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Model-Based Stressed Blood Volume is an Index of Fluid Responsiveness ⋆

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Abstract: Fluid therapy is frequently used to manage acute circulatory failure. This therapy aims to restore cardiac output by fluid administration, which increases the quantity of fluid in the circulation. However, it has been shown to be effective only in certain cases, leading to the need for indices of fluid responsiveness. Total stressed blood volume has recently been shown to be such an index of fluid responsiveness. However, the current methods to determine this parameter require specific procedures. In this work, a more straightforward method is developed using data available in the intensive care unit. A simple three-chamber cardiovascular system model is used, of which total stressed blood volume is a parameter. All model parameters (including total stressed blood volume) are adjusted to pig experimental data during fluid administrations. The resulting value of total stressed blood volume is always negatively associated with the relative change in cardiac output after fluid administration. This finding confirms that total stressed blood volume is an index of fluid responsiveness. Another finding of this study is that the response curves are subject-specific. The method developed in this work can be applied to humans, since the data required is typically available in an intensive care unit.

Keywords: parameter identification, mathematical models, biomedical systems, medical applications.

1. INTRODUCTION

Fluid therapy aims to improve cardiac output (CO) by increasing the quantity of fluid in the circulation and is frequently used to manage acute circulatory failure (Michard and Teboul (2000)). It has been shown to be effective only for some patients. Consequently, clinicians have been searching for various indices of fluid responsiveness.

Maas et al. (2012) showed that total stressed blood volume (SBV), defined as the total pressure-generating blood volume in the circulation, was such an index of fluid responsiveness. However, current methods to determine SBV involve repeated phases of circulatory arrests followed by fluid infusions.

Pironet et al. (2014) previously developed a method to compute a mathematical model-based analogue of SBV. This method has two drawbacks: it requires data from both the systemic and pulmonary circulations and this data has to be obtained during a preload reduction manoeuvre. In this work, these two limitations are removed using a simpler mathematical model, requiring only systemic data in steady conditions. The method is validated against vascular filling experiments data.

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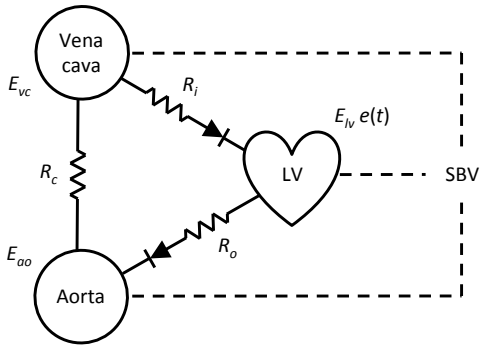

Fig. 1. Schematic representation of the CVS model.

2. METHODS

2.1 Cardiovascular System Model

The cardiovascular system (CVS) model used in this work is presented in Fig. 1. It consists of three elastic chambers representing the left ventricle (lv), the aorta (ao) and one vena cava (vc). The aorta and the vena cava are described by the following equations:

$$P_{ao}(t) = E_{ao}\ V_{S,ao}(t) \quad (1)$$

$$P_{vc}(t) = E_{vc}\ V_{S,vc}(t), \quad (2)$$

where P is pressure, E is elastance and V_S is stressed volume. (Stressed volume is equal to the difference between

actual volume and a constant volume offset, called the unstressed volume (Pironet et al. (2014)).)

The left ventricle is represented using the description of Suga et al. (1973):

$$P_{lv}(t) = E_{lv}\ e(t)\ V_{S,lv}(t) \tag{3}$$

where E_{lv} is the maximum (end-systolic) elastance and $e(t)$ is the normalised pressure-volume ratio, which is a T-periodic function (T being the duration of a heartbeat) ranging from nearly 0 (during filling) to 1 (at end-systole).

