A Pilot Study Evaluating Adaptive Closed-Loop Fluid Resuscitation During States of Absolute and Relative Hypovolemia in Dogs

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Conflict of Interest: B. Gholami has stock ownership in Autonomous Healthcare Inc. He is an inventor on a provisional patent application (assigned to Autonomous Healthcare Inc.) for the presented closed-loop fluid resuscitation system. W. M. Haddad has stock ownership in Autonomous Healthcare Inc. J. M. Bailey has stock options in Autonomous Healthcare Inc. W. W. Muir serves as a consultant for Autonomous Healthcare.

Running Title: Closed-Loop Fluid Resuscitation in Dogs

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Abbreviations

C-L - closed-loop

CO - cardiac output

GDFT - goal directed fluid therapy

HR - heart rate

LRS- lactated Ringers solution

MAC - minimum alveolar concentration

MAP - mean arterial pressure

PPV - pulse pressure variation

PVI - plethysmography variability index

SPV - systolic pressure variation

SVV - stroke volume variation

Abstract:

Objective— To evaluate and determine the performance of a partially automated as well as a fully automated closed-loop fluid resuscitation system during states of absolute and relative hypovolemia.

Design— Prospective experimental trial.

Setting – Research laboratory

Animals— Five adult Beagle dogs.

Methods— Isoflurane anesthetized mechanically ventilated dogs were subjected to absolute hypovolemia (controlled: 2 trials; uncontrolled: 3 trials), relative hypovolemia (2 trials) and the combination of relative and absolute controlled hypovolemia (2 trials). Controlled and uncontrolled hypovolemia were produced by withdrawing blood from the carotid or femoral artery. Relative hypovolemia was produced by increasing the isoflurane concentration (1 trial) or by infusion of intravenous sodium nitroprusside (1 trial). Relative hypovolemia combined with controlled absolute hypovolemia was produced by increasing the isoflurane concentration (1 trial) and infusion of IV sodium nitroprusside (1 trial). Hemodynamic parameters including stroke volume variation (SVV) were continuously monitored and recorded in all dogs. A proprietary closed-loop fluid administration system based on fluid distribution and compartmental dynamical systems administered a continuous infusion of lactated Ringers solution in order to restore and maintain SVV to a predetermined target value.

Measurements and Main Results— A total of 9 experiments were performed on 5 dogs. Hemodynamic parameters deteriorated and SVV increased during controlled or uncontrolled hypovolemia, relative hypovolemia and during relative hypovolemia combined with controlled hypovolemia. Strong volume correlations was restored to baseline values during closed-loop fluid infusion.

Conclusions— Closed-loop fluid administration based on IV fluid distribution and compartmental dynamical systems can be used to provide goal directed fluid therapy during absolute or relative hypovolemia in mechanically ventilated isoflurane anesthetized dogs.

Keywords: Fluid Therapy; Shock; Hemodynamic Monitoring; Fluid Resuscitation

Introduction

Intravenous fluid therapy is usually the first line and most frequently used treatment during surgical procedures and for the treatment of traumatized animals.¹⁻³ The goal of fluid resuscitation is to restore or maintain circulatory blood volume and arterial blood pressure in order to ensure adequate tissue perfusion. One study suggested that hypotensive dogs that responded to IV fluid resuscitation were more likely to be discharged from the hospital than those that remained hypotensive.⁴ The response to fluid administration can vary significantly between patients and even within the same patient due to various disease processes or general anesthesia; this variability may result in under- or over-resuscitation.⁵⁻⁷ Over-resuscitation can produce fluid overload resulting in cardiac and pulmonary complications, emphasizing the importance of judicious, controlled, and context sensitive IV fluid administration.⁸⁻¹⁰

Multiple studies have provided ample evidence that monitoring changes in dynamic hemodynamic indices are superior to static hemodynamic values (ie, arterial or central venous pressures) for determining the response to IV fluid administration (fluid responsiveness).¹¹⁻¹⁴ Fluid therapy regimens that rely on dynamic indices are far less likely to result in fluid overload and have become the basis for providing goal directed fluid therapy (GDFT).¹⁴ Implementation of GDFT is dependent upon hemodynamic manipulations that produce changes in cardiac preload generally by a fluid challenge, mechanical ventilation, passive leg raising or end-expiratory occlusion.¹⁴

Mechanical ventilation increases intra-thoracic pressure during the inspiratory phase of mechanical ventilation resulting in an early increase in stroke volume and arterial pressure due to augmentation of left ventricular end diastolic volume and a decrease in arterial impedance (afterload).¹⁵ Subsequently, stroke volume and arterial pressure decrease due to a decrease in right ventricular filling.¹⁵ Mechanical ventilation, therefore, can be employed experimentally and clinically to increase and decrease a variety of dynamic hemodynamic indices including systolic pressure variation (SPV), pulse pressure variation (PPV), stroke volume variation (SVV), and plethysmography variability index (PVI) in order to assess vascular volume status and fluid responsiveness.^{9,16–21}

Closed-loop control systems, which are widely used in various industries (eg, autopilots in aircrafts), have the potential to assist in GDFT. A closed-loop control system involves a controller that uses real-time feedback information to compensate for errors in the system.

