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Myocardial oxygen balance during acute normovolemic hemodilution: A novel compartmental modeling approach

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ABSTRACT

Background: Hemodilution was introduced initially as a blood conservation technique to reduce allogeneic blood transfusion in patients undergoing surgical procedures. Although the technique has been approved by the National Institute of Health consensus panel, limits of hemodilution under anesthetic conditions have not been established as they have in animal models.

Methods: A novel multi-compartmental modeling approach has been proposed that includes the effect of anesthesia to quantify the effect of hemodilution on myocardial oxygen balance during myocardial ischemia.

Results: The results showed that isovolemic hemodilution would cause detrimental effects around a hematocrit of 15%. Even though the fall in oxygen content caused by the decrease in hemoglobin concentration was compensated by an increase in coronary blood flow induced by hypoxic vasodilation and decreased viscosity, the endocardial tissue received less oxygen compared to the epicardial regions, and this sub-endocardial ischemia eventually led to cardiac failure. Statistical analysis also showed that the type of acellular replacement fluid failed to affect the heart rate, the stroke index or the cardiac index during hemodilution, and supplemental oxygen improved the endocardial oxygen supply.

Conclusion: The model validates the clinical conclusions that sub-endocardial ischemia causes cardiac failure under extreme hemodilution conditions and the model can also be easily integrated into other human simulators.

1. Introduction

Acute Normovolemic Hemodilution (ANH) is a blood conservation technique that involves the extraction of blood from patients' central veins before they undergo the surgical procedure and after they have been anesthetized. The collected blood is stored in blood bags with anticoagulants at room temperature. The extracted blood is replaced with combinations of crystalloids and/or colloids to maintain normovolemia and the blood is transfused back in the operating room in the reverse order of collection after the significant blood loss period is over or when there are indications for transfusion such as a transfusion hematocrit or hemoglobin. The method has several conceptual advantages over allogenic transfusion such as increased oxygen extraction and decreased blood viscosity due to reduced hematocrit. There is a body of clinical research that assesses the safety and the efficacy of the procedure ever since its introduction to perioperative blood management [1–12]. The technique has been recommended by the National Institute of Health (NIH) consensus panel in 1988 among other techniques that allay fears of using allogenic Red Blood Cell (RBC) transfusions and the American Society of Anesthesiologists (ASA) task force was also in agreement with the NIH panel through the published guidelines that were recently updated [8]. Even then, there is diffidence among clinicians to pursue ANH, for the technique is bereft of convincing proof of safety, efficiency and cost-effectiveness compared to other blood management techniques [6].

In order to mitigate these concerns, meta-analyses of multi-centered clinical trials have been performed to understand the effects of the type of surgery involved, the type of crystalloid/colloid used during hemodilution, the volume of hemodilution, drug infusions, monitoring of hemodynamic parameters and RBC transfusion protocols [5,6]. The authors of the meta-analyses concluded that ANH reduced allogenic transfusion. However, heterogeneity in the type of surgeries resulted in an ambiguous interpretation of the technique's efficiency. Throughout the period since the introduction of ANH, the physician community has

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been at odds regarding the volume of hemorrhage (sum of volume that is diluted and volume that is lost through bleeding) that has to occur to have a positive effect in terms of reducing allogenic RBC transfusion and fewer complications. Most studies acquiesce in performing higher volumes of hemodilution to achieve its benefits [3,4]. Furthermore, hemodilution directly affects the blood's physical properties such as viscosity which directly affects the oxygenation of tissues [9,10] and there are some studies that recommend clinicians to heed to potential complications in kidneys and cognitive functions due to hypoxia [11,12]. Furthermore, ANH has proven effective in major liver resection surgeries [1], neurosurgery [2], hip arthroplasty [1] and radical prostatectomy [3]. Although ambiguous evidence exists in cardiac procedures based on the conclusions of meta-analyses, Goldberg et al. [4] concluded that the benefits of ANH can be achieved by performing hemodilution greater than 800 ml.

Despite these advantages, clinical limits of hemodilution have not been established for sedated human subjects similar to animal models [7,13]. One of the major physiological phenomena observed during isovolemic hemodilution in conscious healthy volunteers is the increase in myocardial work due to increased heart rate [14] and the failure of myocardial tissue sets the absolute limit of the isovolemic hemodilution procedure. Certain older clinical recommendations [15] and newer computational studies [16] are consistent with such a surmise. The ASA taskforce advanced the idea that transfusion should be based on complications of anemia rather than a trigger hematocrit and the updated guidelines for perioperative management further endorse this and ask physicians to consider ANH in high blood loss surgeries [8].

Mathematical models have been applied to understand ANH since the 1970s [17–19]. However, these models do not consider the dynamic changes that happen in the cardiovascular system. Recently, Sims et al. [16] proposed the use of a detailed computer model to substitute clinical trials by simulating healthy volunteers' response. However, the reason for cardiac failure and the role of sedation were not explored in this study. Moreover, there have been several computational studies that focused on evaluating hemodynamics of the cerebral and the renal vasculature under hypoxia. Siam et al. [20] developed a model to optimize global oxygen delivery during controlled hemorrhage, a situation that often occurs during the surgical procedure after hemodilution. Dexter and Hindman [21] modeled cerebral oxygenation and computed a transfusion trigger hematocrit based on their model after a focal stroke, a clinical scenario that could be treated with hypervolemic hemodilution. Liang et al. modeled the effect of Circle of Willis anatomy on cerebral perfusion following carotid artery surgery [22]. Similarly, Chen et al. developed a renal medulla model and studied the impact of renal architecture on oxygen transport [23]. Lee et al. developed a detailed 3D model that explained the renal cortex oxygenation and the way oxygen delivery and consumption were affected due to hemodilution and ischemia-reperfusion injury [24]. Even though these models were not developed to understand any specific hemodilution scenario, they provide unique insights into tissue oxygen homeostasis. The present work is a distinct attempt using compartmental models to evaluate hemodynamics and myocardial oxygen balance during isovolemic hemodilution. The integrated model, with both fluid-exchange compartments and cardiovascular compartments, complements the cerebral and the renal models and accepts vital parameters such as pre-load crystalloid infusion, target hematocrit and the type of resuscitation fluid such as 6% hydroxyethyl starch 130/0.4 and 130/0.42, 6% dextran, 4% and 5% human serum albumin, 4% succinylated gelatin and lactated Ringer's solution. The model simulates and compares vital cardiovascular parameters of a patient under ideal isovolemic hemodilution conditions imposed by the parameters. The present work also evaluates the variability in results due to changes in anesthetic conditions imposed by the measures taken during the hemodilution procedure.

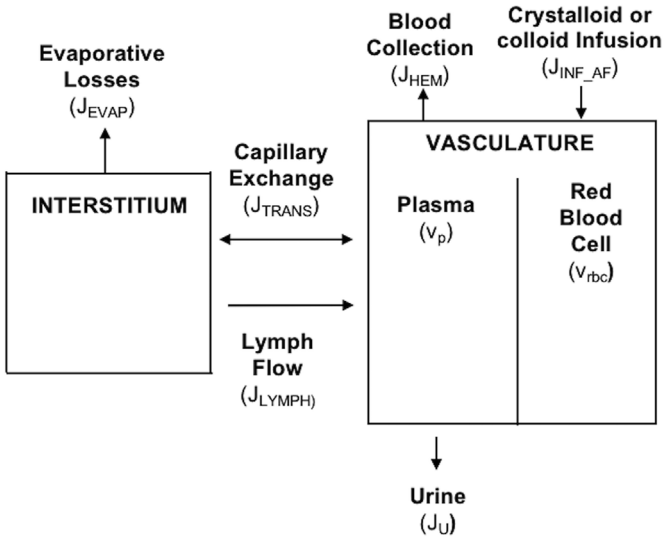

Fig. 1. Block diagram that shows the various compartments of the whole-body fluid dynamics under conditions pertaining to the Acute Normovolemic Hemodilution procedure.

