 mmol/L). Examples include Plasma-Lyte 148 (Baxter Healthcare), a fluid in common use as a CPB circuit primer and under current evaluation as a balanced resuscitation crystalloid solution.⁸ With a relatively small electrolyte-free water content (Table 1),⁹ its hypotonicity as a CPB priming solution should be most evident in the immediate post-haemodilution phase, before equilibration with erythrocytes is completed and before extravascular spread with the remaining total body water. In theory, if 3.2 L of isolated plasma with a sodium concentration of 140 mmol/L and a 7% non-aqueous phase is diluted with 2 L of Plasma-Lyte 148, the predicted result would be a 4 mmol/L reduction in the measured plasma sodium concentration.

We investigated the impact of two CPB priming solutions, both with sodium concentrations of 140 mmol/L, on measured plasma sodium concentrations and calculated plasma tonicity. One priming solution was Plasma-Lyte 148, and the other was a novel bicarbonate-balanced crystalloid solution with a favourable acid–base profile during CPB (Table 1).^{1,10} We hypothesised that both would cause similar plasma sodium reductions, not exceeding 4 mmol/L, immediately after institution of CPB. We further predicted that, since

ABSTRACT

Objectives: We compared effects on plasma sodium concentrations plus calculated plasma tonicity of two “balanced” crystalloid solutions used as 2 L pump primes during cardiopulmonary bypass (CPB): Plasma-Lyte 148 (sodium concentration, 140 mmol/L; potassium concentration, 5 mmol/L) versus a bicarbonate-balanced fluid (sodium concentration, 140 mmol/L; potassium concentration, 0 mmol/L).

Design, setting and participants: We analysed pooled data from two prospective interventional studies performed in university-affiliated hospitals, from 50 patients undergoing elective cardiac surgery.

Interventions: Participants were allocated equally to Plasma-Lyte 148 or bicarbonate-balanced fluid, with plasma electrolytes measured by direct ion selective electrodes immediately before bypass (pre-CPB), within 3 minutes of commencement (T2), and before bypass cessation (end-CPB).

Results: Plasma sodium fell at T2 in 46 patients (92%) ($P < 0.0005$). With Plasma-Lyte 148, the mean sodium decreased by 3.0 mmol/L (SD, 1.7 mmol/L), and with bicarbonate-balanced fluid it decreased by 2.2 mmol/L (SD, 1.1 mmol/L) ($P = 0.002$). The mean tonicity fell by > 5 mOsm/kg for both groups ($P < 0.0005$). At end-CPB, the mean sodium for both groups remained reduced by > 2 mmol/L ($P < 0.0005$). In the group receiving Plasma-Lyte 148, 52% of patients were hyponatraemic (sodium < 135 mmol/L) at T2 and end-CPB.

Conclusions: Sodium reductions were common with both priming solutions, but more severe with Plasma-Lyte 148. Crystalloid priming solutions require sodium concentrations > 140 mmol/L to ensure normonatremia throughout CPB.

Crit Care Resusc 2015; 17: 263–267

Plasma-Lyte 148 contains less electrolyte-free water (due to the presence of potassium [Table 1]),⁹ any associated tonicity reductions would be less severe.

Table 1. Composition of circuit-priming fluids and cardioplegia solution

Electrolyte	Circuit-priming fluid		Cardioplegia solution
	Plasma-Lyte 148	Bicarbonate balanced	
Na ⁺ (mmol/L)	140	140	140
Cl ⁻ (mmol/L)	98	116	256
K ⁺ (mmol/L)	5	0	83
Mg ²⁺ (mmol/L)	1.5	–	40
HCO ₃ ⁻ (mmol/L)	–	24	–
Acetate (mmol/L)	27	–	28
Gluconate (mmol/L)	23	–	24
Electrolyte-free water (mL)	58	91	–309