Within the fluid management context, the goal is to maintain the patient in a clinically acceptable state by changing fluid infusion rates. The controller, which manages the infusion rate, requires feedback signal (eg, SVV measurements) and a desired state for the feedback signal (eg, $SVV = 13\%$). The controller has to periodically compute the correct infusion rate to drive SVV to the desired value. However, the challenge in designing a control system involves guarantees of stability (convergence of SVV to the desired value) and performance (oscillations in SVV and infusion rates over time).

Various approaches to automated (closed-loop) fluid administration that monitor dynamic or static hemodynamic parameters have evolved in order to facilitate IV fluid administration. Closed-loop (C-L) fluid administration systems utilize feedback algorithms that link changes in SPV, PPV, SVV, PVI, cardiac output (CO), heart rate (HR) and mean arterial pressure (MAP) with controllers that use nonlinear decision tables,^{22,23} human data obtained from previously published clinical trials,²⁴⁻²⁶ or proportional integral derivative (PID) and fuzzy logic control frameworks in order to optimize fluid delivery.²⁷

Closed-loop control of fluid administration can address variability in intraoperative fluid management and potentially reduce under- and over-resuscitation. In addition, by automating the labor-intensive process of fluid management, the clinician can attend to more important clinical issues during surgery.

We theorized that an adaptive closed-loop fluid resuscitation system based on a compartmental model of fluid distribution would restore or maintain SVV in isoflurane anesthetized mechanically ventilated dogs subjected to absolute and relative hypovolemia. In contrast to previous heuristic approaches to closed-loop fluid resuscitation, our proposed adaptive control algorithm is based on physiology and provides a mechanism to account for inter-patient and intra-patient variability in the fluid resuscitation process (see Appendix).

In addition to investigating fully automated fluid resuscitation, our study also involved a partially automated mode of operation in two experimental trials. Specifically, in addition to investigating a fully automated fluid resuscitation framework, our goal was to investigate the performance of the proposed fluid resuscitation algorithm in the context of clinical decision support.

Materials and Methods

All procedures were approved by the Institutional Animal Care and Use Committee at QTests Labs Inc and complied with federal guidelines for the care and use of laboratory animals. The study was conducted according to the Guide for the Care and Use of Laboratory Animals.²⁸

Five mature intact Beagle dogs determined to be healthy based on a physical examination and hemogram were included in the experiment. Dogs were individually housed and provided commercial dry dog food and water ad libitum. Each dog and experiment was identified (Table 1). For example, S1-2 represents the second experiment performed on Subject S1. Studies on subjects were performed on different days. Individual trials on the same subject were performed on the same day and a stabilization period was used between trials. All dogs were euthanized with sodium pentobarbital (100 mg/kg, IV) upon completion of the experiments.

Animal Preparation

Food but not water was withheld for 6 hours before each experiment. An intravenous catheter was transcutaneously positioned in the cephalic vein for administration of hydromorphone,^a 0.15 mg/kg IV. Anesthesia was produced ten minutes later by administering 3.5 to 6 mg/kg IV propofol^b to facilitate orotracheal intubation, and initially maintained at a vaporizer setting of 1.5-2% isoflurane^c in oxygen. The dogs were positioned on their right side and mechanically ventilated^d at 10-12 breaths/min and 10-14 mL/kg tidal volume in order to maintain the end-tidal partial pressure of carbon dioxide (ET_{CO2}) between 38 and 48 mm Hg. To avoid potential changes in SVV, tidal volume settings for each subject was not changed during the study. Esophageal temperature was maintained (37°C) with temperature-controlled warm air blankets.^e

Vascular catheters were surgically placed in the left jugular vein and right carotid and femoral arteries after perivascular administration of 0.5-1.0 mL 2% lidocaine. The carotid or femoral artery catheter was connected to a FloTrac sensor^f with low-compliance fluid filled tubing. The FloTrac sensor was connected to a Vigileo monitor^g for determination and continuous monitoring of SVV. The FloTrac sensor was positioned and zeroed at the level of the sternum.²⁹ The pressure line of the FloTrac sensor was flushed with 4 mL/hr of LRS. Heart rate was determined from a Lead II electrocardiogram (ECG). Criteria for obtaining accurate SVV recordings during mechanical ventilation were employed.¹⁴

A 5-Fr Swan-Ganz catheter^h was percutaneously advanced via the right jugular vein (2 dogs) into the pulmonary artery under fluoroscopic guidance for measurement of cardiac output (CO) by thermodilution. Alternatively, CO was determined by a previously implanted flow probeⁱ (3 dogs) positioned around the ascending aorta, proximal to brachio-cephalic trunk for continuous recording of CO.

