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Closed-Loop Fluid Resuscitation Control Via Blood Volume Estimation

This paper presents a closed-loop control of fluid resuscitation to overcome hypovolemia based on model-based estimation of relative changes in blood volume (BV). In this approach, the control system consists of a model-based relative BV (RBV) estimator and a feedback controller. The former predicts relative changes in the BV response to augmented fluid by analyzing an arterial blood pressure (BP) waveform and the electrocardiogram (ECG). Then, the latter determines the amount of fluid to be augmented by comparing target versus predicted relative changes in BV. In this way, unlike many previous methods for fluid resuscitation based on controlled variable(s) nonlinearly correlated with the changes in BV, fluid resuscitation can be guided by a controlled variable linearly correlated with the changes in BV. This paper reports initial design of the closed-loop fluid resuscitation system and its in silico evaluation in a wide range of hypovolemic scenarios. The results suggest that closed-loop fluid resuscitation guided by a controlled variable linearly correlated with the changes in BV can be effective in overcoming hypovolemia: across 100 randomly produced hypovolemia cases, it resulted in the BV regulation error of 7.98 ± 171.6 ml, amounting to 0.18 ± 3.04% of the underlying BV. When guided by pulse pressure (PP), a classical controlled variable nonlinearly correlated with the changes in BV; the same closed-loop fluid resuscitation system resulted in persistent under-resuscitation with the BV regulation error of −779.1 ± 147.4 ml, amounting to −13.9 ± 2.65% of the underlying BV. [DOI: 10.1115/1.4033833]

Introduction

Hypovolemia refers to a state of decreased BV, attributable to many injuries and pathophysiologic conditions such as hemorrhage, burns, trauma, and infections (e.g., sepsis) [1–8]. Patients with hypovolemia require fluid resuscitation to restore their volume state. The ultimate goal of fluid resuscitation is to restore venous return, cardiac output (CO), and essentially BP, by optimizing BV. In many hypovolemic scenarios, early and closely monitored resuscitation is crucial for survival; previous investigations indicate that delayed and inadequate fluid resuscitation was shown to be responsible for increased mortality and morbidity [3,9–11], while over-resuscitation resulted in adverse side effects such as pulmonary edema [12].

Considering the lack of established therapeutic guidelines for fluid resuscitation [13–15], clinicians have used a variety of therapeutic endpoints of his/her own choice to perform fluid resuscitation. Examples include BP, PP, central venous pressure, urine output, PP variability (PPV), and so on [14,16–28]. A big problem associated with today's manual and heterogeneous treatment protocols is that it is very challenging for a clinician to deliver consistent quality in fluid resuscitation across these diverse endpoints and strategies, due to the limited familiarity with all the therapeutic protocols as well as the extreme workload. Therefore, new technological advances in automated closed-loop control for fluid resuscitation may largely improve the treatment efficacy while reducing clinician's workload. Especially, such a technology may find meaningful applications in low-resource settings such as combat/mass casualty care.

Though (perhaps) the first closed-loop control system for fluid resuscitation was reported in early 1980s [29], it is only very recently that closed-loop fluid resuscitation started to receive significant attention, with several closed-loop control and decision-support systems reported in the literatures [14,16–28,30–33]. Similarly to manual fluid resuscitation, the goal in many of these systems is to augment fluid until a physiologic endpoint (such as BP, CO, tissue oxygenation, urine output, and PPV) reaches a target set by the clinician. The underlying assumption is that BV can be optimized (i.e., the sensitivity of BV to additional fluid augmentation is minimized) by regulating these physiologic endpoints to a target. However, the success of the above-mentioned efforts has been modest due to the limited efficacy of the controlled variables used. Most importantly, the controlled variables are not linearly correlated with BV, which may poorly predict fluid responsiveness [22,34–39]. In particular, a few recent reports indicate that PP, a well-known surrogate measure of stroke volume (SV), underestimates SV [40–42]. Thus, a major leap in the closed-loop fluid resuscitation technology must be accompanied by advancement in the monitoring technologies for BV-responsive endpoints. For this reason, we envision that the capability for high-fidelity estimation of BV may enable more effective BV management in hypovolemic patients.

This paper presents a closed-loop control of fluid resuscitation to overcome hypovolemia based on model-based estimation of relative changes in BV (called RBV). In this approach, the control system consists of a model-based RBV estimator and a feedback controller. The former predicts the RBV response to augmented fluid by analyzing an arterial BP waveform and the ECG. Then, the latter determines the amount of fluid to be augmented by comparing target versus predicted RBV. In this way, unlike many previous methods for fluid resuscitation based on controlled variable(s) nonlinearly correlated with the changes in BV (hereafter called as nonlinear surrogate(s)) [25,43–45], fluid resuscitation can be guided by a controlled variable linearly correlated

