Sensitivity Analysis and Parameter Identification of a Cardiovascular Model in Aortic Stenosis

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Abstract

The objective of this study is to propose a model-based method, adapted to patients with severe aortic stenosis (AS), in order to reproduce left ventricle (LV) pressure and volume from patient specific data. A formal sensitivity analysis is proposed, focused on left ventricle volume and pressure. The most influent parameters of this analysis are then selected to be identified in a parameter identification strategy and provide a patient specific pressure curve. This was implemented on 3 AS patients and a close match was observed between experimental and simulated pressure and volume curves. The global root mean square error (RMSE) for pressure and volume curves are respectively 21.8 (±1.8) mmHg and 14.8 (±9.4) ml. The model-based approach proposed shows promising results to generate accurate LV pressure and volume in AS case.

1. Introduction

Aortic stenosis (AS) is the most common valvular heart disease in Western countries [1]. AS is characterized by a reduction of the size of the aortic valve orifice due to a narrowing of the valve opening. This reduction in aortic valve area induces the development of a pressure gradient across the valve and the development of chronic Left Ventricle (LV) pressure overload. Timing and indications for surgical intervention in asymptomatic patients without LV dysfunction remains particularly controversial [2]. Robust indices, independent of loading conditions, are notably required to categorize patients with AS taking into account the impairment of myocardial diastolic and systolic function.

Myocardial work (myocardial function based on speckle tracking imaging) is a promising new tool to assess LV function [3] taking into account loading condition. However, this method requires the estimation of LV pressure, which could be difficult in the case of AS, where high pressure gradients could be observed between LV and the aorta.

Recently our team has proposed a patient-specific model-based approach for the evaluation of myocardial work in the context of AS [4]. The model-based method allows for the integration of physiological knowledge in the evaluation of myocardial work indices. LV pressure and Myocardial work (MW) were estimated from non-invasive data: Aortic Valve Area (AVA), systolic and diastolic pressures. Although a good fitting between model-based and experimental values was observed, we could hypothesis that results might be improved by including LV volume in the identification step. The objectives of this paper were 1) to determine most influent parameters on pressure gradient and stroke volume based on sensitivity analysis and 2) to show the model ability to simulate simultaneously LV pressure and volume for 3 AS patients.

2. Methods

2.1. Dataset

The study was carried out in accordance with the principles outlined in the Declaration of Helsinki on research in human subjects and received specific ethical approval from of the local Medical Ethics Committee.

2.1.1. Clinical measurements

The dataset used in this study contains 3 patients suffering from severe AS (aortic valve area $\leq 1cm^2$). Experimental data include ECG, LV and arterial pressure curves. LV pressure curve (P_{lv}^{exp}) was obtained by left heart catheterization (LHC) performed in all the patients via a retrograde access from the radial artery with a 5 French Judkin R4 catheter (ICU Medical, San Clemente, CA, USA) placed at the mid LV cavity using fluoroscopic screening. The patients underwent a standard transthoracic echocardiography using a Vivid S6, E7 or E9 ultrasound system (General Electric Healthcare,Horten, Norway) to estimate the aortic valve area and extract regional myocardial strain curves.

2.1.2. Volume estimation

Our group has recently proposed a method to estimate LV volume curves from speckle tracking echocardiography [5]. Briefly, the LV knot positions detected for the computation of the regional myocardial strain curves are used. It consists of an extraction of the endocardial wall segmentation points from apical four- and two-chamber followed by a spatial resampling along the long axis of the LV. This defines a 3D volume made of closed splines perpendicular to the long axis (fig.1). Finally, a volume curve (V_{lv}^{exp}) was reconstructed by repeating this procedure during all sample time of the cardiac cycle.

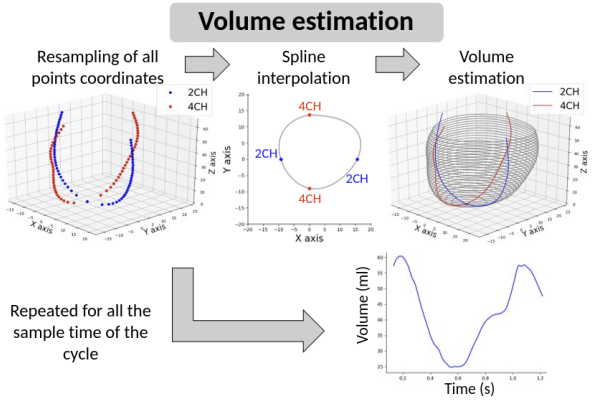

Figure 1: Volume estimation method

2.2. Model description

Four main sub-models, based on previous works of our team [6, 7], were coupled: i) cardiac electrical system, ii) elastance-based cardiac cavities, iii) systemic and pulmonary circulations and iv) heart valves. The proposed model (fig.2) and the equation have been described in detail in the article of Owashi et al. [4]. To sum up:

Cardiac electrical system: A set of interconnected cellular automata, adapted from [6, 7] represents the cardiac electrical activity of the model. Each automaton represents different cardiac regions that cycle between four electrical activation states: slow diastolic depolarization (SDD), upstroke depolarization period (UDP), absolute refractory period (ARP) and relative refractory period (RRP).

