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Model-Based Computation of Total Stressed Blood Volume from a Preload Reduction Experiment ⋆

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Abstract: Total stressed blood volume is an important parameter for both doctors and engineers. From a medical point of view, it has been associated with the success or failure of fluid resuscitation therapy, which is a treatment for cardiac failure. From an engineering point of view, this parameter dictates the cardiovascular system's dynamic behavior. Current methods to determine this parameter involve repeated phases of circulatory arrests followed by fluid administration. In this work, a method is developed to compute stressed blood volume from preload reduction experiments. A simple six-chamber cardiovascular system model is used and its parameters are adjusted to pig experimental data. The parameter adjustment process has three steps: (1) compute nominal values for all model parameters; (2) determine the most sensitive parameters; and (3) adjust only these sensitive parameters. Stressed blood volume was determined sensitive for all datasets, which emphasizes the importance of this parameter. The model was able to track experimental trends with a maximal mean squared error of 11.77 %. Stressed blood volume has been computed to range between 450 and 963 ml, or 15 to 28 ml/kg, which matches previous independent experiments on pigs, dogs and humans. Consequently, the method proposed in this work provides a simple way to compute total stressed blood volume from usual hemodynamic data.

1. INTRODUCTION

In intensive care units (ICUs), patient state is diverse and rapidly changing. In addition, data is scarce because physicians are reluctant to further stress patients with invasive examinations. As a consequence, diagnosis and patient outcome are strongly dependent on the availability and experience of the medical staff. To assist physicians in daily clinical practice, engineers have developed a wide range of modelling and simulation tools, in particular dealing with the cardiovascular system (CVS). For these tools to be usable at an ICU bedside, they have to be fast and to require few data. This requirement has lead to a focus on lumped-parameter models (Smith et al. [2004], Starfinger et al. [2007, 2008], Ellwein et al. [2008], Pope et al. [2009], Revie et al. [2011a,b]).

In such lumped-parameter models of the CVS, whole portions of the system are represented as passive chambers. For simplicity, pressure-volume relationships of these chambers are often assumed linear, that is instantaneous pressure $P_i(t)$ and volume $V_i(t)$ in a chamber i are related with an equation of the form:

$$P_i(t) = E_i \cdot (V_i(t) - V_{U,i}), \tag{1}$$

where E_i is the *elastance* and $V_{U,i}$ represents the (constant) *unstressed volume*, *i.e.* the part of $V_i(t)$ which does not contribute to any increase in pressure. It is common to rewrite Equation 1 as:

$$P_i(t) = E_i \cdot V_{S,i}(t), \tag{2}$$

with $V_{S,i}(t)$ being the *stressed volume*. This approach of working with stressed volumes makes it unnecessary to specify $V_{U,i}$ for every model chamber as it is difficult to measure or identify.

All passive compartments of the CVS are generally described using Equation 2, while for the ventricles and atria, the elastance is time-varying and becomes $E_i(t)$. If the CVS model is closed-loop, one has to know the value of

$$SBV = \sum_i V_{S,i}(t). \tag{3}$$

This value represents the *total stressed volume* in the system and is usually assumed to be constant.

From a medical point of view, the knowledge of SBV is paramount. Indeed, Maas et al. [2012] recently demonstrated that, the lower the SBV, the higher the chance fluid administration would improve cardiac output. Current methods to determine SBV require repeated phases of circulatory arrests (to achieve pressure equilibrium) followed by fluid administration. Complete circulatory arrests have been performed in pigs (Ogilvie et al. [1990])

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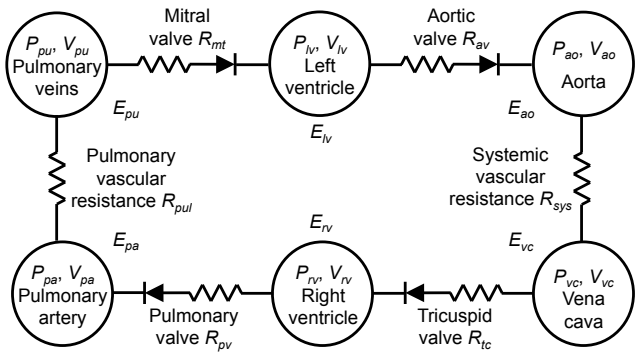

