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In-human subject-specific evaluation of a control-theoretic plasma volume regulation model

Ramin Bighamian [a], Michael Kinsky [b], George Kramer [b], Jin-Oh Hahn [a,*]

[a] Department of Mechanical Engineering, University of Maryland, College Park, MD 20742, USA
[b] Department of Anesthesiology, University of Texas Medical Branch, Galveston, TX 77555, USA

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ABSTRACT

The goal of this study was to conduct a subject-specific evaluation of a control-theoretic plasma volume regulation model in humans. We employed a set of clinical data collected from nine human subjects receiving fluid bolus with and without co-administration of an inotrope agent, including fluid infusion rate, plasma volume, and urine output. Once fitted to the data associated with each subject, the model accurately reproduced the fractional plasma volume change responses in all subjects: the error between actual versus model-reproduced fractional plasma volume change responses was only 1.4 ± 1.6% and 1.2 ± 0.3% of the average fractional plasma volume change responses in the absence and presence of inotrope co-administration. In addition, the model parameters determined by the subject-specific fitting assumed physiologically plausible values: (i) initial plasma volume was estimated to be 36 ± 11 mL/kg and 37 ± 10 mL/kg in the absence and presence of inotrope infusion, respectively, which was comparable to its actual counterpart of 37 ± 4 mL/kg and 43 ± 6 mL/kg; (ii) volume distribution ratio, specifying the ratio with which the inputted fluid is distributed in the intra- and extra-vascular spaces, was estimated to be 3.5 ± 2.4 and 1.9 ± 0.5 in the absence and presence of inotrope infusion, respectively, which accorded with the experimental observation that inotrope could enhance plasma volume expansion in response to fluid infusion. We concluded that the model was equipped with the ability to reproduce plasma volume response to fluid infusion in humans with physiologically plausible model parameters, and its validity may persist even under co-administration of inotropic agents.

1. Introduction

Fluid resuscitation is the central component in the treatment of critically ill patients suffering from blood volume deficit, including infection [1–3], hemorrhage [4], [5], and burn [6–8]. In particular, hemorrhagic shock is responsible for the majority of death among trauma patients [9]. Based on the National Vital Statistics Reports, hemorrhage is the leading cause of death in young population (age 1–44) and the 4th leading cause of death overall in the United States [10]. Given that fluid resuscitation presents a narrow therapeutic window and very large inter-individual differences in response, it must be administered with care. Under-loading or under-resuscitation does not resolve volume deficit and increases mortality and morbidity [11–13], while over-loading causes adverse side effects such as edema and poor oxygen transport [14].

Stringent requirements associated with the precise fluid resuscitation may be fulfilled by autonomous closed-loop control and/or decision-assist systems. From this standpoint, a mathematical model that can describe the blood and plasma volume regulation in response to fluid resuscitation may offer two near-term benefits. First, the majority of physiological closed-loop control and decision-assist systems for fluid resuscitation to date are built upon classical proportional-integral-derivative (PID) controllers with empirically tuned gains [15], [16], and generalized knowledge abstracted into black-box mapping (e.g., fuzzy logic [17] and decision tree [18–20]). Hence, a mathematical model can lead to new opportunities for the development and analysis of closed-loop control and decision-assist systems through the established model-based controller design techniques. Second, there is an ever-increasing interest in effective regulatory approval of closed-loop control and decision-assist systems for medicine, as suggested by the recent discussions at the FDA Public Workshop on Physiological Closed-Loop Controlled Medical Devices [21]. Hence, a credible mathematical model can serve as the basis to enable in-silico pre-clinical evaluation of physiological closed-loop controllers, thereby saving the time and cost associated with the clinical trials.

* Corresponding author.
E-mail address: jhahn12@umd.edu (J.-O. Hahn).

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However, state-of-the-art mathematical models describing plasma and blood volume responses to fluid resuscitation are not ideally suited to offer these benefits. On the one hand, simple low-order models tend to miss physiological mechanisms associated with volume responses such as inter-compartmental fluid shift [22–27]. On the other hand, complex high-order models tend to incorporate excessive details (such as ion and protein kinetics) that cannot be characterized and individualized from routine clinical data collected from real-world patients [28–35]. As a consequence, the former may not allow streamlined interpretation to ascertain patient's plasma and blood volume state, whereas the latter may not allow streamlined design and analysis of physiological closed-loop controllers.

In a recent study, we developed a simple yet interpretable control-theoretic model that can reproduce plasma and blood volume response to fluid resuscitation [36]. This model retains the macroscopic-level physiological implications involved in the plasma volume regulation process while abstracting microscopic-level details into a hypothetical control (i.e., regulatory) action by representing the plasma volume regulation process into a feedback controlled system. In this way, the model could reproduce plasma volume response to fluid infusion with only a few interpretable parameters: absolute plasma volume, inter-compartmental volume distribution ratio, and fluid shift gain(s). In our recent work, we demonstrated the initial proof-of-concept of the model using published population-averaged data. The goal of this study was to conduct a subject-specific evaluation of a control-theoretic plasma volume regulation model in humans. We employed a set of clinical data collected from nine human subjects receiving fluid bolus with and without co-administration of an inotrope agent, including fluid infusion rate, plasma volume, and urine output. We evaluated the control-theoretic plasma volume regulation model for (i) its ability to reproduce plasma volume response in individual subjects, (ii) its ability to reproduce plasma volume response under co-administration of an inotrope, and (iii) physiological plausibility of the model parameters derived in individual subjects.