2. Materials and methods

2.1. Fluid-exchange model

The model has two major components. The first one is a fluid-exchange model that was developed based on models published [25]. This fluid-exchange model is divided into an interstitial compartment and an intravascular compartment, which is further divided into plasma and RBC volume compartments (see Fig. 1). Both interstitial and intravascular compartments have their respective protein compartments in addition to the volume compartments. This model is based on volume or mass balance between the plasma and the interstitial compartments. The model assumes that all native proteins behave similarly to albumin and that the fluid exchange occurs based on the mean values of the descriptive parameters of different capillary tissues. Furthermore, fluid exchange between the intracellular and the interstitial compartments and fluid transport due to ions were ignored. The model also assumes that the fluid transport between the plasma and the interstitial space occurs through the capillaries and the lymph nodes with continuous urine production. Moreover, a set of equations to model the microvascular hematocrit with respect to systemic hematocrit was added to predict the change in capillary hematocrit during hemodilution. The equations were based on hematocrit ratio at different oxygen tensions in normal and vasodilated networks [26]. The capillary-systemic hematocrit ratios with normal and reduced RBC deformability were converted to human scale using allometric conversions and a linear model based on oxygen saturation was generated (see supplemental appendix for the equations).

2.2. Cardiovascular model

The second component is the cardiovascular system which is divided into four vascular compartments-systemic arteries, systemic veins, pulmonary arteries and pulmonary veins and two cardiac compartments, the right and the left heart, based on Ursino's model [27]. Each heart compartment has an atrial and a ventricular segment. All the compartments are connected in the following order: left heart, systemic arteries, systemic veins, right heart, pulmonary arteries, pulmonary veins and left heart (see Fig. 2). Each compartment is governed by mass balance based on the perfusion pressure, the resistance offered to flow and the compliance of the compartment. Some important parameters are summarized in the supplemental appendix. Moreover, the model

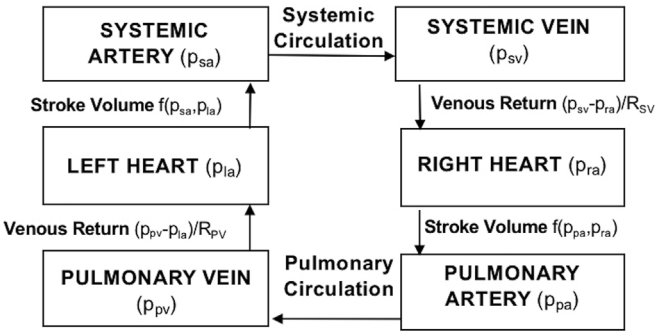

Fig. 2. A block diagram that shows the various compartments of the cardiovascular dynamics model as proposed by Ursino et al. [27].

has control loops that govern the baroreceptor reflex with systemic artery and right atrial pressures as afferent signals and heart period, systemic arterial resistance, systemic venous compliance as effectors through first-order dynamics. Additionally, several algebraic equations that govern stroke volume, viscous resistance-hematocrit relationship, lymph flow, urine production and capillary fluid exchange (Starling's equation) can be found in the supplemental appendix. Ursino's model was chosen over other models in the literature because of the availability of control equations. As the hemodilution procedure causes the change in hematocrit, it is imperative for the model to change its viscous resistance and reproduce the expected homeostatic changes. Moreover, the model is adaptable to the addition of sub-controls that the original model does not include, and it is easier to add forcing functions that are caused by ischemia and anesthetics. Furthermore, Ursino's model including the interaction of the regulatory mechanisms has been validated based on animal data [28], hemorrhagic conditions [28] and hemodialysis [27]. Besides, the model has been extended to pulsatile hemodynamics [29], isocapnic hypoxia [30] and an integrated cardiopulmonary model [31].

2.3. Myocardial relationships

Several practical additions were made in order to simulate the myocardial oxygen balance under anesthetic conditions during hemodilution. Myocardial oxygen supply was estimated based on coronary blood flow and the amount of oxygen present in the blood. The amount of oxygen was calculated based on hematocrit [9]. Coronary blood flow was estimated using the pressure difference between the systemic artery and the arterial capillary compartments and the resistance to flow. Basal left ventricular coronary flow of 0.8 ml min^{-1} g^{-1} was used to set the initial resistance value. Moreover, two vasodilation mechanisms-autoregulation and hypoxic vasodilation, were incorporated into the coronary flow estimation equation. The coronary flow would be maintained over a wide range of perfusion pressure (20–120 mmHg) through autoregulation [32] and hypoxic vasodilation would decrease the resistance with a gain of 3% (% desaturation)$^{-1}$ based on the correlation data between isocapnic hypoxic conditions and increase in coronary flow in humans [33]. Oxygen desaturation was indirectly computed using a polynomial equation fit between arterial oxygen concentration at a range of arterial oxygen tension (1–100 mmHg) and the basal hematocrit (40%). As the arterial oxygen concentration decreased with the decrease in hematocrit, the polynomial equation would generate the equivalent oxygen saturation and the coronary resistance would decrease by 3% (% desaturation)$^{-1}$. Myocardial oxygen consumption was calculated using left ventricular parameters such as pressure, end systolic volume, elastance and heart rate [34]. The authors surmised that the myocardium would fail even when the overall coronary flow had been maintained due to inadequate blood supply to the different layers of myocardium. The oxygen supply to different layers of the myocardium was estimated based on the relationship between the ratio of endocardial and epicardial flow and the ratio of diastolic pressure-time and systolic tension-time indices [35]. The critical value for sub-endocardial ischemia was selected based on previously published data under anemic conditions [35]. This relationship was continuously monitored and the point of cardiac failure for the model was added by forcing the control loops of the cardiovascular model to a paltry gain. The equations that describe the myocardial relationships can be found in the supplemental appendix.

2.4. Anesthesia

Besides the myocardial relationships, effects of sedation were considered. Firstly, preload crystalloid infusion before anesthesia induction (0, 10 or 20 ml kg^{-1} min^{-1}) was incorporated into the model. Secondly, the authors assumed that fentanyl and midazolam were used for sedation. Midazolam and fentanyl were chosen over modern anesthetic agents such as propofol, and sevoflurane along with remifentanil in order to validate the model with the clinical data available. Moreover, propofol's mechanism of action is a matter of debate among the research community [36,37]. The authors also assumed that endotracheal intubation followed the anesthesia induction with a fraction inspired oxygen (F_iO_2) of 0.4. Midazolam is known to decrease the baroreflex heart rate control by 43% [38]. In order to incorporate this effect into the model, the sigmoidal gain of the heart period differential equation (see supplemental appendix) was decreased by 43% and the cardiovascular effects of fentanyl are negligible at therapeutic ranges [39]. Any change in F_iO_2 that would result in a change in baroreflex heart rate control was based on the reduction of heart rate at low hemoglobin concentration studies from Jehovah's Witness patients [40]. Moreover, anesthetic conditions tend to reduce the fluid exchange rate. This was incorporated into the model by calculating the half-life of saline infusion at 1 ml min^{-1} kg^{-1} at various fluid exchange constants (see 'k_f' in the supplemental appendix) [41].

2.5. Volume kinetics

Furthermore, volume kinetics of the replacement fluids was added to the model to change the fluid distribution parameters based on the type of fluid chosen. Linear correlation between oncotic pressure and concentration was computed for each colloid to be included in the Starling's equation [1] and the distribution parameters for each colloid were established based on the respective colloid's molecular weight fractions and hydrodynamic radii [1]. Moreover, colloid elimination rates were added to the model based on half-life analysis data [41,42].

