Critically ill patients are at risk of positive sodium balance due to inadvertent excess administration, which may be over twice the recommended daily sodium intake for healthy individuals,1,2 and decreased sodium clearance.3 A small, single-centre study suggested that the estimated positive sodium balance in intensive care patients is high and that there may be dissociation between estimated sodium balance and fluid balance.4 In patients on mechanical ventilation (MV), cumulative positive fluid balance is associated with worsening oxygenation, prolonged MV and increased morbidity and mortality.5-9 The distribution of water between intracellular and extracellular compartments is strongly influenced by sodium concentration and its relative restriction to the extracellular fluid space. The adverse effects associated with positive fluid balance may, therefore, be related partly to positive sodium balance.

There is limited evidence about factors contributing to sodium balance in critically ill patients and the clinical implications of positive sodium balance.10 The potential for excess sodium to exacerbate interstitial oedema in the systemic and pulmonary circulations, independent of fluid balance, is supported by the recent single-centre reports of an adverse association between estimated positive sodium balance and PaO2/FiO2 ratio, radiological lung injury score and expanded extracellular fluid volumes in critically ill patients.4 The aim of our study was to extend these initial single-centre observations by examining sodium balance and its relationship with oxygenation (PaO2/FiO2 ratio) and length of MV in critically ill patients on MV at multiple centres.

Methods

We conducted a prospective, observational, multicentre study in four mixed medical and surgical Australian intensive care units between April 2012 and September 2013. We included patients receiving invasive MV for less than 48 hours who were anticipated to be on MV for at least another 48 hours. Patients were also required to have an indwelling urinary catheter in situ and a screening serum sodium concentration between 130 mmol/L and 150 mmol/L. Exclusion criteria were age less than 18 years, traumatic brain injury, ICU admission diagnosis of diabetic ketoacidosis–hyperosmolar hyperglycaemic state, Child–Pugh class C liver cirrhosis, pregnancy or anticipated survival less than 24 hours. Patients undergoing renal replacement therapy (RRT)
or expected to require dialysis within the next 48 hours were also excluded due to the potential for inadvertent excess sodium loading.11 Ethics approval was obtained at all participating sites and the study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12612000046808).

Data were collected on Day 1, Day 2 and Day 3 after recruitment, with Day 1 being defined as the day of enrolment, based on the ICU chart time. Data included:
- patient demographics (age, sex, weight and height)
- ICU admission diagnosis and severity of illness (Acute Physiology and Chronic Health Evaluation [APACHE] II and III) score
- daily highest and lowest $\text{PaO}_2/\text{FiO}_2$ ratio
- daily urine output and fluid balance
- daily serum creatinine, urea and albumin levels
- diuretic, steroid, vasopressor and RRT administration
- intravascular devices
- presence of shock (defined as requirement for vasopres-
sor infusion at any dose for more than 6 hours)
- duration of MV, ICU and hospital mortality, and ICU and hospital lengths of stay.

Sodium and fluid intakes were calculated and recorded for all solutions as the type and volume administered over each 24-hour study day. Sodium and fluid sources were classified as:
- intravenous (IV) fluids administered by bolus or infusion for volume expansion and/or resuscitation, including crystalloids and colloids
- transfusion of blood products such as red blood cells, platelets and fresh frozen plasma
- IV infusions given as maintenance or replacement fluids
- IV antibiotics administered as a bolus with its vehicle
- other IV drugs administered by continuous infusion with their vehicle (drug infusions)
- other IV drugs administered by bolus with their vehicle (drug boluses)
- intravascular line flushes associated with haemodynamic monitoring, including arterial lines and central venous catheters
- total parenteral nutrition (TPN)
- enteral nutrition.

The amount of sodium administered was then calculated based on published sodium concentrations of each solution. Therefore, for drug infusions and boluses, the sodium content was calculated from the sodium content of the drug and the type and volume of carrier fluid or diluent. For TPN and enteral nutrition, information on the type and volume of feed was recorded and the sodium content calculated accordingly. As sodium content from sources such as drug boluses, drug infusions, antibiotics and flushes are often occult and may be considered unintentional, they were grouped as “inadvertent” sources.

