

## Clinical paper

# Assessment of intravascular volume by transthoracic echocardiography during therapeutic hypothermia and rewarming in cardiac arrest survivors<sup>☆,☆☆</sup>

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## ARTICLE INFO

## Article history:

Received 8 October 2008

Received in revised form 13 May 2009

Accepted 7 June 2009

## Keywords:

Cardiac arrest

Cardiopulmonary resuscitation

Hypothermia

Haemodynamics

Echocardiography

Intensive care

## ABSTRACT

**Aim:** To study haemodynamic effects and changes in intravascular volume during hypothermia treatment, induced by ice-cold fluids and maintained by ice-packs followed by rewarming in patients after resuscitation from cardiac arrest.

**Materials and methods:** In 24 patients following successful restoration of spontaneous circulation (ROSC), hypothermia was induced with infusion of 4 °C normal saline and maintained with ice-packs for 26 h after ROSC. This was followed by passive rewarming. Transthoracic echocardiography was performed at 12, 24 and 48 h after ROSC to evaluate ejection fraction and intravascular volume status. Central venous pressure (CVP), central venous oxygen saturation (ScvO<sub>2</sub>) and serum lactate were measured. Fluid balance was calculated.

**Results:** Twelve hours after ROSC, two separate raters independently estimated that 10 and 13 out of 23 patients had a decreased intravascular volume using transthoracic echocardiography. After 24 and 48 h this number had increased further to 14 and 13 out of 19 patients and 13 and 12 out of 21 patients. Calculated fluid balance was positive (4000 ml the day 1 and 2500 ml day 2). There was no difference in ejection fraction between the recording time points. Serum lactate and ScvO<sub>2</sub> were in the normal range when echocardiography exams were performed. CVP did not alter over time.

**Conclusions:** Our results support the hypothesis that inducing hypothermia following cardiac arrest, using cold intravenous fluid infusion does not cause serious haemodynamic side effects. Serial transthoracic echocardiographic estimation of intravascular volume suggests that many patients are hypovolaemic during therapeutic hypothermia and rewarming in spite of a positive fluid balance.

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## 1. Introduction

Post-resuscitation brain injury is a major cause of morbidity and mortality in cardiac arrest survivors.<sup>1</sup> Therapeutic hypothermia (32–34 °C) has been shown to improve neurological outcome<sup>2,3</sup> and reduce mortality.<sup>3</sup> Therapeutic hypothermia has become more common in clinical practice<sup>4</sup> and is recommended by both the European Resuscitation Council<sup>5</sup> and American Heart Association.<sup>6</sup>

Induction of hypothermia by intravenous infusion of cold fluid is effective and simple<sup>7,8</sup> and has gained popularity. In addition,

induction of hypothermia with cold fluid infusion is feasible during ongoing cardiopulmonary resuscitation (CPR) in an experimental setting<sup>9</sup> and in recent studies in the clinical setting.<sup>10,11</sup> In these studies no major adverse haemodynamic effects of volume loading were reported. Bernard et al. suggested the infusion of cold fluids may have a beneficial haemodynamic effect.<sup>7</sup> In spite of this, there is still concern that induction of hypothermia with a large amount of cold intravenous infusion is harmful to a heart that has recently undergone ischaemia and reperfusion after cardiac arrest.<sup>12</sup> Moreover, the clinical studies mentioned,<sup>7,8,10,11</sup> were primarily designed to study mortality or the feasibility of the cooling method. Thus, more subtle harmful haemodynamic changes may have passed unnoticed. In a human study, cardiac function after cardiac arrest (assessed by transthoracic echocardiography) was not affected by induction of therapeutic hypothermia by cold fluid infusion.<sup>13</sup> The patients in this study were all examined within 6 h after cardiac arrest. The effects of hypothermia and intravascular volume loading beyond the first few hours after cardiac arrest are still unclear.

<sup>☆</sup> A Spanish translated version of the abstract of this article appears as Appendix in the final online version at doi:10.1016/j.resuscitation.2009.06.035.

<sup>☆☆</sup> Grants: Swedish Heart-Lung Foundation.

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We hypothesise that inducing hypothermia after resuscitation from cardiac arrest by infusing ice-cold solution is possible without haemodynamic disturbances. In contrast to earlier clinical studies<sup>7,8,10,11</sup> we aim to assess left ventricular ejection fraction (LVEF) and intravascular volume status with transthoracic echocardiography together with central venous pressure (CVP). Measurement of central venous jugular oxygenation (ScvO<sub>2</sub>) and serum lactate will provide an indicator of global circulation status.

