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Closed-Loop and Decision-Assist Guided Fluid Therapy of Human Hemorrhage

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Abstract

Objectives—We sought to evaluate the efficacy, efficiency and physiological consequences of automated, end-point directed resuscitation systems and compare them to formula-based bolus resuscitation.

Design—Experimental human hemorrhage and resuscitation

Setting—Clinical Research Laboratory

Subjects—Healthy volunteers

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All experiments and work were performed at the University of Texas Medical Branch, Galveston, Texas.

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Interventions—Subjects (n=7) were subjected to hemorrhage and underwent a randomized fluid resuscitation scheme on separate visits 1) formula-based bolus resuscitation (BR) 2) semi-autonomous (decision-assist, DA) fluid administration and 3) fully autonomous (closed-loop, CL) resuscitation. Hemodynamic parameters, volume shifts, fluid balance, and cardiac function were monitored during hemorrhage and resuscitation. Treatment modalities were compared based on resuscitation efficacy and efficiency.

Measurements and Main Results—All approaches achieved target BP by 60 min. Following hemorrhage, the total amount of infused fluid (BR: 30ml/kg, DA: 5.6 ± 3 ml/kg, CL: 4.2 ± 2 ml/kg, $p < 0.001$), plasma volume, extravascular volume (BR: 17 ± 4 ml/kg, DA: 3 ± 1 ml/kg, CL: -0.3 ± 0.3 ml/kg, $p < 0.001$), body weight and urinary output remained stable under DA and CL and were significantly increased under bolus resuscitation. Mean arterial pressure initially decreased further under bolus resuscitation (-10 mmHg, $p < 0.001$) and was lower under BR than CL at 20 min (BR: 57 ± 2 mmHg CL: 69 ± 4 mmHg, $p = 0.036$). Colloid-osmotic pressure (BR: 19.3 ± 2 mmHg DA, CL: 24 ± 0.4 mmHg, $p < 0.05$) and hemoglobin concentration were significantly decreased after bolus fluid administration.

Conclusions—We define efficacy of decision-assist and closed-loop resuscitation in human hemorrhage. In comparison to formula-based bolus resuscitation, both semiautonomous and autonomous approaches were more efficient in goal-directed resuscitation of hemorrhage. They provide favorable conditions for the avoidance of over-resuscitation and its adverse clinical sequelae. Decision-assist and closed-loop resuscitation algorithms are promising technological solutions for constrained environments and areas of limited resources.

Keywords

closed-loop resuscitation; decision-assist resuscitation; ATLS resuscitation; human hemorrhage

Introduction

Intravenous fluid therapy remains the cornerstone of treating hypovolemia, but the non-systematic use of endpoints to guide volume resuscitation efforts results in heterogeneous scientific conclusions (1–3). Both hypo and hypervolemia result in damage, dysfunction and failure of tissue and end organs, albeit by different mechanisms (4–7). Precise fluid management is favorable to reduce sequelae of under- and over-resuscitation (6,7). Thus, optimizing resuscitation of hypovolemia secondary to hemorrhage remains a challenge (8).

For hemorrhage, several teaching manuals, including the American College of Surgeons (ACS), recommends a fixed-formula-based regimen that replaces 3 mL crystalloid fluid per 1 mL estimated blood loss (3:1 rule)(9). However, most recently, the ATLS working group takes general steps towards recommending less aggressive resuscitation with lower initial volumes (10). Still, while clinical presentation and vital signs initially influence the assessment of hypovolemic severity and recommended fluid amount, the monitoring of resuscitation success remains open-ended, inconclusively defined and subject to wide interpretation (10–11).

Recent concepts introduced end-point or goal directed volume therapy, in which fluid is titrated proportional to the measured value of a specific physiological variable (6,12). Non-invasive blood pressure (NIBP) is one of the most readily accessible surrogate indicator of intravascular volume and can reliably detect hypovolemia (13). While NIBP has limitations, it remains the primary endpoint chosen by the ACS. The advent of precise, portable and reliable measuring devices also make it a promising variable for endpoint resuscitation (14–15). Computed algorithms that analyze endpoint data and continuously adapt fluid therapy through automated infusion pumps have been tested in various animal experiments and for common resuscitation fluids (17–20).