The estimated sodium output was based on combined losses from urine, nasogastric drainage, other gastrointestinal losses and drains. For urinary sodium losses, the sodium concentration was measured each day from 24-hour urine collection. For all other losses, sodium concentration was estimated (for pragmatic reasons) from published values.12

### Statistical analysis

Data are reported as means and standard deviations (SDs) or medians and interquartile ranges (IQRs), as appropriate for the

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>62.8 (14.6)</td>
</tr>
<tr>
<td>Sex (male), n (%)</td>
<td>33 (66%)</td>
</tr>
<tr>
<td>Mean weight, kg (SD)</td>
<td>79.4 (14.4)</td>
</tr>
<tr>
<td>Mean height, cm (SD)</td>
<td>171.5 (8.9)</td>
</tr>
<tr>
<td>Median APACHE II score (IQR)</td>
<td>25 (19–29)</td>
</tr>
<tr>
<td>Median APACHE III (IQR)</td>
<td>82 (61–99)</td>
</tr>
<tr>
<td>Median mechanical ventilation time, hours (IQR)</td>
<td>120 (86.7–182.5)</td>
</tr>
<tr>
<td>Reason for ICU admission, n (%)</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>16 (32%)</td>
</tr>
<tr>
<td>Respiratory disorder</td>
<td>15 (30%)</td>
</tr>
<tr>
<td>Cardiac disorder</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Postoperative disorder</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>Median ICU length of stay, days (IQR)</td>
<td>7.5 (6–12.7)</td>
</tr>
<tr>
<td>Median hospital length of stay, days (IQR)</td>
<td>17.9 (7.8–32.3)</td>
</tr>
<tr>
<td>ICU mortality, n (%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Hospital mortality, n (%)</td>
<td>7 (14%)</td>
</tr>
</tbody>
</table>

SD = standard deviation. APACHE = Acute Physiology and Chronic Health Evaluation. IQR = interquartile range. ICU = intensive care unit.
distribution of each variable. The Shapiro–Wilk test and probability–probability plots were used to assess distribution of data, and the independent sample t test or Wilcoxon signed-rank test were used to compare groups. Repeated-measures analysis of variance was used to analyse data measured over time (Day 1 to Day 3). The Pearson correlation was used to test for the association between continuous variables, and the χ² test was used to compare proportions. Predictor variables predefined for length of MV (age, APACHE II score, weight, PaO₂/FiO₂ ratio, cumulative sodium and fluid balance at Day 3, presence of shock, and IV diuretic and steroid administration) were analysed using stepwise multiple linear regression analyses. Results are reported as the β coefficient, standard error and P. For data analysis we used SPSS, version 19.0 (SPSS Inc). Conventional two-tailed α < 0.05 was used for all tests of significance.

Results

Ninety-two patients were screened for eligibility and 50 patients were enrolled, of whom 33 were men (66%). All patients provided data on fluid and sodium balance for 3 days and no patients were lost to follow-up (Figure 1). Demographic details of patients recruited are shown in Table 1. Sepsis was the most common admission diagnosis (n=16 [32%]), followed closely by patients with a respiratory disorder. Daily physiological and biochemical data are shown in Table 2. More than half the patients received vasopressors on any study day. The mean time between ICU admission and inclusion in the study was 8 hours (SD, 0–17 hours), and between intubation and inclusion was 4 hours (SD, 0–14 hours).

Fluid balance

The fluid balance was positive each day, with a mean cumulative balance of +2668 mL (SD, +875 to +3507 mL) by Day 3 (Table 3). The daily fluid balance was less marked on Day 3 (P=0.01), due to lower fluid input (P=0.04) with an unchanged urine output (P=0.35). By examining the 50 patients on each of the 3 study days we showed that patients who were administered diuretics (n=39) had increased urine output and a lower daily fluid balance, while patients who were administered vasopressors for shock (n=89) or were administered steroids (n=85) had no significant difference in their urine output and daily fluid balance (Table 4).