Experimental Procedures

Five dogs were subjected to 9 experiments. Lactated Ringer's solution^j (LRS) was administered as fluid resuscitation. A variety of experimental hypovolemic conditions were created in order to mimic various clinical conditions (Table 1). Absolute controlled hypovolemia (2 trials) was produced during 1.5 minimum alveolar concentration (MAC:1.27% used throughout) of isoflurane anesthesia by withdrawing 15 mL/kg/15 minutes from either the right carotid or right femoral artery (S1-1).³⁰ There was a 30-minute stabilization period between the end of the C-L fluid resuscitation (S1-1) and the beginning of the second hemorrhage, 40 mL/kg/30 minutes (S1-2). Closed-loop fluid administration was initiated within 10 minutes of completion of each blood withdrawal and continued until SVV reached a predetermined target range equal to or less than $13 \pm 3\%$.

Absolute uncontrolled hypovolemia (S3-1, S4-2, S5-2; 3 trials), designed to simulate blood loss from a severed artery was produced by withdrawal of approximately 50% (40 mL/kg) of the dogs estimated blood volume (80 mL/kg) from the right carotid or right femoral artery over one hour.^{31,32} Five successive 8.0 mL/kg increments of blood were withdrawn

continuously in increments that were completed at approximately 7-8, 18-20, 30-32, 43-45, and 60 minutes after initiating hemorrhage.³² Closed-loop fluid resuscitation was initiated 10 minutes after initiation of absolute uncontrolled hypovolemia (ie, beginning of Stage 2 of blood withdrawal) and continued until SVV reached a predetermined target range equal to or less than $13 \pm 3\%$.

Relative hypovolemia (2 trials) was produced by either increasing the inspired concentration of isoflurane to 2.0-2.5 MAC (S5-1, 1 trial) or administering sodium nitroprusside (5-10 $\mu\text{g/kg/min}$; S4-1, 1 trial) until mean arterial blood pressure was ≤ 50 mm Hg. The target range SVV was set at $13 \pm 3\%$ for S4-1 and $5 \pm 3\%$ for S5-1.

Relative and controlled absolute hypovolemia were produced by increasing the concentration of isoflurane (0.25-0.5%, 1.5-2.0 MAC multiples) in order to decrease MAP by $\geq 30\%$ (S2-1, 1 trial) or administering sodium nitroprusside (1-15 mcg/kg/min ; S2-2, 1 trial) followed by withdrawal of 15 mL/kg/minutes of blood. The target range SVV was set at $13 \pm 3\%$ for S2-1 and S2-2. The subject was resuscitated to the target SVV value in S2-1 and stabilized before initiating the second study (S2-1). Fluid resuscitation started 15 minutes after achieving relative and controlled absolute hypovolemia.

The C-L fluid resuscitation system was employed in a “partial automation” mode (human-in-the-loop) in 2 experimental trials, one involving absolute uncontrolled hemorrhage (S4-2) and

one involving relative hypovolemia from sodium nitroprusside administration (S4-1), where the system displayed the recommended infusion rate every minute and the user manually changed the infusion rate. A Horizon NXT Modular Infusion System pump^k was used in the partial automated mode. While the system was able to provide infusion rate recommendations more frequently, an update interval of 1 minute was chosen to allow sufficient time for the clinical staff to adjust the pump settings manually. Measured SVV values were filtered in all studies, including automated and partially automated modes, using a 1-minute moving window averaging to remove noise.

Closed-loop Fluid Administration

The C-L fluid resuscitation system included 3 components: *i*) a sensor to measure a hemodynamic variable that is correlated with fluid responsiveness (eg, SVV, PPV or PVI), *ii*) a controller that analyzes sensor measurements and computes the appropriate infusion rate; and, *iii*) an infusion pump that administers the fluid at the rate determined by the controller. The closed-loop system continuously recomputed and adjusted the infusion rate. The subject continuously received a fluid infusion and the control system changed the infusion rate every few seconds in response to changes in SVV. Vigileo transmitted the most recent value of the SVV measurement every 2 seconds using serial communication. The laptop was connected to the Vigileo using a Serial to USB cable. The C-L system used a 1-minute moving window averaging to remove noise. The control algorithm was implemented in the Python programming language running on a laptop (Samsung Chrono 7) with the Linux^l operating system. Measurements from Vigileo were recorded by the laptop using serial communication.

The C-L algorithm computed an infusion rate every 11 seconds using the average SVV values in the past 1-minute. The infusion rate was sent by the laptop to an infusion pump^m (supporting flow rates from 0.06 to 4200 mL/hr) using a USB connection.

Performance Metrics

Performance metrics that are of clinical relevance were defined in order to assess the performance of the C-L fluid resuscitation system. Specifically, T_{target} was defined as the duration from start of fluid administration to restoration of an acceptable SVV target range.

We defined the acceptable SVV target range to be equal to $13 \pm 3\%$ with the exception of 2 experiments, namely, S5-2 (uncontrolled hypovolemia) and S5-1 (relative hypovolemia), where the acceptable SVV target range was $10 \pm 3\%$ and $5 \pm 3\%$, respectively. The $R_{\text{in range}}$ was defined as the percentage of time that SVV target value stayed in the acceptable range (ie, duration of time SVV stayed in the acceptable range divided by total duration of resuscitation). Other performance metrics included minimum and maximum infusion rates denoted by u_{min} and u_{max} , respectively, total infused volume to reach the acceptable SVV target range denoted by V_{target} , and, in absolute hypovolemia experiments, the ratio of total fluid volume infused to total blood loss denoted by V_{ratio} . To ensure that the subject can be maintained at the acceptable SVV target range, the resuscitation continued after reaching the acceptable SVV target range, and hence, V_{target} and total infused volume are not equal. Continued resuscitation after reaching V_{target} lasted approximately 15 minutes on average. The

stabilization period between different trials on the same subject started after the completion of the fluid resuscitation of the previous trial.