## 2. Materials and methods

This study was performed at the general intensive care unit at Uppsala University Hospital, Sweden. The study was approved by the Human Ethics Committee of Uppsala, Sweden. Consent for participation was obtained from a legal next of kin, and later by survivors when considered competent.

### 2.1. Inclusion criteria and treatment protocol

Inclusion criteria for the study were patients after cardiac arrest with an age greater than 18 years, systolic pressure greater than 80 mmHg for more than 5 min after restoration of spontaneous circulation (ROSC) and unconscious with Glasgow Coma Scale (GCS) score less than or equal to 7. Patients had to be recruited within 6 h of cardiac arrest to be included. Patients with a terminal disease were excluded.

Hypothermia treatment was started after ROSC with intravenous infusion of 30 ml/kg of 4 °C normal saline. Ice packs were placed in the groins, axillae and along the neck. A target temperature 32–34 °C was maintained until 26 h after cardiac arrest. Patients were then slowly rewarmed (passively) to normothermia (defined as 36.5 °C). During hypothermia treatment patients were sedated with an infusion of propofol at 0.5–2.5 mg/kg/h and fentanyl at 0.5–2 µg/kg/h (at the lowest possible range to keep the patient sedated). If shivering occurred during induction the primary intervention was to give extra boluses of fentanyl and increase the dose of propofol. If unsuccessful, the patients received either intravenous boluses of rocuronium at 0.6 mg/kg or an infusion of 0.15 mg/kg/h. When the target temperature was achieved rocuronium infusion was discontinued. At normothermia sedation was stopped to allow evaluation of neurological status. During mechanical ventilation the aim was to maintain PaO<sub>2</sub> of above 12 kPa and PaCO<sub>2</sub> between 5.0 and 5.5 kPa. The target mean arterial pressure was 65–100 mmHg with inotrope or vasopressor support if required. The inotropes and vasopressors used were dobutamine as a first line medication followed by noradrenaline (norepinephrine) or adrenaline if needed. Furosemide was given, if necessary, to achieve a diuresis of at least 0.5–1 ml/kg/h or if it was considered that the patient was fluid overloaded.

All patients had an arterial catheter in the radial artery and a central venous catheter in the internal jugular bulb.

### 2.2. Monitoring

Core temperature was continuously measured in the bladder and recorded every 15 min (Curity temperature KAD, Coviden/Tyco). Diuresis was measured hourly. Respiratory function was monitored according to our usual practice in the intensive care unit. Arterial blood pressure and heart rate were monitored continuously and recorded every hour. The CVP was also recorded at intervals.

Blood samples were collected as soon as possible in the emergency phase (within 2 h after cardiac arrest) and then repeatedly. Samples were analysed for blood-glucose, arterial blood-gases, electrolytes, central venous oxygen saturation and serum lactate. Fluid balance was calculated every 24 h. Losses (diuresis, stools,

gastric tube and possible drainages) were subtracted from administered fluids (intravenous infusions, medications, enteral nutrition) to yield either a positive or a negative balance. Insensible fluid losses were not estimated and not included in the calculation. Patients were monitored until 108 h after cardiac arrest, or until discharge from the intensive care unit.

Patient records were checked to determine whether the patient died or was discharged from the hospital.

### 2.3. Transthoracic echocardiography

Transthoracic echocardiography was performed twice during hypothermia treatment (at 12 and 24 h after cardiac arrest) and once after rewarming (at 48 h) using a Philips iE33 or 7500 system using a small footprint harmonic imaging multifrequency probe by certified echocardiography technicians or physicians with specialist training in echocardiography. The protocol included parasternal long and short axis views, apical two and four chamber views and a subxiphoid view. Apart from 2D images, zoomed M-mode of mitral ring motion in four positions, continuous wave Doppler over the aortic and pulmonary valves and pulse waves in the left ventricular outflow tract and mitral and tricuspid valves were recorded. Five R–R-intervals of each were sampled and archived digitally. At the end of the study period the patient identities and time stamps in the images were blanked. Two physicians, specialists in echocardiography, assessed recorded images, whilst blinded to the patient identity, chronological order, clinical details and estimations of the other rater. Assessment of intravascular volume status was performed subjectively based on ventricular end-systolic area in available planes, degree of atrial end-diastolic area in the four-chamber view and the inferior vena cava diameter. A 3 point scale was used to record estimations of intravascular volume, where –1 represented a decreased intravascular volume, 0 normal volume and +1 an increased volume. Inter-rater agreement was calculated. Left ventricular ejection fraction (LVEF) was also assessed subjectively based on left ventricular dilatation, mitral ring motion and segmental systolic wall thickening. An effective range of 5–85% was used in order to allow for very low values in highly dilated hearts as well as for supranormal values in the presence of hypovolaemia, hypertrophy, inotropic and or vasopressor drugs and stress. A further blinding of patient recordings was done and after that a second identical LVEF assessment was performed and the mean value of each pair was used.