2. Materials and methods

2.1. Experimental data

We employed a set of experimental data collected from nine human subjects (age 21–50, 3 males and 6 females) receiving fluid bolus with and without co-administration of an inotrope agent, isoproterenol, including fluid infusion rate, plasma volume (PV; measured in terms of plasma dilution; see, e.g., [37]), and urine output (UO). Inotropes augment the force of ventricular contraction, increase cardiac output, and alter the blood-tissue transport of fluids. Hence, these data provide two different physiological states to evaluate the control-theoretic PV regulation model. These experimental data were collected under institutional IRB approval and written informed consent in a previously performed study, the details of which can be found elsewhere [38]. Here, information relevant to this study is summarized.

Each subject was placed in supine position in a hospital bed during the study. The subject underwent two infusion protocols, which were randomly assigned and were separated with each other by at least 7 days: control (CON) and isoproterenol (ISO). In the CON protocol, the subjects received 0.9% saline at 10 mL/h. In the ISO protocol, the subjects received isoproterenol at 0.05 mcg/kg/m. These infusions started from 30 m before to 120 m after the start of saline bolus (25 mL/kg over 20 m). Initial PV was measured via spectrophotometric detection of indocyanine green [37]. The change in PV from its initial value was measured via the change in hematocrit [37]. For hematocrit, arterial blood samples were obtained at the start of the saline bolus, every 2 m during the bolus (first 20 m), then every 5 m for next 40 m, and every 30 m thereafter until the end of the study, or 120 min from the start of the fluid bolus. Cumulative UO was measured at the start and end of the bolus, and at 40 m, 60 m, 90 m, and 120 m in reference to the start of fluid bolus.

2.2. Control-theoretic plasma volume regulation model

We developed a simple yet interpretable control-theoretic PV regulation model [36], by exploiting the physiological principle that the body stores a fraction of the net inputted fluid volume (fluid infusion minus UO) in the intra-vascular compartment (i.e., as plasma) while shifting the remaining fraction to the extra-vascular compartment (i.e., as interstitial fluid) [39]. By denoting the ratio between the changes associated with the intra-vascular and extra-vascular volumes in the steady state as α, the target intravascular volume change $r_P(t)$ to net inputted fluid is given by:

$$r_P(t) = \frac{1}{1+\alpha}\int_0^t [u(\tau) - v(\tau)]d\tau \tag{1}$$

where $u(t)$ and $v(t)$ denote fluid inputted via infusion and lost via UO, respectively ($\int_0^t [u(\tau) - v(\tau)]d\tau$ represents the net inputted fluid volume, and $\frac{1}{1+\alpha}$ implies that the changes associated with the intra-vascular and extra-vascular volumes in the steady state is $1:\alpha$). Note that α can be assumed as a constant in a short time window (i.e., a few hours) [36], although its variability over a long time window (i.e., days) may not be neglected [39].

The fluid shift $q(t)$ between the intra-vascular and extra-vascular compartments is the consequence of the blood flow across the micro-vascular network in the body, determined by a wide range of complex mechanisms such as the vessel permeability as well as hydrostatic and oncotic pressure gradients [39]. To obviate the need to incorporate these complex mechanisms while still capturing the macroscopic consequence of the fluid shift, the model assumes that fluid shift results from a hypothetical, lumped control action to eliminate the error" between the target versus actual changes in PV:

$$q(t) = q(r_P(t) - \Delta V_P(t)) \tag{2}$$

where $\Delta V_P(t)$ is the change in PV from its initial value. Then, the time rate of change in PV can be expressed as follows:

$$\Delta \dot{V}_P(t) = u(t) - v(t) - q(t) \tag{3}$$

which indicates that the time rate of change in PV originates from the net inputted fluid ($u(\tau) - v(\tau)$) minus the fluid shift from the intra-vascular to extra-vascular compartments ($q(t)$).

Invoking the classical control theory [40] and formalizing $q(t)$ as the output of a proportional-integral (PI) controller to the error $e_P(t) = r_P(t) - \Delta V_P(t)$:

$$q(t) = -K_p e_P(t) - K_i \int_0^t e_P(\tau)d\tau \tag{4}$$

where K_p and K_i denote the proportional and integral gains. Then, the time rate of change in PV in Eq. (3) can be reduced to the following:

$$\Delta \ddot{V}_P(t) + K_p \Delta \ddot{V}_P(t) + K_i \Delta \dot{V}_P(t) = [\ddot{u}(t) - \ddot{v}(t)] + \frac{K_p}{1+\alpha}[\dot{u}(t) - \dot{v}(t)] + \frac{K_i}{1+\alpha}[u(t) - v(t)] \tag{5}$$

This model is illustrated in Fig. 1. The intra- (i.e., PV; V_P with initial value V_{P0}) and extra-vascular (i.e., interstitial fluid volume (ISFV); V_{ISF} with initial value V_{ISF0}) compartments are shown as buckets, while the fluid shift is shown as fluid flow through a valve connecting the buckets, which is controlled by the fluid shift mechanism abstracted into a PI controller to eliminate the PV error $e_P(t)$.

Considering that PV is measured as the fractional change from its initial value (V_{P0}) in practice (e.g. [41–45]), Eq. (5) can be rewritten in terms of the fractional change in PV $\Delta \breve{V}_P(t) = \frac{\Delta V_P(t)}{V_{P0}}$ (also called fractional PV″ hereafter) as follows: