Closed-Loop Control of Fluid Therapy for Treatment of Hypovolemia

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Closed-loop algorithms and resuscitation systems are being developed to control IV infusion rate during early resuscitation of hypovolemia. Although several different physiologic variables have been suggested as an endpoint to guide fluid therapy, blood pressure remains the most used variable for the initial assessment of hemorrhagic shock and the treatment response to volume loading. Closed-loop algorithms use a controller function to alter infusion rate inversely to blood pressure. Studies in hemorrhaged conscious sheep suggest that: (1) a small reduction in target blood pressure can result in a significant reduction in volume requirement; (2) nonlinear algorithms may reduce the risk of increased internal bleeding during resuscitation; (3) algorithm control functions based on proportional-integral, fuzzy logic, or nonlinear decision tables were found to restore and maintain blood pressure equally well. Proportional-integral and fuzzy logic algorithms reduced mean fluid volume requirements compared with the nonlinear decision table; and (4) several algorithms have been constructed to the specific mechanism of injury and the volume expansion properties of different fluids. Closed-loop systems are undergoing translation from animal to patient studies. Future smart resuscitation systems will benefit from new noninvasive technologies for monitoring blood pressure and the development of computer controlled high flow intravenous pumps.

Key Words: **Fluid resuscitation, Circulatory shock, Combat casualty care, Autonomous healthcare, Trauma.**

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INTRODUCTION

Hypovolemia due to hemorrhage, burns, trauma, and dehydration either alone or in combination requires fluid therapy to restore vascular volume and normalize venous return, cardiac output (CO) and blood pressure (BP). Although normalization of these endpoints can be reassuring that hypovolemia is not present, excessive edema remains a common complication of fluid therapy, which can increase morbidity and mortality. The challenge is to avoid the administration of too little or too much volume, and appropriately titrate fluid delivery to each individual patient's mechanism of injury, severity, physiologic reserves, and compensatory responses. Combat casualties present additional resuscitation challenges due to the logistical limitations of battlefield supplies, personnel, and medical expertise.

One approach to optimizing fluid therapy is to employ Resuscitation Systems that link sensors of physiologic variables and intravenous (IV) infusion pumps with microprocessors programmed with treatment algorithms. The Department of Defense has been supporting the development of closed-loop systems for treatment of combat casualties under situation in which advanced medical expertise is unavailable or delayed.

Closed-Loop resuscitation systems have been developed and tested in different animal models of hemorrhage and burns (Table 1). Experimental uncontrolled hemorrhagic shock has been treated using closed-loop control of fluid therapy with different endpoints (BP, CO and tissue O_2).[1,2] Studies have evaluated the relative effectiveness of closed-loop resuscitation using normotensive versus hypotensive endpoints and different types of Food and Drug Administration (FDA)-approved fluids.[3,4] Closed-loop resuscitation of experimental burn injury using urinary output has also been evaluated.[5] This manuscript reviews the experimental record of closed-loop resuscitation, and the practical challenges of developing closed-loop fluid therapy technologies for prehospital care with an emphasis on combat casualty care. The record of closed loop resuscitation of burn injury is covered in a separate review in this supplement edition of *The Journal of Trauma.*[6]

Rationale

There is a strong rationale for use of a closed-loop system to guide fluid therapy from transport to the first echelon of multidisciplinary caregivers. Both civilian para-

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Table 1 Closed-Loop Resuscitation of Hemorrhage and Burns

Study Groups	n =	Animal Model	Authors
Fuzzy Logic and PID	18	Conscious sheep subjected to multiple hemorrhage	Ying, 2002
Arterial pressure, cardiac output and skeletal muscle S_TO_2 hourly manual as target endpoints	20	Conscious sheep uncontrolled hemorrhage	Chaisson, 2003; Chaisson, 2004
LR vs. Hextend with Hypotensive vs. Normotensive endpoints	19	Conscious sheep uncontrolled hemorrhage	Rafie, 2004
LR vs. 3% NaCl with Hypotensive vs. Normotensive endpoints	13	Conscious sheep uncontrolled hemorrhage	Vaid, 2006
Use of Urinary Output as endpoint	11	Sheep 40% TBSA burn	Hoskins, 2006

medics and military medics and corpsmen vary in knowledge and clinical experience. Furthermore, the medic has several tasks to focus on in caring for the injured patient or soldier. Fluid therapy is considered only after injury assessment, establishment of airway, and providing emergency hemostasis. Obtaining IV access and being ready to resuscitate with fluids has a high priority only after the above tasks have been completed. Unfortunately, once resuscitation is started, precise adjustment of infusion rate based on a patient's response can and often is interrupted by ongoing overall re-assessments, delivery of medications, airway maintenance, and other medical and nonmedical tasks.

