# COMPARATIVE EVALUATION OF CRYSTALLOID RESUSCITATION RATE IN A HUMAN MODEL OF COMPENSATED HAEMORRHAGIC SHOCK

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ABSTRACT—**Introduction:** The most effective rate of fluid resuscitation in haemorrhagic shock is unknown. **Methods:** We performed a randomized crossover pilot study in a healthy volunteer model of compensated haemorrhagic shock. Following venesection of 15 mL/kg of blood, participants were randomized to 20 mL/kg of crystalloid over 10 min (FAST treatment) or 30 min (SLOW treatment). The primary end point was oxygen delivery ($DO_2$). Secondary end points included pressure and flow-based haemodynamic variables, blood volume expansion, and clinical biochemistry. **Results:** Nine normotensive healthy adult volunteers participated. No significant differences were observed in $DO_2$ and biochemical variables between the SLOW and FAST groups. Blood volume was reduced by 16% following venesection, with a corresponding 5% reduction in cardiac index (CI) ($P < 0.001$). Immediately following resuscitation the increase in blood volume corresponded to 54% of the infused volume under FAST treatment and 69% of the infused volume under SLOW treatment ($P = 0.03$). This blood volume expansion attenuated with time to 24% and 25% of the infused volume 30 min postinfusion. During fluid resuscitation, blood pressure was higher under FAST treatment. However, CI paradoxically decreased in most participants during the resuscitation phase; a finding not observed under SLOW treatment. **Conclusion:** FAST or SLOW fluid resuscitation had no significant impact on $DO_2$ between treatment groups. In both groups, changes in CI and blood pressure did not reflect the magnitude of intravascular blood volume deficit. Crystalloid resuscitation expanded intravascular blood volume by approximately 25%.

KEYWORDS—Blood pressure, blood volume, cardiac index, fluid, haemorrhage, shock, venesection

## INTRODUCTION

Haemorrhagic shock is a clinical syndrome resulting from decreased perfusion of vital organs secondary to a loss of blood volume. The World Health Organization estimated that approximately 5 million people die annually from injury, with haemorrhage contributing to more than one-third of the deaths (1). The current Advanced Trauma Life Support (ATLS) guidelines for the management of haemorrhagic shock advocate rapid infusion of 1–2 L of crystalloid solution in the absence of the matched blood products (2). This traditional teaching of resuscitation appears to be based on expert opinion with minimal supporting evidence from human clinical trials (3).

Furthermore, there is no current consensus regarding exactly what defines a "fluid bolus" and the most effective rate of fluid resuscitation in haemorrhagic shock is unknown.

Although animal studies have shown that resuscitation with a fast fluid infusion had worse outcome compared with a slow fluid infusion in various models of haemorrhagic shock (4–10), prospective research in humans on the same comparison is lacking. While fast crystalloid resuscitation has been associated with increased mortality and complications in patients with severe sepsis (11), there are no human studies to date comparing the rate of crystalloid resuscitation for patients in haemorrhagic shock. Therefore, we evaluated, in a model of compensated haemorrhagic shock, whether a slow (SLOW treatment) or fast (FAST treatment) rate of resuscitation with crystalloid infusion would differ in terms of oxygen delivery ($DO_2$), pressure- and flow-based haemodynamic variables, and clinical biochemistry including N-terminal pro B-type natriuretic peptide (NT-BNP).

## PATIENTS AND METHODS

The Austin Health Research and Ethics Committee approved this study (HREC no: HREC/14/Austin/458) and written informed consent was obtained from all participants. The study was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN: 12615000100594). Inclusion

criteria included normotensive healthy adults, 18 to 50 years of age, BMI <35 kg/m$^2$, normal haemoglobin levels for sex, and no regular medication for comorbid disease.

### Standardization of study protocol

Nine participants were randomized into either a FAST or SLOW fluid resuscitation protocol based on a random allocation sequence generated by a computer-based randomization programme. All participants were fasted for 6 h for solids and encouraged to maintain adequate hydration with clear fluids for 2 h prior to each experiment. The study was conducted in a dedicated Anaesthesia Research Laboratory with standardization of illumination intensity and noise, and with ambient air temperature set to 21°C to avoid distractions that could alter haemodynamics during the continuous measurements. Participants were placed in a supine position on a standard hospital bed with their heads raised at 45 degrees and resting on a pillow for comfort. The Clearsite advanced haemodynamic monitor (Edwards Lifesciences, Irvine, CA) was used for continuous beat-by-beat haemodynamic monitoring. Baseline haemodynamic measurements were obtained after a 10-min resting period. A 16-gauge and 20-gauge cannula were then established aseptically using local anaesthetic solution (Topical Emla Gel and subcutaneous 2% lignocaine and adrenaline) for fluid resuscitation, blood sampling, and venesection. After the insertion of the cannula, blood pressure was allowed to stabilize to baseline values over a further 10-min period. Once haemodynamic variables had returned to precannulation baseline values, 15 mL/kg of blood ideal body weight (12) was venesected over 25 min into purpose venesection bags (Fenwal, PL146 Citrate Phosphate Dextrose 63 mL, Lake Zurich, IL), in accordance with the Australian Red Cross and hospital blood bank venesection protocols. Blood was crosschecked by two study investigators, and immediately placed in a dedicated blood fridge set at 4°C until re-infusion. A total of 450 mL (± 10%) of blood was placed in each bag, in accordance with the manufactures instructions. For incomplete bags, the 63 mL ratio of Citrate Phosphate Dextrose to venesected blood was adjusted accordingly to keep the anticoagulant ratio of blood returned consistent. Calcium chloride was not infused with the return of the venesected blood. After 30 min of continuous haemodynamic monitoring, Plasmalyte (1.3 × total venesected blood volume in milliliter) was infused over 10 min (FAST) or 30 min (SLOW) using dedicated volumetric pumps to control the infusion rate and volume infused. After 2 h of monitoring, and completion of the study protocol, the venesected blood was re-infused over 30 min. Participants were observed for a further 60 min to ensure no adverse effects of the reinfusion blood were reported. After a 2-week period participants returned for the alternate arm of the crossover study.

### Outcomes and data collected

*Primary outcome: oxygen delivery*—The primary outcome variable was change in oxygen delivery ($\Delta DO_2$), comparing $DO_2$ at 120-min post-resuscitation (T6) with the baseline $DO_2$ value. The difference in $\Delta DO_2$ under the FAST and SLOW treatments, $\Delta DO_{2Fast-Slow}$, allowed assessment of resuscitation strategy effectiveness. Additionally, we examined the overall difference between treatments in $DO_2$ over the 120-min monitoring period that followed fluid resuscitation. We assumed that the contribution of free oxygen to the total oxygen delivery was negligible and $DO_2$ was calculated using the following formula (12):

$$DO_2 = CI \times 1.34 \times [Hb] \times SaO_2 \text{ where}$$

- $DO_2$ is arterial oxygen delivery (mLO$_2$/min/m$^2$)
- Hb is concentration of haemoglobin (g/dL)
- SaO$_2$ is haemoglobin oxygen saturation
- CI is cardiac index (L/min)

*Secondary outcomes*—Secondary outcomes included pressure-based haemodynamic variables: mean arterial pressure (MAP), systolic blood pressure (sBP), diastolic blood pressure (dBP); flow-based haemodymanic variables: cardiac index (CI), stroke volume index (SVI), systemic vascular resistance index (SVRI), and pulse rate; blood volume (BV); biochemical variables including, haemoglobin, venous blood gas variables (pH, pCO$_2$, bicarbonate, standard base excess, glucose, and lactate), electrolytes (sodium, potassium, calcium, magnesium, phosphate, and albumin), and N-terminal pro B-type natriuretic peptide (NT-BNP).