Fig. 1. Schematic representation of the CVS model.

and dogs (Drees and Rothe [1974]), but is of course inconceivable in ICU patients. For humans, Maas et al. [2012] recently determined SBV by stopping blood flow in the arm instead of the whole body. However, this procedure is long (more than 20 minutes), requires administration of 500 ml fluid in the patient, and is highly invasive.

From an engineering point of view, SBV represents an important parameter of closed-loop CVS mathematical models. However, this importance is often underestimated, because the effect of SBV only appears in model simulations with changing load conditions. This type of simulations is the most useful, because in real life, load is constantly changing due to breathing, exercise, *etc.* Paradoxically, to our knowledge, few works have sought to determine this value and many authors do not mention the value used in simulation.

This work proposes a method to compute the total stressed blood volume SBV without requiring circulatory arrests and fluid administration.

2. METHODS

2.1 CVS Model

The CVS model used has been previously described by Smith et al. [2004]. It has been validated in several animal experiments (Starfinger et al. [2007, 2008], Revie et al. [2011a]). The model is presented in Fig. 1.

The model consists of six elastic chambers. These chambers represent the arteries and veins, both systemic and pulmonary, ($i = ao$, vc, pa and pu) and the two ventricles ($i = lv$ and rv). They are described by Equation 2, except for the ventricles, whose elastances are time-varying:

$$P_i(t) = E_i(t) \cdot V_{S,i}(t) \text{ for } i = lv \text{ and } rv. \tag{4}$$

Ventricular time-varying elastances $E_i(t)$ were described (Smith et al. [2004]):

$$E_i(t) = E_i \cdot \exp\left\{-B_i \cdot \left[\left((t - C_i) \bmod T\right) - \frac{T}{2}\right]^2\right\} \tag{5}$$

where E_i is the maximum (end-systolic) elastance, B_i describes the width of the Gaussian function used, C_i denotes the time at which $E_i(t)$ is maximal, t is time, T is cardiac period and mod denotes the modulo operator.

In this work, unlike the original model, no direct interaction is modelled between the two ventricles. Also, for simplicity, no end-diastolic pressure-volume relationship was inserted in Equation 4.

The six model chambers are linked by vessel resistances R_j, representing the four heart valves ($j = mt$, av, tc and pv) and the systemic and pulmonary capillaries ($j = sys$ and pul). Flows Q_{sys} and Q_{pul} through the systemic and pulmonary resistances R_{sys} and R_{pul} are described by Poiseuille's equation:

$$Q_j(t) = \frac{\Delta P_j(t)}{R_j} \text{ for } j = sys \text{ and } pul, \tag{6}$$

where ΔP_j is the pressure gradient across the resistance. There is flow through the valves only if the pressure gradient is positive. Hence:

$$Q_j(t) = \begin{cases} \dfrac{\Delta P_j(t)}{R_j} & \text{if } \Delta P_j(t) > 0 \\ 0 & \text{otherwise} \end{cases} \tag{7}$$

for $j = mt$, av, tc and pv.

Finally, the continuity equation gives the rate at which the volume of the chamber i changes:

$$\dot{V}_i(t) = \dot{V}_{S,i}(t) = Q_{in,i}(t) - Q_{out,i}(t), \tag{8}$$

where $Q_{in,i}$ and $Q_{out,i}$ denote flow coming in and going out of the chamber i.

Overall, the model counts 18 parameters (6 elastances E_i, 6 resistances R_j, 2 width parameters B_{lv} and B_{rv}, 2 shift parameters C_{lv} and C_{rv}, the heart period T and SBV). Parameter identification is used to identify parameter values from animal data.