The three chambers are linked by vessel resistances representing the systemic circulation (R_c), the aortic valve (R_o) and the whole right circulation, from the tricuspid to the mitral valves (R_i). Flow Q_c through the systemic circulation is described by Ohm's law:

$$Q_c(t) = \frac{P_{ao}(t) - P_{vc}(t)}{R_c}. \tag{4}$$

The model assumes (i) that there is flow through the valves only if the pressure gradient is positive and (ii) that the flow through an open valve can also be described by Ohm's law. Hence, one has:

$$Q_i(t) = \begin{cases} \dfrac{P_{vc}(t) - P_{lv}(t)}{R_i} & \text{if } P_{vc}(t) > P_{lv}(t) \\ 0 & \text{otherwise,} \end{cases} \tag{5}$$

$$Q_o(t) = \begin{cases} \dfrac{P_{lv}(t) - P_{ao}(t)}{R_o} & \text{if } P_{lv}(t) > P_{ao}(t) \\ 0 & \text{otherwise.} \end{cases} \tag{6}$$

Finally, the continuity equation gives the rate at which the volume of the chambers change:

$$\dot{V}_{S,lv}(t) = Q_i(t) - Q_o(t), \tag{7}$$

$$\dot{V}_{S,ao}(t) = Q_o(t) - Q_c(t), \tag{8}$$

$$\dot{V}_{S,vc}(t) = Q_c(t) - Q_i(t). \tag{9}$$

Summing the previous equations gives:

$$\dot{V}_{S,lv}(t) + \dot{V}_{S,ao}(t) + \dot{V}_{S,vc}(t) = 0. \tag{10}$$

Consequently, the total stressed blood volume contained in the left ventricle, aorta and vena cava is a constant and a model parameter:

$$V_{S,lv}(t) + V_{S,ao}(t) + V_{S,vc}(t) = \text{SBV}. \tag{11}$$

Overall, the model counts eight parameters (three elastances E_{lv}, E_{ao} and E_{vc}, three resistances R_i, R_o and R_c, the cardiac period T and SBV) and one normalised pressure-volume ratio $e(t)$. Parameter identification is used to compute the value of SBV and the other parameters from experimental data.

2.2 Experimental Data

To identify the model parameters, experimental animal data were used. These data came from vascular filling experiments performed on eight anaesthetised pigs, weighing 27.7±6.2 kg. The experiments consisted in 2 to 6 successive administrations of saline solution. Pigs 1 and 2 received slow 500 ml fluid infusions and pigs 3 to 8 received rapid 225 ml fluid boluses. The pigs were mechanically ventilated at a positive end-expiratory pressure of 5 cmH_2O. These experiments were performed with the approval of the Ethics Committee of the Medical Faculty of the University of Liège. Catheters (Transonic, NY) provided continuous recording of:

- left ventricular pressure P_{lv} and volume V_{lv},
- aortic pressure P_{ao},
- vena cava pressure P_{vc} (only for pigs 1 and 2),
- left atrial pressure P_{la} (only for pig 1).

A PiCCO monitor (Pulsion AG, Germany) was also used for pigs 5 to 8, providing beat-to-beat recording of:

- stroke volume (SV),
- mean vena cava pressure $\bar{P}_{vc}$,
- amplitude of the vena cava pressure PP_{vc}.

The PiCCO was recalibrated with three thermodilutions after each fluid administration to avoid any drift in the measured SV. Table 1 summarises the available data for each animal.

Table 1. Summary of the experimental data.

	Catheter data					PiCCO data		
	P_{lv}	V_{lv}	P_{ao}	P_{vc}	P_{la}	SV	$\bar{P}_{vc}$	PP_{vc}
Pig 1	×	×	×	(×)	×			
Pig 2	×	×	×	×				
Pig 3	×	×	×					
Pig 4	×	×	×					
Pig 5	×	(×)	×			×	×	
Pig 6	×	×	×			×	×	×
Pig 7	×	×	×			×	×	×
Pig 8	×	×	×			×	×	×

Since cardio-pulmonary interaction is not accounted for in the model, only data during temporary disconnections of the mechanical ventilator were used. More precisely, the last heartbeat before re-plugging of the ventilator was used, so that the hemodynamics was stabilised after the load change caused by unplugging the ventilator.