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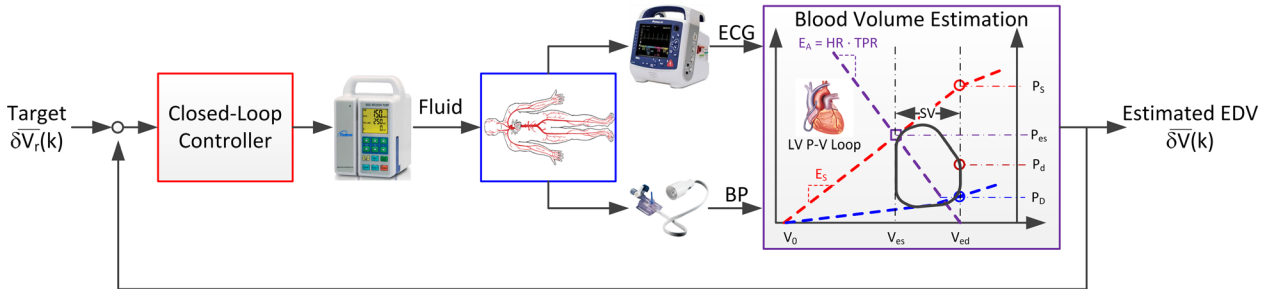

Fig. 1 Closed-loop fluid resuscitation via model-based estimation of relative changes in left-ventricular (LV) end-diastolic volume (EDV) as linear surrogate of relative changes in BV

with the changes in BV (hereafter called as linear surrogate). This paper reports initial design of the closed-loop fluid resuscitation system and its in silico evaluation in a wide range of hypovolemic scenarios.

Closed-Loop Fluid Resuscitation

The closed-loop fluid resuscitation system proposed in this paper is made up of a model-based RBV estimator and a closed-loop controller as well as an infusion pump as an actuator and a BP monitor and ECG as sensors (Fig. 1). The model-based RBV estimator predicts the relative changes in LV EDV as RBV response to fluid, by analyzing an arterial BP waveform and the ECG based on a LV pressure–volume (P–V) loop model [46–51]. The closed-loop controller compares the discrepancy between target versus predicted RBV and computes the amount of fluid that must be augmented to optimize BV. The integration of a RBV estimator and a closed-loop controller enables fluid resuscitation with a linear surrogate of BV, which may outperform many previous fluid resuscitation methods relying on nonlinear surrogates of BV. The RBV estimator and the closed-loop controller are described in detail below.

Model-Based BV Estimation. The model-based RBV estimator predicts the RBV response to fluid by analyzing an arterial BP and the ECG. The estimator is built upon an LV P–V loop model [46–51] (Fig. 2). The model is governed by the end-systolic and end-diastolic P–V relationships given by

$$P_S(V(t)) = E_S(V(t) - V_0) \tag{1a}$$

$$P_D(V(t)) = B[e^{A(V(t)-V_0)} - 1] \tag{1b}$$

where P_S (mmHg) and P_D (mmHg) are the BP values corresponding to the end-systolic and end-diastolic P–V relationships at an LV volume $V(t)$ (ml), E_S (mmHg/ml) is the end-systolic LV elastance, A and B are constants specifying the end-diastolic P–V relationship, and V_0 (ml) is the LV volume corresponding to zero LV pressure. The so-called maximum LV pressure is then given by the weighted average of P_S and P_D

$$P_{\mathrm{LV}}^{\max}(t) = \phi(t)P_S(V(t)) + (1 - \phi(t))P_D(V(t)) \tag{2a}$$

$$\phi(t) = 0.5\left(1 - \cos\frac{\pi t}{T_{\mathrm{es}}}\right) \tag{2b}$$

where $\phi(t)$ is the activation function [46,47] and T_{es} is the ejection duration, which may be derived from the analysis of an arterial BP waveform [52,53]. It is noted that $P_{\mathrm{LV}}^{\max}(t)$ versus $V(t)$

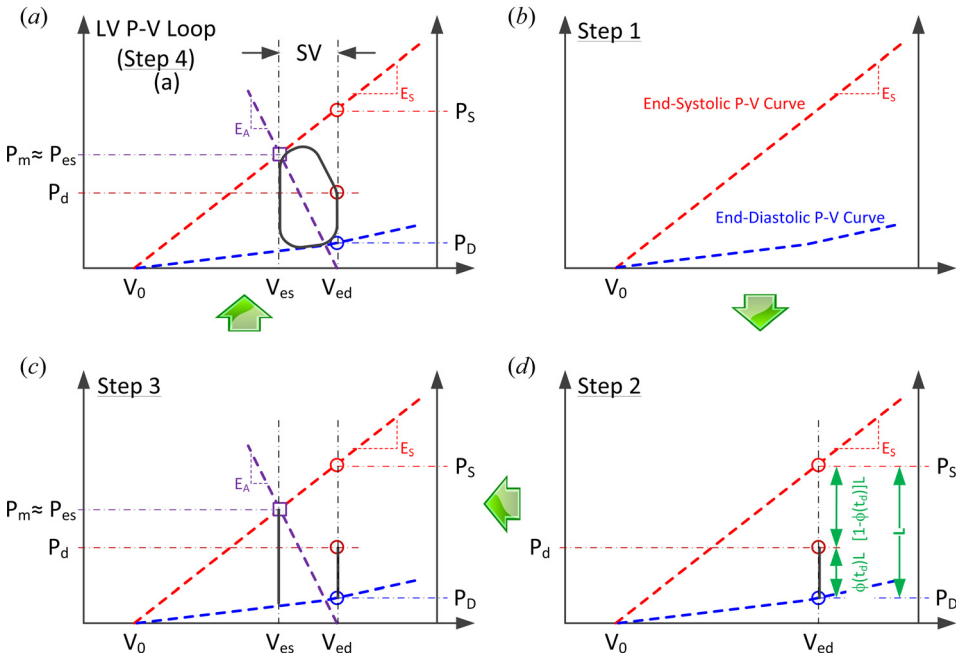

Fig. 2 Model-based RBV estimation: (*a*) LV pressure–volume (*P–V*) loop and (*b*)–(*d*) Estimation of LV *P–V* loop based on BP and ECG