2.2 Experimental Data

To identify the model parameters, experimental animal data was used. These data came from pulmonary embolism experiment on nine pigs (Ghuysen et al. [2008]) performed with the approval of the Ethics Committee of the Medical Faculty of the University of Liège. In this work, only data obtained before the induction of pulmonary embolism, *i.e.* at basal state, was used. Measurements consisted in continuous recording of:

- ventricular volumes $V_{lv}(t)$ and $V_{rv}(t)$,
- ventricular pressures $P_{lv}(t)$ and $P_{rv}(t)$,
- arterial pressures $P_{ao}(t)$ and $P_{pa}(t)$.

The pigs were also weighed at the beginning of the experiment. After the sensors were correctly positioned, preload was reduced by inflating a balloon introduced in the inferior vena cava. For each animal, two preload reduction experiments were performed. For two animals, a third preload reduction manoeuvre was performed. In total, datasets corresponding to twenty preload reduction manoeuvres were available.

Thirteen datasets were discarded, where measurements were not perfectly regular during preload reduction, which is incompatible with Equation 5. In total, seven experimental datasets were thus used.

2.3 Parameter Identification

The parameter identification procedure involves three steps, described in the following three sections. First, nominal values have to be assigned to all 18 model parameters. From these values, an algorithm selects a sensitive subset of parameters to be further identified. Finally, this subset of parameters is identified, using an iterative procedure.

I. Nominal Parameter Values To assign nominal values to the model parameters, the available data was used in combination with the model equations described in Section 2.1. When it was not possible to infer a parameter value directly from the data, reference values published in the literature were used.