*Haemodynamic variables*—Haemodynamic variables were measured continuously beat-to-beat with the noninvasive Edwards Life Science ClearSight monitor that is based on the Nexfin system technology. The Nexfin system gained approval from the Association for the Advancement of Medical Instrument and has been validated against other intermittent noninvasive (13) and continuous invasive haemodynamic monitoring methods (14). This system uses the volume clamp method (15) and the physiocal method (16) to formulate an accurate real-time construction of the pressure based haemodynamic waveform. Using the blood pressure measurements, the Nexfin system derives CI, SVI, and SVRI through validated algorithms. Similar to the measurements of $DO_2$, haemodynamic variables at 120-min post-resuscitation (T6) were compared to baseline values for both the FAST and SLOW groups. This comparison between the groups is denoted as $\Delta$Haemodynamic variable$_{fast-slow}$. We also examined the overall difference between the two groups in blood pressure and flow-based haemodynamic variables for the 120-min post-resuscitation monitoring period.

*Blood volume*—The blood volume at baseline (BV$_o$) was estimated by assuming that the blood volume amounts to 7% of the absolute body weight. The blood volume change ($\Delta BV$) at time $t$ when no bleeding occurred was calculated as follows:

$$\Delta BV_T = BV_o ([Hb_o]/ [Hb_T]) - BV_o$$

where the subscript "o" denotes baseline values, and subscript "T" denotes values at a later time. The amount of fluid retained in the blood (efficacy of the fluid) is given by:

$$\text{fluid retained (\%)} = 100 \times \Delta BV_T / \text{infused volume}$$

To account for withdrawn blood, the total Hb content (total Hb) of BV$_o$ was first calculated, and then all losses of Hb were subtracted from this product. BV$_T$ was then obtained dividing the remaining Hb mass by Hb$_T$:

$$\text{Total Hb}_o = BV_o \times [Hb_o]$$
$$BV_T = (\text{Total Hb}_o - Hb_{loss})/[Hb_t]$$
$$\Delta BV_T = BV_T - BV_o$$

*Biochemistry and blood gases*—A total of 20 mL of blood was collected for the measurements of serum biochemistry and venous blood gases at seven time points: baseline, post-venesection, preresuscitation, 0-min post-resuscitation, 60-min post-resuscitation, 120-min post-resuscitation, and post-blood re-infusion. Serum biochemistry was measured at each time point at 37°C. Calcium, magnesium, phosphate, and albumin were measured with a Cobas analyzer (Roche Diagnostics, Rotkreuz, Switzerland), using a standardized photometric module, linear and non-linear multipoints, and a two-point calibration. Measurements of venous pH, CO$_2$, bicarbonate, glucose, lactate, and routine electrolytes in venous blood were completed on an ABL 800 Blood Gas Analyzer (Radiometer, Copenhagen, Denmark) with a fully automated micromode eliminating risk of user-induced bias or loss of accuracy with very small samples, and an interference-protected lactate analysis. The machine calculates the bicarbonate concentration using the Henderson–Hasselbalch equation and the standard base excess using the Van Slyke Eq. (17).

*N-terminal pro B-type natriuretic peptide*—The venous blood samplings from each experiment were also used for the measurements of NT-pro B-type natriuretic peptide at four time points: baseline, 0-min post-resuscitation, 60-min post-resuscitation, 120-min post-resuscitation with Cobas e602 immunoassay analyzer (Roche Diagnostics).

*Statistics*—Sample calculations were based on comparing two dependent sample populations where a sample size of nine participants provided the desired power of 0.8 and allowed a detection of 75 mL/min/m$^2$ difference in $DO_2$ between the two groups. In the primary outcome analysis to compare $\Delta DO_2$ (the difference between $DO_2$ at 120-min post-resuscitation (T6) and the baseline $DO_2$ value) and all the haemodynamic variables under FAST and SLOW treatments, a Wilcoxon signed-rank test was used to test the hypothesis that there was no difference between the two treatments, i.e., that $\Delta DO_{2Fast-Slow}$ was 0.

For $DO_2$ and the haemodynamic variables, we also used a longitudinal analysis. Due to the cross-over nature of the study, where all the patients have undergone both FAST and SLOW treatments and multiple repeated measures over time were taken under both treatment regimes, there were two levels of "nestedness" in the data: the treatment data was "nested" in the individual time points and the time data was "nested" within individual participants. To appropriately account for this multilevel data structure, we utilized three-level random effect generalized linear regression models with $DO_2$ or the haemodynamic variables as the dependent variable, FAST/SLOW treatment as independent variable, order of treatment and time as adjustment covariates, and time point and participant being random effects. Given the exploratory nature of this study, no formal adjustment for multiplicity of testing was undertaken, and $P = 0.05$ was regarded as significant for every outcome. This may yield a potential increase in Type 1 error rate, which is acceptable given the context of the study.

## RESULTS

Nine participants consented and received crystalloid at the designated rate according to the study protocol. There were no

breaches or violations in the study. One participant had a decrease in ionized calcium from their baseline value (1.1–0.86 mmol/L) immediately after crystalloid resuscitation (attributed to haemodilution). The participant complained of mild tingling of the lips that resolved over 5 min. There were no other adverse events during the experiment or during the 60 min observation period post reinfusion of the blood. One participant noted mild bruising over the cannula sight the following day, which resolved within 72 h. Seven of the participants were male. The median (IQR) age was 27 years (24–39 years). The mean (SD) height and the IBW were 177.6 cm (1.5 cm) and 74.7 kg (14.5 kg), respectively. The mean (SD) venesection volume was 1069 mL (326 mL). The mean crystalloid infusion volume was 1390 mL (424 mL). The mean (SD) infusion rate for the FAST and the SLOW group was 139 mL/min (42.4 mL/min) and 46.3 mL/min (14.1 mL/min), respectively.

### Primary end point: oxygen delivery (DO$_2$)

Changes in oxygen delivery (DO$_2$) at baseline, post-venesection, preresuscitation, 0-min, 60-min and 120-min post-resuscitation are summarized in Table 1. The median (IQR) of $\Delta DO_{2Fast-Slow}$ from baseline values at 120-min was 55 mLO$_2$/min/m$^2$ (−192 to 13 mLO$_2$/min/m$^2$; $P = 0.250$) (Table 2). No statistically significant changes in DO$_2$ between the treatments over the duration of the study were identified. Even after adjusting for gender, BMI, treatment order and time points, no statistically significant differences were observed.

