



## Editorial

## Fluid infusion during CPR and after ROSC—Is it safe?

Fluids are commonly infused during cardiopulmonary resuscitation (CPR) and following return of spontaneous circulation (ROSC). Fluids are given to increase circulating volume during CPR and improve cardiac output and blood pressure after ROSC. More recently, rapid infusions of a large volume ( $30 \text{ mL kg}^{-1}$ ) of cold ( $4^\circ\text{C}$ ) fluid have been used during CPR or in comatose patients after ROSC to induce therapeutic hypothermia.<sup>1</sup> Fluids are often given liberally during CPR, yet after ROSC the fear of giving fluids to a patient with myocardial dysfunction causes some physicians to restrict the use of fluids. Variability in the use of fluids during CPR is not surprising considering the lack of a large evidence base to guide intravenous fluid therapy in any clinical setting.

The evidence supporting the use of intravenous fluid during CPR in primary cardiac arrest is limited. Animal studies show that fluid infusion during CPR causes a decrease in coronary perfusion pressure (CPP = aortic diastolic pressure – right atrial pressure).<sup>2–4</sup> Although fluid infusion raises the right atrial pressure during CPR, there seems to be little effect of fluid infusion on the aortic diastolic pressure. Human studies suggest that a higher CPP during CPR is associated with successful ROSC.<sup>5</sup> Ascertaining the true effects of fluids during CPR is hampered by the fact that most studies do not have a control group that received no fluid. For example, Bender et al. found a non-significant increase in the rate of ROSC and survival to hospital admission when a hypertonic saline/starch solution was infused during out-of-hospital cardiac arrest compared with starch alone (ROSC, 66.7% versus 51.5%,  $p=0.21$ ; admission, 57.6% versus 39.4%,  $p=0.14$ ,  $n=66$ ).<sup>6</sup> Kamarainen et al. showed that a rapid infusion of cold Ringer's acetate ( $1571 \pm 517 \text{ mL}$ ) during CPR in 17 patients with out-of-hospital primary cardiac arrest decreased the nasopharyngeal temperature (initial temperature,  $35.17 \pm 0.57^\circ\text{C}$  (95% CI); hospital admission,  $33.83 \pm 0.77$ ;  $p < 0.001$ ).<sup>7</sup> Return of spontaneous circulation was achieved in 13 patients, 11 survived to hospital admission, and only one patient survived to hospital discharge. Without a definite proven benefit of intravenous fluid use during CPR for primary cardiac arrest, the value of knowing which type of fluid to give, and whether it should be cooled is difficult to judge when studies do not have a control group that receives no fluid infusion.

The use of therapeutic hypothermia has generated many studies assessing the effects of a rapid infusion of cold fluids in comatose patients after ROSC.<sup>8–12</sup> The largest study randomized 125 out-of-hospital cardiac arrest patients with ROSC to out-of-hospital cooling with 2 L of 0.9% sodium chloride at  $4^\circ\text{C}$  compared with standard therapy.<sup>8</sup> Sixty-three patients received cold fluids (0.5–1 L) before hospital arrival and 62 received standard therapy, although it is not entirely clear whether patients in the standard therapy

group received any fluid. Cold fluid infusion resulted in a mean temperature decrease of  $1.24 \pm 1^\circ\text{C}$  compared with a mean temperature increase in the standard therapy group of  $0.10 \pm 0.94^\circ\text{C}$  ( $p < 0.0001$ ) on hospital arrival. Cold fluid infusion did not cause pulmonary oedema (based on the initial chest X-ray) or any adverse haemodynamic effects. Bernard et al. infused  $30 \text{ mL kg}^{-1}$  of ice-cold ( $4^\circ\text{C}$ ) lactated Ringer's solution over 30 min in 22 patients resulting in a significant decrease in median core temperature from  $35.5$  to  $33.8^\circ\text{C}$ , and significant improvements in mean arterial blood pressure, renal function and acid–base analysis. No patient developed pulmonary oedema. These studies suggest that a rapid large volume fluid infusion is tolerated remarkably well in patients who are comatose and receiving ventilatory support soon after ROSC from cardiac arrest.