Results

Five mature intact beagle dogs (3 male, 2 female) weighing between 7.1-12.2 kg (mean 10.2 and standard deviation 2.04 kg) were studied.

Controlled Hypovolemia

Absolute hypovolemia during 1.5 MAC isoflurane anesthesia decreased MAP from 100 to 86 mm Hg (dog S-1) and from 109 to 54 mm Hg (S1-2) after withdrawal of 15 mL/kg and then 40 mL/kg of blood, respectively (Table 2). Heart rate increased and CO decreased after withdrawal of 15 mL/kg and 40 mL/kg of blood (Table 2). In addition, the SVV increased after withdrawal of 15 mL/kg and 40 mL/kg of blood. The SVV returned to the target range ($13\% \pm 3$) after the administration of 7 mL/kg and 66 mL/kg of LRS, respectively (Table 2). The total infused volumes were 189 mL (S1-1: $V_{\text{ratio}} = 1.1$) and 925 mL (S1-2: $V_{\text{ratio}} = 2$), respectively.

Uncontrolled Hypovolemia

Closed-loop fluid administration was initiated during the second stage of blood withdrawal, and continued throughout hemorrhage (S3-1, S4-2, S5-2). Closed-loop fluid administration was stopped approximately 30 minutes after the end of the last (fifth) stage of hemorrhage as this exceeds the average time for fluid equilibration with the interstitial fluid compartment.³³

Mean arterial blood pressure and CO decreased and HR increased during the initial 3-4 stages of uncontrolled hypovolemia (Table 3). Heart rate increased throughout hemorrhage and remained increased throughout hemorrhage and fluid administration (Table 3). The SVV increased during the first stage of uncontrolled hypovolemia and returned toward baseline values thereafter (Table 3). Total infused volumes for S3, S4, and S5 were 1,092 mL ($V_{\text{ratio}} = 2.5$), 1,243 mL ($V_{\text{ratio}} = 2.8$), and 548 mL ($V_{\text{ratio}} = 1.4$), respectively. The fluid administration system was used in a partially-automated (human-in-the-loop) mode for S4, where the recommended infusion rate was displayed to the user every minute and the user manually changed the infusion rate to the recommended value.

Relative Hypovolemia from Vasodilatation

Dogs were made hypotensive by increasing the inspired concentration of isoflurane (S5-1 dog) or by administering sodium nitroprusside (S4-1) until MAP was ≤ 50 mm Hg. The target range SVV was set at $13 \pm 3\%$ for S4-1 and $5 \pm 3\%$ for S5-1. The administration of isoflurane or sodium nitroprusside decreased MAP and increased HR and either did not change or increased CO, respectively (Table 4). Stroke volume variation increased in both dogs (Table 4). C-L resuscitation increased cardiac output and decreased SVV in both dogs. Arterial blood pressure increased during fluid administration in the dog administered sodium nitroprusside (S4-1) but not in the dog administered isoflurane (S5-1) (Table 4). Total infused volumes were 187 mL (nitroprusside: 15 mL/kg) and 265 mL (isoflurane: 28 mL/kg).

Relative Hypovolemia and Controlled Hypovolemia

Increasing the isoflurane concentration from 1.5 to 2.5 MAC (S2-1) or administration of sodium nitroprusside (S2-2) was followed by blood withdrawal (15 mL/kg/15 minutes). The sodium nitroprusside infusion rate started at 1 μ g/kg/min and was increased to 15 μ g/kg/min. The target range SVV was set at $13 \pm 3\%$. Absolute hypovolemia (15 mL/kg/15 min) during 2.5 MAC isoflurane anesthesia decreased MAP from 60 mm Hg before blood withdrawal to 39 mm Hg after blood withdrawal (S2-1). In addition, MAP increased from 39 mm Hg to 46 mm Hg after a 15-minute stabilization period. Heart rate changed minimally (110 vs. 112/min) and CO decreased 20% (1.0 vs. 0.8 L/min) after the production of relative hypovolemia combined with controlled hypovolemia (15 mL/kg/15 min). The SVV increased from 13% at 1.5 MAC to 21% at 2.5 MAC and then to 41% after withdrawal of 15 mL/kg of blood. The SVV decreased to 26% after a 15-minute stabilization period. The SVV returned to the target range ($13\% \pm 3$) at 43 minutes (T_{target}) after the administration of 78 mL/kg of LRS. Total infused volume was 573 mL ($V_{\text{ratio}} = 5.4$). The maximum fluid administration rate (u_{max}) was 113 mL/kg/hr. Heart rate decreased (112 to 99/min) and CO increased to above the baseline value (1.0 vs. 1.2 L/min) after LRS administration but MAP remained relatively unchanged (43 mm Hg) until the isoflurane concentration was decreased.