2.3 Parameter Identification

The parameter identification procedure aims to reproduce the measured signals with the model. Since the model only represents the systemic circulation, the parameter identification only requires measurements coming from the systemic circulation, which is an improvement with respect to Pironet et al. (2014). The only exception in this work is the use of left atrial pressure for pig 1, which will be justified further.

The parameter identification procedure involved four steps, described in the following four sections. First, nominal values had to be assigned to all eight model parameters. Then, an error vector was defined. From the error vector computed using the nominal parameter values, an algorithm selected a sensitive subset of parameters to be further identified. Finally, this subset of parameters was identified using an iterative procedure.

I. Nominal Parameter Values To assign nominal values to the model parameters, approximate formulae derived from the model equations were used in combination with

the available data. The derivation of these approximate formulae is given in Appendix A.

1. The cardiac period T was computed as the distance between two minima of the aortic pressure signal.
2. The nominal value of the systemic resistance R_c was computed as:
$$R_c \approx \frac{\bar{P}_{ao}}{\mathrm{CO}}, \tag{12}$$
where $\bar{P}_{ao}$ is the mean aortic pressure over one heartbeat.
3. Aortic elastance E_{ao} was estimated by fitting the following equation to aortic pressure during diastole:
$$P_{ao}(t) \approx \exp\left(-\frac{E_{ao}(t-t_{BD})}{R_c}\right) P_{ao}(t_{BD}). \tag{13}$$
where t_{BD} denotes the beginning of diastole.
4. Left ventricular end-systolic elastance E_{lv} has been computed as:
$$E_{lv} \approx \max_T \frac{P_{lv}(t)}{V_{lv}(t)}. \tag{14}$$
The normalised pressure-volume ratio $e(t)$ was then obtained as:
$$e(t) \approx \frac{P_{lv}(t)}{E_{lv}\ V_{lv}(t)}. \tag{15}$$
5. Aortic valve resistance was initialised using:
$$R_o = \frac{\int_{P_{lv}(t)>P_{ao}(t)} (P_{lv}(t) - P_{ao}(t))\ \mathrm{d}t}{\mathrm{SV}}. \tag{16}$$
6. The resistance of the right circulation was initialised using:
$$R_i \approx \frac{\int_{\bar{P}_{vc}>P_{lv}(t)} (\bar{P}_{vc} - P_{lv}(t))\ \mathrm{d}t}{\mathrm{SV}}. \tag{17}$$
When Equation 16 or 17 could not be used (missing or inconsistent data), nominal valve resistances values were taken from Revie et al. (2013):
$$R_o = 0.04 \text{ mmHg s/ml} \tag{18}$$
$$R_i = 0.05 \text{ mmHg s/ml}. \tag{19}$$
7. Venous elastance E_{vc} was estimated using:
$$E_{vc} \approx 2\frac{PP_{vc}}{\mathrm{CO}\ T}. \tag{20}$$
When PP_{vc} was not available, it was estimated to be equal to 9 mmHg (Barbier et al. (2000)).
8. To determine the nominal value of SBV, the following equation was used:
$$\mathrm{SBV} \approx \bar{V}_{lv} + \frac{\bar{P}_{ao}}{E_{ao}} + \frac{\bar{P}_{vc}}{E_{vc}}. \tag{21}$$
When part of the data necessary to compute this nominal value of SBV was missing, results published by Pironet et al. (2014) were used. From these results, SBV was estimated to be equal to 593 ml.

In the previous computations, parameters T and E_{lv} 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 vector was:
$$\mathbf{p} = (\mathrm{SBV} \quad E_{ao} \quad E_{vc} \quad R_c \quad R_i \quad R_o). \tag{22}$$

II. Error Vector When available, the following experimental data were used for parameter identification:

- mean left ventricular volume ($\bar{V}_{lv}$),
- left ventricular SV (SV_{lv}),
- mean aortic ($\bar{P}_{ao}$) and vena cava pressures ($\bar{P}_{vc}$),
- aortic (PP_{ao}) and vena cava (PP_{vc}) pulse pressures.