In this issue of Resuscitation, two further studies attempt to further our knowledge about fluid infusion in comatose survivors of cardiac arrest receiving post-resuscitation care. Firstly, Jacobshagen et al. retrospectively studied the effects of large volume, ice-cold intravenous fluid infusion on cardiorespiratory function in 52 cardiac arrest survivors of whom 35 were discharged alive.<sup>13</sup> Patients were infused with  $3427 \pm 210 \text{ mL}$  ice-cold 0.9% sodium chloride over  $4.1 \pm 0.5 \text{ h}$  (cooling rate  $0.48^\circ\text{C h}^{-1}$ ) to achieve a target temperature of  $32\text{--}24^\circ\text{C}$ . The study patients had impaired left ventricular function (ejection fraction  $35.8 \pm 2.2\%$ ) and respiratory function on intensive care unit (ICU) admission. Rapid infusion of cold fluid was associated with a small, but statistically non-significant, worsening of oxygenation ( $\text{PaO}_2/\text{FiO}_2$   $290 \pm 24.1$  on ICU admission,  $247.5 \pm 18.4$  at  $34^\circ\text{C}$ ,  $224.3 \pm 16.3$  at  $33^\circ\text{C}$ ) and preservation of myocardial function. Indeed, follow-up echocardiography in 16 patients also showed improved left ventricular function (ejection fraction  $47.8 \pm 2.6\%$ ). All these patients also received other post-resuscitation care interventions such as percutaneous coronary intervention, inotropes and vasopressors infusion, and adjustments in ventilator settings to achieve target blood gas values ( $\text{PaO}_2$  of 100 mmHg and  $\text{PaCO}_2$  of 40 mmHg).

Secondly, Nordmark et al. prospectively assessed intravascular volume using transthoracic echocardiography by two independent assessors with good inter-observer reliability, during therapeutic hypothermia and rewarming in a total of 24 comatose cardiac arrest survivors.<sup>14</sup> Thirteen out of 23 patients, 14 out of 19, and 13 out of 21 patients were assessed to have a decreased intravascular volume at 12, 24 and 48 h respectively. This was despite the use of a  $30 \text{ mL kg}^{-1}$  infusion of cold fluid to induce hypothermia and a median positive fluid balance at 24 and 48 h of 4056 (3272–5018) mL and 2500 (1844–3075) mL respectively. The median ejection fraction was 0.56 at 12 h, 0.62 at 24 h and 0.59

at 48 h after cardiac arrest. All these patients also received inotropic and, or vasopressor support.

These two studies together with previous studies suggest that comatose ventilated patients require and tolerate large volumes of intravenous fluids in the first few days after ROSC when the fluids are infused as part of a package of post-resuscitation care that includes therapeutic hypothermia and cardiovascular support.<sup>15</sup> Laurent et al. described reversible myocardial dysfunction after cardiac arrest and showed that out-of-hospital cardiac arrest survivors initially required a cumulative crystalloid volume of 5 L (3.5–6.5 L) over the first 24 h to maintain a central venous pressure of 12 mmHg.<sup>16</sup> In another observational study, patients receiving a package of care after ROSC that improved survival compared with a historical control group also had a positive fluid balance (3.5 ± 1.6 L) in the first 24 h, with a central venous pressure goal of 8–12 mmHg.<sup>17</sup> In a study of early goal-directed haemodynamic optimization combined with therapeutic hypothermia in 18 comatose survivors of out-of-hospital cardiac arrest, the average volume of intravenous fluid infused over the first 12 h was 5761 mL (range 2250–14,795 mL).<sup>18</sup> This was associated with an improvement in survival to discharge versus a historical control group that was not statistically significant ( $p = 0.16$ ).

Resuscitation from cardiac arrest is associated with a systemic inflammatory response syndrome (SIRS). The use of intravenous fluids as part of treatment after ROSC is rationale considering that intravenous fluid therapy is used for the treatment of SIRS from other causes such as sepsis.<sup>19</sup> The studies available suggest that the presence of myocardial dysfunction should not lead to restriction of fluids in patients with ROSC after cardiac arrest. The use of cold fluids in comatose and ventilated patients after ROSC to induce therapeutic hypothermia and improve haemodynamic status has shown only minimal adverse effects in patients who are already critically ill. The overall safety of fluids in the peri-arrest setting is difficult to assess. Studies have included few subjects and most do not have appropriate control groups. Also the use of fluids is just one of the many interventions that can be used during post-resuscitation care.<sup>20</sup> It is therefore difficult to tease out the exact role of fluids in terms of benefit and harm.

Further well designed, large-scale studies of intravenous fluid infusion are necessary in all critical care settings given the lack of evidence for the optimum dose, timing, type of fluid and endpoints to guide fluid infusion. The limited evidence available suggests that fluid infusion could be detrimental during CPR for primary cardiac arrest. After ROSC, however, the infusion of large volumes of fluid is tolerated remarkably well by patients when fluids are used as part of a comprehensive package of post-resuscitation care.

#### Conflict of interest statement

No conflicts of interest.

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