Absolute hypovolemia (15 mL/kg/15 min) during 1.5 MAC and sodium nitroprusside administration decreased MAP from 113 to 92 mmHg prior to blood withdrawal (S2-2). MAP was 101 mm Hg after blood withdrawal. Heart rate changed minimally and cardiac output decreased 25% (1.3 vs. 1.0 L/min) after the production of relative hypovolemia combined with controlled hypovolemia (15 mL/kg/15 min). The SVV increased from 10% to 15% after sodium nitroprusside administration and then to 22% after withdrawal of 15 mL/kg of blood. The SVV returned to the target range ($13\% \pm 3$) at 26 minutes (T_{target}) after the administration

of 46 mL/kg of LRS. The maximum fluid administration rate ($u_{\max}$) was 108 mL/kg/hr.

Cardiac output increased to above the baseline value (1.3 vs. 2.1) after LRS administration and MAP increased to near the baseline value (Table 5). Total infused volume was 400 mL ($V_{\text{ratio}} = 3.7$). Stroke Volume variation values and infusion rates for four experiments are shown in Figures 1 and 2, respectively.

Discussion

The designed closed-loop fluid resuscitation system uses the compartmental modeling framework to compute fluid infusion rates. In order to model the microvascular exchange system to characterize the distribution of fluids in the body, we can use a two-compartment dynamical system model as discussed in the literature (see the Appendix). A critical drawback of using a model-based approach to compute a patient's fluid requirement is that accurate physiological parameter values are needed for the model. However, high-fidelity models do not exist and current models cannot fully account for the physiology and response of the patient to fluids. Literature reports average values for these parameters, however, there is no "average patient." The two-compartment model of the microvascular exchange system discussed in the appendix involves many parameters that are generally unknown and different from patient to patient. In addition, the two-compartment model is only an approximation of the fluid distribution in the body, and hence, modeling error exists.

Our proposed adaptive control algorithm uses the compartmental characteristics of the fluid distribution to the body. However, to address modeling error and unknown parameters of the compartmental model governing fluid distribution, the proposed adaptive algorithm uses a

“function approximator.” The function approximator is characterized by a set of parameters, which are continuously estimated by the closed-loop system in real-time. Hence, the closed-loop fluid resuscitation system re-computes the fluid infusion rate periodically. The function approximator uses the values of infusion rates and SVV measurements to estimate the dynamics of fluid distribution. The controller performance was evaluated with computer simulations on a two-compartment model prior to conducting the animal study. The results presented in this paper is the first attempt to use the proposed algorithm in live subjects.

Data from this pilot study confirmed that an adaptive closed-loop fluid administration system based on a compartmental model of fluid distribution provided targeted GDFT in dogs subjected to experimental conditions that mimicked clinical scenarios of absolute (controlled, uncontrolled), relative hypovolemia or a combination of relative hypovolemia and absolute controlled hypovolemia. Stroke volume variation was restored and maintained to within a preselected normal target range in less than one hour after initiating fluid administration.

Larger volumes of blood loss (40 vs. 15 mL/kg) increased the V_{ratio} required to restore SVV to the target range but remained below amounts based upon LRS distribution.³⁴ In scenarios of intravascular volume loss the retention of crystalloid (ie, LRS) will be increased and will not follow the typical fluid distribution characteristic of euvoletic states. Based on the data generated as part of this pilot study we observed that closed-loop fluid administration restored SVV to the target range following isoflurane induced relative hypovolemia but did not improve MAP. Previous observations in isoflurane anesthetized dogs reported a similar observation and emphasized the inability of MAP to predict fluid requirements during anesthetically induced relative hypovolemia.³⁵ The total time and rate of fluid administration

required to restore SVV to the target range ($13, 10$ or $5 \pm 3\%$) increased with greater blood loss or the combination of blood loss and relative hypovolemia.

The determination of when (timing), how much (mL/kg), and how fast (mL/kg/h) to administer IV fluids is a focus of intense experimental and clinical research due to its potential contribution to increases in both morbidity and mortality caused by fluid overload.^{6,7,36-41} Current recommendations for IV fluid administration suggest that a goal directed approach that monitors a dynamic variable (eg, SVV, PPV, SPV, PVI) is more sensitive and specific for determining fluid responsiveness and limiting fluid overload than static determinations of cardiac output, or arterial blood pressure.⁴²⁻⁴⁴ Central venous pressure, although a good indicator of preload, is not a good indicator of fluid responsiveness.⁴⁵

We chose to measure SVV as an indicator of fluid responsiveness and selected a threshold value of $13, 10$, or $5 \pm 3\%$ as indicative of normovolemia. Threshold values for the various dynamic indices display different sensitivities to hypovolemia dependent upon cause.¹⁸ Most threshold values vary between $5-15\%$ and higher threshold values are more indicative of the need for fluid replacement therapy.⁴⁶ The sensitivity of SVV for predicting acute hemorrhage and the effects of transfusion is more sensitive than most other dynamic indices suggesting that SVV is a better indicator of the effective circulating blood volume.¹⁹ Studies investigating blood loss in isoflurane anesthetized dogs suggest that increases in SVV of more than 10% are predictive of hypovolemia.¹⁹