The error vector $\mathbf{e}$ was built as the relative error between simulated and measured values (superscripts mes) of the previous signals:
$$\mathbf{e} = \left(1 - \frac{\bar{V}_{lv}}{\bar{V}_{lv}^{mes}} \quad 1 - \frac{SV_{lv}}{SV_{lv}^{mes}} \quad 1 - \frac{\bar{P}_{ao}}{\bar{P}_{ao}^{mes}} \quad ...\right). \tag{23}$$
Ventricular pressures were not included in the error vector since they had already been used to compute E_{lv} and $e(t)$. However, for pig 5, measured left ventricular volume was unreliable, which prevented correct estimation of E_{lv} and $e(t)$ as explained in the previous section. Consequently, for this animal, E_{lv} was inserted in the parameter vector $\mathbf{p}$, while $\bar{P}_{lv}$ and PP_{lv} were inserted in the error vector $\mathbf{e}$.

Additionally, measured mean vena cava pressure was negative for pig 1, which cannot be reproduced by the model. Since it was available, mean left atrial pressure was used instead, even if this substitution does not agree with the hypotheses underlying the model.

III. Subset Selection Algorithm A subset of the parameter vector $\mathbf{p}$ was selected for optimization using a dedicated algorithm, introduced by Burth et al. (1999). This algorithm performs a sensitivity analysis on the error vector $\mathbf{e}$ and selects the ρ parameters to which $\mathbf{e}$ is the most sensitive. In this work ρ was selected as the i (> 1) that maximised the ratio of two successive eigenvalues of the Hessian matrix h_i/h_{i+1}, when they were sorted in decreasing order, *i.e.* $h_i \geq h_{i+1}$.

IV. Iterative Adjustment of the Selected Parameters The ρ selected parameters were computed by an iterative procedure. The objective of this procedure was to minimise the mean absolute error (MAE), defined as
$$\mathrm{MAE} = \frac{1}{N}\sum_{i=1}^{N} |e_i|, \tag{24}$$
where N is the number of components in $\mathbf{e}$, equal to 4, 5, 6 or 7 in function of the available data. This task was performed using the simplex method for nonlinear optimisation combined with a custom implementation of the proportional method of Hann et al. (2010). The initial values needed by this algorithm were the ones computed in step I. All computations were performed using Matlab (2010a, MathWorks, Natick, MA).

3. RESULTS AND DISCUSSION

3.1 Subset Selection Algorithm

Figure 2 shows the frequency of parameter selection by the algorithm. As can be seen from this figure, SBV and R_c have been selected by the algorithm for all 37 datasets, allowing the estimation of these parameters in all cases. This result emphasises the importance of the

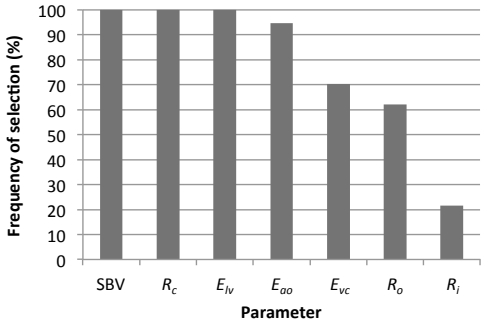

Fig. 2. Frequency of parameter selection by the subset selection algorithm.

SBV parameter for CVS model simulations, as previously pointed out by Pironet et al. (2014).

As mentioned in the previous section, E_{lv} was only submitted to the subset selection algorithm for pig 5. For this animal, E_{lv} has also been selected for all datasets.

The valve resistances R_i and R_o were the least frequently selected parameters. They are indeed difficult to identify (from the data used), as already noted by Revie et al. (2013) and Pironet et al. (2014).