In the present study, we assess, the efficacy and efficiency of two main concepts: closed-loop (CL) resuscitation, an autonomously operating and recursive circuit of endpoint measurement and therapy adjustment; and Decision-assist (DA) resuscitation, which, based on endpoint measurements, recommends therapy adjustments that have to be confirmed and entered manually. We compared both systems to formula-based fluid resuscitation in humans undergoing hemorrhage.

Methods

This study was approved by the Institutional Review Board (IRB) of the University of Texas Medical Branch at Galveston (IRB# 07-371). Seven healthy volunteers underwent 3 different randomized fluid resuscitation regimens for experimentally induced hemorrhage of 10ml/kg bodyweight separated by at least 4 weeks. The resuscitation regimens were (supplemental Figure 1):

- BR; bolus resuscitation: A fixed 30 mL/kg fluid bolus was administered over 20 min based on previous ATLS 3:1 resuscitation guidelines(9).
- DA; Semi-automated care: Resuscitation was based on NIBP measurements obtained through a Wireless Vital Signs (WVSM, AthenaGTX, Johnson IA) monitor, routed to a computerized algorithm decision interface, which prompted the user to confirm or override the calculated infusion rate facilitated through a Zoll powerinfuser (Zoll Medical Chelmsford MA).
- CL; Autonomous care: Fluid therapy was based on intra-arterial blood pressure measurements obtained through an Impact Lightweight Trauma Monitor (LTM, Impact – Zoll Medical Chelmsford MA) processed through a computerized algorithm interface and the calculated autonomous infusion facilitated through a Zoll Powerinfuser.

The computerized algorithm for DA used a decision table linking deficit in blood pressure to infusion rate; while the CL algorithm used a non-linear equation linking blood pressure to infusion rate. Both algorithms automatically administered or recommended aggressive fluid resuscitation volumes when blood pressure was furthest from target, whereas, when target–pressures were approached, fluid volumes were reduced towards zero to facilitate a “soft landing approach”. The algorithm was developed for tight blood pressure control for head injury – thus a target MAP of 70 mmHg was used; we appreciate that lower MAP endpoints could also be chosen for more hypotensive resuscitation (MAP=50 mmHg).

Figure 1 illustrates the experiment. On the day of the experiment, subject weight was recorded. A peripheral IV, arterial line and hemodynamic monitors were placed. Subjects were induced and maintained under general anesthesia (GA, (T-30 = Tminus30)), while spontaneously breathing via a laryngeal mask airway (LMA, size 4 female and size 5 male). After thirty minutes of GA, 10 mL/kg of blood were removed over 20 minutes (T0–T20). After onset of hemorrhage, the respective fluid infusion was initiated. The effects of fluid resuscitation on volume spaces, hemodynamic parameters, urinary output and cardiac function were followed for 120 minutes (T120). At T120, the blood collected during the hemorrhage from the subject was re-infused over 10–20 min. Body weight was recorded and the subject discharged when safety criteria were met.

General Anesthesia

Propofol (2–3 mg/kg) was used to induce general anesthesia. During induction, a patent airway was confirmed and the LMA was inserted into the oral pharynx. General anesthesia was maintained with a continuous infusion of propofol (75–150 µg/kg/min). A bispectral index (BIS) monitor (Covidien, Minneapolis MN) was used to titrate anesthesia depth to a BIS index of 50 throughout the study (21). BIS and propofol infusion rate were recorded every 15 minutes.

Calculation of dilution of fluid spaces and volume changes

Total fluid infused was recorded. Plasma volume (PV) was determined using an indocyanine green (ICG, Akorn Inc., Buffalo Grove, IL, USA) dilution and mass balance approach as previously described (22–24). Hct was corrected for the F-cell ratio (0.91); blood volume (BV) and red cell volume (RBCV) were derived as:

$$BV = PV / (1 - Hct) \quad \text{and} \quad RBCV = BV - PV$$

BV and PV at any given time t (BVt and PVt) were calculated by indicator dilution accordingly.