During ambulance or life-flight evacuations there are multiple distractions and physical barriers to patient access that complicate initial care. If a decision assist or closed-loop system could lessen the burden of physical and mental chores for the medics, greater focus on other key tasks could be employed. Additionally, titrating fluid therapy to a defined endpoint or target level may reduce total fluid needs providing both logistic benefits and reduced incidences of hypovolemia and hypervolemia. Over resuscitation at all echelons of care has become recognized as a significant contribution to morbidity and extended intensive care unit (ICU) care.[7–9]

Overview of Endpoint Variable

The first challenge for developing closed-loop systems is the choice of the variable(s) to be controlled. Endpoint resuscitation occurs when fluid therapy is titrated proportional to the measured values of a specific physiologic variable or endpoint.[10] The use of endpoint resuscitation has largely been restricted to the intensive care unit and operating room environments where continuous monitoring and an experienced staff allow careful titration of therapy to a target variable level or range.[11–13] With the development of new portable monitoring technologies and computer-controlled infusion pumps, automated "closed-loop" titrated endpoint resuscitation is technically feasible for prehospital and emergency room use.

There are several physiologic variables that provide indices of hypovolemia fluid need and can be used as a resuscitation endpoint. These range in complexity from standard noninvasive vital signs (eg, BP, heart rate, saturation of arterial hemoglobin, and respiratory rate) to variables derived from primary vital signs (eg, pulse wave transit time, heart rate variability, and the shock index) (Table 2). Invasive bladder catheterization and blood sampling add the use of urinary output, lactate, central venous oxygen saturation, hematocrit, and blood gases. These variables are available for emergency department care (Table 3). Additional endpoint variables can be made available, but are less used and require specialized sensor technology (eg, tissue O_2 and CO_2 measured with near infrared spectroscopy [NIRS] for skeletal muscle or brain, and electrodes for transcutaneous O_2 and CO_2). In the operating room and ICU, a number of advanced

Table 2 Basic Vital Signs For Field and Initial Transport—All are Noninvasive Used in Field or Transport

Variable	Pro	Con
Mentation, Glasgow Coma Score, GCS)	SOC, requires no instrumentation	Low mentation score can occur without hemorrhage
Systolic and Mean Arterial Blood Pressure (SBP, MAP)	SOC, can be estimated by palpitation, low SBP predicts need for LSI	Late indicator of hypovolemia
Heart Rate (HR)	SOC, Easily measured	Not always indicative of hypovolemia
Arterial Pulse Oxygenation (SpO_2)	SOC, Easily measured	Measures lung function not cardiovascular function
ECG	SOC, Easily measured	Indicates cardiac dysfunction value limited for fluid therapy
End tidal CO_2 ($ETCO_2$)	Generally requires intubation	Value limited to severe shock
Pulse wave transit time (PWTT)	Continuous BP calculated	Accuracy in trauma is not proven
Shock Index (SI) = HR/SPB	SOC, Easily calculated	VND
Heart Rate Variability (HRV)	Based on non-invasive ECG	Not ordinarily available, VND

SOC = standard of care; VND = value not defined.

Table 3 Variables Available At First Echelon of Team Care-Emergency Room/Battalion Aid Station

Variable	Pro	Con
Lactate or base deficit	Baseline values well defined, predicts need for LSI	Requires blood sampling, spot measurement
Hematocrit (Hct)	Defines blood loss in previously healthy trauma patients	Requires blood sampling, spot measurement
Urinary output (UO)	Primary variable for guiding burn resuscitation	Time delay, renal failure, and drugs complicate interpretation
Central venous oxygenation $S_{cv}O_2$	Global perfusion index sensitive to change in cardiac output, use impacts outcome in RCT	Pre-injury baseline values vary, $$
Muscle Oxygenation	Perfusion index, end organ monitor	Pre-injury baseline values vary, $$
Cutaneous O_2/CO_2	Perfusion index easily measured, end organ monitor	Specificity for fluid therapy not defined, $$
Central venous pressure (CVP)	Sensitive to volume change	Pre-injury baseline values vary
Arterial pressure by transducer	Real-time continuous	Compensatory mechanisms of hypovolemia delay changes

$$ = expensive technology and not widely used; LSI = livesaving intervention.

hemodynamic monitors offer methods for measuring CO, mixed venous oxygen saturation, and oxygen delivery, along with such variables as stroke volume variability, extravascular lung water, intrathoracic blood volume, and corrected flow time (Table 4). The validation of such variables to predict the need for lifesaving interventions and for use as target endpoints to guide fluid therapy is ongoing in both experimental animals and patients.