3.2 Quality of the Parameter Adjustment

After parameter adjustment on the 37 datasets, the MAE amounts to 8.58 % on average and ranges from 0.89 to 33.23 %. The quality of the parameter adjustment is thus very good, which also implies that the very simple 3-chamber CVS model used can capture the diversity of the experimental measurements obtained. For instance, pig 6 presented a *pulsus paradoxus* (alternance of strong and weak beats), which caused the highest MAE of 33.23 %, but this condition was still correctly reproduced by the model. Additionally, Pig 8 was diagnosed in shock, but this did not prevent the model to correctly represent this animal's condition (average MAE for this pig is 3.31 %).

A representative example of parameter adjustment is displayed in Figure 3. The MAE for the corresponding dataset is 8.86 %. Simulated and measured pressures and volumes are thus in good agreement.

A frequent source of errors can be evidenced using Figure 3: during a whole cardiac cycle, measured aortic pressure (top, dashed light grey line) is nearly always higher than measured left ventricular pressure (top, dashed black line). The simple valve model used in this work cannot reproduce such a situation, since the model requires aortic pressure to be lower than left ventricular pressure for the valve to open (Equation 6).

The parameter identification method presented in this work is robust, since it was able to fit the model to various experimental data, as shown in Table 1:

- PiCCO data available or not,
- left atrial/vena cava pressure data available or not,
- vena cava pulse pressure data available or not,
- unreliable left ventricular volume data.

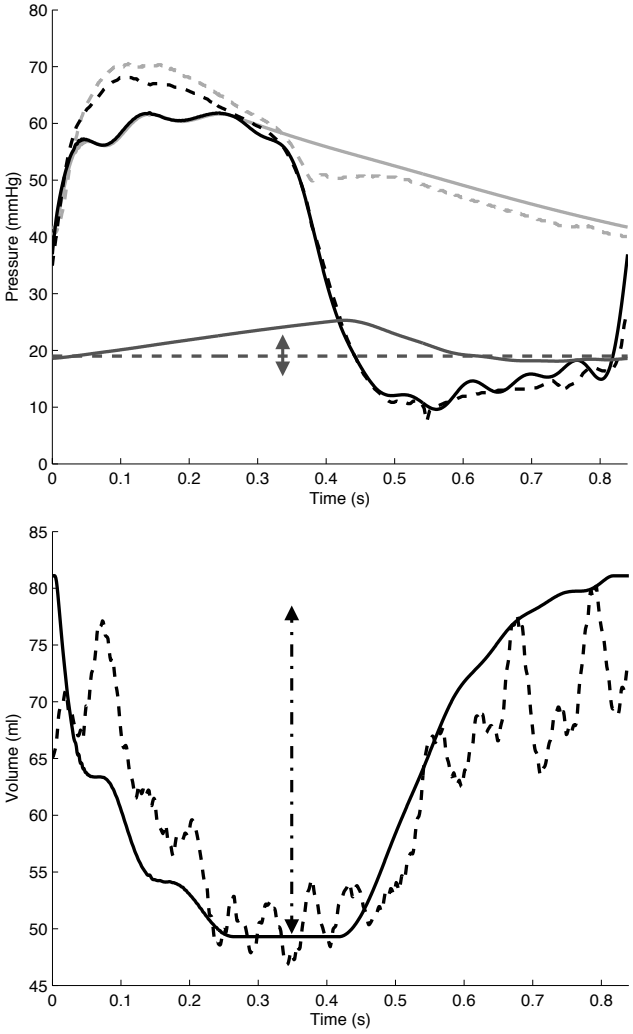

Fig. 3. Identification result for pig 8, after 225 ml fluid administration. *Top:* simulated (*full lines*) and measured (*dashed lines*) left ventricular (*black*), aortic (*light grey*) and vena cava (*dark grey*) pressures. The arrow represents vena cava pulse pressure measured by the PiCCO. *Bottom:* simulated (*full line*) and measured (*dashed line*) left ventricular volumes. The arrow represents SV measured by the PiCCO.

This robustness and adaptability to the available data makes the method a serious candidate for application to intensive care unit patient data.