### Secondary end points

*Pressure-based haemodynamic variables (MAP, sBP, and dBP)*—Changes in haemodynamic variables at baseline, post-venesection, preresuscitation, 0, 60, and 120-min post-resuscitation are summarized in Table 1. Comparing the 120-min post-resuscitation haemodynamic values to the baseline values, the median (IQR) of $\Delta MAP_{Fast-Slow}$, $\Delta sBP_{Fast-Slow}$, and $\Delta dBP_{Fast-Slow}$ was 3 mm Hg (−5 to 8 mm Hg; $P = 0.516$); 3 mm Hg (−7 to 12 mm Hg; $P = 0.289$); and 3 mm Hg (−4 to 6 mm Hg; $P = 0.621$), respectively (Table 2). Longitudinal analysis showed that MAP, sBP, and dBP were all significantly higher under the FAST treatment compared with the SLOW treatment ($P = 0.035$; $P = 0.046$; $P = 0.035$) (Table 2).

*Flow-based haemodynamic variables (CI, SVRI, SVI)*—Changes in these haemodynamic variables at baseline, post-venesection, preresuscitation, 0, 60, and 120-min post-resuscitation are summarized in Table 1. At 120-min post-resuscitation, compared with baseline values, the median (IQR) of $\Delta CI_{Fast-Slow}$ and $\Delta SVRI_{Fast-Slow}$ was 0 L/min/m$^2$ (−0.4 to 0.3 L/min/m$^2$; $P = 0.883$) and 150 dyne s m$^2$/cm$^5$ (−172 to 296 dyne s m$^2$/cm$^5$; $P = 0.426$), respectively (Table 2). There were no differences in CI or SVRI between the two groups based on our longitudinal analysis ($P = 0.432$; 0.964). Changes in cardiac index from baseline to 120-min post-resuscitation are presented graphically in Figure 1. During the resuscitation phase (time period between Shock and Resus Complete in Fig. 1), CI paradoxically declined in eight participants (89%) under the FAST treatment in the last quarter of this phase. These findings were coupled with reporting of abdominal discomfort, chest, and facial fullness during resuscitation in six participants (67%) under the FAST treatment, compared with none under the SLOW treatment. Similar to the pattern change found in CI during the resuscitation phase, four participants (44%) under the FAST treatment also had a decrease in SVI during during the final stages of resuscitation. This is in contrast to the SLOW treatment group where all participants had a consistent increase in the SVI throughout the resuscitation phase, which peaked within 30 min post-resuscitation.

*Pulse rate*—Changes in pulse rate at baseline, post-venesection, preresuscitation, 0, 60, and 120-min post-resuscitation are summarized in Table 1. At 120-min post-resuscitation, compared with baseline values, the median (IQR) $\Delta HR_{Fast-Slow}$ and $\Delta SVI_{Fast-Slow}$ was −4 bpm (−11 to 3 bpm) and −1 mL/b/m$^2$ (−6 to 10 mL/b/m$^2$), respectively, ($P = 0.191$; $P = 0.562$) (Table 2). Longitudinal analysis indicated that the pulse rate under the FAST treatment was significantly higher than under the SLOW treatment ($P = 0.022$). The pulse rate was uniformly increased under the FAST treatment during the resuscitation period, compared with an increase in <50% of the participants under the SLOW treatment.

*Intravascular blood volume (BV)*—The estimated mean (SD) BV$_o$ was 5.1 (1.0) L before venesection commenced. Figure 2 shows the change in BV with the change in CI over the period of the study. In both groups, venesection reduced the BV by 16%, while CI decreased by only 5% ($P < 0.0011$). During the resuscitation phase, the SLOW and FAST infusions increased BV by 720 (210) and (920) (223) mL, respectively ($P < 0.03$). This increase in BV corresponds to 54 (7%) and 69 (16%) of the infused volume of crystalloid fluid. The immediate BV expansion was attenuated with time, and represented 24% and 25% of the infused volume 30 min post-resuscitation. The retransfusion of the venesected blood increased CI by a similar magnitude as the infused volume (1.05 L).

*Biochemistry, oxygen saturations, venous blood gas, and N-terminal pro B-type natriuretic peptide (NT-BNP)*—Changes in the above variables are summarized in Tables 3 and 4. No statistically significant differences were found in venous acid base variables, electrolytes, oxygen saturations, haemoglobin, glucose, lactate, or BNP-NT values between the FAST and SLOW treatment regimes at any time point

## DISCUSSION

### Key study findings

To date, there are no human studies that compare rates of crystalloid resuscitation in a haemorrhagic shock model. In this randomized crossover study to compare the effects of FAST and SLOW crystalloid resuscitation in a model of compensated haemorrhagic shock, we found that despite higher pulse rates and blood pressure values in the FAST group, there were no differences in DO$_2$, flow-based haemodynamic parameters, BV, and clinical biochemistry. However, during the resuscitation phase, CI and SVI decreased under the FAST treatment before resuscitation was complete, suggesting a degree of impaired myocardial performance.

Throughout the experiment we observed important physiological findings. During venesection under both treatments, the amount of withdrawn blood was not fully accounted for by the

Table 1. **Oxygen delivery and haemodynamic variables in a human model of compensated haemorrhagic shock**