constitute the LV P–V loop (the black solid loop in Fig. 2(*a*)). It hits the end-systolic P–V relationship at the end systole upon the aortic valve closure, at which $V(t)$ corresponds to end-systolic volume (ESV) V_{es}. In addition, it overlaps with the end-diastolic P–V relationships during the LV filling period, at the end of which $V(t)$ becomes EDV V_{ed}. Considering the triangle constructed by the $(V(t),\ P(t))$ coordinates $(V_0,\ 0)$, $(V_{es},\ P_{es})$, and $(V_{ed},\ 0)$, the following relationships hold at the end-systole:

$$P_{es} = E_S(V_{es} - V_0) \tag{3a}$$

$$P_{es} = E_A(V_{ed} - V_{es}) = E_A \mathrm{SV} \tag{3b}$$

where E_A (mmHg/ml) is called the arterial elastance [46,47], and SV is SV (ml). Under the assumption that end-systolic BP is very close to mean BP [54–56], Eq. (3*b*) can be rewritten as follows:

$$P_m = R \cdot F_{HR} \cdot \mathrm{SV} = E_A \mathrm{SV} \tag{3c}$$

where P_m (mmHg) is mean BP, R (mmHg min/ml) is total peripheral resistance (TPR), and F_{HR} (bpm) is heart rate (HR). It is obvious from Eq. (3*c*) that $E_A = R \cdot F_{HR}$.

The above governing equations for the LV P–V loop form the basis for the model-based RBV estimator as described in detail below. The model-based RBV estimator predicts the trends of V_{ed}, V_{es}, and SV values in four steps, by analyzing the measurements of an arterial BP and the ECG (Figs. 2(*b*)–2(*d*)). The underlying assumption is that the values of A and B in the end-diastolic P–V relationship in Eq. (1*b*) are known a priori. Since the estimator predicts V_{ed}, V_{es}, and SV in the absence of any BV and/or blood flow measurements, it can only predict scaled (rather than absolute) BV values. In Step 1, a value is assumed for E_S (this is necessary because only BP but not BV and/or blood flow is available). This allows the end-systolic P–V relationship to be constructed (Fig. 2(*b*)). In Step 2, $V_{ed} - V_0$ is predicted using Eq. (2) based on the measurement of diastolic BP (Fig. 2(*c*))

$$P_{LV}^{\max}(t_d) = P_d = \phi(t_d)P_S(V_{ed}) + (1 - \phi(t_d))P_D(V_{ed}) \tag{4}$$

where P_d is the diastolic BP measurement, while t_d is the time instant corresponding to the occurrence of diastolic BP relative to the beginning of systole, computed as the time interval between the ECG R-wave and the corresponding diastolic BP. Note that $V(t_d) = V_{ed}$. This step may be interpreted as predicting the value of V_{ed} corresponding to P_d for a specified E_S (this in turn implies that the value of predicted V_{ed} depends on the assumed value of E_S). In Step 3, $V_{es} - V_0$ is predicted using Eq. (3*a*) based on the measurement of mean BP (Fig. 2(*d*)) assuming that $P_{es} \cong P_m$. Finally, in Step 4, the LV P–V loop is constructed and SV is predicted as $\mathrm{SV} = V_{ed} - V_{es}$ (Fig. 2(*a*)). In this way, scaled BVs (including EDV, ESV and SV) can be predicted solely based on an arterial BP waveform and the ECG measurements, where the scaling depends on the value of E_S assumed.

It is noted that the adverse impact of the assumed E_S on the fidelity of predicted volumes may be minimal. As can be seen in Fig. 2(*a*), changes in E_S are accompanied by the corresponding changes in V_{ed} and V_{es}: as E_S becomes larger, V_{ed} and V_{es} become smaller (which can also be verified from Eqs. (3*a*) and (4)). To illustrate, consider the triangle constructed by the $(V(t),\ P(t))$ coordinates $(V_0,\ 0)$, $(V_{es},\ P_{es})$, and $(V_{ed},\ 0)$. An increase in E_S leads to a linearly proportional decrease in V_{ed} and V_{es} (here the decrease in V_{ed} is not strictly linear, since it is subject to both end-systolic and end-diastolic P–V relationships as shown in Eq. (4); yet, the contribution of end-diastolic P–V relationship is typically small at diastolic BP). Thus, E_S primarily affects the scaling associated with the predicted volumes, but the volumes thus predicted still exhibit (approximately) linear correlation with the actual volumes.