Of the above invasively measured variables, only a few have been proven of value in randomized controlled clinical trials. These include $S_{CV}O_2$, oxygen delivery, and corrected flow time.[12,14,15] We are unaware that the use of BP to guide fluid therapy has been proven to impact clinical outcome, but hypotension in hemorrhaged trauma patients is an established indication for fluid therapy per standard of care as found in the Advanced Trauma Life Support (ATLS) guidelines. All the variables in Tables 2, 3, and 4 are used more or less to guide clinical decision making. The values of such variable alone or together are receiving increased attention as part of multiple evidenced-based clinical practice protocols.[13] The value of such decision support paradigms is not the current standard of care, but is gaining increased acceptance in the ICU environment. Microprocessor power will continue to increase as will our understanding of the fundamental relationship between measured variables and pathologic processes, and how current and innovative therapies affect both. It is inevitable that effective decision support and closed-loop systems will be developed for many aspects of clinical care and be increasingly used.

There are several possible endpoint variables that could be used for initial acute resuscitation. All have practical advantages, and limitations. Although future smart closed-loop systems may integrate multiple variables for all echelons of trauma care, to date, most work has focused only on the use of a single variable at a time to guide fluid therapy. This review will discuss three variables in some detail that we have evaluated experimentally using our closed-loop systems.

Cardiac Output as Endpoint

From one perspective, CO is the ideal or "gold standard" of cardiovascular function as it is a precise measure of a total body perfusion. Unfortunately, CO does not lend itself to prehospital monitoring with present day equipment and is rarely available even in the emergency department or trauma operation room environment. A noninvasive CO monitor based on impedance plethysmography is available, but rarely used before surgery, nor to our knowledge has been clinically tested in the prehospital or emergency department. Cardiac

Table 4 Variables Available in Operating Rooms and Intensive Care Units Using Advanced Monitoring

Variable	Pro	Con
Cardiac-output (CO)	Excellent for trending, sensitive to preload and blood loss	Pre-injury baseline values vary, $$
Oxygen delivery (DO_2)	Sensitive to CO, lung function and anemia	Requires several independent measurements
Stroke volume variation (SVV)	Real time sensitive to preload	Requires mechanical ventilation, sensitivity and specificity not defined, $$
Plasma or blood volume (PV, BV)	Should provide definitive volume	Clinical interpretation is not defined. Not easily measured, $$
Corrected flow time (Ftc)	Use impacts outcomes in RCTs, minimally invasive	Not widely used nor appreciated, $$
Intrathoracic blood volume (ITBV)	Measure of blood volume surrogates	Not widely used nor appreciated, $$
Global end diastolic volume (GEDV)		

$$ = expensive technology and not widely used; RCT = randomized clinical trial.

output can potentially be measured noninvasively in the field via Doppler ultrasound, specialized radar or radio frequency. Approaches such as these are currently under advanced development.

However, even if CO is measured, it is limited as an endpoint variable for early resuscitation because, in a clinical setting, baseline preinjury levels of CO of a specific trauma patient are unavailable. Further, baseline CO may be an unreliable estimate of the needed CO after injury, since baseline hematocrit, and arterial O_2 content are reduced by asanguineous resuscitation. Conceivably, a soldier's values for baseline CO and tissue O_2 could be encoded in a "smart" digital dog tag or implanted in a radio frequency identification chip along with other medical history. Ready availability of such data would provide help to diagnose and guide therapy for a variety of medical conditions. Such electronic medical record technology could provide a means for the effective use of CO as an endpoint for initial trauma care.

Blood Pressure

BP is a logical endpoint candidate for closed-loop care, and represents the standard of care in almost all trauma centers. Most closed-loop resuscitation studies have used BP as an endpoint. BP for trauma patients can be measured noninvasively with automated pressure cuffs, but the cuffs can fail at systolic blood pressures below 60 mm Hg because of loss of peripheral blood flow and pulses. However, if BP is undetectable, infusion of fluids is likely to be needed to augment blood volume, restored venous return, CO, and blood pressure. The development of a reliable beat-to-beat noninvasive BP monitor is needed to optimize the use of BP as an endpoint. An assessment of mentation and peripheral perfusion (extremity temperature and transcapillary refill), and evidence of hemorrhage should all be considered as additional indicators for initiation of closed-loop fluid therapy with blood pressures as endpoint variable. Hundreds of experimental animal studies involving resuscitation of hemorrhage have used BP as both a measure of shock as well as a primary endpoint to resuscitation.