| | Group | Baseline | Post-venesection | Pre-Resuscitation | 0 min Post-Resuscitation | 60 min Post-Resuscitation | 120 min Post-Resuscitation | p-value |
|---|---|---|---|---|---|---|---|---|
| Oxygen delivery (mLO$_2$/min/m$^2$) | Fast | 663 (581, 614, 705, 813) | 581 (508, 556, 710, 766) | 596 (508, 518, 655, 753) | 689 (487, 538, 787, 908) | 679 (491, 539, 699, 762) | 670 (643, 651, 825, 832) | 0.169 |
| | Slow | 703 (551, 608, 792, 851) | 592 (508, 552, 633, 681) | 596 (494, 514, 618, 638) | 631 (529, 562, 726, 799) | 629 (398, 534, 700, 728) | 630 (304, 540, 732, 774) | |
| Mean arterial pressure (mm Hg) | Fast | 91 (84, 86, 98, 104) | 89 (67, 82, 92, 97) | 92 (80, 84, 94, 96) | 94 (75, 81, 97, 100) | 91 (78, 82, 101, 102) | 91 (82, 85, 94, 100) | 0.035 |
| | Slow | 92 (74, 85, 98, 104) | 88 (59, 80, 91, 93) | 89 (70, 84, 91, 95) | 86 (69, 76, 91, 102) | 91 (66, 78, 94, 96) | 94 (70, 78, 96, 98) | |
| Systolic blood pressure (mm Hg) | Fast | 125 (104, 109, 132, 135) | 121 (93, 104, 123, 127) | 121 (104, 111, 128, 133) | 126 (100, 112, 135, 141) | 124 (110, 115, 136, 143) | 121 (108, 111, 129, 141) | 0.046 |
| | Slow | 123 (96, 114, 135, 140) | 115 (92, 105, 120, 123) | 116 (101, 109, 122, 129) | 122 (103, 109, 129, 146) | 120 (89, 109, 128, 141) | 120 (97, 111, 127, 142) | |
| Diastolic blood pressure mm Hg | Fast | 73 (68, 70, 79, 90) | 74 (55, 68, 76, 85) | 74 (67, 69, 78, 87) | 73 (62, 65, 77, 79) | 75 (62, 69, 79, 87) | 71 (61, 70, 77, 81) | 0.035 |
| | Slow | 73 (57, 68, 79, 84) | 71 (48, 65, 79, 82) | 74 (57, 66, 79, 81) | 70 (54, 58, 75, 80) | 73 (53, 60, 75, 85) | 76 (53, 60, 75, 79) | |
| Cardiac index (L/min/m$^2$) | Fast | 3.3 (2.5, 3.0, 3.7, 3.8) | 3.2 (2.5, 2.8, 3.7, 3.9) | 3.1 (2.5, 2.8, 3.6, 3.7) | 4.4 (3.2, 3.4, 4.5, 4.9) | 4.0 (2.7, 3.3, 4.1, 4.8) | 3.5 (3.0, 3.1, 4.0, 4.0) | 0.432 |
| | Slow | 3.5 (2.6, 3.2, 3.7, 4.1) | 3.1 (2.4, 2.8, 3.5, 4.1) | 3.2 (2.4, 2.8, 3.3, 4.4) | 4.1 (3.1, 3.6, 4.4, 5.6) | 3.7 (2.1, 3.1, 3.9, 4.6) | 3.9 (1.6, 3.3, 4.1, 4.4) | |
| Stroke volume index (mL/b/m$^2$) | Fast | 49 (33, 44, 54, 57) | 42 (29, 39, 46, 50) | 45 (32, 38, 51, 55) | 53 (45, 47, 62, 68) | 56 (37, 42, 57, 58) | 46 (38, 45, 55, 59) | 0.355 |
| | Slow | 54 (39, 48, 60, 62) | 43 (30, 38, 49, 56) | 44 (32, 39, 48, 55) | 54 (42, 49, 61, 67) | 55 (27, 42, 59, 64) | 52 (22, 47, 56, 64) | |
| Systemic vascular resistance index (dyne s m$^2$/cm$^5$) | Fast | 1913 (1706, 1793, 2219, 3070) | 1987 (1885, 1926, 2358, 3101) | 2131 (1987, 2032, 2540, 3037) | 1530 (1056, 1366, 1842, 2198) | 1735 (1299, 1401, 2103, 2782) | 1792 (1339, 1732, 2082, 2291) | 0.964 |
| | Slow | 1973 (1465, 1726, 2051, 2460) | 2141 (1579, 1845, 2323, 2797) | 2299 (1562, 1859, 2510, 2864) | 1598 (985, 1230, 1812, 2062) | 1698 (1251, 1453, 2022, 3349) | 1715 (1209, 1367, 1992, 4498) | |
| Pulse rate (bpm) | Fast | 69 (65, 65, 73, 77) | 77 (50, 71, 83, 87) | 73 (60, 65, 74, 79) | 78 (65, 74, 82, 84) | 74 (70, 71, 78, 82) | 72 (69, 70, 73, 86) | 0.022 |
| | Slow | 66 (56, 65, 68, 71) | 73 (62, 67, 77, 79) | 72 (67, 68, 75, 77) | 75 (64, 73, 80, 83) | 69 (58, 63, 75, 84) | 72 (64, 70, 77, 80) | |

Values are medians in absolute values (minimum, 25% percentile, 75% percentile, maximum). P values obtained from longitudinal analyses with the random effect generalised linear regression model; $P < 0.05$ represent statistically significant findings.

TABLE 2. **Difference in oxygen delivery and haemodynamic variables in a human model of compensated haemorrhagic shock at 120-min post-resuscitation from baseline in the FAST and SLOW groups**

| | FAST group | SLOW group | Effect size | P value |
|---|---|---|---|---|
| Oxygen delivery (mLO$_2$/min/m$^2$) | −46 (−82 to 8) | −110 (−154 to 2) | 55 (−192 to 13) | 0.250 |
| Mean arterial pressure (mm Hg) | −2 (−9 to 2) | −5 (−8 to 3.5) | 3 (−5 to 8) | 0.516 |
| Systolic blood pressure (mm Hg) | 2 (−14 to 11.5) | −2 (−10 to 1) | 3 (−7 to 12) | 0.289 |
| Diastolic blood pressure (mm Hg) | 0 (−8 to 3) | −3 (−6 to 3.5) | 3 (−4 to 6) | 0.621 |
| Cardiac index (L/min/m$^2$) | 0.2 (0.1 to 0.4) | 0.1 (−0.2 to 0.6) | 0 (−0.4 to 0.3) | 0.883 |
| Stroke volume index (mL/b/m$^2$) | 1 (−2 to 3) | −4 (−7 to 2) | −1 (−6 to 10) | 0.562 |
| Systemic vascular resistance index (dyne s m$^2$/cm$^5$) | −124 (−354 to 66) | −203 (−343 to 59) | 150 (−172 to 296) | 0.426 |
| Pulse rate (bpm) | 2 (−1 to 7) | 6 (2.5 to 12) | −4 (−11 to 3) | 0.191 |

Values are medians in absolute values (IQR); effect size as mean in absolute values (95% CI). $P < 0.05$ represent statistically significant findings.

observed decrease in blood volume. This is likely attributed to physiological compensation by capillary refill observed in hypovolaemia induced by exsanguination (18). This result is consistent with findings in conscious sheep, where one-third of the lost blood volume is compensated by capillary refill within the first 30 min after haemorrhage, after which compensation diminishes (19). This spontaneous compensation observed in animals is consistent with our study, where approximately 300 mL of the venesected blood was promptly replaced by capillary refill by the end of the venesection, after which restoration slowed until the resuscitation commenced. While colloid infusion is thought to be more effective in intravascular expansion compared with crystalloid infusion (20), we observed that the immediate plasma volume expanding effect of crystalloid fluid is close to what is expected from a colloid fluid (21). By 30 min after the crystalloid infusion, fluid kinetics between the intravascular and the interstitial space reached equilibrium, where the final plasma volume expansion was only 25% of the transfused volume, a finding consistent with most medical textbooks. Our results also show that the crystalloid fluid, after complete distribution, expands the blood volume by 25% even when volunteers are hypovolaemic. In contrast, hydroxyethyl starch (22) and autologous plasma (23) given to replace blood that has just been withdrawn from volunteers seem to remain there.
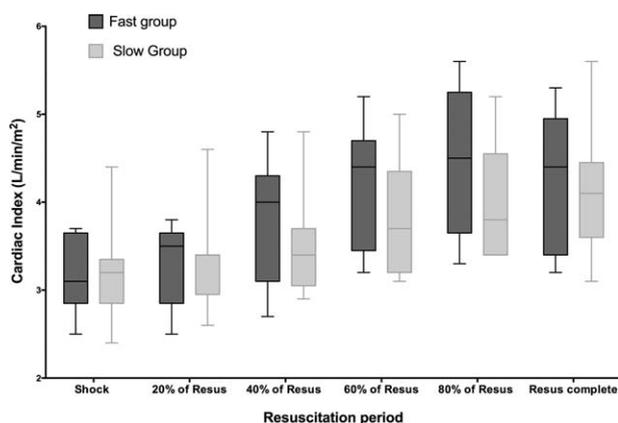
We did not find any significant correlation between changes in CI and blood volume. Importantly, the CI did not decrease to the same proportion as the blood volume in response to venesection. In addition, CI increased to 20% above baseline in response to the crystalloid resuscitation despite the failure to restore hypovolaemia to baseline. The discrepancy between the change in CI and blood volume is likely related to the stress response induced by a single hypovolaemic episode, evident by the mild tachycardia, hyperglycaemia, and improvement in cardiac contractility (20% increase in CI) for several hours. Unlike animal studies that have shown that the MAP is higher and more effectively maintained in a SLOW fluid resuscitation (6, 9), we found that the pressure-based haemodynamic variables were better preserved in the FAST group in our study. In accordance with the increasing evidence suggesting that blood pressures does not accurately reflect oxygen delivery and tissue perfusion (24), we found that the higher blood pressures resulted from the FAST resuscitation did not yield superiority in DO$_2$.