The ability of closed-loop or manually assisted semi-closed-loop fluid administration systems to provide GDFI is only as good as the method used to assess fluid needs or responsiveness. The diagnostic accuracy of most dynamic indices currently being used to assess fluid responsiveness have been statistically evaluated by “grey zone analysis.”¹⁸ In the grey zone analysis approach, fluid responders and non-responders can be identified with high certainty while no specific conclusion on fluid responsiveness of cases in the grey zone can be made. Thresholds for fluid administration have been established for people and are being developed for dogs.^{18–20,46} We employed the Vigileo Flo-Trac sensor to estimate SVV. Although this system has been shown to overestimate CO in isoflurane anesthetized dogs due to a higher degree of dependence on arterial blood pressure, it has been shown to be a sensitive indicator of dynamic circulating blood volume changes.^{47,48}

Various approaches based on decision table algorithms, population data, proportional-integral-derivative (PID) controllers, and fuzzy logic have been employed to design and construct closed-loop fluid delivery systems.^{22–24,26,27,49,50} PID controllers, which have been widely used in industrial applications, generate the control signal (eg, fluid infusion rate) based on applying a series of operations on an error signal (eg, the difference between current SVV and the target SVV). However, a critical issue with PID control algorithms is that nominal parameter values are needed for the controller design. Specifically, a mathematical model describing the response of the patient to fluids and its corresponding parameter values

are required for controller design. Currently, a comprehensive mathematical model that can accurately describe the response of a patient to fluids does not exist. In addition, “tuning” the parameters of a PID controller involves a trial and error process and in the end no guarantees of stability exist. Similarly, other heuristic approaches such as fuzzy logic,⁵⁰ decision tables,^{22,23} or reliance on population data from previous clinical trials to guide fluid therapy,^{22,24,26} assume the existence of an “average patient”. In contrast, our proposed adaptive control algorithm is based on physiology and the parameters of the model are estimated in real-time. This framework provides a mechanism to account for inter-patient and intra-patient variability in the fluid resuscitation process.

Previously reported closed-loop control algorithms for fluid delivery do not provide any guarantees of closed-loop stability. Rather, they assume that stability follows from the microvascular exchange system model governing fluid distribution. However, this is not the case since these controllers do not account for full model uncertainty, unmodeled dynamics, and system nonlinearities.⁵¹ In contrast, the adaptive control framework employed in the current study guarantees closed-loop stability in the face of system nonlinearities and system uncertainty using *Lyapunov theory*.⁵¹ Stability of a closed-loop system ensures that system variables and states do not deviate from desired values over time. One method to prove the stability of a system is to find an energy-like function, referred to as a Lyapunov function, and show that the “energy” of the closed-loop system decreases over time, and hence, the system will remain stable. As an example, a mechanical system consisting of a swinging pendulum is stable as the mechanical energy is continuously dissipated due to the air resistance as well as friction at the pivot.

The proposed adaptive controller design assumes that body fluid distribution is governed by a compartmental model (see Appendix).^{52–54} The closed-loop system uses the compartmental model to compute the required infusion rate to drive an endpoint of resuscitation (eg, SVV or PPV) to a desired set value. The adaptive control framework starts with an estimate of the compartmental model parameters and iteratively re-estimates the parameters during the resuscitation process.

The rate and volume of administered fluids by C-L fluid administration systems relies on sensing technologies that monitor static (MAP, CO, CVP) or dynamic (SVV, PPV, PVI) indices. Threshold and grey zone values (sensitivity, specificity) for most indices are influenced by several prominent confounders including spontaneous breathing, high respiratory rates, small tidal volumes, pulmonary disease (low lung compliance), an open chest, cardiac arrhythmias, right heart failure, and increased abdominal pressure.¹⁴ Our use of mechanical ventilation and mode of ventilation could also have influenced the results. Nevertheless, the experimental procedures employed mimicked clinical conditions.⁵⁵ Closed-loop fluid administration systems that rely on monitoring a continuous or periodically computed dynamic index (eg, SVV) when used in conjunction with clinical signs and additional measures of hemodynamic stability (e.g. arterial blood pressure) should provide a superior method for fluid administration and reduce the potential for fluid overload.⁵⁶

In conclusion, an adaptive C-L fluid administration system based on a compartmental model of fluid distribution computed an infusion rate to drive an endpoint of resuscitation (eg, SVV) during both absolute (controlled or uncontrolled), relative hypovolemia or a combination of relative hypovolemia and absolute controlled hypovolemia. Fluid rates and volumes delivered approximated values recommended by studies that have modeled different fluid rates and volumes required to restore and maintain blood volume after acute hemorrhage.^{10,53,57} The proposed adaptive control framework did not require subject-specific information (eg, age, gender, weight, diagnosis). Furthermore, the framework did not require an accurate model of the subjects' fluid dynamics. Additional trials are required in animals with naturally occurring causes for absolute and relative hypovolemia in order to assess the clinical utility for an adaptive closed-loop fluid administration system.