Table 2. Patient characteristics according to study fluid group

Patient characteristic	Bicarbonate-balanced (N=25)	Plasma-Lyte 148 (N=25)	P
Mean age, years (SD)	66 (9.3)	68 (9.1)	0.49*
Male, n (%)	20 (80%)	16 (64%)	0.35 [†]
Surgical type, n (%)			1.00 [†]
CABG	18 (72%)	18 (72%)	
Valve	7 (28%)	7 (28%)	
Median CPB time, minutes (range)	78 (26–177)	78 (60–128)	0.80 [‡]
Median clamp time, minutes (range)	45 (17–145)	54 (36–109)	0.52 [‡]
Mean cardioplegia solution volume, mL (SD)	315 (122)	339 (94)	0.45*
Mean extra Plasma-Lyte 148, mL (SD)	533 (731)	508 (745)	0.84*
Median euroSCORE, (range)	4 (0–11)	4 (0–10)	0.86 [‡]
Median Parsonnet score, (range)	10 (3–25)	8 (1–26)	0.64 [‡]
Hospital survival, n (%)	25 (100%)	25 (100%)	1.00 [†]

CABG = coronary artery bypass graft. Valve = cardiac valve surgery with or without CABG. EuroSCORE = European System for Cardiac Operative Risk Evaluation. * Using unpaired *t* test. [†] Using Fisher exact test. [‡] Using Wilcoxon rank-sum (Mann–Whitney) test.

Materials and methods

We conducted a pooled-data analysis from two published studies^{1,10} reporting the acid–base properties of both priming solutions during CPB (ACTRN12610000267055). Both protocols were approved by the research ethics committee of the Princess Alexandra Hospital, and written informed consent was obtained from all patients before enrolment.

There were 50 elective cardiac surgical patients. Exclusion criteria included venous plasma HCO₃⁻ concentration < 22 mmol/L or > 27 mmol/L, hypercarbic respiratory failure, plasma creatinine concentration > 120 micromol/L, diabetes mellitus and chronic liver disease.

One group received 2 L of Plasma-Lyte 148 priming solution. The other group received 2 L of bicarbonate-balanced fluid mixed in the pump by addition of 0.9% sodium chloride 1130 mL, 0.45% sodium chloride 822 mL (Baxter Healthcare) and 8.4% sodium bicarbonate 48 mL (Astra Pharmaceuticals). Allocation in one study was by computerised random number generation (*n* = 20),¹ and in the other by convenience (*n* = 30).¹⁰

Arterial blood was sampled at three time points:

- T1 (pre-CPB): after anaesthesia induction, before starting CPB
- T2: 2–3 minutes after starting CPB, before cardioplegia solution administration
- end-CPB: before CPB separation.

After the T2 sample was taken, cardioplegia solution was administered to all patients, and some patients also then received supplementary fluid boluses of Plasma-Lyte 148. Fluid compositions (including administered cardioplegia solution) are set out in Table 1.

Direct ion selective electrodes (ABL 600 [Radiometer] or Rapidlab 865 [Siemens Medical Solutions]) measured plasma concentrations of sodium, potassium and glucose. Use of indirect ion selective electrode analysers was avoided to prevent the measurement error introduced by preanalytic dilution.¹¹

Calculation of plasma tonicity

The plasma tonicity (effective osmolality) was calculated from measured electrolyte concentrations (in mmol/L) by omitting urea concentration from a standard osmolality algorithm:¹²

$$\text{Tonicity (mOsm/kg)} = 1.89[\text{Na}] + 1.38[\text{K}] + 1.08[\text{glucose}] + 7.45$$

Statistical analysis

Between-group baseline characteristics were compared using exact, rank-sum or unpaired *t* tests. A linear analysis-of-covariance model evaluated main effects with interactions for fluid group across time points, using a population-averaged generalised estimating equation (GEE) approach.¹³ The model adjusted for volumes of cardioplegia solution and extra Plasma-Lyte 148 as well as for age, sex, European System for Cardiac Operative Risk Evaluation (EuroSCORE)¹⁴ and valve surgery versus coronary artery surgery.

The proportion of subjects with hyponatraemia (plasma sodium < 135 mmol/L) over time was evaluated using a similar GEE logistic model.

Results

CPB data

Groups were similar with respect to mean baseline plasma concentrations of sodium, potassium and glucose, age, sex, operative type, CPB times, clamp times, EuroSCORE and Parsonnet indices,¹⁴ volumes of administered cardioplegia solution, and volumes of extra Plasma-Lyte 148 administered (Table 2 and Table 3).