The discrepancies between the findings in animal studies and our findings are not surprising. In contrast to our controlled compensated haemorrhagic shock model, most of the animal studies adopted haemorrhagic shock model that involved uncontrolled bleeding and more significant blood loss secondary to large vessels and solid organ injuries (4–10). Moreover, a variety of resuscitation fluids were infused at arbitrarily predetermined rates in these animal studies. Unfortunately, the combination of the differences in physiology and in the experimental protocols precludes direct comparison.

The higher blood pressures observed under the FAST treatment can be attributed to the rapid increase in ventricular preload, increased SV, and higher pulse rate compared with the SLOW treatment. This increase in pulse rate may be a result of an increase in body temperature due to the warm crystalloid being rapidly infused during the resuscitation period in addition to the participants' anxiety associated with receiving the FAST resuscitation. Despite the pressure-based haemodynamic variables being higher under the FAST treatment, a more critical analysis of haemodynamic variables during the actual resuscitation period showed that CI peaked late during resuscitation and then decreased before the resuscitation was complete (Fig. 1). This finding was not observed under the SLOW treatment, where CI and SVI continued to increase throughout the resuscitation period.
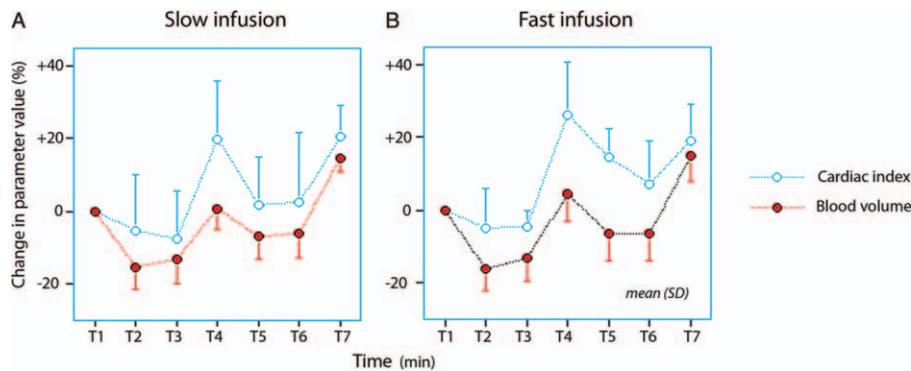


Fig. 1. **Box-and-Whisker plot showing median changes in cardiac index observed during FAST (20 mL/kg crystalloid over 10 min) and SLOW (20 mL/kg crystalloid over 30 min) resuscitation in a human model of compensated haemorrhagic shock.**

FIG. 2.  **Changes in percentage in cardiac index in relation to blood volume in a human model of compensated haemorrhagic shock.** A, fast infusion. B, slow infusion. T1 indicates baseline; T2, post-venesection; T3, preresuscitation; T4, 0-min post-resuscitation; T5, 60-min post-resuscitation; T6, 120-min post-resuscitation; T7, post-blood transfusion.

The decline in CI might be simply reflective of a baroreceptor response to a rise in blood pressure, which would fit with our observations that there were no elevations in NT-BNP. The stretching of the myocardial wall from the increased venous return is directly responsible for the release of NT-BNP. Studies have reported that the level of NT-BNP increases as the resuscitation volume increases, suggesting that NT-BNP may be a useful marker of fluid overload from resuscitation (25, 26). Following fluid resuscitation NT-BNP levels may increase at least 12 h after the fluid intervention; therefore, our study might not have allowed sufficient time (2 h) to capture the accurate level of NT-BNP. The initial choice between BNP and NT-BNP to detect the stretching of myocardial wall induced by fluid overload from resuscitation was based on assay availability at our institution and the sensitivity of these two hormones. BNP has a shorter half-life (22 min) than that of NT-BNP (120 min) (27) and might have been sufficient to detect any measurable responses in our study; however, we preferred NT-BNP for its higher sensitivity and stability (28). Nevertheless, not extending the collection of NT-BNP for at least 12 h is a limitation of the present study.

The decrease in SVI and CI during the end of the resuscitation phase under the FAST treatment could also be due to over resuscitation from aggressive fluid intervention. Stretching of the myocardial walls by the FAST resuscitation might have exceeded the optimal contractility point on the Frank–Starling curve. Following the Frank–Starling theory, a rapid increase in venous return theoretically should have increased the LVEDV, which should in turn have increased the SV. In our study, during the resuscitation period this was not observed. Instead, there was a decline in both SVI and CI (despite a significant increase in HR) in the FAST group most noticeable before the end of the resuscitation. These clinical observations in hemodynamics changes support the postulation that the myocardial wall of the ventricle was possibly overfilled and stretched beyond the optimal contractile response, consequently leading to underperformance by the myocardium. Finally, a rapid dilution of serum calcium in the FAST group could also have affected the changes observed in CI at the end of the resuscitation. We consider this to be less likely, as the magnitudes of the decreases in serum calcium from baseline were similar in both groups.

### Study implications

Our findings contradict current resuscitation practices, which are based on presumption that FAST crystalloid resuscitation is superior to SLOW crystalloid resuscitation (2, 3). There were no significance differences in $DO_2$ between the FAST and SLOW treatments groups, and changes in CI and blood pressure did not reflect the magnitude of intravascular blood volume deficit. Crystalloid resuscitation expanded intravascular blood volume by approximately 25%. This was associated with a reduction in CI and SVI during the resuscitation phase, again supporting the theory of over resuscitation and suboptimal myocardial performance. In the view of the increasing prevalence of cardiovascular disease with advancing age, the impact of FAST resuscitation on the CI observed in this study, which is of most relevance to combat casualties, might be more profound in the current aging population or patients with preexisting cardiac dysfunction. Older subjects have a more poorly functioning adrenergic system, although stress hormones are generally higher than in younger subjects, which makes them more sensitive to changes in preloading and more prone to hypotension in hypovolaemia. Finally, the discrepancy between changes in blood volume and CI could mislead the clinician who tries to maintain the blood volume by monitoring CI alone. Neither did the reduction in CI proportionally reflect the degree of blood loss from the venesection, nor did the increase in CI accurately reflect the persisting hypovolemic state.

There are several limitations to our study. We did not use invasive techniques to measure arterial blood pressure, CVP, and cardiac output. However, the accuracy of the Nexfin cardiac output technology has been validated against pulmonary thermodilution, transpulmonary thermodilution (29), transoesophageal and transthoracic echocardiography (30, 31), and inert gas rebreathing (32). Percentage errors range from 23% to 39%, comparable to more invasive methods (33, 34). Measurement of central venous pressure via a central venous catheter would have been useful in identifying the effects of resuscitation on preload and in more accurately calculating SVRI, but was considered too invasive in a healthy volunteer population.