2.6. Simulation protocol and statistics

This system of equations was solved with MATLAB_R2017b software (The MathWorks Inc., Natick, USA) on a MacBook Pro that uses a 2.6 GHz Intel Core i5 processor (Apple Inc., Cupertino, USA) using the trapezoidal rule that uses a free interpolant. In order to assess the parameters in Table 1, the model was programmed to accept various parameters such as crystalloid infusion to maintain preload before anesthesia induction, target hematocrit, acellular fluid resuscitation options, colloid replacement volume and blood extraction rate. The model was utilized to implement an ANH protocol that was successfully performed in dogs [7]. The protocol used in this model followed a single dose of fentanyl and midazolam with no crystalloid infusion preceding the sedation. This was followed by the removal of blood and the simultaneous replacement of the collected blood and the losses with 6% hydroxyl ethyl starch 130/0.4 and a balanced crystalloid solution respectively to maintain normovolemia until myocardial failure. The parameters listed in Table 1 were compared with published data [7] after the application of allometric conversions. Furthermore, the model and the extrapolated published data were statistically analyzed for relevance by computing Pearson's correlation coefficient. Additionally,

Table 1
Parameters that are under observation during isovolemic hemodilution.

Parameter name	Abbreviation	Description
Mean arterial pressure	MAP	Pressure in the systemic artery compartment
Left atrial pressure	LAP	Pressure in the left heart compartment
Cardiac index	CI	Total blood pumped by the heart per minute per m^2 of body surface area
Systemic vascular resistance index	SVRI	Systemic vascular resistance per m^2 of body surface area
Stroke volume index	SVI	Stroke volume of the left heart per beat per m^2 of body surface area
Heart rate	HR	Heartbeat per minute
Left ventricular myocardial oxygen supply	LVMOS	Oxygen supplied to the left ventricular myocardial tissue by the coronary arteries per minute per 100 g
Left ventricular myocardial oxygen demand	LVMOD	Oxygen required by the left ventricular myocardial tissue per minute 100 g
Left ventricular myocardial blood flow	LVMBF	Blood flow per minute per 100 g supplied to the myocardium of the left ventricle
Endo/epicardial flow ratio	ENDO/EPI	Ratio of myocardial blood flow between the endocardial and epicardial layers of the heart
Total systemic oxygen supply	TSOS	Total systemic oxygen supply per minute per kg of bodyweight

the model was used to predict capillary hematocrit (CH) when the systemic hematocrit is reduced from the baseline value of 40%.

Subsequently, a random set of 84 body weights (68.85 ± 3.11 kg), heights (169 ± 15.84 cm) and basal parameters such as heart rate (71.5 ± 5.79 bpm), mean blood pressure (100.32 ± 3.08 kg), hematocrit (39.84 ± 1.27%), plasma and interstitial protein concentrations (6.97 ± 0.32% and (3.01 ± 0.07%), coronary flow reserve (5 ± 0.14 were generated based on a meta-analysis [5] and known standard deviations. Each colloid and crystalloid group had 12 samples. The number of samples was chosen based on a previous clinical study [43]. The model simulations were run for the set of fluid distribution parameters and cardiovascular compliances using the generated body weights and the body surface areas were calculated based on the generated body weights and the heights. These body surface areas were then used to further compute SVI, HR and CI. A paired *t*-test was conducted between data from 6% hydroxyethyl starch 130/0.4 and that from other colloids or crystalloid to check for the null hypothesis that the change in CI, SI and HR was not statistically significant when the type of replacement of fluid was changed during gradual isovolemic hemodilution. Moreover, sensitivity analysis of LVMBF, LVMOS, LVMOC, ENDO/EPI, CI, SVRI, SI, HR and CH was performed at mild (40%–35%), moderate (28%–25%), severe (20%–17%) and extreme (10% to cardiac failure) hemodilution.

Additionally, the 84 sets of parameters were used to simulate changes in the anesthetic conditions imposed by surgical management. Increase in F_iO_2 to low hematocrit is a common clinical adaption. This was simulated with an increase in F_iO_2 from 0.4 to 1 at 20% or 15% hematocrit or lower with 24 simulations for 0.4 F_iO_2 scenario and 60 simulations for 1 F_iO_2 scenario. Furthermore, changes in the effect of midazolam on the baroreflex control were analyzed with 24 simulations for 43% reduction and 48 cases for both 51% and 38% reduction cases respectively. Moreover, the change in fluid exchange rate under anesthesia with infusion half-life from 20 min to 55.20, 69.67 and 88.27 min was analyzed with 21 simulations each.

3. Results

3.1. Model validation

The model predicted the response of an ideal 70 kg man to graded isovolemic hemodilution following the published protocol. The MAP decreased over the period of gradual hemodilution. Cardiac failure occurred at 8.745% hematocrit as seen in Fig. 3. However, the LAP increased over the period of gradual hemodilution. Even though the increase in LAP was not as high as the increase in the animal data at the point of cardiac failure, there was a strong statistically significant correlation between the model predicted data and the extrapolated published data (see Fig. 3B).

Other cardiovascular parameters such as CI, SVI, HR and SVRI distinctly varied in response to graded hemodilution under fentanyl and midazolam (see Fig. 4). CI increased until cardiac failure. The increase in CI was due to the increase in SVI. The stroke volume also increased to compensate for the decrease in heart rate due to midazolam affecting the baroreflex control of heart rate. Though the HR decreased initially, it increased as the heart needed to augment the cardiac output to counteract the decrease in oxygen content in the blood. The decrease in stroke volume and the failure of the reflex control loop that controls the heart period caused the drop in cardiac output at the point of failure. Similar to the animal data, the SVRI decreased over gradual hemodilution.

Additionally, the parameters that signify oxygen balance also showed good agreement with the published data [7]. LVMOS remained almost the same as the basal value until 26.91% hematocrit and the hypoxic vasodilatory response increased the oxygen supply to the left ventricle through an increase in LVMBF until the heart failure (see Fig. 5). LVMOC also consistently increased until the heart failure and LVMOS was maintained even though TSOS decreased progressively over time (see Fig. 6). Although the total oxygen supply to the myocardium was maintained throughout the period of progressive hemodilution, cardiac failure occurred at extreme hemodilution. The heart failure was due to unequal blood flow to the sub-endocardium during extreme hemodilution. The model was able to predict the ENDO/EPI based on diastolic and systolic pressure-time indices. The ENDO/EPI was well maintained until 15% hematocrit with only a modest decline. However, the sub-endocardium started receiving less blood compared to the epicardial layers once the hematocrit was progressively reduced below 15%. It ultimately led to cardiac failure.

The model predictions for capillary hematocrit showed that the capillary hematocrit was between 87.3% and 99.4% of the systemic hematocrit under normal RBC deformability scenario. There was also an 8.2% reduction in the systemic hematocrit at the moment the systemic arteries dilated. But the overall capillary hematocrit stayed between a small range of the systemic hematocrit. However, under reduced RBC deformability, the model predicted that the capillary hematocrit would consistently decrease until the activation of vasodilators. The capillary hematocrit reduced to 61.9% of the systemic hematocrit at this point. Furthermore, the effect of vasodilation also increased the capillary hematocrit to 115.76% of the systemic hematocrit and maintained the hematocrit at the same level until cardiac failure. Another important aspect of the model predictions is that the hematocrit ratios are subject to a 30% error based on the source of the data used to model [26]. The model predictions along with the error lines, are shown in Fig. 7.