Indeed, even if experimental measurements include left ventricular pressure and volume, which are not routinely measured in the intensive care unit, these measurements are only used to obtain the nominal parameter values. The parameter adjustment is performed using only the vector $\mathbf{e}$, which contains data available in the intensive care unit.

3.3 Relation between Total Stressed Blood Volume before Fluid Administration and Change in Cardiac Output after Fluid Administration

Figure 4 shows the relation between relative change in CO after each fluid administration and the identified SBV value before the fluid administration, for all 8 animals. The figure shows that, the higher the SBV, the lower the

relative change in CO. This relation was to be expected, since SBV represents the volume status of a subject. For instance, a high SBV value means that the subject has a large intra-vascular blood volume. In this case, a fluid administration is not required and will probably not be beneficial. Note that the worst correlation ($R = -0.38$) is observed for pig 6, which presented a *pulsus paradoxus*. As explained in the previous section, this condition was associated with a larger MAE, which might have impacted the quality of the estimated SBV and could explain the poor relation between SBV and relative change in CO after fluid administration.

Such a negative correlation between SBV and relative change in CO after fluid administrations was previously observed by Maas et al. (2012) in intensive care unit patients. In the study of Maas et al. (2012), SBV was determined using a succession of 10 sequential 50 ml fluid administrations and local circulatory arrests, a time-consuming procedure, which may also be harmful if these *a priori* fluid administrations are actually not required. In contrast, the procedure presented in this work does not require *a priori* fluid administration or circulatory arrests to compute the SBV value. Furthermore, it is based on data available in an intensive care unit.

3.4 Predictive Value of Total Stressed Blood Volume

Figure 4 also emphasises that neither SBV nor CO changed monotonously during the filling experiments, which can be attributed to the numerous regulatory mechanisms acting on the CVS. This observation underlies the complexity of predicting the effects of fluid administration.

Various definitions of a positive response to vascular filling exist in the literature. Maas et al. (2012) define a positive response as a relative change in CO larger than 12 %. According to this definition, 10/37 (27 %) of the fluid administrations performed in the present study were associated to a positive response.

The receiver operating characteristic (ROC) curve was plotted to investigate if a SBV lower than a given threshold could predict a relative change in CO larger than 12 %. The best threshold for SBV was found to be 145 ml and is represented in Figure 4. The threshold was associated with a sensitivity of 0.75 and a specificity of 0.70. The area under the ROC curve was 0.70. This analysis was conducted only using data from pigs 3 to 8 since pigs 1 and 2 received different volumes of fluid, administered in a different fashion.

The moderately high values of sensitivity and specificity can be understood by noticing that the relation between SBV and relative change in CO seems to be subject-specific. (The slope of the relation between SBV and relative change in CO ranges from -0.0013 to -0.0088 ml^{-1}.) Maas *et al.* determined only one SBV value for each subject, and thus, could not make such an observation.

4. CONCLUSION

This work presented a mathematical model-based method to compute SBV. This index was estimated using a simple CVS model, whose parameters were adjusted to data from vascular filling experiments in pigs. The identified SBV value presented a consistent association with the relative change in cardiac output after fluid administration, as expected theoretically and from the results of a previous study.

The method can be applied to humans, since it does not require *a priori* fluid infusions and the data required for parameter identification can be obtained in an intensive care unit. A human trial is planned in the near future.

REFERENCES

Barbier, P., Solomon, S., Schiller, N.B., and Glantz, S.A. (2000). Determinants of forward pulmonary vein flow: an open pericardium pig model. *Journal of the American College of Cardiology*, 35(7), 1947–1959.

Burth, M., Verghese, G.C., and Velez-Reyes, M. (1999). Subset selection for improved parameter estimation in on-line identification of a synchronous generator. *IEEE Transactions on Power Systems*, 14(1), 218–225.

Hann, C., Chase, J., Desaive, T., Froissart, C., Revie, J., Stevenson, D., Lambermont, B., Ghuysen, A., Kolh, P., and Shaw, G. (2010). Unique parameter identification for cardiac diagnosis in critical care using minimal data sets. *Computer Methods & Programs in Biomedicine*.