TABLE 3. Venous blood gas variables in a human model of compensated haemorrhagic shock

| | Group | Baseline | Post-venesection | Preresuscitation | 0min Post-Resuscitation | 60min Post-Resuscitation | 120min Post-Resuscitation |
|---|---|---|---|---|---|---|---|
| pH (N: 7.32–7.43) | Fast | 7.37 (7.32, 7.35, 7.38, 7.40) | 7.38 (7.36, 7.37, 7.40, 7.41) | 7.39 (7.37, 7.38, 7.40, 7.43) | 7.38 (7.35, 7.36, 7.38, 7.40) | 7.38 (7.36, 7.37, 7.39, 7.41) | 7.39 (7.36, 7.39, 7.40, 7.42) |
| | Slow | 7.35 (7.33, 7.34, 7.37, 7.39) | 7.35 (7.33, 7.34, 7.37, 7.40) | 7.38 (7.35, 7.36, 7.39, 7.40) | 7.37 (7.34, 7.37, 7.41, 7.42) | 7.37 (7.34, 7.36, 7.40, 7.42) | 7.38 (7.36, 7.37, 7.41, 7.43) |
| $pCO_2$ (N: 41–50 mm Hg) | Fast | 51 (47, 48, 53, 56) | 50 (43, 44, 51, 54) | 45 (40, 43, 47, 50) | 47 (46, 46, 52, 53) | 48 (44, 46, 50, 52) | 46 (42, 43, 48, 53) |
| | Slow | 52 (43, 49, 53, 59) | 53 (42, 50, 56, 56) | 47 (44, 44, 49, 51) | 46 (41, 44, 49, 51) | 48 (42, 45, 50, 51) | 49 (41, 44, 51, 52) |
| Bicarbonate (N: 24–28 mmol/L) | Fast | 29 (28, 28, 29, 30) | 28 (26, 27, 29, 29) | 27 (25, 26, 28, 28) | 28 (26, 27, 28, 28) | 28 (27, 27, 28, 29) | 28 (25, 27, 28, 29) |
| | Slow | 28 (26, 27, 29, 30) | 28 (25, 28, 29, 30) | 27 (26, 27, 27, 28) | 27 (25, 26, 27, 28) | 27 (26, 27, 28, 28) | 28 (27, 27, 28, 29) |
| Standard base excess (−5–+5) | Fast | 3.8 (2.8, 3.0, 4.2, 5.2) | 3.4 (1.5, 2.0, 4.0, 4.3) | 2.2 (0.4, 1.7, 3.1, 3.3) | 3.0 (1.7, 2.0, 3.2, 3.4) | 3.1 (2.4, 2.5, 3.6, 4.0) | 3.1 (0.7, 2.4, 3.3, 4.0) |
| | Slow | 3.0 (1.3, 1.6, 3.5, 4.8) | 2.9 (1.1, 2.8, 3.4, 4.6) | 2.2 (1.6, 1.7, 2.4, 2.6) | 2.1 (1.1, 1.3, 2.4, 2.8) | 2.6 (2.1, 2.2, 3.0, 4.1) | 2.9 (2.2, 2.4, 3.5, 3.7) |
| Glucose (3.0–5.4 mmol/L) | Fast | 5.3 (5.2, 5.2, 5.9, 6.1) | 5.6 (5.2, 5.3, 5.9, 6.0) | 5.8 (5.3, 5.4, 5.9, 6.4) | 5.2 (4.9, 5.1, 5.3, 5.4) | 5.6 (5.1, 5.3, 5.8, 6.0) | 5.6 (5.3, 5.4, 5.8, 5.9) |
| | Slow | 5.7 (5.1, 5.1, 5.8, 6.9) | 5.5 (4.9, 5.0, 5.8, 6.7) | 5.7 (4.9, 5.2, 6.3, 6.9) | 5.2 (4.6, 5.0, 5.5, 5.6) | 5.5 (4.9, 5.1, 6.0, 6.5) | 5.5 (4.9, 5.2, 6.4, 7.0) |
| Lactate (0.5–2.0 mmol/L) | Fast | 0.9 (0.7, 0.7, 1.3, 1.5) | 0.9 (0.7, 0.8, 1.0, 1.3) | 0.9 (0.7, 0.7, 1.1, 1.3) | 0.9 (0.7, 0.7, 1.0, 1.1) | 0.8 (0.7, 0.7, 0.9, 0.9) | 0.8 (0.6, 0.7, 0.8, 0.9) |
| | Slow | 1.1 (0.7, 0.8, 1.3, 2.1) | 1.0 (0.8, 0.8, 1.3, 1.7) | 1.1 (0.7, 0.8, 1.1, 1.2) | 1.1 (0.6, 0.7, 1.1, 1.3) | 0.8 (0.6, 0.7, 0.9, 1.2) | 0.9 (0.5, 0.7, 1.2, 1.8) |
| Calcium (ionized) (1.1–1.3 mmol/L) | Fast | 1.21 (1.17, 1.18, 1.24 1.27) | 1.19 (1.16, 1.18, 1.22 1.27) | 1.19 (1.16, 1.17, 1.23 1.26) | 1.08 (1.05, 1.06, 1.14 1.19) | 1.12 (1.10, 1.12, 1.17, 1.19) | 1.15 (1.11, 1.13, 1.18, 1.21) |
| | Slow | 1.21 (1.20, 1.21, 1.23 1.26) | 1.20 (1.19, 1.20, 1.24 1.27) | 1.19 (1.18, 1.19, 1.22 1.27) | 1.14 (1.08, 1.14, 1.15 1.16) | 1.14 (1.13, 1.14, 1.19 1.20) | 1.15 (1.15, 1.15, 1.18 1.19) |

Values are medians in absolute values (minimum, 25% percentile, 75% percentile, maximum).

TABLE 4. Electrolytes, haemoglobin, and oxygen saturation values in a human model of compensated haemorrhagic shock