3.2. Statistical analysis

The results of the correlation analysis suggest that the model predictions were statistically correlated with the published data. All the parameters had a strong statistical correlation (see Figs. 3–6). The paired t-tests did not reject the hypothesis ($p > 0.05$). Although different fluids were used to induce progressive isovolemic hemodilution, the changes in the SVI, the HR and the CI were not statistically different

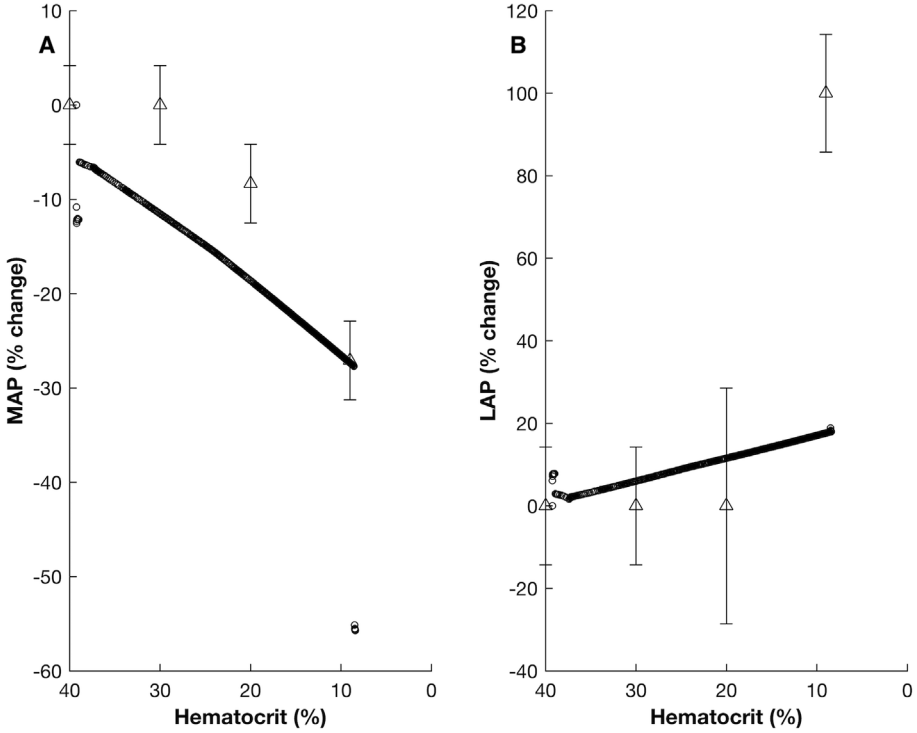

Fig. 3. Model predictions for change in Mean Arterial Pressure (MAP) ○ in comparison with clinical animal data △ (r = 0.7372, p < 0.001, 95% confidence interval 0.6884–0.7793) due to graded isovolemic hemodilution with hydroxyethyl starch (HES) 130/0.4 B) Model predictions for change in Left Atrial Pressure (LAP) ○ in comparison with clinical animal data △ (r = 0.8713, p < 0.01, 95% confidence interval 0.8452–0.8932) due to graded isovolemic hemodilution with hydroxyethyl starch (HES) 130/0.4.

in all the sets of data at different hematocrit levels except one scenario.

The change in F_iO_2 from 0.4 to 1 at 20% hematocrit (group 1) decreased the HR (p = 0.0268), CI (p = 0.0256) and LVMOC (p = 0.0127), increased the SVRI (p = 0.0059), LVMOS (p < 0.001) and ENEP (p < 0.001) and had no effect on TSOS (p = 0.3305). Similarly, the change in F_iO_2 at 15% hematocrit (group 2) also decreased the HR (p = 0.0535), CI (p = 0.0374) and LVMOC (p = 0.0077), increased the SVRI (p = 0.0033), LVMOS (p < 0.001) and ENEP (p < 0.001) and had no effect on TSOS (p = 0.7301). Fig. 8 shows the absolute change in parameters for these two scenarios. Even though the change in the HR was not significant in group 2, the statistical test was designed to have 80% power and the p-value is very close to the chosen significance level (0.05). Moreover, there was no significant change in the MAP in both the scenarios.

Fig. 9 shows the results of variability in the effect of midazolam on the baroreflex control. The change in baroreflex control from 43% reduction to 38% reduction (group1) decreased the HR reduction (p = 0.0130), the SVI increase (p = 0.1350) and the SVRI reduction (p = 0.7220) at midazolam infusion and did not affect ENEP at 9% hematocrit (p = 0.7500) while the change in baroreflex control from

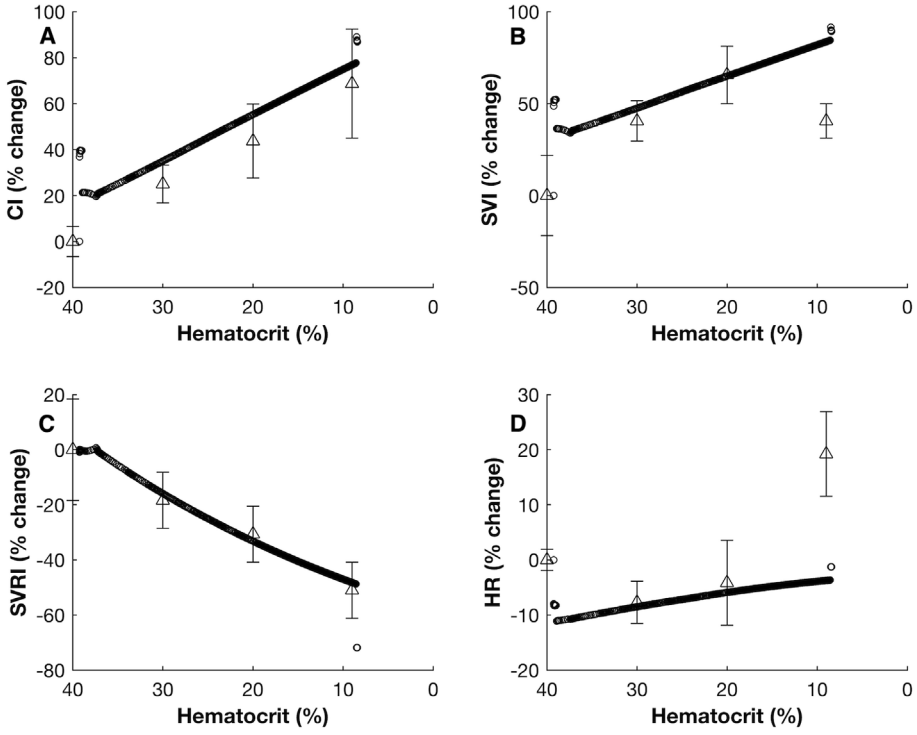

Fig. 4. Model predictions for **A)** Change in Cardiac Index (CI) ○ in comparison with clinical animal data △ (r = 0.9189, p < 0.01, 95% confidence interval 0.9019–0.9330) due to graded isovolemic hemodilution with hydroxyethyl starch (HES) 130/0.4 **B)** Change in Stroke Volume Index (SVI) ○ in comparison with clinical animal data △ (r = 0.8235, p < 0.01, 95% confidence interval 0.7887–0.8529) due to graded isovolemic hemodilution with hydroxyethyl starch (HES) 130/0.4 **C)** Change in Systemic Vascular Resistance Index (SVRI) ○in comparison with clinical animal data △ (r = 0.9590, p < 0.01, 95% confidence interval 0.9502–0.9663) due to graded isovolemic hemodilution with hydroxyethyl starch (HES) 130/0.4 **D)** Change in Heart Rate (HR) ○ in comparison with clinical animal data △ (r = 0.9167, p < 0.01, 95% confidence interval 0.8993–0.9312) due to graded isovolemic hemodilution with hydroxyethyl starch (HES) 130/0.4.