Klabunde, R. and Dalley, A. (2004). *Cardiovascular physiology concepts*. Lippincott Williams & Wilkins.

Maas, J.J., Pinsky, M.R., Aarts, L.P., and Jansen, J.R. (2012). Bedside assessment of total systemic vascular compliance, stressed volume, and cardiac function curves in intensive care unit patients. *Anesthesia & Analgesia*, 115(4), 880–887.

Michard, F. and Teboul, J.L. (2000). Using heart-lung interactions to assess fluid responsiveness during mechanical ventilation. *Critical Care*, 4(5), 282–289.

Pironet, A., Desaive, T., Chase, J.G., Morimont, P., and Dauby, P.C. (2014). Model-based computation of total stressed blood volume from a preload reduction experiment. In *Proceedings of the 19th IFAC World Congress*, 5641–5646.

Revie, J.A., Stevenson, D.J., Chase, J.G., Hann, C.E., Lambermont, B.C., Ghuysen, A., Kolh, P., Shaw, G.M., Heldmann, S., and Desaive, T. (2013). Validation of subject-specific cardiovascular system models from porcine measurements. *Comput Methods Programs Biomed*, 109(2), 197–210.

Suga, H., Sagawa, K., and Shoukas, A.A. (1973). Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. *Circulation Research*, 32(3), 314–322.

Appendix A. DERIVATION OF THE NOMINAL PARAMETER VALUES

A.1 Systemic Vascular Resistance R_c

The systemic vascular resistance R_c was computed using the definition of Klabunde and Dalley (2004):

$$R_c = \frac{\bar{P}_{ao} - \bar{P}_{vc}}{CO}. \tag{A.1}$$

For simplicity, $\bar{P}_{vc}$ was neglected with respect to $\bar{P}_{ao}$ and thus set to zero in Equation A.1, yielding Equation 12.

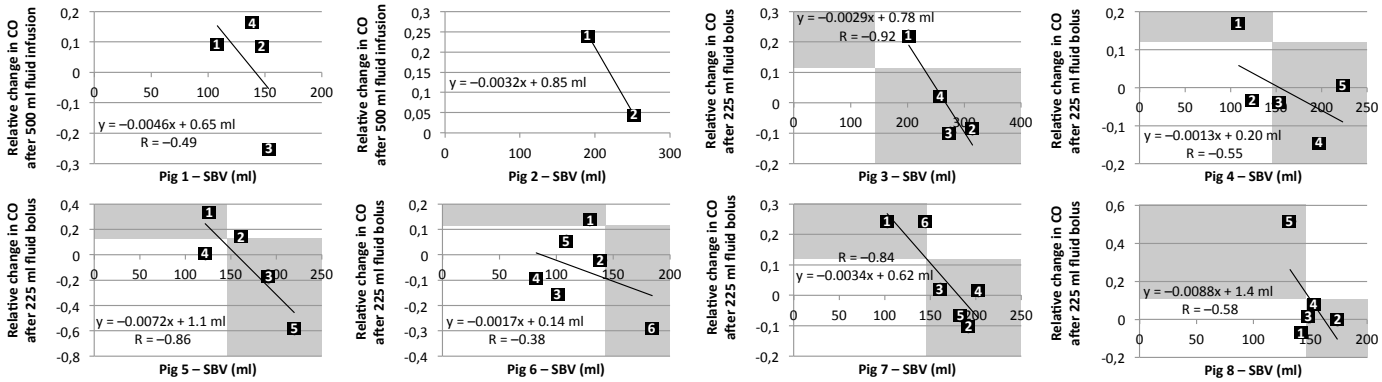

Fig. 4. Relative change in CO after each fluid administration plotted versus the identified SBV value before administration. The numbers in the squares indicate the sequence of fluid administrations. The grey areas divide the plane along the lines SBV = 145 ml and relative change in CO = 12 %.