| | Group | Baseline | Post-venesection | Preresuscitation | 0 min Post-Resuscitation | 60 min Post-Resuscitation | 120 min Post-Resuscitation |
|---|---|---|---|---|---|---|---|
| Potassium (3.6–5.0 mmol/L) | Fast | 4.0 (3.7, 3.9, 4.3, 4.6) | 4.1 (3.8, 3.8, 4.4, 4.5) | 4.2 (3.9, 3.9, 4.4, 4.5) | 3.9 (3.8, 3.9, 4.4, 4.4) | 3.9 (3.7, 3.7, 4.0, 4.2) | 3.9 (3.7, 3.7, 4.1, 4.4) |
| | Slow | 4.0 (3.8, 3.9, 4.4, 4.5) | 4.0 (3.7, 3.8, 4.1, 4.2) | 4.2 (3.9, 3.9, 4.5, 4.8) | 4.1 (3.7, 3.8, 4.4, 4.9) | 4.0 (3.8, 3.8, 4.2, 4.3) | 3.9 (3.4, 3.6, 4.0, 4.3) |
| Sodium (132–142 mmol/L) | Fast | 140 (137, 139, 141, 141) | 139 (136, 138, 140, 142) | 139 (136, 137, 140, 141) | 138 (136, 138, 140, 140) | 139 (136, 138, 140, 141) | 138 (136, 138, 140, 141) |
| | Slow | 139 (138, 139, 141, 142) | 139 (138, 138, 140, 142) | 138 (137, 138, 140, 141) | 138 (137, 137, 139, 140) | 138 (137, 138, 139, 140) | 138 (137, 138, 139, 140) |
| Chloride (101–111 mmol/L) | Fast | 105 (104, 105, 107, 108) | 106 (105, 106, 108, 108) | 105 (104, 105, 105, 107) | 105 (104, 105, 106, 108) | 105 (104, 105, 106, 108) | 105 (105, 105, 106, 108) |
| | Slow | 105 (103, 104, 106, 107) | 105 (101, 104, 106, 108) | 106 (104, 106, 108, 108) | 105 (104, 105, 107, 108) | 106 (104, 105, 107, 107) | 104 (104, 104, 105, 105) |
| Calcium (2.18–2.58 mmol/L) | Fast | 2.29 (2.21, 2.23, 2.37, 2.41) | 2.24 (2.16, 2.20, 2.34, 2.37) | 2.23 (2.13, 2.15, 2.31, 2.40) | 1.88 (1.78, 1.82, 2.08, 2.28) | 2.04 (1.96, 1.99, 2.19, 2.26) | 2.08 (1.96, 2.01, 2.19, 2.28) |
| | Slow | 2.28 (2.23, 2.25, 2.42, 2.48) | 2.24 (2.14, 2.20, 2.34, 2.38) | 2.25 (2.07, 2.17, 2.29, 2.34) | 1.96 (1.85, 1.89, 2.11, 2.20) | 2.08 (1.95, 2.02, 2.22, 2.26) | 2.12 (1.91, 2.06, 2.24, 2.28) |
| Phosphate (0.8–1.5 mmol/L) | Fast | 1.0 (0.8, 0.9, 1.2, 1.3) | 0.9 (0.8, 0.9, 1.2, 1.3) | 1.0 (0.9, 0.9, 1.2, 1.3) | 0.9 (0.8, 0.8, 1.0, 1.3) | 0.9 (0.8, 0.9, 1.0, 1.3) | 1.0 (0.8, 0.9, 1.1, 1.4) |
| | Slow | 1.1 (0.7, 1.0, 1.2, 1.3) | 1.1 (0.7, 0.9, 1.2, 1.2) | 1.1 (0.6, 0.9, 1.2, 1.2) | 1.0 (0.6, 0.9, 1.1, 1.1) | 1.0 (0.7, 0.8, 1.1, 1.1) | 1.0 (0.8, 0.9, 1.1, 1.1) |
| Magnesium (0.75–0.95 mmol/L) | Fast | 0.88 (0.84, 0.85, 0.92, 0.96) | 0.85 (0.80, 0.82, 0.91, 0.93) | 0.86 (0.79, 0.81, 0.90, 0.94) | 0.88 (0.81, 0.85, 0.92, 0.95) | 0.88 (0.82, 0.84, 0.93, 0.96) | 0.86 (0.78, 0.83, 0.92, 0.95) |
| | Slow | 0.88 (0.74, 0.83, 0.92, 0.93) | 0.85 (0.75, 0.79, 0.88, 0.93) | 0.86 (0.73, 0.77, 0.88, 0.90) | 0.87 (0.78, 0.80, 0.90, 0.93) | 0.88 (0.76, 0.81, 0.90, 0.91) | 0.86 (0.77, 0.80, 0.88, 0.92) |
| Albumin (32–55 mmol/L) | Fast | 41 (38, 40, 44, 46) | 40 (35, 37, 41, 42) | 38 (34, 36, 39, 42) | 29 (25, 26, 32, 24) | 34 (30, 32, 36, 38) | 35 (30, 32, 36, 38) |
| | Slow | 42 (27, 40, 44, 45) | 40 (36, 37, 41, 42) | 38 (35, 36, 39, 41) | 31 (29, 29, 32, 34) | 35 (32, 32, 36, 37) | 35 (32, 32, 36, 38) |
| Haemoglobin (female: 123–157 g/L; male: 140–174 g/L) | Fast | 153 (127, 144, 162, 177) | 149 (126, 136, 155, 168) | 145 (114, 132, 151, 160) | 120 (92, 108, 128, 135) | 132 (108, 124, 142, 147) | 131 (107, 123, 140, 145) |
| | Slow | 155 (132, 143, 165, 172) | 147 (120, 135, 158, 160) | 143 (116, 132, 153, 155) | 122 (101, 112, 132, 133) | 135 (109, 123, 142, 144) | 134 (105, 122, 141, 144) |
| Oxygen saturation (N: 95–100%) | Fast | 98 (97, 97, 98, 100) | 98 (96, 98, 98, 100) | 98 (96, 97, 98, 100) | 98 (95, 97, 98, 100) | 99 (97, 97, 100, 100) | 99 (95, 97, 99, 100) |
| | Slow | 98 (94, 97, 99, 100) | 99 (96, 97, 100, 100) | 99 (97, 97, 100, 100) | 99 (98, 98, 100, 100) | 99 (97, 98, 99, 100) | 99 (97, 98, 99, 100) |
| N-terminal pro B-type natriuretic peptide (N:0–125 ng/L) | Fast | 11 (8, 9, 41, 47) | Not measured | Not measured | 12 (8, 8.5, 32, 43) | 14 (7, 9, 37, 48) | 21 (8, 11, 35, 48) |
| | Slow | 21 (9, 13, 30, 38) | Not measured | Not measured | 20 (7, 13, 25, 30) | 21 (8, 15, 26, 29) | 20 (8, 14, 24, 28) |

Values are medians in absolute values (minimum, 25% percentile, 75% percentile, maximum).

Use of transthoracic echocardiography would have allowed valuable noninvasive and focused estimations of cardiac function, preload, and fluid responsiveness. However, its continuous use over the entire duration of each experiment ($>3\,h$) was not pragmatic. Finally, Plasma-Lyte was the choice of crystalloid solution used in this study for its physiological-like properties and its accessibility at our institution. The effects of FAST and SLOW infusion on $DO_2$, pressure- and flow-based haemodynamic variables, biochemistry, and NT-BNP are likely to be similar from those yielded from any crystalloid solutions of different electrolyte compositions, e.g., Hartmann's solution or saline 0.9%.

## CONCLUSION

In a healthy volunteer model of compensated haemorrhagic shock, FAST or SLOW fluid resuscitation had no significant impact on $DO_2$ between treatments groups. In both groups, changes in CI and blood pressure did not reflect the magnitude of intravascular blood volume deficit. Crystalloid resuscitation expanded intravascular blood volume by approximately 25%.