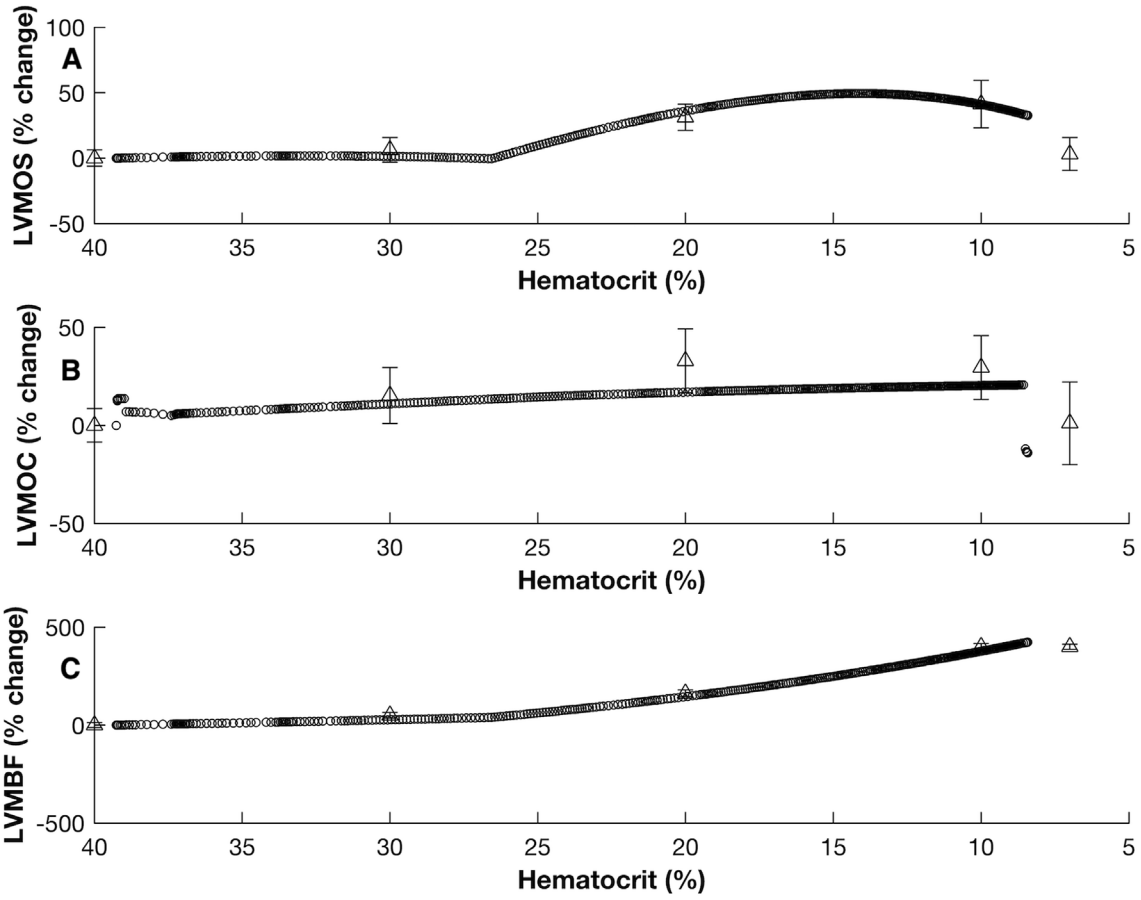

Fig. 5. Model predictions for **A)** Change in Left Ventricular Myocardial Oxygen Supply (LVMOS) ○ in comparison with clinical animal data △ ($r = 0.9556$, $p < 0.01$, 95% confidence interval 0.9461–0.9635) due to graded isovolemic hemodilution with hydroxyethyl starch (HES) 130/0.4 **B)** Change in Left Ventricular Myocardial Oxygen Consumption (LVMOC) ○ in comparison with clinical animal data △ ($r = 0.8831$, $p < 0.01$, 95% confidence interval 0.8571–0.9047) due to graded isovolemic hemodilution with hydroxyethyl starch (HES) 130/0.4 **C)** Change in Left Ventricular Myocardial Blood Flow (LVMBF) ○ in comparison with clinical animal data △ ($r = 0.9940$, $p < 0.01$, 95% confidence interval 0.9927–0.9951) due to graded isovolemic hemodilution with hydroxyethyl starch (HES) 130/0.4.

43% reduction to 51% reduction (group 2) increased the HR reduction ($p < 0.001$), decreased the SVRI reduction ($p = 0.4177$) and did not affect the SVI ($p = 0.7452$) at midazolam infusion. However, increased baroreflex control reduction increased ENEP at 9% hematocrit ($p = 0.0038$).

The change in the fluid exchange rate decreased the total volume of infused maintenance saline from 90.1069 ± 9.6708 ml kg^{-1} in 20-min group to 38.4094 ± 7.2139 ml kg^{-1} ($p < 0.001$), 30.6448 9.8082 ml kg^{-1} ($p < 0.001$) and 29.9361 7.7286 ml kg^{-1} ($p < 0.001$) in 55.20-min, 69.67-min, 88.27-min groups respectively. Other parameters such as HR, SVI and CI were not expected to change based on the previous result.

3.3. Sensitivity analysis

In addition to the statistical analysis, a sensitivity analysis at various levels of hemodilution (see Table 2) helped understand the variation of the cardiovascular parameters under different scenarios. During mild hemodilution, the change in parameters is only modest. This can be attributed to the presence of more RBCs, albeit lower than the normal volume, compared to the more extreme scenarios. The major noticeable variations are the changes in SVI and HR. The effect of midazolam is quite evident on the HR sensitivity. However, this decrease is compensated by an increase in SV and maintains the required cardiac output.

During moderate hemodilution, the oxygen-carrying capacity was reduced. However, the LVMBF increased substantially compared to the moderate case to maintain the overall oxygen supply. In spite of increased oxygen supply, as evident from the LVMOS sensitivity, there was a subtle decrease in blood supply to the sub-endocardium as evident from the ENDO/EPI sensitivity. As the SVRI decreased due to decreased viscosity, the heart increased its stroke volume easily because of decreased afterload. The increase in SVI compensated the drop in overall oxygen concentration with minor increases from the HR as well. The CH also decreased more during moderate hemodilution in comparison with mild hemodilution.

Although the oxygen-carrying capacity of the blood decreased further during severe hemodilution, the LVMBF increased further with the help of vasodilation to counteract the effects of low oxygen concentration. However, the increase in LVMOS was not as high as the increase during the mild hemodilution scenario. The decrease in subendocardial flow is substantial during this period and the overall oxygen requirements of the heart were higher than the previous two scenarios. The increase in CI due to an increase in SVI and a mild increase in HR was enough to maintain the blood supply to the epicardial layers. Additionally, the CH increased substantially during severe hemodilution.

Under the extreme hemodilution scenario, the sensitivities of all parameters except CH changed abruptly due to cardiac failure. Even though the LVMBF increased during this period, the heart was already facing a fall in oxygen supply, as evident from the LVMOS. The decrease in ENDO/EPI caused total heart failure and abruptly decreased the

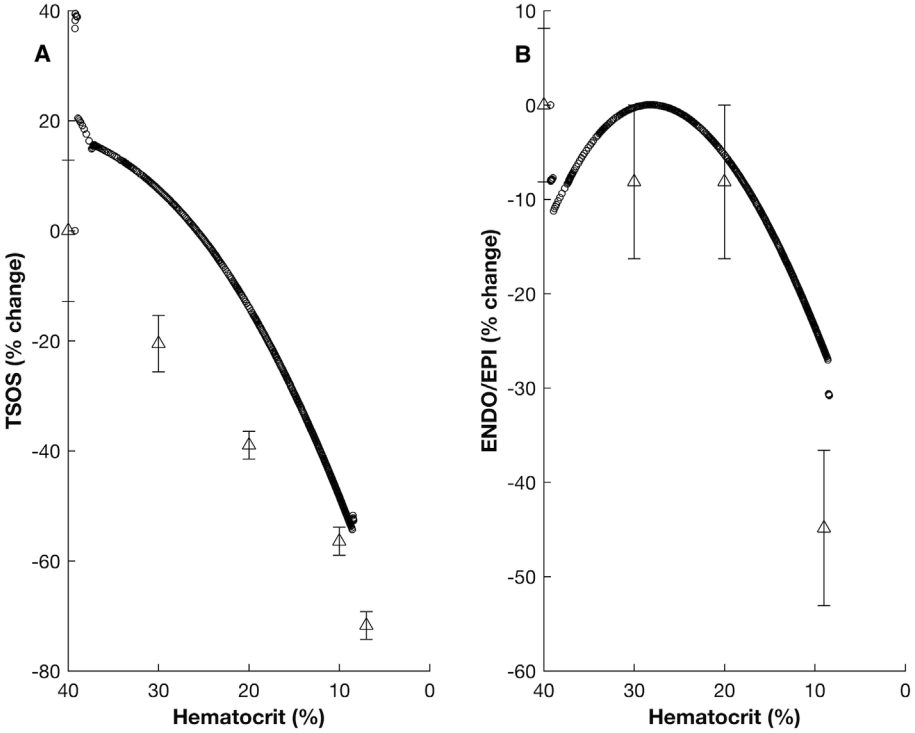

Fig. 6. Model predictions for **A)** Change in Total Systemic Oxygen Supply (TSOS) ○ in comparison with clinical animal data △ (r = 0.9691, p < 0.01, 95% confidence interval 0.9624–0.9746) due to graded isovolemic hemodilution with hydroxyethyl starch (HES) 130/0.4 **B)** Change in Endo/Epicardial Flow Ratio (ENDO/EPI) ○ in comparison with clinical animal data △ (r = 0.9335, p < 0.01, 95% confidence interval 0.9194–0.9451) due to graded isovolemic hemodilution with hydroxyethyl starch (HES) 130/0.4.