1. The cardiac period T was computed by dividing the duration of the dataset by the number of cycles it contains.
2. The systemic vascular resistance was computed using the usual formula (Klabunde and Dalley [2004]):
$$R_{sys} = \frac{\bar{P}_{ao} - \bar{P}_{vc}}{CO} \tag{9}$$
where $\bar{P}_{ao}$ and $\bar{P}_{vc}$ are, respectively, mean aortic and vena cava pressure and CO is cardiac output. For simplicity, we assumed $\bar{P}_{vc}$ to be negligible with respect to $\bar{P}_{ao}$. The computation was made on the first beat of the preload reduction experiment.
3. The pulmonary vascular resistance was estimated using the pulmonary counterpart of Equation (9):
$$R_{pul} = \frac{\bar{P}_{pa} - \bar{P}_{pu}}{CO} \tag{10}$$
where $\bar{P}_{pa}$ and $\bar{P}_{pu}$ respectively denote mean pulmonary arterial and venous pressures. Here also, $\bar{P}_{pu}$ was neglected with respect to $\bar{P}_{pa}$.
4. During diastole, blood flow out of the aorta is described by the following equation:
$$\dot{V}_{S,ao}(t) = -\frac{P_{ao}(t) - P_{vc}(t)}{R_{sys}} \tag{11}$$
If, once again, P_{vc} is neglected with respect to P_{ao} and Equation 2 is used, one gets:
$$\dot{V}_{S,ao}(t) \approx -\frac{E_{ao} \cdot V_{S,ao}(t)}{R_{sys}}. \tag{12}$$
Solving this equation yields:
$$V_{S,ao}(t) \approx \exp\left(-\frac{E_{ao} \cdot t}{R_{sys}}\right) \cdot V_{S,ao}(t_{BD}). \tag{13}$$
where t_{BD} denotes the beginning of diastole. Multiplying both sides of Equation 13 by E_{ao} yields:
$$P_{ao}(t) \approx \exp\left(-\frac{E_{ao} \cdot t}{R_{sys}}\right) \cdot P_{ao}(t_{BD}). \tag{14}$$
Since R_{sys} can be computed from Equation 9, E_{ao} has been determined by fitting the measured $P_{ao}(t)$ curve during ejection to Equation 14. The same procedure has been applied to compute E_{pa}.
5. E_{lv} (and left ventricular unstressed volume $V_{U,lv}$ as a byproduct) has been determined by linear regression of the end-systolic pressure-volume points, according to the method of Kass et al. [1987]. The experimental time-varying elastance has then been computed using Equation 4:
$$E_{lv}(t) = \frac{P_{lv}(t)}{V_{lv}(t) - V_{U,lv}} \tag{15}$$
and parameters B_{lv} and C_{lv} were estimated by fitting Equation 5 to the previously computed curve. Right-side parameters E_{rv}, $V_{U,rv}$, B_{rv} and C_{rv} were computed by an analogous procedure.
6. Valve resistances R_{mt}, R_{av}, R_{tc} and R_{pv} were initialized at values provided by Revie et al. [2011b] in another study performed on the dataset used in the present work:
$$\begin{aligned} R_{mt} &= 0.05 \text{ mmHg} \cdot \text{s/ml} \\ R_{av} &= 0.04 \text{ mmHg} \cdot \text{s/ml} \\ R_{tc} &= 0.04 \text{ mmHg} \cdot \text{s/ml} \\ R_{pv} &= 0.03 \text{ mmHg} \cdot \text{s/ml}. \end{aligned} \tag{16}$$
7. According to Zanzinger et al. [1996], inferior vena cava elastance for pigs is 0.44 mmHg/(ml/kg). Half of this value is used to account for the two vena cavae in parallel. The nominal value used for E_{vc} is thus 0.22 mmHg $\cdot$ kg/ml divided by the pig's weight.
8. No experimental study assessing the elastance of a pulmonary vein in pigs was found. What was found, is an experimental study giving reference values for the minimum and maximum pulmonary vein pressure in pigs (Barbier et al. [2000]). Using this data, the amplitude of the pulmonary vein pressure was computed to be approximately 9 mmHg and E_{pu} was estimated by:
$$E_{pu} \approx \frac{9 \text{ mmHg}}{SV} \tag{17}$$
where SV is the stroke volume. Note that this formula underestimates E_{pu} because it assumes that all the stroke volume contributes to a pressure increase in the pulmonary veins, whereas part of it flows directly into the hart during diastole.
9. To determine the nominal value of SBV, experimental results on dogs published by Drees and Rothe [1974] are used. From these results, SBV is estimated to be equal to 31.95 ml/kg.

In the previous computations, parameters T, B_{lv}, B_{rv}, C_{lv}, C_{rv}, E_{lv} and E_{rv} were computed by directly fitting the model to the data. Consequently, it was assumed that the parameter identification process would not largely alter these parameter values. They were thus excluded from the following sensitivity analysis procedure, and the remaining parameter set was:
$$\begin{aligned} \mathbf{p} = \{&SBV, E_{ao}, E_{vc}, E_{pa}, E_{pu}, \\ &R_{sys}, R_{pul}, R_{mt}, R_{av}, R_{tc}, R_{pv}\}. \end{aligned} \tag{18}$$

II. Subset Selection Algorithm To reproduce the preload reduction experiments with the model, it was first simulated with the previously computed parameter values. A first simulation on 100 heart beats was performed to let the model reach steady state and then the value of the tricuspid valve resistance R_{tc} was abruptly doubled to reduce preload. (We chose to multiply R_{tc} by two to stick to the experimental settings in which only one of the two venae cavae is occluded.) The model was then re-simulated for 12 to 17 supplementary heart beats (in accordance with the data).