Feedback Control. It is well known that the fluid augmented to the body is distributed in blood and interstitial fluid in both hypovolemic and normovolemic states [57,58]. However, most of the fluid augmented beyond a certain hypervolemic level is not stored in blood but is shifted to interstitial fluid [59]. This leads to a decrease in the sensitivity of BV to augmented fluid as BV increases. Noting that EDV predicted by the RBV estimator is a scaled value, a closed-loop controller may be designed so that the relative change in EDV is regulated at a reference target in a run-to-run fashion. In this approach, each resuscitation run starts when BV response to fluid bolus from the prior run has reached a steady state. In each resuscitation run, our closed-loop controller performs three tasks: (1) it predicts RBV; (2) it refines the predicted RBV via a smoothing technique; and (3) it computes and then applies fluid bolus required to drive the RBV to its target value.

As described in the "Model-Based BV Estimation" section, the RBV estimator predicts the EDV response (denoted as $\mathrm{EDV}(k)$) to the fluid $V_F(k)$ at the end of kth resuscitation run by analyzing an arterial BP and the ECG. Then, the RBV $\overline{\delta V}(k)$, defined as the relative change in EDV, at the kth resuscitation run is computed as follows:

$$\overline{\delta V}(k) = \frac{\mathrm{EDV}(k) - \mathrm{EDV}(k-1)}{\mathrm{EDV}(k-1)} \frac{\overline{V}}{V_F(k)} \tag{5}$$

where $\mathrm{EDV}(k-1)$ is the EDV response associated with the $(k-1)$-th resuscitation run, and $\overline{V}$ is a normalizing volume to reflect the fact that RBV also depends on $V_F(k)$: $\overline{\delta V}(k)$ is proportional to $V_F(k)$. $\overline{\delta V}(k)$ is compared with the reference $\overline{\delta V}_r(k)$, and the fluid to be augmented during the $(k+1)$-th run $V_F(k+1)$ is determined by the closed-loop controller based on the error between $\overline{\delta V}_r(k)$ and $\overline{\delta V}(k)$.

In this paper, the target is defined as 15% change in EDV in response to 500 ml fluid augmentation in the steady-state ($\overline{\delta V}_r(k) = 0.15$ and $\overline{V} = 500$ ml; note that a target of 15% used here is commensurate with the targets used in the previous investigations [60–64]). In our initial effort to demonstrate the feasibility of the proposed approach, we employed a classical proportional–integral–derivative (PID) controller as the closed-loop controller. In each resuscitation run, the PID controller compares $\overline{\delta V}(k)$ with $\overline{\delta V}_r(k)$ to determine the fluid to be augmented. The control command is computed by

$$u(k) = K_p e(k) + K_i \sum e(k) + K_d \frac{\{e(k) - e(k-1)\}}{T_s} \tag{6}$$

where k is the sequence of fluid administration, $e(k) \triangleq r(k) - y(k) = \overline{\delta V}_r(k) - \overline{\delta V}(k)$, K_p, K_i and K_d are the PID gains, respectively, and T_s is the sampling interval.

Noting that LV elastance decreases as BV increases [65–67], the closed-loop fluid resuscitation system may benefit from appropriate updating of the value of E_S in the RBV estimator, so that RBV can be predicted more accurately. An increase in BV may result in a decrease in HR via autonomic-cardiac regulation, thereby increasing the ejection duration [68–70]. Since quantitative relationship between the decrease in E_S and the associated increase in ejection duration during fluid resuscitation does not seem to be established, we incorporated a simple updating rule for E_S shown in Eq. (7) into the closed-loop fluid resuscitation system

$$E_S(k) = \frac{T_{es}(0)}{T_{es}(k)} E_S(0) \tag{7}$$

where $E_S(k)$ is the value of LV elastance assumed by the RBV estimator in the kth run, and $T_{es}(k)$ is the associated ejection duration.

Our preliminary in silico simulation showed that the sequence of $\overline{\delta V}$ predicted by the model-based RBV estimator ($\overline{\delta V}(k)$, $k = 1, \cdots, N$) was often subject to inaccuracy due to errors associated with the estimation of EDV ($\mathrm{EDV}(k)$, $k = 0, \cdots, N$; presumably caused by the simplifying assumptions for the RBV estimator,

including the use of population-averaged A and B, mean BP as surrogate of end-systolic BP, and the errors associated with Eq. (7)), which often led to premature under-resuscitation or over-resuscitation (see Fig. 3 for an example of under-resuscitation). To improve the robustness of the controller to the inaccuracy in $\overline{\delta V}(k)$, a model-based smoothing is employed. Our in silico simulation results suggest that the sequence of $\overline{\delta V}(k)$ may be adequately fitted using the following power function:

$$\overline{\overline{\delta V}}(k) = \alpha_1(k)\left[\sum_{i=1}^{k} V_F(i)\right]^{\alpha_2(k)} + \alpha_3(k) \tag{8}$$

where $\overline{\overline{\delta V}}(k)$ is the smoothed $\overline{\delta V}(k)$, and $\alpha_1(k)$, $\alpha_2(k)$ and $\alpha_3(k)$ are the parameters to be tuned. The smoothing model in Eq. (8) is updated at every resuscitation run. More specifically, once $\overline{\delta V}(k)$ is computed using Eq. (5) at the end of kth run, the parameters $\alpha_1(k)$, $\alpha_2(k)$ and $\alpha_3(k)$ in the smoothing model are updated by fitting the model in Eq. (8) to the sequence $\overline{\delta V}(j), j = 1, \ldots, k$