### 2.4. Analysis and statistics

Changes in values over time were analysed using the Friedman ANOVA test for non-parametric values. Values were expressed as median ± first and third quartile. Significance was set at the <0.05 level. Inter-rater agreement was measured to get an unweighted kappa value. Statistical analyses were calculated using the STATISTICA 7.0 program (Statsoft, Scandinavia, Sweden).

## 3. Results

The study was performed between November 2004 and May 2007. During this period, 45 patients presented to the hospital with CA and 24 patients were enrolled in the study. Twenty-one patients were not included because of; death before inclusion ( $n=1$ ), researcher responsible not notified ( $n=9$ ), terminal disease or trauma ( $n=5$ ) and failure to accomplish echocardiography ( $n=6$ ). The protocol was initiated within 4 h of cardiac arrest. Twelve out of the 24 (50%) included patients survived to hospital discharge. Characteristics of the patients are presented in Table 1.

**Table 1**  
Characteristics of patients (n = 30). Values are median (with first and third quartile), or n (%).

Average age (years)	63 (55–71)
Sex	
Female	5 (21%)
Weight (kg)	82 (71–88)
Previous cardiovascular morbidity	13 (54%)
Previous diabetes mellitus	3 (12%)
Presenting rhythm	
Ventricular fibrillation	14 (58%)
Asystole	17 (29%)
Pulseless electrical activity	3 (13%)
Presumed cause of cardiac arrest	
Cardiac	21 (88%)
Asphyxia	2 (8%)
Anaphylaxis	1 (4%)
Place of arrest	
Out-of-hospital	21 (87%)
In-hospital	3 (13%)
Interval between cardiac arrest and ROSC <sup>a</sup> (min)	20 (10–27)
Percutaneous Coronary Intervention (PCI) during intensive care	9 (38%)

<sup>a</sup> Restoration of spontaneous circulation.

### 3.1. Temperature

Patients reached target temperature (34°C) after 6.5 h (3.0–10 h) following cardiac arrest. No patient failed to reach the target temperature and all patients remained in target temperature range (32–34°C) during hypothermia treatment. The time from cardiac arrest until normothermia (36.5°C) after rewarming was 36 h (35–36.5 h). The duration of time spent in the target temperature range was 24 h (21–27 h).

### 3.2. Haemodynamics

#### 3.2.1. Mean arterial pressure, central venous pressure (CVP) and heart rate

Values are presented in Table 2. No differences over time were detected for mean arterial pressure or CVP. Heart rate was stable during hypothermia and increased during rewarming ( $p < 0.001$ ) with stabilisation at a higher level during normothermia.

#### 3.2.2. Central venous oxygen saturation (ScvO<sub>2</sub>), arterial oxygen saturation and serum lactate

ScvO<sub>2</sub> values are expressed in Table 2. Median ScvO<sub>2</sub> values were above or equal to 70%. There was no difference over time. Arterial oxygen saturation was between 95 and 99%. Lactate was increased during the first hour after cardiac arrest. Lactate levels then declined (Table 2).

### 3.3. Fluid balance and diuresis

The patients had a positive calculated median fluid balance for the first and the second day of 4056 (3272–5018) ml and 2500 (1844–3075) ml respectively. On days 3–5 the fluid balance was negative at –900 to –1000 ml/day.

Diuresis is presented in Table 2. Diuresis was greatest during the first few hours after cardiac arrest.

On the first day no furosemide was given. On the second day the patients received 10 (0–15) mg and on day 3 the patients received 15 (0–26) mg. Thereafter the amount of furosemide declined to 0 (0–10) mg on days 4 and 5.