An error vector $\mathbf{e}$ was built as the relative error between simulated and measured values. The first eight components of $\mathbf{e}$ are computed on the last heart beat before simulation of the vena cava occlusion. More precisely, this vector was built as follows:

$$\begin{aligned} e(1) &= 1 - \frac{\bar{V}_{lv}^{sim}}{\bar{V}_{lv}^{ref}} \\ e(2) &= 1 - \frac{\max(V_{lv}^{sim}) - \min(V_{lv}^{sim})}{\max(V_{lv}^{ref}) - \min(V_{lv}^{ref})} \\ &\vdots \end{aligned} \tag{19}$$

That is, the first component is the absolute error between simulated (sim) and measured (ref) mean left ventricular volumes (during one cardiac period). The second component contains the absolute error between simulated and measured amplitudes of left ventricular volume (during one cardiac period). Components 3 to 8 of the error vector contain the same formulae, applied to aortic pressure, right ventricular volume and pulmonary artery pressure. The last eight components (indices 9 to 16) of $\mathbf{e}$ are analogous to the previous ones, but are computed on the last heart beat after simulation of the vena cava occlusion. (Ventricular pressures are not included in the error vector since they have already been used to compute parameters T, B_{lv}, B_{rv}, C_{lv}, C_{rv}, E_{lv} and E_{rv}.)

In one dataset, measured pulmonary artery pressure was negative. Consequently, components 7, 8, 15 and 16 of the error vector were deleted. Similarly, measured pulmonary artery pressure at the end of the preload reduction experiment was negative in three supplementary datasets. Then, components 15 and 16 were deleted.

The subset selection algorithm used in this work was introduced by Burth et al. [1999] and was used in cardiovascular modeling by Pope et al. [2009]. Briefly, this algorithm works as follows:

- Compute the Jacobian matrix: $\mathbf{J} = \partial\mathbf{e}/\partial\mathbf{p}$ by a finite difference approximation.
- Approximate the Hessian matrix by: $\mathbf{H} \approx \mathbf{J}'\mathbf{J}$.
- Compute the eigenvalues λ_i of $\mathbf{H}$.
- Choose a number ρ such that ρ eigenvalues of $\mathbf{H}$ are larger than the others.
- Find the ρ parameters corresponding to the ρ eigenvalues through a QR decomposition of $\mathbf{H}$.
- Select these ρ parameters for optimization. The remaining parameters are kept at their nominal values.

In this work ρ was selected as the i (> 1) that maximized the ratio of two successive eigenvalues λ_i/λ_{i+1}, when they were sorted in decreasing order, *i.e.* $\lambda_i \geq \lambda_{i+1}$.

III. Iterative Adjustment of the Remaining Parameters The ρ selected parameters were computed by an iterative procedure. The objective of this procedure was to minimize the square of the Euclidean norm of the error vector $\mathbf{e}$. This task was performed using the direct search method with random-generated search directions and random polling (Conn et al. [2009]). The initial values needed by this algorithm were the ones computed in step I. All computations were performed using MATLAB (2011a, MathWorks, Natick, MA).

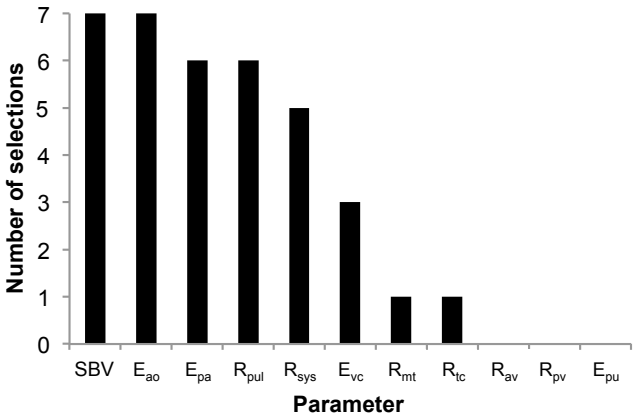

Fig. 2. Frequency of parameter selection by the subset selection algorithm.

3. RESULTS AND DISCUSSION

3.1 Subset Selection Algorithm

As can be seen from Figure 2, SBV and aortic elastance E_{ao} have been selected by the algorithm for all seven datasets, emphasizing the importance of SBV for CVS model simulations. Pulmonary artery elastance E_{pa} and systemic vascular resistance R_{sys} have been selected in all but one dataset, and pulmonary vascular resistance R_{pul} in all but two. Consequently, vascular resistances and arterial elastances are the most important parameters in a CVS model. This outcome is related to the widespread use of two-parameter windkessel models, including only an arterial elastance and a vascular resistance.