Table 2. Daily physiological and laboratory data*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean serum sodium, mmol/L (SD)</td>
<td>140.2 (5.3)</td>
<td>141.1 (5.2)</td>
<td>141.4 (5.5)</td>
</tr>
<tr>
<td>Mean serum albumin, g/L (SD)</td>
<td>27.6 (5.1)</td>
<td>26.4 (5.1)</td>
<td>25.4 (4.6)</td>
</tr>
<tr>
<td>Mean serum creatinine, mmol/L (SD)</td>
<td>103.9 (51.9)</td>
<td>103.4 (59.7)</td>
<td>90.6 (50.1)</td>
</tr>
<tr>
<td>Mean serum urea, mmol/L (SD)</td>
<td>10.5 (5.6)</td>
<td>11.4 (5.8)</td>
<td>10.9 (5.6)</td>
</tr>
<tr>
<td>Mean lowest PaO₂/FiO₂ ratio (SD)</td>
<td>171.3 (85.8)</td>
<td>192.8 (77.6)</td>
<td>204.4 (77)</td>
</tr>
<tr>
<td>Mean highest temperature, °C (SD)</td>
<td>37.4 (1.1)</td>
<td>37.4 (0.7)</td>
<td>37.2 (0.7)</td>
</tr>
<tr>
<td>Mean CVP, mmHg (SD)</td>
<td>14.5 (3.7)</td>
<td>14.6 (4)</td>
<td>13.3 (3.9)</td>
</tr>
<tr>
<td>Vasopressors administered, n (%)</td>
<td>32 (64%)</td>
<td>31 (62%)</td>
<td>26 (52%)</td>
</tr>
</tbody>
</table>

CVP = central venous pressure. * All values are the highest recorded on the study day, except PaO₂/FiO₂, which was the lowest recorded.

Sodium balance

The sodium balance was positive on all study days (Table 3), with a cumulative balance of 717 mmol (SD, 422–958 mmol) at the end of Day 3. The daily sodium balance reduced each day (P=0.03) due to a lower sodium input (P=0.01) and increased urinary sodium losses (P=0.05), but it remained positive on all 3 study days. Patients who were administered vasopressors due to shock or were administered steroids on the study day had reduced urinary sodium losses and a higher daily sodium balance; administration of diuretics made no difference to their urinary sodium losses or daily sodium balance (Table 4).

Contributions to fluid and sodium

The sources of administered fluid and sodium each day are shown in Table 5. For both, the main source on Day 1 was fluid boluses, which provided 50.3% of total fluid and

Table 3. Daily and cumulative sodium and fluid balance

<table>
<thead>
<tr>
<th>Parameter, median (IQR)</th>
<th>Day 1*</th>
<th>Day 2</th>
<th>Day 3*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily balance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluid administered, mL</td>
<td>2874 (1992–3788)</td>
<td>2995 (2144–3551)</td>
<td>2443 (1887–2845)</td>
</tr>
<tr>
<td>Urine output, mL</td>
<td>1325 (918–2270)</td>
<td>1500 (1130–2285)</td>
<td>1493 (923–2364)</td>
</tr>
<tr>
<td>Fluid balance, mL</td>
<td>1054 (516–1650)</td>
<td>1130 (69–1788)</td>
<td>619 (53–1388)</td>
</tr>
<tr>
<td>Sodium administered, mmol</td>
<td>322 (213–504)</td>
<td>227 (178–357)</td>
<td>199 (153–256)</td>
</tr>
<tr>
<td>Sodium administered, mmol*</td>
<td>299 (212–464)</td>
<td>212 (116–319)</td>
<td>158 (94–227)</td>
</tr>
<tr>
<td>Sodium balance, mmol†</td>
<td>299 (212–464)</td>
<td>565 (327–796)</td>
<td>717 (422–958)</td>
</tr>
<tr>
<td>Fluid balance, mL</td>
<td>1054 (516–1650)</td>
<td>2091 (413–2918)</td>
<td>2668 (875–3507)</td>
</tr>
</tbody>
</table>