Change in extravascular volume (EVV) was calculated by subtracting changes in plasma volume and cumulative urinary output from volume infused at each time point:

$$\Delta EVV = \Delta PV - \text{cumulative fluid infused} - \text{urinary output}.$$

Urinary output

As previously published, urinary output throughout the study was measured by bladder ultrasound (Bladderscan, Diagnostic Ultrasound Corporation, Bothell, WA) (24).

Blood sampling

Baseline hemoglobin (Hb) and hematocrit (Hct) samples were taken during the stabilization period (T-60 to T-30) prior to GA and hemorrhage. Arterial blood samples were measured in duplicate for Hb and Hct at T0, T5, T10, T15, T20, T30, T60, T90 and T120. Samples for plasma protein concentrations (total protein and albumin) to calculate colloid osmotic

pressure (24) were taken at similar time points. The total blood for plasma volume determination and for blood samples was 55 mL.

Echocardiography

End-diastolic (EDV) and end-systolic volume (ESV) measurements were obtained from a 3.5 MHz transducer and ultrasound system (Vivid 7 PRO BT04, GE Medical Systems, Milwaukee, WI) in two-chamber, apical parasternal long-axis view at T-30, T0, T20, T60 and T120. The modified Simpson's rule was applied for calculating EDV, ESV, stroke volume (SV) and ejection fraction (EF%).

Hemodynamic Monitoring

Specific hemodynamic measurements included mean arterial pressure (MAP, measured by arterial catheter), cardiac output (CO, measured by echocardiography), heart rate (measured by ECG) and systemic vascular resistance (calculated from $MAP/CO \times 80$).

All data are presented as Mean $\pm$ SD unless noted otherwise. Statistical analyses were performed using GraphPad Prism version 7.00 for Windows (GraphPad Software, La Jolla CA). Paired repeated parametric measurements were analyzed with 2-way ANOVA and Tukey's correction for multiple comparisons. Statistical significance was accepted at $p < 0.05$.

Results

DA and CL infusion reached and maintained target MAP of 70 ± 5 mm Hg after a median 15 and 10 minutes respectively, BR after 60 minutes, without significant differences between the groups through log rank comparison. Area under the curve (AUC) analysis of MAP showed significantly lower AUC for BR versus CL (AUC BR: 2173 ± 144 AUC CL: 3034 ± 198 , $p < 0.01$, supplemental Figure 4), representing less time at target blood pressure. During administration of BR bolus fluid, MAP paradoxically decreased significantly from 66 ± 2 mmHg (T-15/0; post anesthesia/pre-hemorrhage) to 56 ± 2 mmHg (T15/20; post hemorrhage/complete bolus administration; $p < 0.001$, Figure 4). MAP did not decrease following initiation of CL or DA resuscitation. At 20 minutes after hemorrhage and resuscitation, MAP was significantly lower in the BR group versus CL fluid group (BR: 57 ± 2 mmHg CL: 69 ± 4 mmHg, $p = 0.036$, Figure 4). The total amount of infused fluid (Figure 2), plasma volume (supplemental Figure 2) and extravascular volume expansion (Figure 3) and urinary output (supplemental Figure 3) remained steady throughout DA and CL infusion and were significantly increased in the BR group. Hemoglobin concentration was unchanged during DA and CL infusion, but transiently decreased following BR fluid administration, before returning towards normal values at T 30 (supplemental Figure 5). Colloid-osmotic pressure remained unchanged under DA and CL infusion and was significantly and persistently reduced following hemorrhage and resuscitation in the BR group (Figure 5). Systemic vascular resistance and heart rate decreased following the induction of anesthesia and hemorrhage, but showed no significant differences between the groups. Echocardiographic evaluation showed a significant increase in EDV at 20 minutes (end of hemorrhage and BR resuscitation) in the BR group compared to DA and CL (BR: 143 ± 4 ml DA: 107 ± 4 ml CL: 120 ± 5 ml, $p_{BR:DA} < 0.0001$, $p_{BR:CL} = 0.0018$, supplemental Figure 6),

before returning to baseline at 60 minutes. ESV and CO did not differ significantly between the groups. Supplemental Table 1 shows detailed echocardiographic function results.