Vena cava elastance E_{vc} was selected in 3 out of 7 datasets, while pulmonary vein elastance E_{pu} was never selected. Atrioventricular valve resistances R_{mt} and R_{tc} were selected once, while semilunar valve resistances R_{av} and R_{pv} were never selected. This outcome emphasizes the fact that valve resistances are difficult to identify (from the data used), as already noted by Revie et al. [2011b].

It should also be noted that Ellwein et al. [2008] performed a parameter sensitivity analysis in a different CVS model including 11 compartments and 52 parameters. Mitral valve resistance was the 42$^{\text{nd}}$ most sensitive parameter and aortic valve resistance, the 46$^{\text{th}}$, which matches the results here. Note that their model did not include tricuspid and pulmonary valve resistances.

3.2 Parameter Adjustment

Table 1 shows the computed values of SBV, along with the pig weights and final values of the mean squared error $\|\mathbf{e}\|^2/N$ for all seven datasets. (N is the number of components in $\mathbf{e}$, equal to 12, 14 or 16 as explained in section 2.3.) The largest value of the mean squared error is 11.77 % for dataset number 4. For this dataset, $N = 12$ and not 16 because measured pulmonary artery pressure was negative. The overall poor quality of this dataset could justify the highest $\|\mathbf{e}\|^2/N$ value.

For all other datasets, the average squared error is much lower. Consequently, the parameter adjustment can be qualified as good.

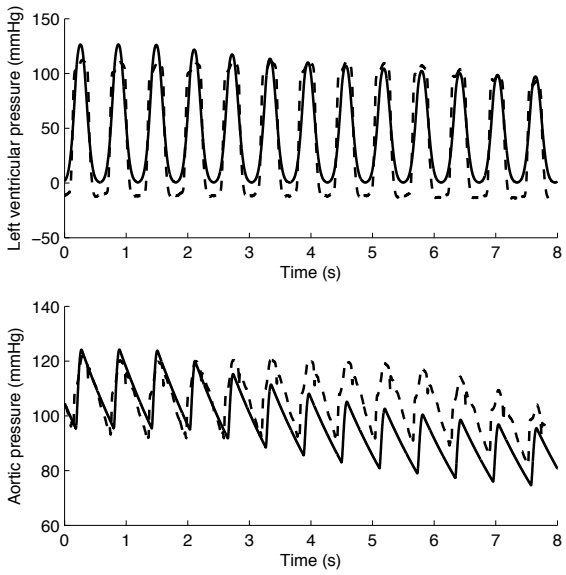

Fig. 3. Simulated (*full line*) and measured (*dashed line*) left ventricular (*top*) and aortic (*bottom*) pressures during a preload reduction experiment (dataset number 5).

To further emphasize this statement, Figure 3 shows simulated and measured left ventricular and aortic pressures for dataset number 5. As can be seen on this figure, simulated and measured pressures are in acceptable agreement all along the preload reduction manoeuvre.

In general, the errors between measurements and simulations are due to two main causes, exemplified on Figure 3. First, for all datasets but number 6, measured left ventricular pressure is negative during diastole, which physiologically happens (Sabbah and Stein [1981]) but cannot be reproduced by the model. Second, for datasets number 4 and 5, measured aortic pressure is always higher than left ventricular pressure, which is physiologically impossible, since it would prevent emptying of the ventricle. This second outcome probably comes from an error in the calibration of the pressure catheters. Despite these discrepancies, the model is able to track the pressure changes when preload is reduced and the trends appear accurately reproduced, which is clinically valuable.