## REFERENCES

1. Kauvar DS, Lefering R, Wade CE: Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations. *J Trauma* 60(6 Suppl):S3–S11, 2006.
2. American College of Surgeons Committee on Trauma. Advanced Trauma Life Support for Doctors. 9th ed. American College of Surgeons: Chicago, IL; 2012
3. Hilton AK, Bellomo R: A critique of fluid bolus resuscitation in severe sepsis. *Crit Care* 16(1):302, 2012.
4. Bickell WH, Wall MJ, Pepe PE, Martin RR, Ginger VF, Allen MK, Mattox KL: Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med* 331(17):1105–1109, 1994.
5. Krausz MM, Hirsh M: Bolus versus continuous fluid resuscitation and splenectomy for treatment of uncontrolled hemorrhagic shock after massive splenic injury. *J Trauma* 55(1):62–68, 2003.
6. Stern SA, Kowalenko T, Younger J, Wang X, Dronen SC: Comparison of the effects of bolus vs. slow infusion of 7.5% NaCl/6% dextran-70 in a model of near-lethal uncontrolled hemorrhage. *Shock* 14(6):616–622, 2000.
7. Leppäniemi A, Soltero R, Burris D, Pikoulis E, Waasdorp C, Ratigan J, Hufnagel H, Malcolm D: Fluid resuscitation in a model of uncontrolled hemorrhage: too much too early, or too little too late? *J Surg Res* 63(2):413–418, 1996.
8. Yu TC, Yang FL, Hsu BG, Wu WT, Chen SC, Lee RP, Subeq YM: Deleterious effects of aggressive rapid crystalloid resuscitation on treatment of hyperinflammatory response and lung injury induced by hemorrhage in aging rats. *J Surg Res* 187(2):587–595, 2014.
9. Wang P, Ba ZF, Koo DJ, Cioffi WG, Bland KI, Chaudry IH: Continuous resuscitation after hemorrhage and acute fluid replacement improves cardiovascular responses. *Surgery* 129(5):559–566, 2001.
10. Lilly MP, Gala GJ, Carlson DE, Sutherland BE, Gann DS: Saline resuscitation after fixed-volume hemorrhage. Role of resuscitation volume and rate of infusion. *Ann Surg* 216(2):161–171, 1992.
11. Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, Nyeko R, Mtove G, Reyburn H, Lang T, et al.: FEAST Trial Group: mortality after fluid bolus in African children with severe infection. *N Engl J Med* 364(26):2483–2495, 2014.
12. Pai MP, Paloucek FP: The origin of the "ideal" body weight equations. *Ann Pharmacother* 34(9):1066–1069, 2000.
13. Eeftinck Schattenkerk DW, van Lieshout JJ, van den Meiracker AH, Wesseling KR, Blanc S, Wieling W, van Montfrans GA, Settels JJ, Wesseling KH, Westerhof BE: Nexfin noninvasive continuous blood pressure validated against Riva-Rocci/Korotkoff. *Am J Hypertens* 22(4):378–383, 2009.
14. Martina JR, Westerhof BE, van Goudoever J, de Beaumont EM, Truijen J, Kim YS, Immink RV, Jöbsis DA, Hollmann MW, Lahpor JR, et al.: Noninvasive continuous arterial blood pressure monitoring with Nexfin. *Anaesthesiology* 116(5):1092–1103, 2012.
15. Penaz J: Criteria for set point estimation in the volume clamp method of blood pressure. *Physiol Res* 41(1):5–10, 1992.
16. Wesseling K, De Wit B, Van der Hoeven G, Van Goudoever J, Settels J: Physiocal, calibrating finger vascular phyisology for Finapres. *Homeostasis* 36:67–82, 1995.
17. Kellum J, Elbers P: Stewart's Textbook of Acid-Base. 2nd ed. Amsterdam, The Netherlands: Acidbase.org; pp 267–279, 2009.
18. Lister J, Mcneill IF, Marshall VC, Plzak LF, Dagher FJ, Moore FD: Transcapillary refilling after hemorrhage in normal man: basal rates and volumes; effect of norepinephrine. *Ann Surg* 158:698–712, 1963.
19. Hahn RG, Brauer L, Rodhe P, Svensén CH, Prough DS: Isoflurane inhibits compensatory intravascular volume expansion after hemorrhage in sheep. *Anesth Analg* 103(2):350–358, 2006.
20. Weil MH: Crystalloids, colloids, and fluid compartments. *Crit Care Med* 27(1):3, 1999.
21. Hahn R: Why are crystalloid and colloid fluid requirements similar during surgery and intensive care? *Eur J Anaesthesiol* 30(9):515–518, 2013.
22. James MF, Latoo MY, Mythen MG, Mutch M, Michaelis C, Roche AM, Burdett E: Plasma volume changes associated with two hydroxy ethyl starch colloids following acute hypovolaemia in volunteers. *Anaesthesia* 59(8):738–742, 2004.
23. Betnzer P, Thomas OD, Westborg J, Johansson PI, Schött U: The volume expanding effects of autologous liquid stored plasma following hemorrhage. *Scand J Clin Lab Invest* 72(6):490–494, 2012.
24. Dünser MW, Takala J, Brunauer A, Bakker J: Re-thinking resuscitation: leaving blood pressure cosmetics behind and moving forward to permissive hypotension and a tissue perfusion-based approach. *Crit Care* 17(5):326, 2013.
25. Zhang Z, Zhang Z, Xue Y, Xu X, Ni H: Prognostic value of B-type natriuretic peptide (BNP) and its potential role in guiding fluid therapy in critically ill septic patients. *Scand J Trauma Resusc Emerg Med Scand J Trauma Resusc Emerg Med* 20(1):86, 2012.
26. Friese RS, Dineen S, Jennings A, Pruitt J, McBride D, Shafi S, Frankel H, Gentilello LM: Serum B-type natriuretic peptide: a marker of fluid resuscitation after injury? *J Trauma* 62(6):1346–1350, 2007.
27. Kemperman H, van den Berg M, Kirkels H, de Jonge N: B-type natriuretic peptide (BNP) and N-terminal proBNP in patients with end-stage heart failure supported by a left ventricular assist device. *Clin Chem* 50(9):1670–1672, 2004.
28. Vanderheyden M, Bartunek J, Claeys G, Manoharan G, Beckers JF, Ide L: Head to head comparison of N-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide in patients with/without left ventricular systolic dysfunction. *Clin Biochem* 39(6):640–645, 2006.
29. Broch O, Renner J, Gruenewald M, Meybohm P, Schottler J, Caliebe A, Steinfath M, Malbrain M, Bein B: A comparison of the Nexfin and transcardiopulmonary thermodilution to estimate cardiac output during coronary artery surgery. *Anaesthesia* 67(4):377–383, 2012.
30. Chen G, Meng L, Alexander B, Tran N, Kain Z, Cannesson M: Comparison of noninvasive cardiac output measurements using the Nexfin monitoring device and the esophageal Doppler. *J Clin Anaesth* 24(4):275–283, 2012.
31. Bartels S, Stok S, Boksem R, Van Goudoever J, Cherpanath T, van Lieshout J, Westerhof BE, Karemaker JM, Ince C: Noninvasive cardiac output monitoring during exercise testing: Nexfin pulse contour analysis compared to an inert gas rebreathing method and respired gas analysis. *J Clin Monit Comput* 25(5):315–321, 2011.
32. Van der Spoel A, Voogel A, Folkers A, Boer C, Bouwman R: Comparison of noninvasive continuous arterial waveform analysis (Nexfin) with transthoracic Doppler echocardiograhy for monitoring of cardiac output. *J Clin Anaesth* 24(4):304–309, 2012.
33. Alhashemi J, Cecconi M, Hofer C: Cardiac output monitoring: an integrative perspective. *Crit Care* 15(2):214, 2011.
34. Bubenek-Turconi S, Craciun M, Miclea I, Perel A: Noninvasive continuous cardiac output by the Nexfin before and after preload-modifying maneuvers: a comparison with intermitten thermodilution cardiac output. *Anesth Analg* 117(2):366–372, 2013.