$$\begin{aligned}\{\alpha_1^*(k), \alpha_2^*(k), \alpha_3^*(k)\} &= \text{argmin}\sum_{j=1}^{k}\left(\overline{\delta V}(j) - \overline{\overline{\delta V}}(j)\right)^2 \\ &= \text{argmin}\sum_{j=1}^{k}\Bigg(\overline{\delta V}(j) \\ &\quad - \left\{\alpha_1(k)\left[\sum_{i=1}^{j} V_F(i)\right]^{\alpha_2(k)} + \alpha_3(k)\right\}\Bigg)^2\end{aligned} \tag{9}$$

Then, the closed-loop controller computes the error $e(k)$ as follows so that the volume is optimized in an aggressive fashion (in that $e(k)$ becomes maximally negative to result in maximal control action in this way)

$$e(k) = \overline{\delta V}_r(k) - \max\left\{\overline{\overline{\delta V}}(k), \overline{\delta V}(k)\right\} \tag{10}$$

The fluid resuscitation is completed when both $\overline{\overline{\delta V}}(k)$ and $\overline{\delta V}(k)$ fall below $\overline{\delta V}_r(k)$, that is, $u(k) = 0$ if $e(k) \geq 0$. Hence, assuming that the model-based RBV estimator provides reasonably accurate prediction of RBV, the closed-loop system is stable as far as BV is concerned because BV cannot grow indefinitely under the proposed control law. On the other hand, steady-state error in BV may persist because fluid inappropriately infused due to the inaccuracy associated with the prediction of RBV cannot be withdrawn.

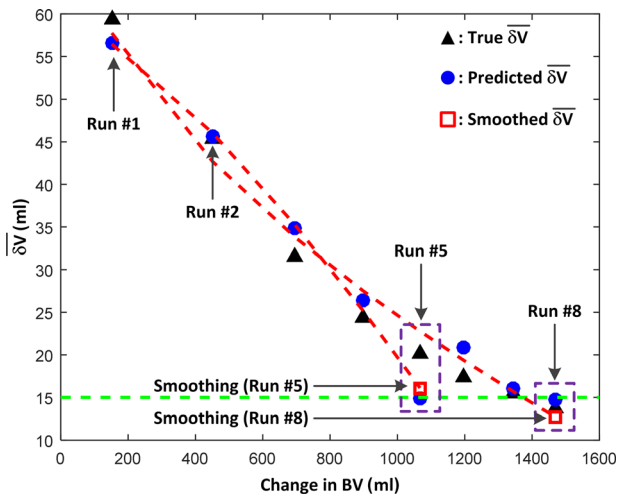

Fig. 3 Model-based smoothing of RBV. The RBV predicted by the model-based RBV estimator at the end of fifth fluid resuscitation run ($\overline{\delta V}(5)$ = 14.8% < 15% target) was not accurate, resulting in premature fluid resuscitation that was stopped after fifth run. The model-based smoothing predicted $\overline{\overline{\delta V}}(5)$ = 16.1% > 15% and the fluid resuscitation continued up to eighth run, preventing premature fluid resuscitation.

Methods

The validity of the closed-loop fluid resuscitation system proposed in this paper was tested via a rigorous in silico simulation study. A high-fidelity cardiovascular physiology model reported in a previous study [71–73] was implemented and refined to be applicable to the in silico simulation. Then, this model was used to produce a total of 100 hypovolemia cases with wide-ranging physiologic conditions. The closed-loop fluid resuscitation system was simulated on the 100 hypovolemic cases to evaluate the model-based RBV estimator and run-to-run closed-loop fluid resuscitation controller. Details follow.

In Silico Model. A mathematical model was employed that incorporates the heart, systemic and pulmonary circulations (both arterial and venous) and the autonomic-cardiac regulation mechanisms for TPR, systemic venous unstressed volumes, HR and E_S [71–73]. Each of the left and right hearts was modeled as a variable elastance model [71]. The systemic and pulmonary circulations were modeled as lumped 5- and 3-compartment systems, respectively. Each compartment employed lumped flow resistance, compliance, and unstressed volume. The autonomic-cardiac regulation model included afferent and efferent pathways as well as the actions of effector mechanisms. In sum, the in silico model was described by a set of 22 nonlinear ordinary differential equations.

The change in BV due to hypovolemia and fluid resuscitation was simulated by altering the systemic arterial BV. It was assumed that fluid augmented to the patient is distributed to the blood and interstitial fluid at a constant ratio of 1:2.3 in the steady state [59].

In Silico Closed-Loop Control Simulation. To evaluate the proposed closed-loop fluid resuscitation system, a total of 100 hypovolemia cases was created by randomly perturbing the key model parameters from the respective nominal value, including the autonomic-cardiac regulation gains (up to ±50%), flow resistances (up to ±50%), LV and RV elastances (up to ±50%), HR (up to ±20%), venous unstressed volumes (up to ±10%), and end-diastolic P–V relationship parameters A and B (up to ±20%). These ranges were determined via trial and error so that the in silico model could produce reasonable key hemodynamic responses of BP, HR, and CO both before and after fluid resuscitation (see "Results and Discussion" section).