Skeletal Muscle Oxygenation

Saturation of muscle hemoglobin ($SkMusSO_2$) is a measure of tissue perfusion and a logical index of the effectiveness of cardiovascular function. Skeletal muscle O_2 can be measured noninvasively with NIRS. Skeletal muscle blood flow is sensitive to increased sympathetic tone and could be a sensitive indicator of compensatory responses to hypovolemia,[16] and would be proportional to $SkMusSO_2$. A practical question is, is $SkMusSO_2$ response proportional to vascular volume over the full range of severe shock through resuscitation and stabilization? As with CO, baseline muscle O_2 between individuals is extremely variable, such that one patient's normal value may be another patient's value with moderate hemorrhage. Current NIRS tissue O_2 technologies are expensive, not easily adapted for prehospital use, require 110-volt power and weigh several pounds. However tissue oximeters could be used in ambulances. For this technology to have military field application it would have to be battery-powered and greatly reduced in size and weight. Transcutaneous O_2 and CO_2 as endpoints have been used in some clinical studies.[17] Skin is the most sensitive organ to sympathetic vasoconstriction, and level of sympathetic activity is proportional to level of hypovolemia and inversely proportional to oxygen delivery to the skin. Transcutaneous O_2 and CO_2 technologies, although not portable, are less complex than NIRS oximeters and may lend themselves to miniaturization.

Animal Studies of Different Endpoint Variables for Closed-Loop Control

Only a limited number of closed loop control studies comparing different endpoint variables have been performed. Chaisson et al.[1,2] resuscitated sheep subjected to severe uncontrolled hemorrhage using computer-controlled, closed-loop control of fluid therapy in three groups of animals with infusion rate adjusted to different endpoints: mean arterial pressure (MAP), CO and noninvasively measured skeletal muscle O_2 saturation ($SkMusSO_2$), respectively. A nonlinear decision table algorithm was used to control infusion rate according to the endpoints. Animals were prepared a week before a study with chronic vascular catheters for pressure monitoring, fluid infusions, blood sampling and hemorrhaging. A transit time Doppler flow probe was placed around the pulmonary artery to allow measurement of CO. A Teflon-coated wire was sutured through a 3–4 mm length of the infrarenal ventral aortic wall and exteriorized for later induction of immediate aortotomy in conscious sheep. The day of the study a NIRS fiber optic oxygen sensor patch (INVOS 4100, Somanetics Corp., Troy, MI) was glued on the flank over the external oblique muscle to measure $SkMusSO_2$.

Aortotomy caused a very rapid hemorrhage, ~50% blood volume in 2–3 minutes, with MAP and CO decreasing to 25–35 mm Hg and 10–20% of baseline, respectively, within two minutes. During a twenty-minute period of no treatment, MAP and CO increased modestly but still remained severely subnormal. Resuscitation was started 20 minutes after the aortotomy. Target levels of MAP = 90 mm Hg, baseline CO, and $SkMusSO_2$ = 50%. Note that animals had baseline levels of MAP = 95–100 mm Hg and $SkMusSO_2$ = 60–65%, so only the CO group had an endpoint target equal to prehemorrhage values.

Chaisson et al. used a nonlinear decision algorithms designed to promptly and severely lower infusion rates when the endpoint variable was approaching the target level. With such a control paradigm the term target can be a misnomer as targets are asymptotically reached and the endpoint values may hover somewhat below target depending on the algorithm. Another way of characterizing such a nonlinear algorithm is that it provides a 'soft landing' on the target. The rationale is to prevent rapid increases in BP and hemodynam-

ics once the animal is out of a critical range of cardiovascular dysfunction. Aortotomy models of uncontrolled hemorrhage demonstrate rebleeding with rapid increases in blood pressure.[18,19] However, there was minimal rebleeding during resuscitation using the closed-loop as measured with flow probes placed on the aorta directly above and below the aortotomy nonlinear algorithm.

All animals resuscitated by closed-loop control received substantially less crystalloid fluid than prescribed by ATLS guidelines (3× shed blood volume). Both the MAP and $SkMusSO_2$ endpoint groups required about half the volume compared with the CO group. The $SkMusSO_2$ endpoint group had a level of 50%, well below baseline levels of 57–66%. Total volume requirements were 63 ± 9 mL/kg in the CO group and 35 ± 8 mL/kg in the $SkMusSO_2$ group. In this case, the target of subnormal $SkMusSO_2$ insured limited resuscitation, and reduced fluid volume. The MAP endpoint group had a target of 90 mm Hg, which was only slightly below baseline levels of 95–100 mm Hg, yet also produced low volume requirements, 30 ± 7 mL/kg. Taken together, these data suggest that a target blood pressure slightly below baseline may save substantial volume compare to ATLS guidelines, ~90 mL/kg for 30 mL/kg blood loss, or resuscitation to normal blood pressure. These data suggest that nonlinear control algorithms may limit re-bleed. A nonlinear algorithm using a 90-mmHg target was chosen for future experimentation.