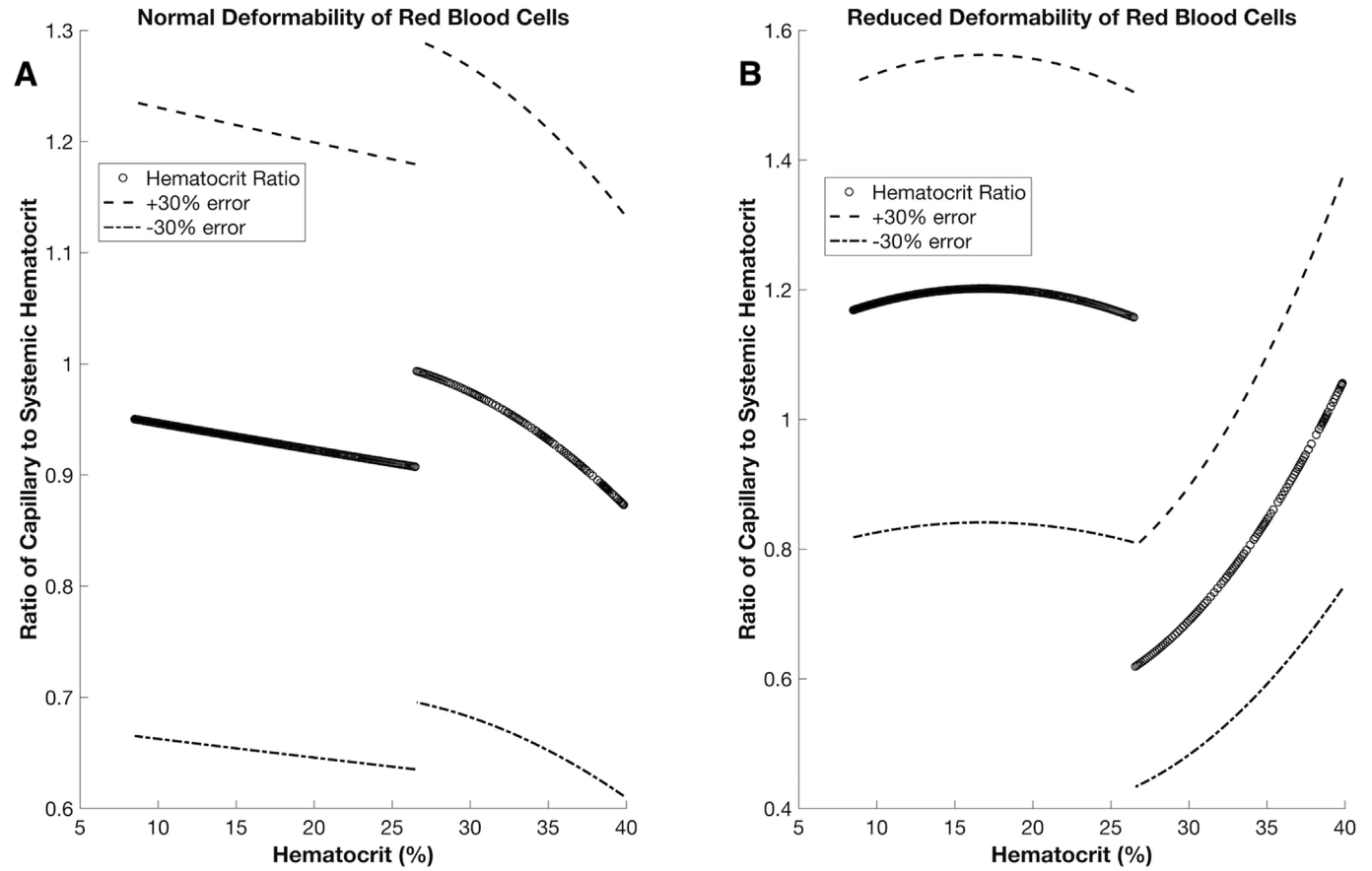

Fig. 7. Model predictions for the ratio of the capillary to systemic hematocrit with **A)** normal deformability of Red Blood Cells ○ during graded isovolemic hemodilution with hydroxyethyl starch (HES) 130/0.4 **B)** reduced deformability of Red Blood Cells ○ during graded isovolemic hemodilution with hydroxyethyl starch (HES) 130/0.4. The dashed and the dotted lines indicate the maximum error.