3.3 Value of the Total Stressed Blood Volume

Table 1 shows that SBV values for pigs range from 450 to 863 ml. Taking the pig weights into account, these results correspond to a range of 15 to 28 ml/kg. In an experimental study on pigs, Ogilvie et al. [1990] reported mean values of 29, 34 and 41 ml/kg for three different experimental protocols. It is worth noticing that the pigs used in this study were smaller (average weight: 27.9 kg) than those used here, but the values are normalized. No other experimental study on pigs was available to compare these results. Also, no mathematical model of the CVS applied to pigs published in the literature provided the SBV value used. However, other experimental results obtained on different animals are available. For instance, Drees and Rothe [1974] found a value of 32 ml/kg for dogs and Maas et al. [2012] report a value of 19.6 ml/kg for humans. The fact that all these values are of the same order of magnitude and similar range as our results is encouraging, but comparisons with other porcine studies would be better, if available.

Table 1. Computed Values of SBV

Dataset No.	Pig No.	SBV (ml)	Weight (kg)	$\|\mathbf{e}\|^2/N$
1	1	530.3	35	3.51 %
2	1	541.6	35	3.30 %
3	2	862.7	31	7.75 %
4	3	449.7	29	11.77 %
5	3	709.4	29	6.10 %
6	4	697.8	31	4.33 %
7	5	643.7	32.5	2.29 %

The quite large range obtained for SBV expressed per unit mass comes from the fact that there is no apparent correlation between the weight of the pigs and the computed SBV value. This outcome is due to the fact that SBV is not necessarily constant in a given animal. Compare, for example, SBV values of pigs 1 and 3 in Table 1. Consequently, it is probably inappropriate to define a stressed blood volume per unit mass. This further highlights the need to identify this subject and condition-specific parameter directly.

Even if the model assumes SBV to be constant, unmodelled effects can change its value. For instance, stressed blood volume can be modified by sympathetic actions, time-dependent vascular properties and fluid exchanges through the capillaries, and others (Drees and Rothe [1974]).

LIMITATIONS AND EXTENSIONS

It is likely that the computed SBV value could change according to how fast the vena cava is occluded and how well the animal copes with the preload reduction manoeuvre. In addition, the way this preload reduction manoeuvre is mathematically represented probably influences the obtained SBV value. In this work, it was assumed that the preload reduction manoeuvre could be simply modelled as a sharp doubling of the right ventricular input resistance R_{tc}. However, there exist many other options: the transition could be made smoother; the factor 2 could be modified; and another model resistance could be used. Investigation of all these influences is needed to assess the reproducibility of the method.

To validate the method, it would be very useful to compare values of SBV computed by the previously described methods and by other usual ones. As mentioned in the introduction, these other methods are much more invasive and risky, as they involve repetitive circulatory arrests in all or part of the CVS and multiple fluid administrations. If the method provided here correlates well with these other approaches, it could be used as a faster replacement, also avoiding the need for circulatory arrests.

Finally, the method presented could be made non-invasive by suppressing the need for ventricular pressures and volumes. As we have shown, SBV is the most sensitive parameter. Therefore, it is likely to be identifiable only from aortic pressure measurements. The second step to make the method non-invasive would be to replace the vena cava occlusion by another preload reduction manoeu-

vre, for example raising a patient's legs. These changes would result in a fully non-invasive method to compute a patient's volume status.

CONCLUSIONS

This research proposed a simple method to compute total stressed blood volume, SBV, from usual hemodynamic data. This methods consists in fitting a simple six-chamber CVS model to data from a preload reduction experiment. Because data is limited and not perfect, a sensitivity analysis was used to select a subset of parameters to fit. Stressed blood volume was always selected by the algorithm, which confirms the important role of this parameter. Its value could then be computed for all available datasets.

The method can be adapted to operate from different available measurements and would likely still be able to compute SBV. If this set of available measurements is reduced to aortic pressure only, the method could provide a non-invasive way to compute SBV. Non-invasive measurements are critical to enable easy identification of a patient's volume status and whether fluid resuscitation should be performed, which is central to monitoring and treating CVS dysfunction.

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