For each simulated hypovolemia case, the closed-loop fluid resuscitation system first employed the RBV estimator to predict scaled EDV, assuming nominal (population-averaged) $E_S(0)$, A and B parameters: $E_S(0) = 3$ mm Hg, $A = 0.014$ ml^{-1}, and $B = 1.5$ mmHg. It then augmented 500 ml fluid ($= V_F(1)$) and assessed the RBV response, as the relative change in scaled EDV, via the RBV estimator ($\overline{\delta V}(1)$). In case the RBV was greater than 15% per 500 ml fluid, the closed-loop fluid resuscitation system computed the fluid to be augmented in the next run using Eq. (6). The fluid thus computed was augmented, and the RBV response was again assessed via the RBV estimator. This iterative control action was repeated until the RBV response to fluid resuscitation dropped to below 15% per 500 ml fluid. The PID controller gains were tuned by rigorous trial and error to yield a fluid volume ranging from 400 ml to 1 l in all the hypovolemia cases, so that the administration of extremely large/small volume of fluid could be prevented.

To further investigate the efficacy of the proposed closed-loop fluid resuscitation system, the closed-loop controller in Eq. (6) was run with PP as controlled variable instead of RBV.

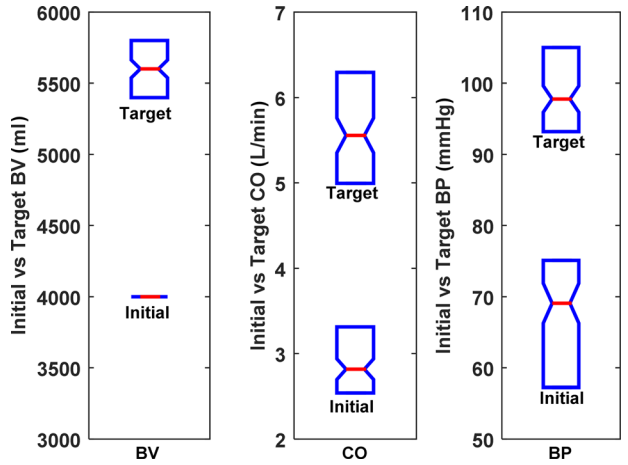

Fig. 4 Distributions of the initial and target BV, CO, and BP

Data Analysis. For each simulated hypovolemia case, the predicted EDV and RBV values as well as other physiologic responses (such as BP) were archived across the run-to-run closed-loop fluid resuscitation. Then, the proposed closed-loop fluid resuscitation system was evaluated by analyzing the following aspects. First, the model-based RBV estimator was evaluated based on the predicted BV measures (V_{ed}, V_{es} and SV in Fig. 2(*a*)). Noting that these measures are relative, they were calibrated to their true counterparts. Then, the goodness of the measures was quantified by their correlations to the respective true counterparts. Second, the closed-loop controller was evaluated based on its volume optimization performance. The desired amount of fluid augmentation was computed as the total volume of fluid augmented by the time the measured RBV attained 15% per 500 ml fluid challenge. The actual volume of fluid augmented was computed as the total volume of fluid augmented by the closed-loop controller in Eq. (6) based on the predicted RBV as feedback. Then, the actual fluid volume was compared with its desired counterpart.

The RBV-based versus PP-based closed-loop fluid resuscitation systems were compared via the accuracy in predicting BV as well as the errors associated with the volume optimization.

Results and Discussion

Closed-loop automated fluid resuscitation may make contributions in improving the efficacy of hypovolemia treatment as well as in reducing clinician's workload. Many existing treatment protocols rely on nonlinear surrogates of BV, often leading to limited volume optimization performance. In this paper, we proposed a closed-loop fluid resuscitation system based on RBV, a linear surrogate of BV. Reported in this paper are the initial design and in silico testing of the proposed closed-loop fluid resuscitation system.

In Silico Simulation. Figure 4 shows the distributions of the initial and target BV, CO, HR, and BP spanned by the 100 in silico hypovolemia cases. Despite the constant initial BV of 4 l, initial CO (2.9 ± 0.7 lpm), HR (129 ± 19 bpm), and BP (64 ± 17 mmHg) as well as target BV (5.6 ± 0.25 l), CO (5.7 ± 1.0 lpm), HR (84 ± 11 bpm), and BP (99 ± 9.1 mmHg) are widely distributed, suggesting that the randomly produced in silico hypovolemia cases encompass wide-ranging hypovolemic conditions, enabling a rigorous in silico testing of the closed-loop fluid resuscitation system.