Changes in plasma sodium concentrations

Acute sodium reductions were experienced at T2 by 23 of the 25 patients in each group ($P < 0.0005$, Figure 1). With the bicarbonate-balanced priming solution, plasma sodium decreased by a mean of 2.2 mmol/L (SD, 1.1 mmol/L), and with Plasma-Lyte 148 it decreased by 3.0 mmol/L (SD, 1.7 mmol/L) ($P = 0.002$). Ten of the 25 patients receiving Plasma-Lyte 148 experienced acute sodium reductions of 4–7 mmol/L.

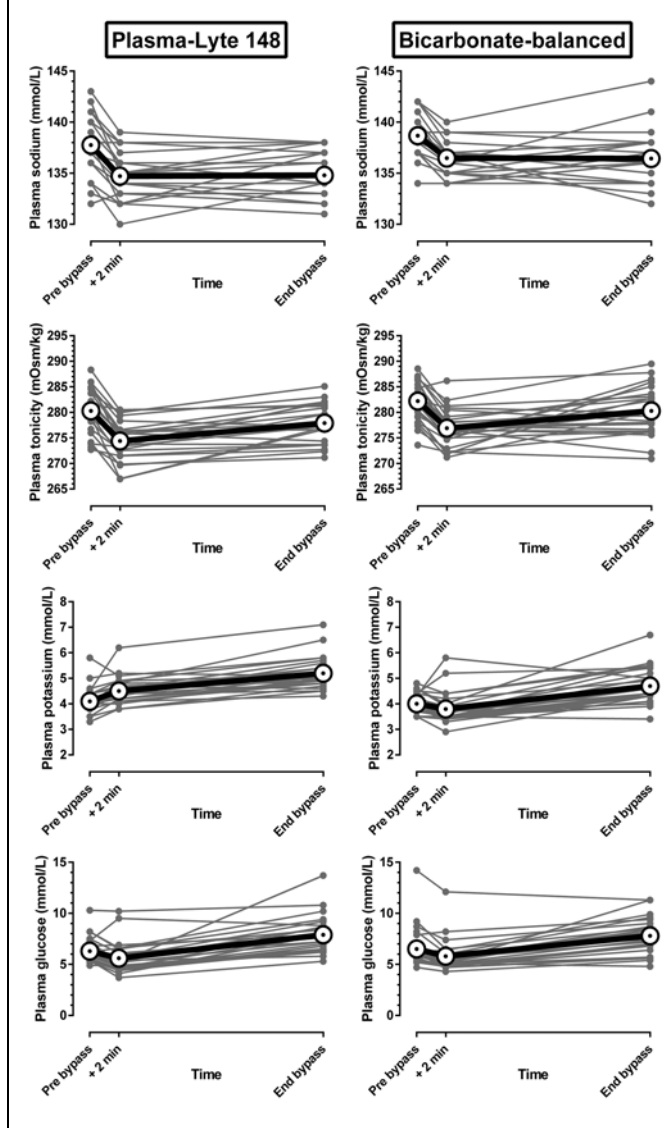
In both groups, mean sodium reductions > 2 mmol/L relative to T1 ($P < 0.0005$) were maintained until end-CPB, although the differential greater reduction in the Plasma-Lyte 148 group was less prominent ($P = 0.19$, Figure 1).

Development of hyponatraemia

Mild baseline hyponatraemia ($[Na] < 135$ mmol/L) was present in undifferentiated proportions (bicarbonate-balanced group, 1/25 [4%]; Plasma-Lyte 148 group, 4/25 [16%]; $P = 0.35$) (Figure 2). At T2, there was a substantial increase in the prevalence of hyponatraemia in the Plasma-Lyte 148 group to 52% ($P = 0.001$), which was maintained until end-CPB ($P < 0.0005$).

In contrast, there was a delayed onset of hyponatraemia in the bicarbonate-balanced group at T2 and end-CPB (12% at T2, $P = 0.18$; 20% at T3, $P = 0.04$). Hyponatraemia was differentially more prevalent with Plasma-Lyte 148 at T2 ($P = 0.003$) and end-CPB ($P = 0.01$).