Algorithms

Closed-loop algorithms can be constructed from a variety of controller paradigms such as nonlinear decision tables, proportional integral derivative (PID), and fuzzy logic. Their design must be based on sound physiologic principles and clinical expertise such as provided by the guidelines of ATLS, Pre-Hospital Life Support, Advanced Burn Life Support, or Tactical Combat Casualty Care (TCCC). Algorithms must be specific and appropriate for the mechanism of injury. Target levels of BP vary per TCCC guidelines for head injury, uncontrolled penetrating hemorrhage and controlled hemorrhage.[20]

Different Target Levels of Blood Pressure

Clinical targets of BP vary depending on the mechanism of injury. For example, even a single period of hypotension deleteriously impacts outcome in brain injured patient.[21] For such patients, fluid therapy must be administered as aggressively as needed to restore and maintain near normal MAP to insure adequate cerebral perfusion as traumatic injured brains exhibit deficient auto-regulation of blood flow. Alternatively, if there is no direct head injury but penetrating truncal injury is present then infusion rates should be less aggressive with a lower hypotensive target blood pressure to prevent exacerbation of bleeding before surgical hemostasis.

Hypotensive Resuscitation

A key strategy of fluid therapy of penetrating injury, particularly for military trauma, is use of hypotensive resuscitation, in which the goal or resuscitation endpoint is a subnormal blood pressure. The original rationale for using hypotensive resuscitation was to reduce the risk and occurrences of excessive bleeding that can occur with rapid increases of blood pressure and clot disruption. There is not a consensus on how low a target BP should be for effective hypotensive resuscitation. Resuscitation studies in anesthetized animal models of uncontrolled hemorrhage (aortotomy or tail ligation) suggest that target mean arterial pressures of 40 to 60 mm Hg are ideal.[22,23] Other studies using conscious animals suggest that target pressures should be above 65 mm Hg perhaps because anesthetized animals benefit from reduced metabolic needs.[3,24] Although, the perfect target pressure remains to be determined, there is a significant rationale for the use of some form of limited resuscitation. Some military units practice hypotensive resuscitation using pulse strength and level of consciousness as an approximate measure of blood pressure, and adequacy of vital organ perfusion (eg, brain).

Experimental animal studies of hypotensive resuscitation and different fluids have been reported in a variety of endpoint guided, and closed-loop strategies using different target blood pressures, and different FDA-approved fluids.[3,4,25] Employing a hypotensive resuscitation strategy to treat combat casualty care offers the practical benefit of greatly reducing volume needs. The impact of such a strategy may or may not be beneficial to outcomes. Many animal models of uncontrolled hemorrhage show reduced mortality with hypotensive resuscitation strategies, but other more recent animal models suggest that mortality can be increased when certain hypotensive strategies are employed. Notably, Sondeen et al. showed a 100% 24-hour survival rate in conscious hemorrhaged swine when an initial large volume of LR was used per ATLS guidelines followed by rapid replacement (within 2 hours) of the shed blood, but survival rates were reduced to 33% to 50% when hypotensive strategies were used with either LR or Hextend to treat hemorrhaged swine and the shed blood returned after the 24-hour hypotensive period.[26] Further, conscious hemorrhaged animals treated with limited resuscitation have suggested that such strategies can be less efficacious than standard ATLS guidelines with respect to survival and that these methods do not adequately normalize lactate levels.[24,27] Sondeen and Dubick achieved the highest survival rates when using whole blood for endpoint resuscitation.[28,29]

The subsequent testing by our group presented below used a controlled hemorrhage model of multiple hemorrhages. Adult sheep (30–40 kg) were surgically prepared one week before a study with chronic catheters for BP monitoring, blood sampling, and hemorrhaging. Continuous cardiac output was monitored with a transit time Doppler flow probe on the pulmonary artery. The day of the experiment a period

Table 5 Required Comparative Volumesto Resuscitate a 25 ml/kg Hemorrhage Using Normal (NT) and Hypotensive Targets (HT) (Rafie et al., 2003, Vaid et al., 2006)

Solutions	Fluid Volume In (mL)	Maximum Base Deficit (mmol/L)	Mortality
LR-NT, n = 12	62.5 ± 9.2	7 ± 1	0/12
LR-HT, n = 7	18.0 ± 5.9	13 ± 2	1/7
Hextend-NT, n = 6	19.2 ± 2.2	7 ± 2	0/6
Hextend-HT, n = 7	11.6 ± 1.9	13 ± 4	1/7
3% NaCl-NT, n = 7	19.6 ± 2.2	11 ± 3	0/7
3% NaCl-HT, n = 6	13.3 ± 5.7	13 ± 2	1/6

of baseline data was recorded; and then sheep were hemorrhaged a total of 35 mL/kg over three separate bleeds. All events are referenced to the start of the first hemorrhage, t = 0 minutes. The first bleed simulated a major hemorrhage of 25 mL/kg over 15 minutes, t = t − 0 to 15 minutes. Closed-loop resuscitation was started at t = 30 minutes. The second and third bleeds were 5 mL/kg over 3–5 minutes starting at t = 50 and t = 70 minutes. These modeled secondary bleeding that can occur with resuscitation and patient transport. Resuscitation continued until t = 180 minutes.