A.2 Aortic Elastance E_{ao}

During diastole ($Q_o = 0$), volume change of the arterial compartment is described by Equations 4 and 8:

$$\dot{V}_{S,ao}(t) = -\frac{P_{ao}(t) - P_{vc}(t)}{R_c}. \tag{A.2}$$

If, once again, venous pressure is neglected with respect to aortic pressure, using Equation 1, one gets:

$$\dot{V}_{S,ao}(t) \approx -\frac{E_{ao}\ V_{S,ao}(t)}{R_c}. \tag{A.3}$$

Solving this differential equation yields:

$$V_{S,ao}(t) \approx \exp\left(-\frac{E_{ao}\ (t - t_{BD})}{R_c}\right) V_{S,ao}(t_{BD}) \tag{A.4}$$

where t_{BD} denotes the beginning of diastole. Multiplying both sides of Equation A.4 by E_{ao} yields Equation 13.

A.3 Left Ventricular End-Systolic Elastance E_{lv} and Normalised Pressure-Volume Ratio $e(t)$

Equations 14 and 15 are obtained from Equation 3, assuming that measured left ventricular volume $V_{lv}(t)$ is equal to the model left ventricular stressed volume $V_{S,lv}(t)$. This assumption is equivalent to stating that left ventricular unstressed volume is zero. Since preload, afterload and cardiac frequency are not changing in the present simulations, the left ventricular pressure-volume loops are not changing, which makes it unnecessary to precisely determine the left ventricular unstressed volume.

A.4 Aortic Valve Resistance R_o

Equation 6, integrated on one heartbeat, gives:

$$\int_T Q_o(t)\ \mathrm{d}t = \frac{\int_{P_{lv}(t) > P_{ao}(t)} (P_{lv}(t) - P_{ao}(t))\ \mathrm{d}t}{R_o} \tag{A.5}$$

By definition, the integral of the flow going out of the heart during one heartbeat is equal to the SV, hence giving Equation 16.

A.5 Resistance of the Pulmonary Circulation R_i

Equation 5, integrated on one heartbeat, gives:

$$\int_T Q_i(t)\ \mathrm{d}t = \frac{\int_{P_{vc}(t) > P_{lv}(t)} (P_{vc}(t) - P_{lv}(t))\ \mathrm{d}t}{R_i}. \tag{A.6}$$

Here also, the integral of the flow going into the heart during one heartbeat is equal to the SV. For simplicity, $P_{vc}(t)$ was assumed constant and replaced by its mean value $\bar{P}_{vc}$, which gives Equation 17.

A.6 Venous Elastance E_{vc}

During systole ($Q_i = 0$), Equation 9 reads:

$$\dot{V}_{S,vc}(t) = Q_c(t). \tag{A.7}$$

Flow through the capillaries is assumed to be constant and equal to its mean value *i.e.* CO:

$$\dot{V}_{S,vc}(t) \approx \mathrm{CO}. \tag{A.8}$$

Integrating this equation from beginning (t_{BS}) to end (t_{ES}) of systole gives:

$$V_{S,vc}(t_{ES}) - V_{S,vc}(t_{BS}) \approx \mathrm{CO}\ (t_{ES} - t_{BS}). \tag{A.9}$$

Multiplying both sides by E_{vc} and using Equation 2 gives:

$$P_{vc}(t_{ES}) - P_v(t_{BS}) \approx E_{vc}\ \mathrm{CO}\ (t_{ES} - t_{BS}). \tag{A.10}$$

Finally, assuming $P_{vc}(t_{ES}) - P_{vc}(t_{BS}) = PP_{vc}$ and $t_{ES} - t_{BS} = T/2$, one obtains Equation 20.

A.7 Stressed Blood Volume SBV

Equation 11 is averaged on one heartbeat, giving:

$$\bar{V}_{S,lv} + \bar{V}_{S,ao} + \bar{V}_{S,vc} = \mathrm{SBV}. \tag{A.11}$$

Then, Equations 1 and 2 are also averaged, yielding Equation 21.