Figure 1. Concentrations of plasma sodium, tonicity, potassium and glucose during cardiopulmonary bypass



Changes in calculated plasma tonicity

The mean plasma tonicity decreased in both groups by > 5 mOsm/kg at T2 ($P < 0.0005$), with no intergroup difference ($P = 0.11$) (Figure 1). By end-CPB, plasma tonicity returned towards baseline, but remained below pre-CPB levels for both bicarbonate-balanced fluid ($P = 0.09$) and Plasma-Lyte 148 ($P = 0.001$).

Potassium and glucose changes

Patients receiving bicarbonate-balanced fluid exhibited a small mean potassium reduction (-0.2 mmol/L, $P = 0.02$), and patients receiving Plasma-Lyte 148 showed an increase at T2 of about 0.4 mmol/L ($P < 0.0005$) (Figure 1). At end-

Plasma characteristic, mean (SD)	Bicarbonate-balanced	Plasma-Lyte 148	P*
Sodium, mmol/L	139 (2.0)	138 (2.7)	0.18
Potassium, mmol/L	4.0 (0.37)	4.1 (0.51)	0.51
Glucose, mmol/L	6.5 (2.0)	6.3 (1.3)	0.62
Tonicity, mOsm/kg	282 (3.8)	280 (4.2)	0.10

* Using unpaired t test.

CPB, both groups had mean plasma potassium concentrations at least 0.7 mmol/L above baseline ($P < 0.0005$), with a persisting differential elevation with Plasma-Lyte 148 ($P = 0.02$).

There was a reduction in mean plasma glucose of about 0.7 mmol/L at T2 ($P < 0.0005$), followed by an increase over mean baseline values of about 1.5 mmol/L, with no differential Plasma-Lyte 148 effect ($P \geq 0.69$).

Discussion

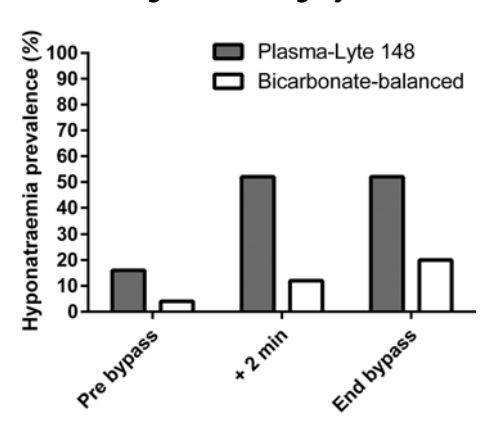
We showed that haemodilution with 2 L of CPB priming solutions consisting of either Plasma-Lyte 148 or a trial bicarbonate-balanced fluid, both with sodium concentrations of 140 mmol/L, was followed by immediate reductions in mean plasma sodium concentrations, confirming a degree of priming hypotonicity in both cases. As predicted, the mean sodium decline with both priming solutions was < 4 mmol/L, consistent with the start of equilibration beyond the plasma water phase by the time of sampling.

Against predictions, mean sodium reductions of > 2 mmol/L were still present with both priming solutions at end-CPB. This was despite subsequent administration of cardioplegia solution (which has a sizeable negative electrolyte-free water content [Table 1]), and relatively small further Plasma-Lyte 148 fluid loads (Table 2). Also against predictions, initial sodium reductions and hyponatraemia at T2 and end-CPB were more prominent with Plasma-Lyte 148, although falls in calculated tonicity were similar due to differential potassium alterations.

No plasma sodium fell below the quoted clinically relevant threshold of 125 mmol/L¹⁵ at T2 or at end-CPB. Whether these less severe but persistent reductions might have clinical consequences in the context of cardiac surgery is unclear. Extracellular sodium concentrations and tonicity are important modifiers of brain water partitioning and intracranial pressure,^{16,17} and cardiac surgical patients as a group have a high prevalence of post-CPB cerebral oedema^{18,19} and an increased neurological risk.²⁰ Also worth noting is that experimental haemodilution-induced tonicity reductions of similar magnitude increased mean intracranial pressure by > 4 mmHg,¹⁷ and that acute plasma sodium increases of equivalent degree can terminate hyponatraemic seizures.²¹

To our knowledge, the only previous report of plasma sodium measurements with Plasma-Lyte 148 prime is that