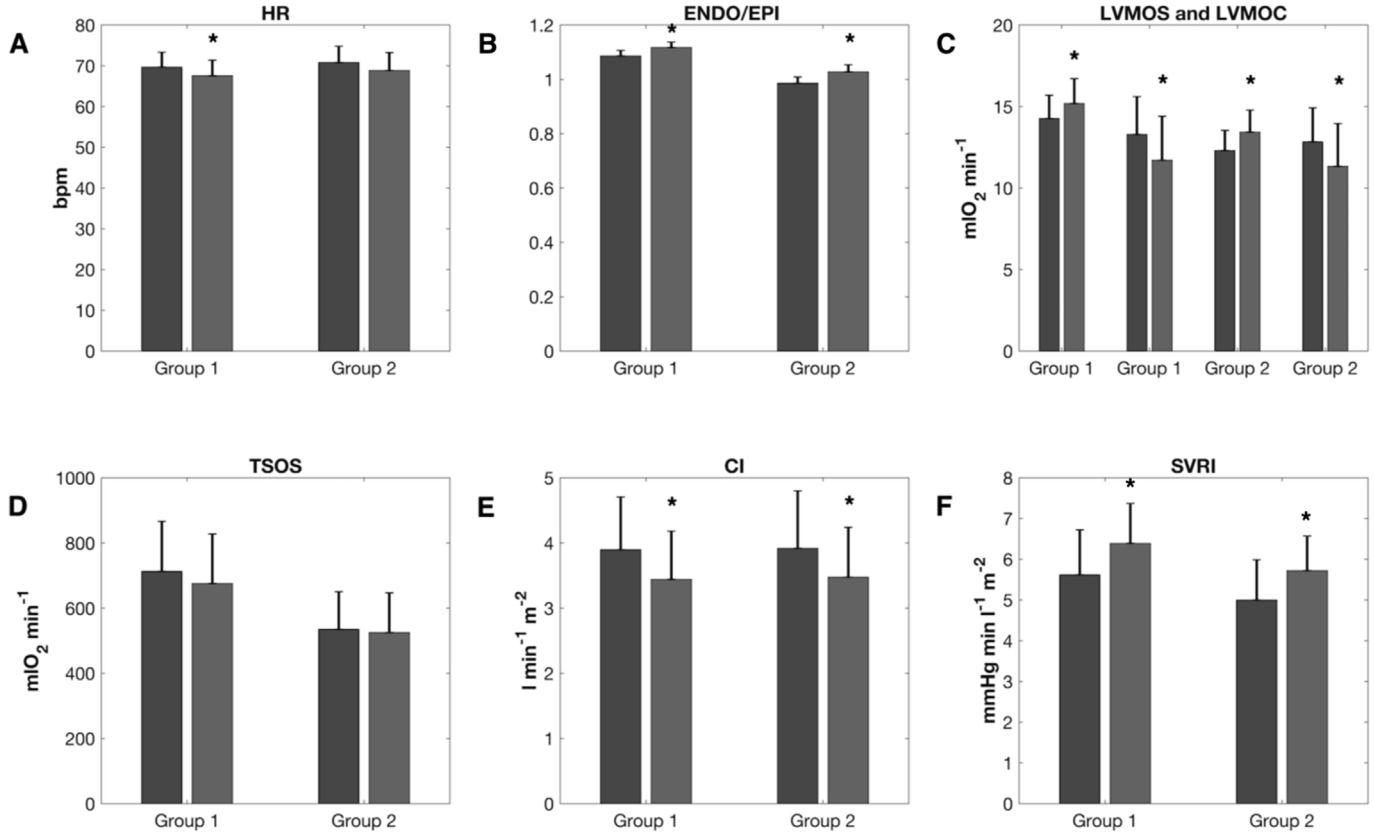

Fig. 8. Comparison of **A)** Heart Rate (HR) **B)** Endo/Epicardial Flow Ratio (ENDO/EPI) **C)** Left Ventricular Myocardial Oxygen Supply (LVMOS) and Left Ventricular Myocardial Oxygen Consumption (LVMOC) **D)** Total Systemic Oxygen Supply (TSOS) **E)** Cardiac Index (CI) **F)** Systemic Vascular Resistance Index (SVRI) due to increase in Fraction Inspired Oxygen (F_iO_2) from 0.4 to 1 at 20% hematocrit (group 1) and 15% hematocrit (group2) respectively (* represents $p < 0.05$).

gains of all control loops. This is clearly observed from the sudden fall in all other parameter sensitivities during the extreme hemodilution scenario.

4. Discussion

4.1. Significance

The simulated cardiovascular parameters showed a good association with the animal data. The MAP decreases moderately until cardiac failure due to a decrease in viscous resistance (Fig. 4C). Even though the MAP was lower than that of the animal data, MAP predictions followed the experimental data trend with a strong correlation. The uncertainty of the effect of midazolam on the MAP of dogs could be the reason for the difference in MAP predictions. The model predictions followed both the increase in SVI and the decrease in SVRI. When the results of SVRI and SVI are considered along with the MAP, it should be clear that the model predictions are valid for the change in hematocrit. Moreover, if the model predictions are considered after the induction of midazolam, the model data would exactly follow the animal experimental data.

When the effects of afterload, midazolam and hemodilution are considered together, decreased hematocrit abates the oxygen-carrying capacity of the blood. This is compensated by increased CI (Fig. 4A). However, midazolam decreases the baroreceptor reflex control of HR [38]. Therefore, the cardiac output should increase through an increase in stroke volume as evident from the decreased afterload due to decreased MAP. This also aids in reduced LVMOC in comparison with non-sedated scenarios. Similar to the MAP, the increase in the LAP is modest and the increased LAP helps in filling more volume into the ventricles and increases the stroke volume (Fig. 4B). Although the HR initially decreases due to induction with midazolam, it increases (Fig. 4D) over gradual hemodilution because midazolam affects only the reflex gain of the control loop and does not shut down the entire mechanism. The increase in HR augments the CI which is validated by the sensitivity values over various scenarios.

Further analysis of oxygen balance shows that LVMOS is maintained even when there is a growing decline in TSOS (see Fig. 6A). The increase in LVMBF (Fig. 5C) during moderate hemodilution is not as high as the increases in the later stages due to minimal oxygen concentration decrease (because of 0.4 F_iO_2) during moderate hemodilution. As oxygen desaturation increases progressively, hypoxic vasodilation increases gradually. Sensitivity calculations during moderate and severe hemodilution corroborate this fact. Simultaneously, the increase in LVMBF is not sufficient to maintain the baseline oxygen supply during mild and moderate hemodilution phases, albeit this insufficiency does not cause an oxygen deficit. Moreover, the increase in LVMBF after 28% hematocrit increases the oxygen supply to meet the demand (see Fig. 5). But, the increase in LVMBF is inadequate to counteract the decrease in oxygen supply once the hematocrit falls below 15%.

Additional analysis of the distribution of the LVMBF based on clinical animal and human data reveals unequal sub-endocardial flow distribution. Since the endocardium receives its blood only during diastole, decrease in the diastolic period due to increasing HR will eventually cause a deficit of blood flow to the internal sub-endocardial layers [7,35,44]. Furthermore, blood oxygen concentration is directly proportional to ENDO/EPI [35]. Clearly, Fig. 6B and the sensitivity analysis table show that the blood flow to the sub-endocardium is maintained above 15% hematocrit and the sub-endocardial ischemia sets in beyond 15% hematocrit. The model also predicted that capillary hematocrit would remain close to systemic hematocrit when the RBCs deform normally. However, the reduction in deformability of the RBCs is expected to reduce the capillary hematocrit (Fig. 7). The sensitivities

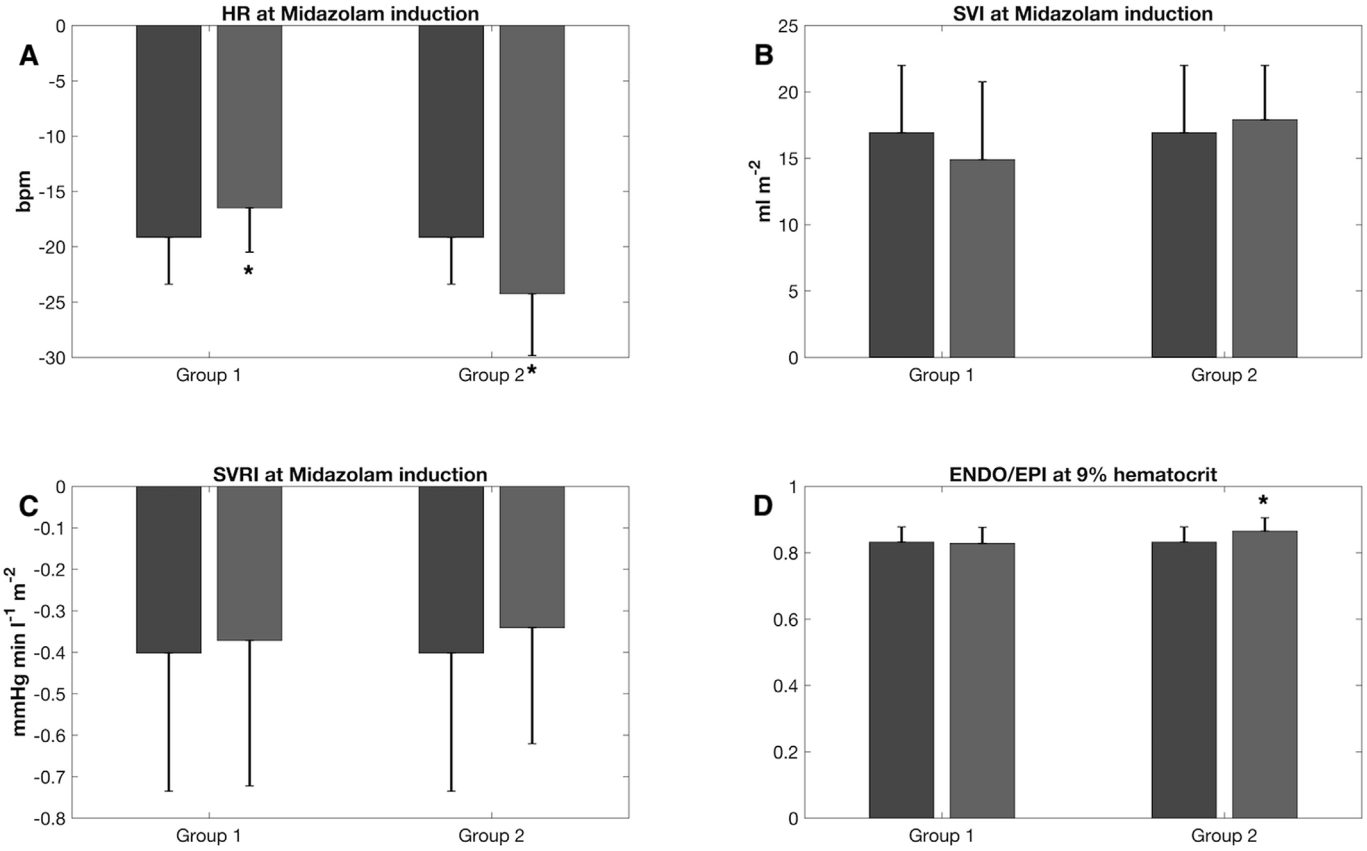

Fig. 9. Comparison of **A)** change in Heart Rate (HR) at Midazolam induction B) change in Stroke Volume Index (SVI) at Midazolam induction C) change in Systemic Vascular Resistance Index (SVRI) at Midazolam induction and D) change in Endo/Epicardial Flow Ratio (ENDO/EPI) at 9% hematocrit due to change in baroreflex control from 43% reduction to 51% reduction (group 1) and 38% reduction (group 2) respectively (* represents $p < 0.05$).