**Table 2**  
Haemodynamic parameters.

	Hours after cardiac arrest									
	E.p.*	4	6	12	24	36	48	60	72	108
Mean arterial pressure (mmHg)	64 (60–84)	86 (71–93)	77 (63–87)	74 (67–87)	67 (64–74)	74 (65–89)	80 (68–87)	80 (64–89)	85 (73–86)	76 (69–81)
Central venous pressure (mmHg)	N/A	10 (9–12)	10 (7–12)	9 (7–12)	10 (8–12)	11 (9–14)	12 (9–15)	11 (8–14)	10 (8–13)	11 (9–14)
Central venous oxygen saturation (%)	N/A	70 (65–80)	70 (64–74)	76 (70–81)	77 (72–80)	80 (74–83)	79 (76–82)	N/A	76 (71–80)	74 (71–79)
Heart rate (beats/min)	90 (76–100)	78 (66–90)	78 (60–85)	67 (60–85)	75 (56–94)	100 (81–117)	100 (86–110)	100 (94–110)	95 (90–105)	85 (80–92)
Diuresis (ml/h)	N/A	200 (110–257)	160 (95–260)	100 (50–240)	42 (25–75)	62 (40–96)	150 (62–195)	95 (55–245)	71 (55–155)	80 (61–101)
Dobutamine (mg/kg/h)	N/A	N/A	N/A	0.02 (0–0.2)	0.20 (0.1–0.4)	N/A	0 (0–0.2)	0 (0–0)	0 (0–0)	0 (0–0)
Norepinephrine (µg/kg/h)	N/A	N/A	N/A	0 (0–1)	2.1 (0–3.5)	N/A	1.4 (0.4–7)	0 (0–0)	0 (0–0)	0 (0–0)
Serum lactate (mmol/l)	3.4 (2.2–7.4)	2.0 (1.3–5.3)	2.0 (1.1–3.5)	2.2 (1.4–3.1)	2.1 (1.4–3.5)	1.8 (1.5–2.5)	1.8 (1.1–2.3)	N/A	1.2 (0.9–1.4)	1.3 (0.9–1.6)
Number of patients observed	17	24	24	23	24	24	22	20	17	9

Median values (with first and third quartile) of mean arterial pressure, central venous pressure, central venous oxygen saturation, serum lactate, heart rate, diuresis and use of inotropic/vasopressor support after restoration of spontaneous circulation following cardiac arrest. n = number of patients. E.p.\*; Emergency phase.

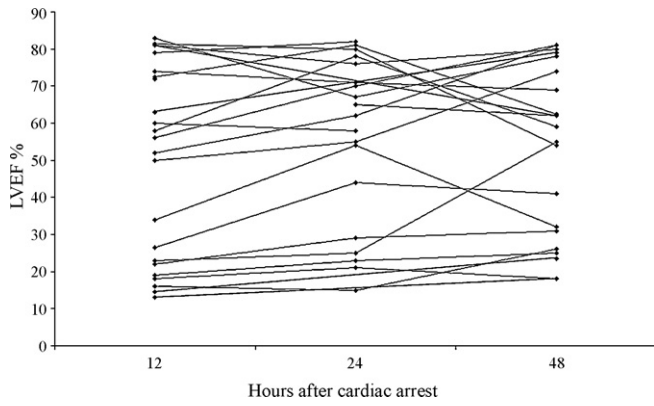


Fig. 1. Left ventricular ejection fraction (LVEF) for each individual.

3.4. Echocardiography

Of the 24 patients included, 16 patients fulfilled the entire echocardiography protocol, with examinations at 13 (12–16)h, 25 (24–26)h and 48 (48–49)h after cardiac arrest. Of the remaining patients, 4 underwent exams at 12 and 48 h, 2 at 12 and 24 h, 1 at 24 and 48 h and 1 at 12 h only.

In Fig. 1 individual LVEF values are plotted. Median LVEF was 0.56 at 12 h, 0.62 at 24 h and 0.59 at 48 h after cardiac arrest. LVEF did not change over time.

Results from the estimation of intravascular volume are presented in Fig. 2a and b. At the first measurement, 10 (rater 1) and 13 (rater 2) out of 23 patients (44 and 57%) had a decreased intravascular volume. At the second and third time point, this number had

increased further to 14 and 13 out of 19 patients (74 and 69%) and, 13 and 12 out of 21 patients (62 and 58%) respectively. The inter-rater agreement for intravascular volume was 77% giving an unweighted kappa value of 0.61.