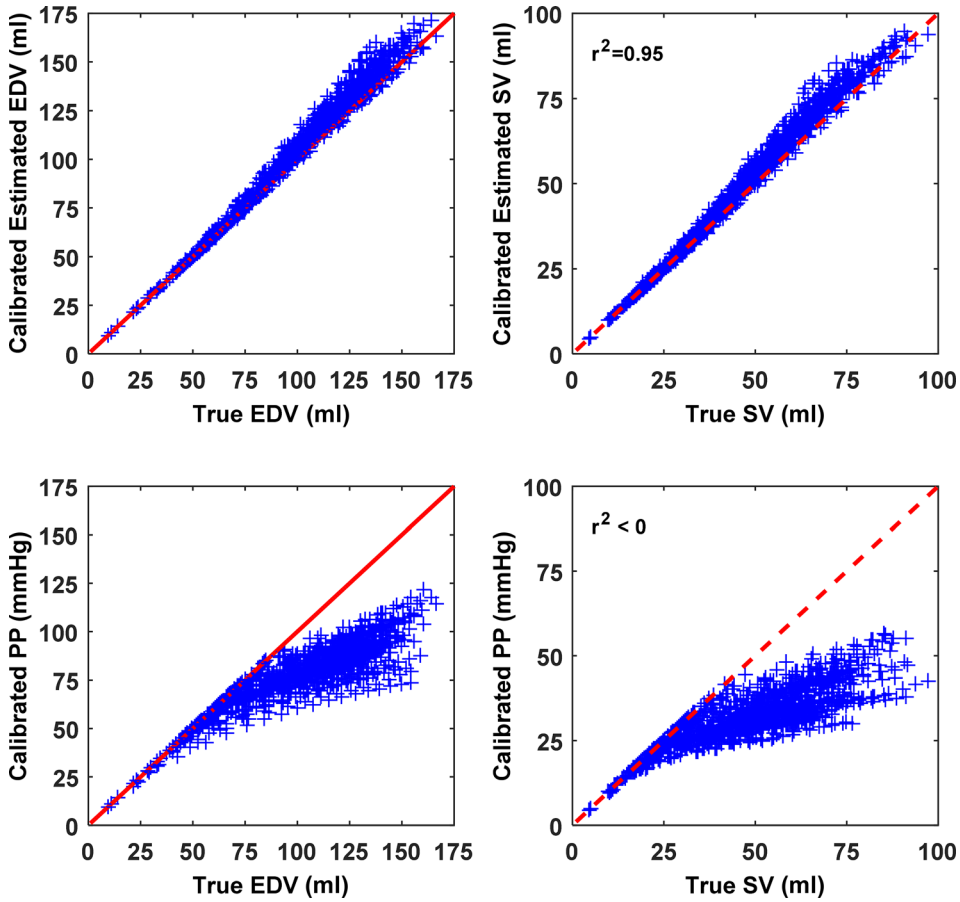

Fig. 5 True versus predicted EDV and SV: (*a*) Model-based RBV estimator and (*b*) PP

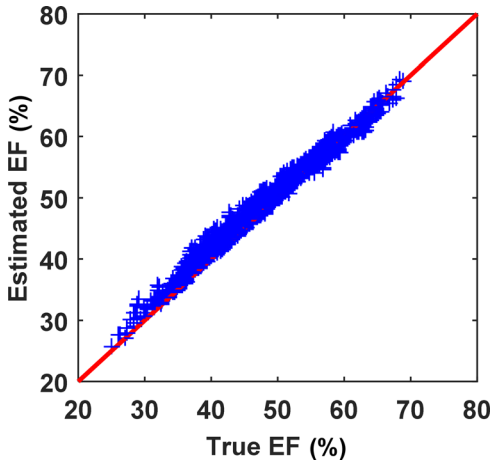

Fig. 6 True versus predicted EF

Model-Based BV Estimation. Figure 5 shows the correlation between true versus predicted EDV values across the closed-loop fluid resuscitation in all the subjects (Fig. 5(*a*)) and the correlation between true EDV versus PP calibrated to EDV (Fig. 5(*b*)). The model-based RBV estimator could yield scaled EDV and SV that correlated well with the true EDV and SV after calibration to account for the unknown E_S (see Fig. 2(*b*)). In contrast, PP largely underestimated both EDV and SV due to the nonlinear LV P-V relationship: in particular, the slope of the diastolic *P–V* relationship gets steeper as EDV increases whereas its systolic counterpart gets more gradual with EDV (Fig. 2), which essentially reduces the change in PP relative to EDV.

The efficacy of the model-based RBV estimator may also be demonstrated by its ability to predict the LV ejection fraction (EF), an important inotropic measure of the heart [74]. Figure 6 shows that the EF predicted by the model-based RBV estimator correlates well with the true EF even without calibration. As mentioned earlier, the RBV estimator can only estimate scaled (rather than absolute) BV measures since it utilizes only BP but not BV or blood flow (which is why E_S must be assumed in Fig. 2(*a*)). Regardless, noting that EF is the ratio between SV and EDV (EF = SV/EDV), the RBV estimator was able to predict the absolute value of the EF by canceling the unknown scaling factor imposed on EDV and SV due to E_S. This result suggests that the model-based RBV estimator preserves the absolute scaling relationship between EDV and SV it predicts, making them credible and consistent surrogates of the BV status.