Figure 2. Prevalence of hyponatraemia (< 135 mmol/L) with 95% CIs at three times during cardiac surgery



of Liskaser and colleagues,² who also found immediate reductions in median sodium concentrations persisting to the late rewarming phase. Although reductions were smaller (2 mmol/L) than in our study (3 mmol/L), the median sodium concentration at baseline was lower at 135 mmol/L, and the priming volume was 1.5 L versus 2 L. By contrast, other priming fluids with higher sodium concentrations (up to and including 154 mmol/L) have been associated with no change^{2,3} or a slight increase⁴ in plasma sodium.

Acute plasma sodium reductions at T2 were expected, on the basis that both priming fluids are mildly

hypotonic compared with normal plasma water, and contribute electrolyte-free water relative to isotonic saline (Table 1). The persistence of reductions to end-CPB perhaps reflected a retarded rate of priming solution equilibration with the total body water while on CPB. The more prominent sodium reductions with Plasma-Lyte 148 are more difficult to explain as Plasma-Lyte 148 contains less electrolyte-free water (Table 1), a calculation which includes potassium.⁹ There was no glucose surge at T2 or end-CPB (Figure 1), and the transient acetate surges associated with a Plasma-Lyte 148 prime¹⁰ do not predispose to sodium reductions on current evidence.

Baxter quality control using flame photometry showed consistent sodium concentrations in Plasma-Lyte 148 samples, with little variation from 140 mmol/L (G Lauder, Regional Director Quality Assurance, Baxter Healthcare, personal communication, November 2012). Higher-than-intended sodium concentrations in the bicarbonate-balanced trial fluid cannot be excluded, since final pump concentrations were not monitored by direct testing. Another possibility is that there was a shorter equilibration time in the Plasma-Lyte 148 group due to inadvertent earlier T2 sampling.

We conclude that 2 L CPB primes of Plasma-Lyte 148 and a novel bicarbonate-balanced fluid, both with designated sodium concentrations of 140 mmol/L, were associated with acute reductions in plasma sodium concentrations and calculated tonicity of uncertain clinical significance, to the extent that half of the patients receiving Plasma-Lyte 148 prime were hyponatraemic throughout CPB. Precise maintenance of plasma normonatraemia and normotonicity by crystalloid CPB pump primes requires sodium concentrations exceeding 140 mmol/L.

If higher sodium concentrations were adopted in a balanced prime, an equivalent chloride increase would be necessary to maintain that balance. For example, if the sodium concentration of the bicarbonate-balanced crystalloid solution in Table 1 was increased from 140 mmol/L to the isotonic value of 154 mmol/L, the chloride concentration would have to be reset at 130 mmol/L to retain a balanced effective strong ion difference of 24 mEq/L.²² Since chloride restriction may improve outcomes,^{6,23} an alternative is to leave the chloride concentration unaltered at 116 mmol/L. The effective strong ion difference would then increase to 38 mEq/L, which is still 12 mEq/L lower than that of Plasma-Lyte 148. Any metabolic alkalosis generated by a 2 L haemodilution with such a prime would be minimal. The other alternative is to include a non-volatile weak acid such as albumin with the sodium increase. To illustrate the chloride-sparing effects of albumin, a commercial preparation of 4% albumin (Albumex 4 [CSL]) retains in vitro acid-base effects equivalent to those of 0.9% sodium chloride, despite its modified saline vehicle, in which the chloride concentration is 12 mmol/L lower than the sodium concentration.²⁴

Competing interests

None declared.

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References

- Morgan TJ, Power G, Venkatesh B, Jones MA. Acid-base effects of a bicarbonate-balanced priming fluid during cardiopulmonary bypass: comparison with Plasma-Lyte 148. A randomised single-blinded study. *Anaesth Intensive Care* 2008; 36: 822-9.
- Liskaser FJ, Bellomo R, Hayhoe M, et al. Role of pump prime in the etiology and pathogenesis of cardiopulmonary bypass-associated acidosis. *Anesthesiology* 2000; 93: 1170-3.