Discussion

Herein we demonstrate for the first time the efficacy and efficiency of semiautonomous (decision-assist) and autonomous (closed-loop) NIBP-controlled resuscitation in a setting of human hemorrhage under general anesthesia.

Effectiveness of resuscitation is expressed by successful maintenance of vital organ perfusion in order to preserve their function. Whether a certain MAP can be restored and maintained following hemorrhage could serve as a surrogate parameter for the success of resuscitation efforts. Our systems of DA and CL infusion achieved normotensive MAP after median 10 and 15 minutes, respectively, and maintained it thereafter. DA and CL systems maintained a normal plasma volume, extravascular volume, urinary output, hemoglobin concentration and colloid-osmotic pressure, suggesting that feedback using MAP as an end-point, adequately replaces the physiologic volume deficit over the course of resuscitation.

Various clinical situations similar to our experimental approach could initially or definitively benefit from this form of end-point directed fluid replacement: elective or emergency surgical procedures under general anesthesia, in which estimated blood loss has been shown to be both poorly reproducible and underestimated (21,22); sustained head injury, in which avoidance of hypotension is one of the most powerful predictors of outcome (23,24); subclinical gastrointestinal bleeding in sedated ICU patients who require tight continuous blood pressure control and resuscitation (25); conservatively treated blunt abdominal trauma (26), or the stationary phase following initial burn shock resuscitation (27). We assert that volume-intensive settings such as acute septic and burn shock resuscitation, penetrating trauma with substantial blood loss, uncontrolled hemorrhage of any kind or other similar events are explicitly not a target for the specific approach we used. Nonetheless, we believe that the efficiency and simplicity of (semi-) automated end-point resuscitation can be advantageous under certain circumstances. Conservation of limited resources is of importance in field care, transportation of critically ill patients, or in an event of mass casualty. Furthermore, autonomous resuscitation systems with built in algorithms provide the ability to export expertise. This could be advantageous in treating large numbers of patients by fewer and less experienced personnel, as required characteristically following natural disasters, terrorist attacks or military emergencies (28–30).

Our experimental model confirms a major shortcoming of formula-based resuscitation, in which adherence to the recommended ratio of lost-to-infused volume inevitably entails over-resuscitation of smaller deficits. We demonstrate that, under formula-based 3:1-resuscitation, total volume administered, plasma volume, extravascular volume and urinary output are significantly increased while parameters indicating hemodilution, such as hemoglobin concentration and colloid-osmotic pressure are reduced throughout the experiment. Temporary cardiac strain, although clinically irrelevant in a population of healthy volunteers, was evident through increased EDV following bolus infusion. Interestingly, the small

increase in cardiac output for the BR group was offset by a drop in hemoglobin, which would leave effective oxygen delivery unchanged.

The proven detrimental sequelae of fluid overload such as generalized and pulmonary edema (31,32), exacerbation of congestive heart failure (33), organ perfusion deficits (34), as well as dilution of clotting factors, electrolytes and administered medication (35) lead to increased morbidity and mortality in critically ill patients (36). Therefore, the critical care community has grown increasingly sensitive to the advantages of less aggressive resuscitation approaches as proposed for instance by the Surviving Sepsis Campaign and many others (36–38). In light of these developments, another critical and little described finding of this experiment is the further decrease in blood pressure of 10–15 mmHg that persisted for 20 minutes after and despite administration of a large fluid bolus. We hypothesize this effect could be mediated by capillary shear stress and nitric oxide release (39), a reduction in blood viscosity (40), or the release of atrial natriuretic peptide (ANP) following the volume-induced stretching of the atrial wall (41). In a clinical scenario, in which ongoing resuscitation measures are based on blood pressure improvement, this paradoxical effect could induce a feedback loop in which “fluid begets more fluid” and the consequences of over-infusion exacerbate.

There are limitations to this experiment. We acknowledge that few clinicians would actually resuscitate the hemorrhage volume proposed in this experiment with the recommended 3:1 infusion ratio; at the same time, we stress that ATLS continues to assert this rule regardless of hemorrhage extent (9). Further, we wanted to test our algorithms that were designed to treat patients with traumatic brain injury, and thus more aggressive as episodic hypotension worsens outcomes (23,24). Therefore, formula based resuscitation was chosen as a control group for this experiment not primarily to emphasize superiority of (semi)autonomous approaches, but to provide perspective towards its physiological implications.