IQR = interquartile range. * Data collections on Day 1 and Day 3 were over a median of 23 hours (interquartile range, 16–24 hours) and a mean of 23.3 hours (SD, 3.9 hours). † Sodium balance is estimated from all sodium sources minus combined sodium losses from urine, nasogastric drainage, other gastrointestinal losses and drains.
43.7% of total sodium intake. This was followed by inadvertent sources (fluid, 22.2%; sodium, 29.9%). The contribution of fluid boluses to the total daily fluid and sodium intake declined significantly over the study period, to 11.6% and 9.9%, respectively, on Day 3 ($P<0.001$). Inadvertent sources of fluid administration were unchanged over the 3 days (between 22.1% and 24.8% for Day 1 to Day 3 ($P=0.84$). The total daily sodium administered which was attributed to inadvertent sources increased significantly to about 50% of the total sodium intake ($P=0.003$).

The contribution of infusions to the total daily fluid administration doubled between Day 1 (14.8%) and Day 3 (32.5%); in contrast, infusions consistently contributed only 9.5% to 13.8% of the total daily sodium intake. There was a consistent increase in the contribution of enteral nutrition to the total fluid and sodium intake over the 3 days (Table 5).

### Oxygenation and length of MV

The cumulative estimated sodium balance had a negative correlation with the next day $\text{PaO}_2/\text{FiO}_2$ ratio ($\rho=-0.36$, $P=0.001$) (Figure 2). Factors which related to the length of MV ($\rho^2 = 0.56$) were age ($\beta$ coefficient, 1.3; standard error (SE), 2.3; $P<0.01$) cumulative estimated sodium balance at Day 3 ($\beta$ coefficient, 0.91; SE, 0.06; $P<0.01$), and steroid administration ($\beta$ coefficient, 0.44; SE, 3; $P<0.001$). The cumulative fluid balance neither correlated with oxygenation ($\rho=0.10$, $P=0.23$), nor was it a predictor for the length of MV in the linear regression analysis.

### Discussion

The main findings of our study are that sodium intake in the first 3 days of critical illness is about 200–300 mmol/day and inadvertent sources such as drug boluses and intravascular flushes are the main contributors. The positive cumulative estimated sodium balance (717 mmol) was associated with a worse $\text{PaO}_2/\text{FiO}_2$ ratio and an increased length of invasive MV. These adverse respiratory outcomes were not related to the cumulative fluid balance.

Our study is the first multicentre study to report the estimated sodium balance in critically ill patients on MV. Although the daily estimated balance decreased from 299 mmol on Day 1 to 158 mmol on Day 3, there was a large cumulative estimated positive sodium balance (717 mmol). This amount is more than double the amount we previously reported in our single-centre study of cumulative sodium and water balance in 10 patients on MV (about 300 mmol over 3 days). However, in our current study, more patients were receiving vasopressors for shock (59%) or received intravenous steroids (57%); both of which we found to be associated with sodium retention.

The average daily fluid administered in our study population was nearly 3L, resulting in a cumulative positive fluid balance of 2.7 L. A positive fluid balance has previously been shown to be adversely associated with outcomes in
critically ill patients. Several studies have described the association between a positive fluid balance and increased mortality and morbidity (prolonged ventilation, poor gas exchange, renal failure and prolonged ICU stay); presumed to be due to increased interstitial oedema, reduced cellular oxygen delivery and delayed recovery of failed organs. In our study we did not find a similar relationship between the cumulative fluid balance and either the PaO2/FiO2 ratio or our study, serum sodium remained unchanged over the 3 days.

Calculations using distribution of free water across various circulations, independent of fluid balance. We have previously reported that total body water decreases over time in patients on MV but there is an increase in the interstitium. Therefore, a high sodium intake may exacerbate interstitial oedema in the systemic and pulmonary circulations, independent of fluid balance. We have previously reported that total body water decreases over time in patients on MV but there is an increase in the relative volume of fluid distributed to the extracellular compartment. This rise in extracellular fluid volume is also correlated with estimated positive sodium, but not fluid balance. Similar results have been reported in longitudinal observations of haemodynamically stable and critically ill patients on MV early in the course of their illness, suggesting that fluctuations in body weight may be due to changes in body water and extracellular overhydration, amid progressive cellular dehydration.