Feedback Control. Figure 7(*a*) shows the results of closed-loop control across the 100 hypovolemia cases. The closed-loop controller, when used with the RBV estimator, could offer a tight regulation of BV at the desired relative change of 15% per 500 ml fluid challenge. On the contrary, the same controller, when used with PP, performed poorly by drastically under-resuscitating all the cases. As illustrated in Fig. 5(*b*), this is due to the underestimation of EDV by PP. In fact, the RBV at the last fluid resuscitation run with PP ranged between 22% and 34%, which is largely higher than the desired value of 15%. This contrasting target regulation capability associated with the RBV estimator versus PP entailed a large difference in their volume optimization efficacy: the BV regulation error at the end of the fluid resuscitation was 7.98 ± 172 ml and -779 ± 147 ml for the RBV estimator and PP, respectively, which amounted to $0.18 \pm 3.04\%$ and $-13.9 \pm 2.65\%$ of the desired BV (Fig. 7(*b*)). Across the 100 cases, the desired change in BV was 1616 ± 249 ml. In the case of the RBV estimator, the actual change in BV after the completion of fluid resuscitation was above the target in 50 cases, with the over-resuscitated BV of only 146 ± 87 ml. The actual change in BV was below the target in the remaining 50 cases, with the under-resuscitated BV of only 130 ± 113 ml. In the case of PP, the actual change in BV was below the target in all 100 hypovolemia cases, with the large under-resuscitated volume of 779 ± 147 ml. In sum, the in silico testing results strongly suggested the potential advantage of exploiting linear surrogates of BV in optimizing BV via closed-loop fluid resuscitation.

Limitations. The study conducted in this paper has a few limitations. First, the RBV estimator has several weaknesses. It involved population-averaged parameters A and B in the end-diastolic *P–V* relationship in Eq. (1*b*) that may incur inaccuracy in predicting EDV and RBV. In addition, the activation function $\phi(t)$ was assumed to be perfectly known. It has been suggested from previous work on LV *P–V* loop models [47,50,75] that this may be the case. However, any errors associated with $\phi(t)$ may compromise the fidelity of EDV and RBV predicted by the RBV estimator. Further, it was also assumed that E_S may be tracked accurately from the ejection duration (see Eq. (7)), which is essentially an approximation that must be validated experimentally. Follow-up work to investigate these weaknesses of the RBV estimator is required to rigorously justify these simplifications (and improve if necessary), ideally based on experimental study. Second, the tuning of the controller gains in this paper was empiric. The focus of this paper was to investigate a new approach to closed-loop fluid resuscitation guided by a linear surrogate of BV. Thus, primary effort was made toward initial design and in silico testing of the proposed closed-loop fluid resuscitation system rather than optimizing each element in the system. In the follow-

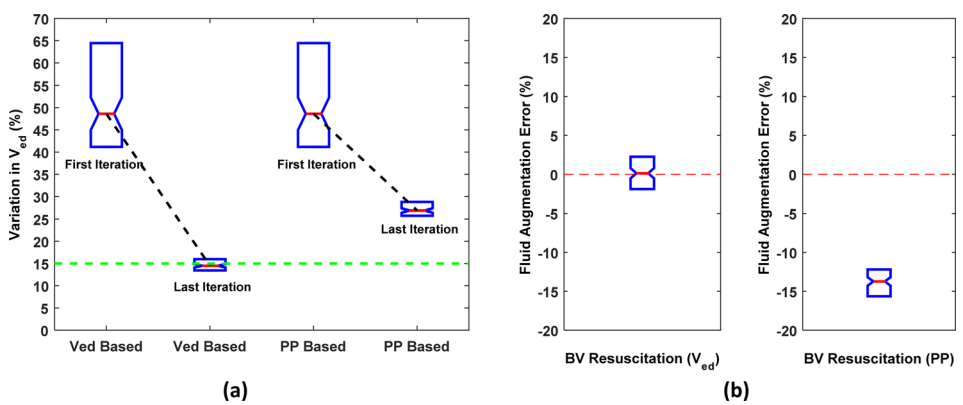

Fig. 7 Efficacy of run-to-run closed-loop fluid resuscitation based on predicted RBV versus PP. (*a*) The relative (percent) change in true EDV at the first and the last runs. The control objective was to regulate the change in the last run at 15% (green horizontal line). (*b*) Percent BV regulation error.

up study, more systematic model-based control design and analysis must be conducted to optimize the performance of the closed-loop controller. Third, some crucial physiological elements were not considered in the in silico model used in this paper for controller testing. In particular, the in silico model used in this paper did not include models to reproduce urine excretion. More rigorous in silico testing of the proposed closed-loop fluid resuscitation system is desired. Fourth, potential real-world challenges in implementing the proposed closed-loop fluid resuscitation system were not examined. These challenges include, among others, the robustness of the system to sensor noise, beat-to-beat variability in BP and ECG, and time-varying fluid distribution between blood and interstitial fluid. The closed-loop fluid resuscitation system must ultimately be validated in experimental investigations.

Conclusion and Future Work

In this paper, we presented and conducted an in silico evaluation of a closed-loop control system for fluid resuscitation guided by a linear surrogate of BV. Rigorous in silico study showed that the proposed closed-loop fluid resuscitation system is effective in optimizing volume to overcome hypovolemia by virtue of its ability to predict and exploit a linear surrogate of BV via the model-based RBV estimator. Future effort will be directed to further improvement and more rigorous model-based and experimental investigation of the proposed closed-loop fluid resuscitation system.

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