We found significant volume sparing [particularly with lactated Ringer's solution (LR)] when a target MAP of 65 mm Hg was used[3,30–32] (Table 5), versus a normotensive target MAP of 90 mm Hg. The MAP of 65 mm Hg is reasonable target since Sondeen et al. found that rebleeding occurred above that pressure in an uncontrolled swine model of hemorrhage.[33] Despite the benefit of reduced volume requirements with a hypotensive resuscitation regimen, some deaths and higher lactate levels were found with all tested fluids, including LR, Hextend, or 3% NaCl. Hypotensive resuscitation is likely not the best means to restore the depressed metabolic and cardiovascular function in shock. On the other hand, the risks of increased bleeding during aggressive resuscitation in penetrating injury are real. How best to implement a strategy of promptly restoring perfusion, and metabolic function, while limiting risk of re-bleeding has yet to be established. The compromise between adequate perfusion and maintaining hemostasis has been approached based on the test results of animal studies of hypotensive blood pressure targets. The ideal risk/benefit ratio of hypotensive resuscitation strategy for severe trauma has not been adequately addressed and may never be due to the concerns over patient safety in trauma studies with waiver of informed consent. Based on retrospective clinical consensus and animal experimentation the guidelines of Pre-Hospital Trauma Life Support and TCCC have established flow chart algorithms for hypotensive resuscitation. An added benefit of a computer controlled resuscitation system is that the real world detailed data can be collected to define the detailed time course of relationships between volumes infused, endpoint responses, and outcomes.

Different Fluids and Different Infusion Regimens

Present day civilian as well as military treatment of hemorrhage and trauma is to administer asanguineous fluids (ie, crystalloids or colloids). In US trauma centers, large volumes of crystalloids, particularly LR, are used for resuscitation of hemorrhage. Each liter of LR only expands blood volume by 20–30% of infused volume; stated another way 3–5 L of LR equal one liter of blood. Therefore, several liters of fluid are required to restore near normal blood volume after a major hemorrhage.[34–36] Such volumes are logistically untenable for most prehospital combat casualty care scenarios. Currently, for field resuscitation, the US Army's Special Operations units use colloids such as Hextend or plasma, which can effectively reduce volume requirements by 60–80%, compared with LR. One liter of hetastarch is equivalent to one liter of plasma in expanding blood volume. Another approach is the use of FDA-approved hypertonic 3% saline, which mobilizes cellular water and can also reduce volume needs. However, there is a limit to how much hetastarch or hypertonic saline can safely be infused, as coagulopathies are known to occur with doses over 20 mL/kg[37] or result in hypertonicity, respectively. Another limitation of hypertonic saline is that its volume expansion is more transient than that of a colloid.

A key point in consideration of correcting volume deficits is the needed volume expansion per time. Both colloids and 3% hypertonic NaCl can expand blood 3× as effectively as crystalloid LR.[38] Hypertonic saline expands volume rapidly, but transiently, while colloids expand volume at a slower rate, but with more sustainment. If 1 L of Hextend were delivered in 10 minutes, it would have the physiologic impact of a 300-mL/min infusion of LR, an infusion rate that is rarely achieved in prehospital care and could be deleterious until hemorrhage is controlled. Severe hemorrhage with continuous rapid bleeding could require such aggressive infusion, but without a prompt simultaneous establishment of hemostasis, such acute and unsustainable resuscitation would likely be futile. If an identical algorithm were used for LR and Hextend that provided an identical infusion rate at a specific blood pressure, then the algorithms would be fundamentally different and produce different physiologic responses and clinical results. Such different goals would be arbitrary and are not in keeping with a rational guideline or best clinical practice goal.

For example, dangerous acute fluid overload was demonstrated when a powerful volume expander (7.5% NaCl-Hespan) was infused at the same set rates and volumes as a crystalloid bolus.[39] Since the full effects of volume expansion with colloid can take a minute or two to be exerted, the probability of overshooting an endpoint target with rapid infusion of colloid is more likely and not in keeping with limited or hypotension strategies.

Algorithm Designs and Fluid Requirements

Ying et al.[3,40] compared the performance of three algorithms and how they impacted volume requirements in the

severe multiple bleed hemorrhage model described above. The controller output was an analog signal connected to a clinical IV infusion pump (Power Infuser, Infusion Dynamics, Inc., Plymouth Meeting, PA). The Power Infuser is a small (320 g), battery-operated IV pump designed for combat casualty care that can infuse rates as high as 100 mL/min or 6 L/hr. The goal of the experiments was to restore and maintain a MAP of 90 mm Hg by controlling the infusion rate of LR. The maximum infusion rate was set at a clinically realistic 100 mL/min per 70 Kg. BP Sampling and screen display of the input signal was at 10 Hz, while data were passed to the controller algorithm at a rate programmed by the user via a screen control. Values used varied from 5 seconds to 60 seconds.