The use of general anesthesia itself accounted for a blood pressure decrease of 20% in all groups before hemorrhage. Blood pressure in conscious subjects does not decrease significantly enough following similar hemorrhage due to preserved compensatory sympathetic responses (42). Furthermore, anesthesia attenuates the hemodynamic response to blood loss by increasing the unstressed venous volume, thereby reducing venous return (43). The combination of both effects made anesthesia a unique and realistic model to study the physiology of human hemorrhage under these exact conditions. While we did not elect to study a non-resuscitation group in the present study, we previously showed that mild hemorrhage (7 mL/kg) under general anesthesia in a similar model results in the inability to restore blood pressure to pre-hemorrhage levels by 120 min (44). Thus, we show that small amounts of fluid are needed to achieve target MAP following hemorrhage. We cannot, from current data, conclude that the observed further drop in MAP following fluid bolus administration is unrelated to anesthesia-induced dysregulation of endogenous MAP feedback control. We are thus bound to describe the effect which warrants further research.

NIBP is often deemed a non-optimal target for resuscitation and surrogate parameter for fluid load (45). There is, however, ample evidence suggesting that non-invasively measured MAP is a better indicator of invasive blood pressure than non-invasive systolic blood

pressure alone (45–47). While to solve this partial discrepancy is beyond the scope of this study, it has been shown recently that the difference of NIBP and invasive arterial blood pressure is clinically negligible in both adults and children with few exceptions (48,49); NIBP continues to be widely used by ICU physicians (50), and NIBP is proportional to intravascular volume during hemorrhage (12). It is furthermore readily and feasibly available to professionals of all levels of experience and causes few complications (51). While blood pressure is a robust and reliable parameter for most cases, there is an age-dependence regarding its readings and circumstances such as severe occlusive arterial disease, missing extremities, or mismatches between cuff and patient size may lead to erroneous readings and infusion, warranting additional caution (52).

The concept of subjecting humans to experimental hemorrhage may seem cavalier, but is well documented in the literature (53,54). The induced hemorrhage was large enough to produce a realistic clinical scenario of mild-to-moderate hemorrhage (up to 1 Liter under anesthesia), yet small enough to ensure subject safety. Non-resuscitative methods of studying volume shifts during hypovolemia in humans involve implementing lower body negative pressure (55), which does not require the physical removal of blood from subjects to simulate hypovolemia. We assert that our model offers more realistic experimental conditions as true fluid shifts occur since red blood cell mass is removed and actual resuscitation with realistic quantities of fluid is performed. Models of extensive hemorrhage in humans remain ethically questionable and difficult to design.

In conclusion, we believe that the gradual replacement of indiscriminate formula-based resuscitation with end-point directed semiautonomous or autonomous infusion systems may be one means of providing standardized and individualized fluid therapy at the same time to patients undergoing hemorrhage.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Study design. Subjects are treated for induced hemorrhage with 3:1 resuscitation formula (BR), decision-assist infusion (DA) and autonomous closed-loop (CL) infusion at separate time points (min. 4 weeks apart). Endpoint measurements are taken at various time points before and after hemorrhage. A-Line: arterial line. PIV: peripheral intravenous line. ICG: Indocyanine Green. GA: general anesthesia. Hb: Hemoglobin. Hct: Hematocrit.

Figure 2. Fluid requirements after hemorrhage. Comparable, stable volumes between DA and CL; increased total volume of fluid administered with BR ($p<0.0001$).

Figure 3.

Fluid balance: Stable extravascular volume after resuscitation with DA and CL, increased under BR without return to baseline ($p < 0.0001$). Mean difference in body weight (ΔBW) between T0 and T120 increased under BR, no significant changes under DA or CL.

Figure 4.
MAP during resuscitation: Significant drop of MAP at T20 under BR compared to baseline (T0) and to DA or CL ($p<0.05$).

Figure 5.
Dilution effects of bolus resuscitation. Decreased colloid osmotic pressure after BR vs. DA or CL without return to baseline ($p < 0.05$). No differences between DA and CL.