- Hayhoe M, Bellomo R, Liu G, et al. The aetiology and pathogenesis of cardiopulmonary bypass-associated metabolic acidosis using polygeline pump prime. *Intensive Care Med* 1999; 25: 680-5.
- Himpe D, Neels H, De Hert S, Van Cauwelaert P. Adding lactate to the prime solution during hypothermic cardiopulmonary bypass: a quantitative acid-base analysis. *Br J Anaesth* 2003; 90: 440-5.
- Liskaser F, Story DA, Hayhoe M, et al. Effect of pump prime on acidosis, strong-ion-difference and unmeasured ions during cardiopulmonary bypass. *Anaesth Intensive Care* 2009; 37: 767-72.
- Shaw AD, Raghunathan K, Peyerl FW, et al. Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with SIRS. *Intensive Care Med* 2014; 40: 1897-905.
- Rose BD, Post TW. Clinical physiology of acid-base and electrolyte disorders. 5th ed. Wellesley, Massachusetts: McGraw-Hill, 2001.
- Reddy SK, Bailey MJ, Beasley RW, et al. A protocol for the 0.9% saline versus Plasma-Lyte 148 for intensive care fluid therapy (SPLIT) study. *Crit Care Resusc* 2014; 16: 274-9.
- Carlotti AP, Bohn D, Mallie JP, Halperin ML. Tonicity balance, and not electrolyte-free water calculations, more accurately guides therapy for acute changes in natremia. *Intensive Care Med* 2001; 27: 921-4.
- Davies PG, Venkatesh B, Morgan TJ, et al. Plasma acetate, gluconate and interleukin-6 profiles during and after cardiopulmonary bypass: a comparison of Plasma-Lyte 148 with a bicarbonate-balanced solution. *Crit Care* 2011; 15: R21.
- Dimeski G, Morgan TJ, Presneill JJ, Venkatesh B. Disagreement between ion selective electrode direct and indirect sodium measurements: estimation of the problem in a tertiary referral hospital. *J Crit Care* 2012; 27: 326 e9-e16.
- Bhagat CI, Garcia-Webb P, Fletcher E, Beilby JP. Calculated vs measured plasma osmolalities revisited. *Clin Chem* 1984; 30: 1703-5.
- Gardiner JC, Luo Z, Roman LA. Fixed effects, random effects and GEE: what are the differences? *Stat Med* 2009; 28: 221-39.
- Baretti R, Pannek N, Knecht JP, et al. Risk stratification scores for predicting mortality in coronary artery bypass surgery. *Thorac Cardiovasc Surg* 2002; 50: 237-46.
- Arief Al, Llach F, Massry SG. Neurological manifestations and morbidity of hyponatremia: correlation with brain water and electrolytes. *Medicine (Baltimore)* 1976; 55: 121-9.
- Strange K. Regulation of solute and water balance and cell volume in the central nervous system. *J Am Soc Nephrol* 1992; 3: 12-27.
- Tommasino C, Moore S, Todd MM. Cerebral effects of isovolemic hemodilution with crystalloid or colloid solutions. *Crit Care Med* 1988; 16: 862-8.
- Harris DN, Bailey SM, Smith PL, et al. Brain swelling in first hour after coronary artery bypass surgery. *Lancet* 1993; 342: 586-7.
- Harris DN, Oatridge A, Dob D, et al. Cerebral swelling after normothermic cardiopulmonary bypass. *Anesthesiology* 1998; 88: 340-5.
- Roach GW, Kanchuger M, Mangano CM, et al. Adverse cerebral outcomes after coronary bypass surgery. Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation Investigators. *N Engl J Med* 1996; 335: 1857-63.
- Adrogué HJ, Madias NE. Hyponatremia. *N Engl J Med* 2000; 342: 1581-9.
- Morgan TJ. The ideal crystalloid — what is 'balanced'? *Curr Opin Crit Care* 2013; 19: 299-307.
- Yunos NM, Kim IB, Bellomo R, et al. The biochemical effects of restricting chloride-rich fluids in intensive care. *Crit Care Med* 2011; 39: 2419-24.
- Morgan TJ, Vellaichamy M, Cowley DM, et al. Equivalent metabolic acidosis with four colloids and saline on ex vivo haemodilution. *Anaesth Intensive Care* 2009; 37: 407-14. □