of CH change according to the severity of hemodilution. As the hematocrit decreases, the reduction in capillary hematocrit gradually increases (see mild and moderate hemodilution in Table 2) until the vasodilatory mechanisms become active. As the vasodilators become active, capillary hematocrit increases substantially and maintains oxygen flow to tissues. Once the systemic hematocrit reduces to extremely low levels, vasodilation mechanisms become inadequate to dilate the vessels further and the capillary hematocrit decreases until cardiac failure.

Besides these simulations, statistical analysis of simulations of populations reveals that an increase in CI is not affected by the type of acellular fluid used under isovolemic conditions. Statistical results are not surprising if cogent reviews are considered [45]. Similarly, the increase in SI, the initial decrease in HR and the later increase in HR are also identical under isovolemic conditions. Even under non-isovolemic conditions, 6% hydroxyethyl starch 130/0.4 and 4% succinylated gelatin have similar volume expansion characteristics and similar serum ion and hemoglobin concentrations [43]. A myriad of factors should be taken into account to prescribe a particular colloid or crystalloid [46].

The results of an increase in supplied oxygen simulations show the beneficial effect of providing 100% F_iO_2 under severely anemic conditions. The increase in oxygen supply has a direct effect on SVRI and HR (see Fig. 8). The decrease in HR and the increase in SVRI cause a decrease in CI so that TSOS is maintained even when oxygen supply is increased from 0.4 to 1. The augmented F_iO_2 directly increases LVMOS and the change in HR leads to a significant reduction in LVMOC. Even though the CI is decreased during supplemental oxygen supply, the increase in LVMOS and an insignificant decrease in LVCF reveal that pronounced vasoconstriction may occur at different parts of the periphery. The use of supplemental oxygen at 15% or 20% hematocrit does not affect the hemodynamic improvements during severe anemic conditions. However, this also escalates concerns of oxygen toxicity which is beyond the scope of the paper.

The extreme effects of midazolam on the HR control causes

Table 2
Effect of severity of hemodilution on the cardiovascular parameters.

Hematocrit change	Parameter Sensitivity % $\%^{-1}$								
	LVMBF	LVMOS	LVMOC	ENDO/EPI	CI	SVRI	HR	SVI	CH
Mild 40%–35%	2.69	0.39	0.41	−0.22	3.22	−1.78	−1.98	5.83	−0.47
Moderate 28%–25%	6.12	0.89	0.86	−0.38	1.65	−2.38	0.43	1.2	−1.62
Severe 20%–17%	8.17	1.68	0.98	−1.57	1.55	−2.3	0.38	1.15	3.12
Extreme 10%–8.745%	6.11	−3.36	−40.11	−9.02	−12.29	−39.84	5.59	−16.71	−0.93

contrasting, albeit expected results. The extreme decrease in the HR due to midazolam helps in decreasing LVMOC since HR is the major component of oxygen consumption in the heart. This also leads to higher endocardial flow at very low hemoglobin concentrations (see Fig. 9) and prevents the heart from failing due to inadequate endocardial flow. However, the weaker decrease in HR leads to results similar to the 43% control case. The decrease in fluid exchange under anesthetic conditions causes less maintenance saline infusion which abates concerns of edema. However, the volume of fluid infused during and after a specific surgical procedure may aggravate edema symptoms which are beyond the scope of this study.

4.2. Model novelty

Previous mathematical analysis studies [17–19] do not take into account the dynamics of cardiovascular parameters. Pliskow et al. [1] implemented a computational approach similar to the current approach to recommend important parameters such as ideal colloid infusion volume and the volume of ANH. However, hemodynamic parameters were not included to validate the results. The present study takes into account all the important clinically relevant cardiovascular parameters. In addition, the present multi-compartmental study also validates the results of previous animal studies [7,13]. Moreover, the Sims et al. [16] computational study establishes the limits of hemodilution in conscious healthy volunteers. The present study went a step further by incorporating the role sedation plays under such circumstances. Sedation helps decrease the oxygen uptake which furthers the limit of hemodilution. The Sims et al. study concluded that the safe limit was 55–75 $g\,l^{-1}$ as there was no increase in coronary flow beyond that point. The present study also shows that sub-endocardial ischemia starts to set around 56.25 $g\,l^{-1}$ (15% hematocrit). However, coronary flow was not maximal at this point and continued to rise until eventual cardiac failure at 32.79 $g\,l^{-1}$ (8.745% hematocrit). Additionally, the data from the model agree with relevant clinical knowledge. Meta-analysis on postoperative mortality in patients with very low post-operative hematocrit finds 75% mortality rate at hemoglobin concentrations below 4 $g\,dl^{-1}$ [47] and our model fails between 3.2 and 3.4 $g\,dl^{-1}$. Furthermore, the role of supplemental oxygen on the results are in line with clinical procedures to manage severely anemic patients where the SVRI increases and the HR decreases at low hematocrit while there is no significant effect on MAP [40]. Another interesting model prediction is that the capillary hematocrit in vascular networks with RBC has reduced deformability. The hematocrit of patients after a surgical procedure and re-transfusion of collected blood is lower than the normal hematocrit [48]. Depending on how active the vasodilators are and how the morphology of the stored RBC is changed, the model shows that capillary hematocrit is reduced even though the systemic hematocrit is maintained at an acceptable level.

4.3. Future work and conclusion

Several high blood loss surgeries involve performing moderate hemodilution [5,6]. A higher volume of hemodilution resulted in reducing allogenic transfusion in cardiac surgery [4]. The sensitivity analysis in Table 2 validates these clinical results under the conditions assumed in the model. However, certain vital parameters have to be considered for complete corroboration of the model. Propofol is commonly used to induce general anesthesia and the sedation may be maintained with sevoflurane. Propofol decreases the MAP [36,37] and sevoflurane is a known coronary vasodilator that also affects the MAP [49]. Besides the effects of anesthetics, there is no clinical data to validate the time course of fluid distribution data other than the plasma volume and the interstitial volume. Moreover, animal models have revealed that the kidneys are highly vulnerable to decrease in oxygen supply [11]. The future course of work will be to assess the oxygen balance of the brain, lungs, liver, kidneys and other vital organs during gradual hemodilution by including the effects of propofol, sevoflurane and a pulsatile cardiovascular model. Moreover, the addition of coagulation mechanisms and the effects of heparin and protamine sulfate can make the model more suitable for simulation of coronary artery bypass graft surgeries. Furthermore, the model is very interactive and can be easily added to existing human subject simulators to help train medical staff, students and paramedics. The model can also be an inexpensive alternative to animal experimentation.

Even though a model cannot include all homeostatic loops, it will help understand the dynamics of parameters that can be utilized to assess an individual's fluid state and find the limits of hemodilution that cannot be performed on animal models or patients. In conclusion, the proposed model is novel and can be clinically useful, since it integrates both validated body-fluid and cardiovascular models as well as the effect of anesthesia, and there is a strong correlation between model predictions and published experimental data.

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Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.compbiomed.2018.12.009.

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