Despite a large cumulative estimated sodium balance in our study, serum sodium remained unchanged over the 3 days. Calculations using distribution of free water across various compartments and sodium concentration reveal that the extracellular fluid has potentially increased up to 4.5 L during the study period. This increase is not explained by the cumulative fluid balance, suggesting that a transcellular shift of approximately 2 L may account for the static serum sodium concentration.

In critically ill patients, activation of the renin–angiotensin–aldosterone system predisposes to sodium retention. This is particularly so in patients on MV, for whom positive-pressure ventilation and positive end-expiratory pressure both raise the intrathoracic pressure and reduce the venous return, leading to complex neurohumoral responses with sodium and water retention. Upadaya and colleagues have reported that although a positive cumulative fluid balance can predict weaning failure, achieving a negative fluid balance using diuretics is not independently associated with weaning success. Our finding that administration of diuretics increases urine output but not urinary sodium losses may partly explain their results. Also, half the patients in our study were in shock, which not only leads to sodium retention but has also been shown, in primate lungs, to increase the propensity of pulmonary interstitial collagen to adsorb sodium. This may explain the adverse association of a positive sodium balance with the length of MV.

The main sodium sources on Day 1 were fluid boluses. On subsequent days, inadvertent sources contributed more to the total administered sodium. Over the 3-day study period, about 740 mmol of sodium was administered, of which a mean of 43.4% was from inadvertent sources. These inadvertent sources can be a potential target for sodium restriction strategies in the future, such as using 5% dextrose as a vehicle for drug boluses and infusions when possible. Previous studies have shown that 0.9% saline is the most commonly used vehicle for IV drug boluses (75.6%) and infusions (64.4%), and heparinised saline was the most commonly used IV flush fluid (98.1%). Furthermore, inadvertent sources and infusions (maintenance or replacement fluids) were responsible for more than 50% of fluid sources by Day 3. All of these are potentially modifiable and should be investigated in future studies.

The findings of our study need to be considered in the light of several limitations. First, our sample was a convenience sample and was small and represented mostly medical ICU patients. However, it confirms the findings of our pilot study describing the adverse association between estimated sodium balance and respiratory function. Second, it should be noted that the sodium balance after 3 days was unknown. Finally, we did not study chloride administration. Sodium administration is often coupled with chloride and recent evidence suggests that chloride restriction may have a positive impact on clinical outcomes, particularly the incidence of acute kidney injury and the need for dialysis. We did not evaluate renal dysfunction, and the effect of chloride on MV and respiratory failure is unclear.
Conclusions
Sodium intake in patients on MV is high and is predominately attributed to fluid boluses and inadvertent sources such as drug infusion and boluses. A cumulative positive sodium balance is associated with adverse effects on respiratory function. Further research into the optimal sodium balance is warranted. Sodium restriction strategies may also represent a novel therapeutic approach for patients on MV in the future.

Competing interests
None declared.

Author details
Shailesh Bihari, Lecturer,1 and Intensivist2
Sandra L Peake, Associate Professor,3 Adjunct Associate Professor,4 and Senior Staff Specialist5
Shivesh Prakash, Senior Registrar2
Manoj Saxena, Research Fellow6
Victoria Campbell, Intensivist7
Andrew Bersten, Professor,1 and Head of Department2
1 Department of Critical Care Medicine, Flinders University, Adelaide, SA, Australia.
2 Department of Critical Care Medicine, Flinders Medical Centre, Adelaide, SA, Australia.
3 School of Medicine, University of Adelaide, Adelaide, SA, Australia.
4 ANZIC Research Centre, Monash University, Melbourne, VIC, Australia.
5 Department of Intensive Care Medicine, The Queen Elizabeth Hospital, Adelaide, SA, Australia.
6 Critical Care and Trauma Division, The George Institute for Global Health, Sydney, NSW, Australia.
7 Intensive Care Unit, Nambour General Hospital, Nambour, QLD, Australia.

Correspondence: biharishailesh@gmail.com

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