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Footnotes

- a. Hydromorphone, West-Ward Pharmaceuticals.
- b. Propofol, Abbott Laboratories, North Chicago, IL.
- c. Isoflurane, Piramal Healthcare Limited, Andhra Pradesh, India.
- d. Hallowell EMC 2002, Pittsfield, MA.

- e. 3M Bair Hugger, Patterson Veterinary Supply, Inc. Columbus, OH.
- f. FloTrac sensor, Edwards Lifesciences, Irvine, CA.
- g. Vigileo Monitor, Edwards Lifesciences, Irvine, CA.
- h. Swan-Ganz catheter, Edwards Lifesciences, Irvine, CA.
- i. PS series ultrasonic transit-time flow probe, Transonic Systems Inc., Ithaca, NY.
- j. Lactated Ringer's Solution, Baxter International. Inc., Deerfield, IL.
- k. Horizon NXT Modular Infusion System, B. Braun Medical Inc., Bethlehem, PA
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Table 1. Study subject information and experiment summary

Subject	Weight (kg)	Study 1	Study 2
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S1	11.6	CH	CH
S2	7.1	RAH	RAH
S3	10.8	UH	-
S4	12.2	RH	UH
S5	9.3	RH	UH

CH=controlled hypovolemia, UH=uncontrolled hypovolemia, RH=relative hypovolemia, RAH=relative and absolute hypovolemia

Table 2. Hemodynamic data and performance metrics for controlled hypovolemia study.

T_{target} denotes the duration from start of fluid administration to restoration of an acceptable SVV target range, u_{min} and u_{max} denote minimum and maximum infusion rates, respectively, and V_{target} denotes total infused volume to reach the acceptable SVV target range.

	Baseline		Before Resuscitation		After Resuscitation	
ml/kg bled	15	40	15	40	15	40
CO (L/min)	1.5	2.1	1.3	0.8	2.1	1.6
MAP (mmHg)	100	109	86	54	109	63
HR (bpm)	85	108	107	187	108	154
SVV (%)	6	15	19	42	13	16

Performance Metrics

Study	T_{target} (min)	u_{min} (ml/kg/hr)	u_{max} (ml/kg/hr)	V_{target} (ml/kg)
S1-1 (15ml/kg)	6.6	26	64	7

S1-2

(40 ml/kg) 50.3 70 87 66

Table 3. Hemodynamic data and performance metrics for uncontrolled hypovolemia study. $u_{\min}$ and $u_{\max}$ denote minimum and maximum infusion rates, respectively, and $R_{\text{in range}}$ the percentage of time that SVV target value stayed in the acceptable range.

	Baseline	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	End
CO (L/min)	1.5 (1.1-1.7)	0.8 (0.5-1.5)	0.8 (0.3-1.4)	1.0 (0.4-1.4)	0.9 (0.4-1.7)	1.0 (0.7-1.7)	1.3 (1.1-2.0)
MAP (mmHg)	81 (62-85)	59 (55-91)	66 (35-87)	65 (45-67)	68 (50-72)	68 (53-78)	59 (44-83)
HR (bpm)	118 (113-121)	134 (120-171)	132 (108-170)	132 (117-174)	135 (117-170)	139 (116-168)	137 (107-167)
SVV (%)	8 (6-12)	21 (17-25)	17 (12-19)	15 (11-16)	14 (11-16)	15 (10-15)	10 (8-18)
Performance Metrics							
Dog	$u_{\min}$ (ml/kg/hr)	$u_{\max}$ (ml/kg/hr)	$R_{\text{in range}}$ (%)				
S3-1	44	115	54				
S4-2	40	82	71				

S5-2	39	64	100
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Table 4. Hemodynamic data and performance metrics for the relative hypovolemia study.

T_{target} denotes the duration from start of fluid administration to restoration of an acceptable SVV target range, u_{min} and u_{max} denote minimum and maximum infusion rates, respectively, V_{target} denotes total infused volume to reach the acceptable SVV target range, and $R_{\text{in range}}$ the percentage of time that SVV target value stayed in the acceptable range. I = isoflurane; SN = sodium nitroprusside

	Baseline	Before Resuscitation	After Resuscitation
CO (L/min)	0.8 I; 1.4 SN	0.8 I; 1.6 SN	1.4 I; 2.0 SN
MAP (mmHg)	62 I; 69 SN	45 I; 47 SN	35 I; 94 SN
HR (bpm)	84 I; 89 SN	87 I; 115 SN	89 I; 126 SN
SVV (%)	7 I; 9 SN	10 I; 17 SN	6 I; 8 SN

Performance Metrics

Study	T_{target} (min)	u_{min} (ml/kg/hr)	u_{max} (ml/kg/hr)	V_{target} (ml/kg)	$R_{\text{in range}}$ (%)
S4-1	3	11	67	3	100
S5-1	4	63	73	5	90

Table 5. Hemodynamic data **and performance metrics** for the relative hypovolemia and controlled hypovolemia study. T_{target} denotes the duration from start of fluid administration to restoration of an acceptable SVV target range, u_{min} and u_{max} denote minimum and maximum infusion rates, **respectively**, V_{target} denotes total infused volume to reach the acceptable SVV target range, and $R_{\text{in range}}$ the percentage of time that SVV target value stayed in the acceptable range. I = isoflurane; SN = sodium nitroprusside