The PID controller was programmed and tuned in a series of pilot studies using the above protocol. These experiments produced the most stable performance when the algorithm was reduced to a PI controller.[40] All three algorithms were designed to dramatically reduce infusion rates once MAP exceeded 80 mm Hg and to halt it at 90 mm Hg. The parameters of the fuzzy controller were fine tuned in pilot animal experiments. The parameters were then fixed for the experiments. All protocols were designed to provide a "slow" approach to target pressure.

Figure 1 shows MAP and CO from the three treatment groups. All protocols restored and maintained MAP up to near target and maintained pressure between 80–90 mm Hg except for transient dips to 65–75 mm Hg with the second and third hemorrhage. Cardiac outputs rapidly decreased to 40–50% baseline after the first hemorrhage and then slowly recovered over the first hour without any significant dips during the first and second hemorrhages. Volumes required were less in all groups compared with the ATLS guidelines (3× shed blood volume) (Fig. 2).[41] Most striking was that different algorithms could restore and maintain a target variable with near identical performance. The efficiency or volume needs of the PI and fuzzy logic algorithms were superior compared with the decision table with respect to volume sparing, despite the identical hemodynamics.

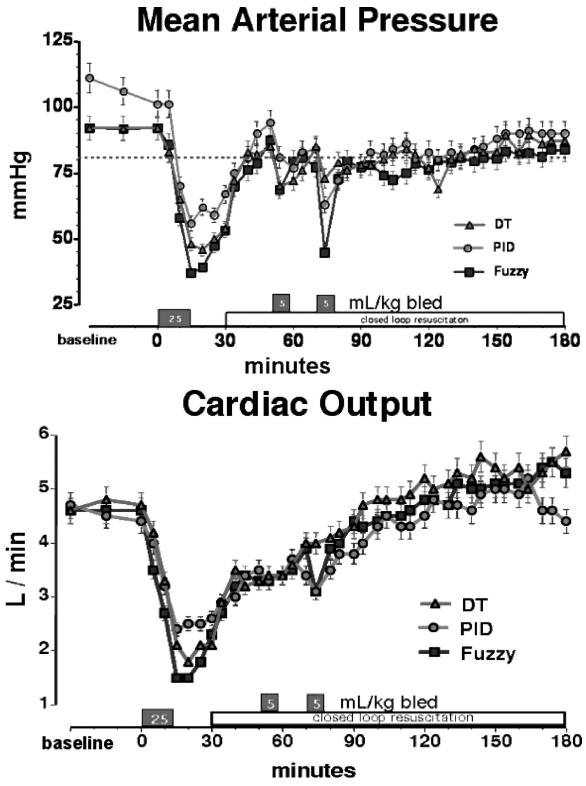

Fig. 1. *Graphs showing three groups of conscious sheep that were subjected to a 25 mL/kg hemorrhage. Closed-loop resuscitation with a target MAP of 80 mm Hg was started 30 minutes from the beginning of the hemorrhage. Two additional hemorrhages at 5 mL/kg were conducted during resuscitation. All three algorithms (nonlinear decision table, PI controller and a fuzzy logic controller) equally restored MAP and cardiac output.*

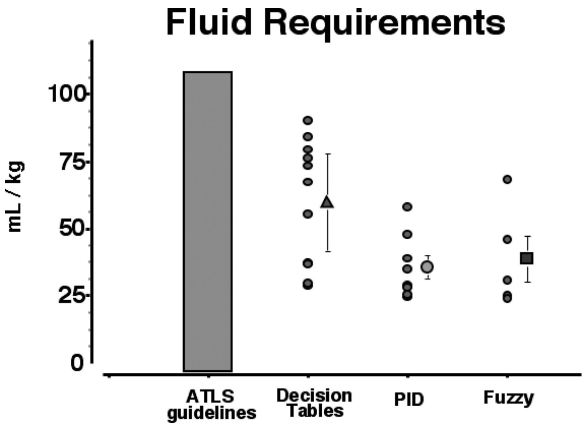

Fig. 2. *Graph showing three groups of conscious sheep as in Figure 1. PID and fuzzy logic algorithms reduced fluid volume needs compared with a nonlinear decision table and ATLS 3:1 guidelines.*

Blood Pressure Measurements and Monitors

Despite the potential for the use of a variety of surrogate endpoints to guide initial resuscitation, it will likely be a combination of clinical assessments (mentation, mechanism of injury, or suspected blood loss) and BP that are use to determine initial infusion rate with changes in blood pressure, and mentation used to guide changes in fluid therapy. BP greater than systolic of 90 mm Hg or an alert mentation indicates blood volume is adequate for vital organ perfusion. At or above target blood pressure levels fluid infusion rates can be minimal until a smart monitoring system alerts for a fall in BP or a medic input of decreased mentation or other indication of increasing blood loss.