3.5. Inotropic and vasopressor support

All patients needed inotropic and/or vasopressor support. Dobutamine was given to all patients but one, who was directly started on an adrenaline-infusion. The amount of dobutamine infused was 9.7 mg/kg (4.8–17.9) during a time period of 38 (27–49) h (Table 2).

Twelve patients received noradrenaline in addition to dobutamine. The amount given was 0.11 (0.04–0.20) mg/kg over a period of 28 (22–38) h (Table 2).

Four patients received adrenaline infusion. The amount of adrenaline given was 0.11 (0.07–0.17) mg/kg over 27 (22–35) h.

4. Discussion

In this study we have demonstrated that hypothermia treatment and induction of hypothermia by intravenous infusion of cold (4 °C) saline at 30 ml/kg appeared to be possible without harmfully increasing the intravascular volume. Instead, many patients tended to have a decreased intravascular volume after cardiac arrest, indicating that volume loading might even be beneficial. In addition there were no evidence of harmful effects of volume loading on ejection fraction either during hypothermia treatment, or during the rewarming phase.

Fluid loading during resuscitation might be beneficial. Experimentally it has been shown that systemic haemodynamics and tissue perfusion improve following a fluid bolus dose during resuscitation.<sup>14</sup> This study was performed during normothermic conditions and with 4 ml/kg of hypertonic saline–dextran, which makes it difficult to compare with the method of 30 ml/kg isotonic fluid used in our study. Nevertheless, this study is in line with our findings, as about half of the patients, in our study, were estimated to have a decreased intravascular volume at the first observation and this had increased at 24 h after cardiac arrest. Although all patients had a calculated positive fluid balance on days 1 and 2 after resuscitation, only, at most, 14% (rater 1 at 48 h after cardiac arrest) were considered to have an increased intravascular volume. In addition CVP values were not markedly influenced by intravascular volume status evaluated by echocardiography. One possible explanation to this is that monitoring CVP is considered to be a rudimentary way of estimating intravascular volume.<sup>15</sup>

There are several reasons why patients could have a decreased intravascular volume, in spite of volume loading to induce hypothermia. After successful resuscitation from cardiac arrest, a “sepsis-like” syndrome with high levels of circulating cytokines and the presence of plasma endotoxin and the potential for fluid loss from the capillaries has been described.<sup>16</sup> It has also been shown that during surface cooling to 28 °C there is a shift of plasma from the circulation to the interstitial space.<sup>17</sup> This observation, on the other hand, is contradicted by findings of Jurkovich et al.<sup>18</sup> who found decreased post-ischaeic capillary permeability in hypothermia treated animals. Another possible explanation for patients to have a decreased intravascular volume could be the phenomenon of cold diuresis. However, the high diuresis during the first hour after cardiac arrest was followed by normalisation and diuresis subsequently was even low during hypothermia treatment. The fact that there was no obvious cold diuresis strengthens the hypothesis that there was a relative hypovolaemia caused by post-resuscitation capillary leakage.

Ejection fraction after cardiac arrest has been shown to be unaltered before and 1 h after infusion of cold fluid.<sup>13</sup> In our