	Baseline	Before Resuscitation	After Resuscitation		
CO (L/min)	1.0 I; 1.3 SN	0.8 I; 1.0 SN	1.2 I; 2.1 SN		
MAP (mmHg)	93 I; 113 SN	46 I; 101 SN	40 I; 115 SN		
HR (bpm)	110 I; 134 SN	112 I; 114 SN	99 I; 108 SN		
SVV (%)	13 I; 10 SN	26 I; 22 SN	15 I; 21 SN		
Performance Metrics					
Study	T _{target} (min)	u _{min} (ml/kg/hr)	u _{max} (ml/kg/hr)	V _{target} (ml/kg)	R _{in range} (%)
S2-1	43	88	113	78	100
S2-2	26	66	108	46	53

Figures

Figure 1. Infusion rate for S1-1 (controlled hemorrhage), S1-2 (controlled hemorrhage), S3-1 (uncontrolled hemorrhage), and S4-1 (relative hypovolemia).

Figure 2. Filtered SVV values for S1-1 (controlled hemorrhage), S1-2 (controlled hemorrhage), S3-1 (uncontrolled hemorrhage), and S4-1 (relative hypovolemia).

Figure 3. Schematic diagram of a two-compartment model characterizing fluid distribution.

Appendix. A Compartmental Model of Fluid Distribution

In order to model the microvascular exchange system to characterize the distribution of fluids in the body, we can use a two-compartment dynamical system model as discussed in the literature.^{54,57,58} Specifically, the compartments include circulation (blood) and the interstitial tissue, and the states of the dynamical system include volume of fluids and albumin mass in each compartment (a total of four states). As shown in Figure 3, the circulation exchanges fluid with the environment (IV infusion, urine production, and hemorrhage) as well as with the interstitial compartment. The interstitial compartment may lose fluids to the environment through evaporation or other insensible water losses.

A mass balance equation for fluid and protein for a two-compartment dynamical system model is given by

$$\dot{v}_c(t) = u(t) + J_L(t) - J_t(t) - J_{\text{urine}}(t) - J_{\text{blood}}(t),$$

$$\dot{a}_c(t) = Q_L(t) - Q_t(t) - a_{\text{blood}}(t),$$

$$\dot{v}_t(t) = J_t(t) - J_L(t) - J_{\text{evaporation}}(t),$$

$$\dot{a}_t(t) = -Q_L(t) + Q_t(t),$$

where $u(t)$ is the volume of infused fluid, $J_L(t)$ is the rate of volume transfer from interstitial tissue to circulation, $J_t(t)$ is the rate of volume transfer from circulation to interstitial tissue, $J_{\text{urine}}(t)$, $J_{\text{blood}}(t)$, and $J_{\text{evaporation}}(t)$ denote loss of fluid volume due to urine production, hemorrhage, or evaporation (and other types of insensible water loss), respectively. Furthermore, $a_{\text{blood}}(t)$ denotes the rate of loss of protein (albumin) mass from hemorrhage, $Q_t(t)$ is the rate of albumin mass transfer from circulation to interstitial tissue, and $Q_L(t)$ is the rate of albumin mass transfer from interstitial tissue to circulation.

The above equation can be rewritten in state space form, namely,

$$\dot{v}_c(t) = f_1(v(t)) + u(t), \quad v_c(0) = v_{c,0}, \quad t \geq 0 \quad (1)$$

$$\dot{a}_c(t) = f_2(v(t)), \quad a_c(0) = a_{c,0} \quad (2)$$

$$\dot{v}_t(t) = f_3(v(t)), \quad v_t(0) = v_{t,0} \quad (3)$$

$$\dot{a}_t(t) = f_4(v(t)), \quad a_t(0) = a_{t,0} \quad (4)$$

where for $t \geq 0$, $v(t) = [v_c(t), a_c(t), v_t(t), a_t(t)]^T$, and system states $v_c(t)$, $a_c(t)$, $v_t(t)$, and $a_t(t)$ denote fluid volume in circulation, albumin mass in circulation, fluid volume in interstitial

tissue, and albumin mass in interstitial tissue, respectively. In addition, $f_1(v)$ and $f_3(v)$ denote functions characterizing the rate of fluid exchange in circulation and tissue compartments, respectively, and $f_2(v)$ and $f_4(v)$ denote functions characterizing the rate of change of albumin in circulation and tissue compartments, respectively. Note that variables indicating exchange of volume or mass with the outside environment including $J_{\text{urine}}(t)$, $J_{\text{blood}}(t)$, $J_{\text{evaporation}}(t)$, and $a_{\text{blood}}(t)$ have been incorporated into functions $f_1(v)$, $f_2(v)$, and $f_3(v)$. In addition, $v_{c,0}$, $a_{c,0}$, $v_{t,0}$, and $a_{t,0}$ denote volume and albumin mass in circulation and interstitial tissue at $t=0$, respectively. This mathematical model of fluid distribution captures the general structure of fluid distribution dynamics, which can be used in controller design.

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