Closed-loop resuscitation systems require reliable and accurate measurements of blood pressure. Measurement of noninvasive BP (NIBP) can be problematic in severe shock with systolic blood pressure less than 70 mm Hg since the devices can fail to acquire accurate values due to peripheral vasoconstriction. Most methods of NIBP use inflatable cuffs, which limit the frequency at which BP can be measured.

When rapid BP changes are occurring, measurements no faster than every 1 to 2 per minute can be a limitation. The use of pulse wave transit time algorithms may allow estimates of BP between BP measurements.[42] Noninvasive beat-to-beat BP technologies are commercially available and others are under development. Commercial beat-to-beat BP devices on the market are the volume clamp Portapres Technology, which although shown to be accurate is extremely expensive. Limited motion tolerance and multi-component Portapres is not amendable for prehospital care in its present configuration. Wrist tonometric NIBP technologies are accurate and produce excellent arterial waveforms, but are highly sensitive to accurate positioning, obesity, motion, and are not applicable to prehospital utility in their present form. These limitations have resulted in sparse clinical acceptance of these devices even in a stable operative environment.

Artifactual measurements or failure due to sound or motion is another factor that limits the practical utility of prehospital NIBP. A variety of motion tolerant algorithms have been developed. Acceptance of auscultations or oscillations per gating with R-wave detection of electrocardiogram is one widely used strategy. The high noise and vibration prone environment of ground and air transport is particularly problematic for military medicine where streets and highways are more often replaced with paths or dirt roads. Military aircraft have less sound deadening and are flown with fewer considerations for level and smooth flight. Innovative and more motion tolerant technologies for assessing BP are under advanced development and may become available in the next two years. Early studies monitoring patients using novel NIBP devices have suggested greater accuracy than that achieved with standard NIBP technologies.[43] Further enhanced motion tolerance systems have been described but not commercialized.[44]

IV Pumps

A closed-loop fluid resuscitation system will require use of computer controlled pumps that can provide resuscitation infusion rates of at least 100 mL/min or 6 L/h. For brief periods of time, to deliver a rapid bolus, even higher infusion rates are desirable. Currently, there are no commercially available computer controlled pumps on the market that meet these requirements. There is only one prehospital pump that can deliver these flow rates as high as 100 mL/min and that is the manually controlled Power Infuser (Zoll Medical Corp.). Ying et al.[40] used a modified version of a Power Infuser with an analog controller for closed-loop control using mean arterial BP. All current standard in-hospital IV pumps deliver maximum infusion rates of 17 mL/min or 1 L/hr, and there are only a few that can be controlled by computer. We are unaware of any published studies on the use of clinical fluid balance pump controllers other than studies that have used Gemini pumps in experimental burn injury or automated fluid balance monitoring in burn patients.[45] The FDA-approved IV pumps (Gemini PC-2 and PC-4) have been accurately and continuously employed for burn patients for up to 72-hour. However, to achieve high flow rates needed for resuscitation of large burns multiple Gemini pumps need to be used simultaneously. Rapid infusers have the advantage of blood/fluid warming and can deliver fluids at rates near 500 mL/min, but they are large and not easily adaptable to early care except with the guidance of a full multi-person trauma team with an anesthesiologist. At present only the modified Power Infuser pump appears appropriate for initial trauma care, although a variety of new small pumps have recently been introduced and are under development.

CONCLUSIONS

There are varieties of endpoints that can be used to guide fluid therapy, but from a practical viewpoint, BP is likely to be used first for clinical application of closed-loop control for treatment of prehospital trauma patients. Different control algorithms have been shown to restore BP equally well during multiple hemorrhages. Although blood pressures were similar total volume requirements varied depending on algorithm design. A key component of an algorithm will be its efficiency or how much volume is required to achieve target goals. Unique algorithms must be employed for different fluids based on hemodynamic and volume expansion properties of each fluid. Closed-loop algorithms used to treat hemorrhage and burns have reduced fluid requirements compared with ATLS and Advanced Burn Life Support guidelines, and manual resuscitation.

While it is logical that closed-loop systems can positively impact outcomes, to date, there are only animal data to support this hypothesis. Much work remains. Immediate goals are: (1) to prototype Resuscitation System using FDA-approved monitors, IV pumps, and algorithms based on accepted guidelines of trauma care utilizing standard vital signs and clinically accepted endpoints; (2) to test such systems and their components in animal models and in human trials; and (3) to evaluate systems under real world conditions. More distant goals are to incorporate new sensors and multivariable algorithms into systems and to evaluate their impact on both clinical and logistic outcome.

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