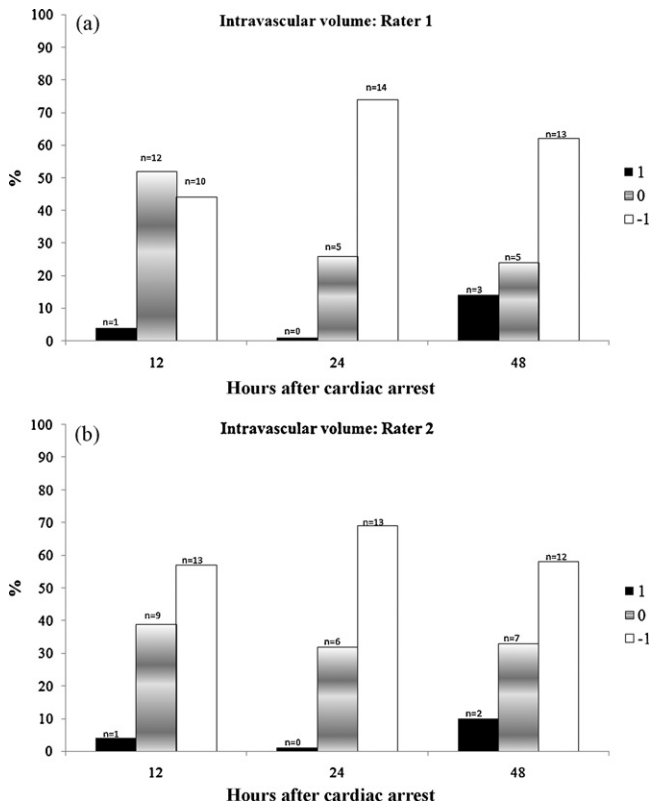


Fig. 2. Percentage of cases with different intravascular volume at 12, 24 and 48 h after cardiac arrest. Volume degree 1 = increased intravascular volume; volume degree 0 = normal volume state; volume degree -1 = decreased intravascular volume. n = number of patients. (a) Assessments by rater 1 and (b) assessments by rater 2.

study no evidence of a change in LVEF was found, neither over an extended time (total of 48 h) after cardiac arrest nor when comparing hypothermic to normothermic conditions. As the measurements in our study were made after hypothermia was induced, conclusions regarding the influence of volume loading on LVEF are impossible to make. However, ScvO<sub>2</sub> and lactate was in the normal range at the time for all echocardiographic exams indicating a sufficient global circulation. In addition evaluating differences of LVEF during the different recording times was difficult as inotropic and vasopressor support was used to maintain an adequate cardiac output. There were also big differences between the patients. Some patients had very low LVEF probably caused by a seriously damaged myocardium or a poor myocardium even before the insult. Others, on the other hand, had high values that may have been caused by an over-use of inotropes.

#### 4.1. Limitations

There are several limitations with this study that might have affected our results.

First, there was no control group as hypothermia treatment after cardiac arrest is our normal clinical practice and a normothermic control group could not be justified.

The small number of patients in our study makes overall safety of the intervention difficult to assess. Out of the 24 patients included only 16 patients fulfilled the entire echocardiography protocol. However, only three patients were not examined during both hypothermic and normothermic conditions.

Assessment of intravascular volume using transthoracic echocardiography is used in intensive care practice<sup>19</sup> and we chose to use the method as it is non-invasive, fast and feasible. However, the method is not well validated. There are studies showing the value of transthoracic echocardiography to assess intravascular volume both clinically<sup>20,21</sup> as well as experimentally.<sup>22</sup> The quantification of intravascular filling on a 3 point scale using transthoracic echocardiography assessment has not been previously used. It was introduced to enable a comparison of echocardiography findings for individual patients and also between patients. The unweighted kappa value of 0.61 shows agreement<sup>23</sup> between the first and second rater and supports the use of our scale. The use of a transthoracic echocardiography, which is not universally accepted as a method to assess intravascular volume, and a non-validated scale of intravascular volume is an obvious weakness of our study.

A number of confounding factors probably had an effect on our results. For example, the use of sedatives can cause vasodilatation and influence the interpretation of intravascular volume. The dose of sedative was kept to the lowest possible level and was used in all patients. The use of vasopressors would have partly opposed the vasodilatation caused by sedatives.

When fluid balance was calculated, insensible fluid losses were not included. This may have caused an over-estimate of any positive fluid balance.

Evaluation of LVEF may have been affected by the use inotropic and vasopressor support. There was an increased need for inotropic and vasopressor support during hypothermia treatment compared to after rewarming. This could be caused by decreased intravascular volume, hypothermia in itself, post-resuscitation myocardial dysfunction<sup>24,25</sup> or different doses of sedation.

## 5. Conclusion

Our results from a small number of patients support the hypothesis that inducing hypothermia after resuscitation following cardiac arrest, using rapid cold intravenous fluid infusion does

not cause serious haemodynamic side effects. Serial transthoracic echocardiographic estimation of intravascular volume suggests that many patients are hypovolaemic during therapeutic hypothermia and rewarming in spite of a positive fluid balance.

## Disclosure

None.

## Conflict of interest

None.

## Acknowledgements

The authors express their gratitude to Elisabeth Pettersson, research assistant for her excellent assistance and Lisa Wernroth, biostatistician at Uppsala Clinical Research Centre (UCR) for help with evaluation of statistics.

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