Elastance-based cardiac cavities: Cardiac cavity pressure is represented by a combination of end-systolic (es) and end-diastolic (ed) pressure-volume relationships [8,9]. These relations are driven by time-varying elastances E_{es} and E_{ed} that represent contraction and relaxation phases. For the right and left ventricles, a "double Hill" driving function e was selected [10] with parameters n_1, n_2, α_1 and α_2, while a gaussian function was used for right and left atria with parameter C and B.

$$P_{es}(V) = E_{es}(V - V_d) \tag{1a}$$

$$P_{ed}(V) = P_0(e^{\lambda(V-V_0)} - 1) \tag{1b}$$

$$P(V) = e(t)P_{es}(V) + (1 - e(t))P_{ed}(V) \tag{1c}$$

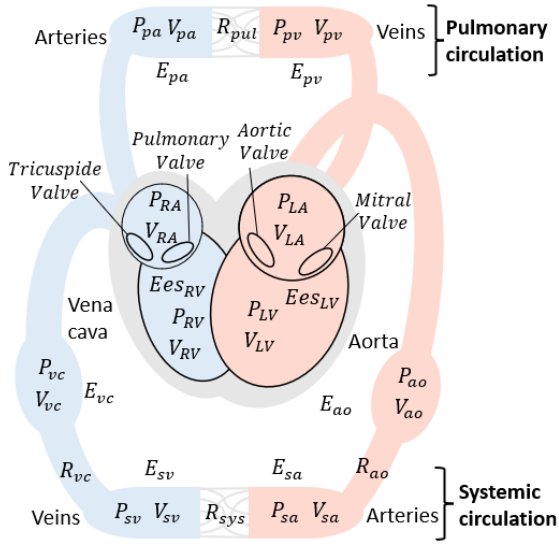

Figure 2: Cardiovascular model. P:pressure, V:volume, R:resistance, E:elastance, pa:pulmonary arteries, pv:pulmonary veins, ao:aorta, sa:systemic arteries, sv:systemic veins, vc:vena cava, LA:left atrium, LV:left ventricle; RA:right atrium, RV:right ventricle

Systemic and pulmonary circulations: The model integrates the pulmonary and systemic arteries, capillaries and veins [11]. Arteries and veins compartments pressure P is calculated using a linear relationship between its volume P and its elastance E. The pressures are then used to calculate blood flow between two chambers as $Q = \Delta P/R$, where ΔP is the pressure gradient between the chambers and R the corresponding resistance.

Cardiac valves : A detailed model of heart valves (mitral, aortic, tricuspid and pulmonary) was integrated [12]. Briefly, the relation between the pressure gradient ΔP and the fluid flow Q across an open valve is approximated by the Bernoulli equation:

$$\Delta P = Bq|q| + L\frac{dq}{dt}, \quad \text{with} \quad L = \rho\frac{l_{eff_{ao}}}{A_{eff}} \tag{2}$$

The cardiac valve model integrates the effective cross-sectional area of the valve A_{eff} with its dynamic ξ:

$$A_{eff}(t) = (A_{eff,max} - A_{eff,min})\xi(t) + A_{eff,min} \tag{3}$$

where $A_{eff,max} = Mst_{ao}.Aann_{ao}$ and $A_{eff,min} = Mrg_{ao}.Aann_{ao}$ correspond respectively to the maximum and minimum valve areas and $Aann_{ao}$ to the estimation of the aortic valve area.

2.3. Sensitivity analysis

Sensitivity analysis through the Morris 'screening method [13] was performed to determine the most influen-

tial parameters of two model outputs: LV pressure gradient (ΔP) and stroke volume (SV). This method consists in generating several random trajectories through the parameter space. Each trajectory is associated with an estimation of the Elementary Effects EE_i, defined for a parameter x_i:

$$EE_i = |\frac{Y(x_1, ..., x_i, ...x_k) - Y(x_1, ..., x_i + \Delta, ...x_k)}{\Delta}| \tag{4}$$

where Y is an output of the model and Δ is the variation of the parameter. EE_i are calculated r times and the mean of absolute value μ_i* and standard deviation σ_i of these r realisations are then computed for each parameter i. SM_i index gathered this two-sensitivity measure. In this study the sensitivity analyses were applied on 80 parameters with ranges selected from previous work and literature $\pm 30\%$.

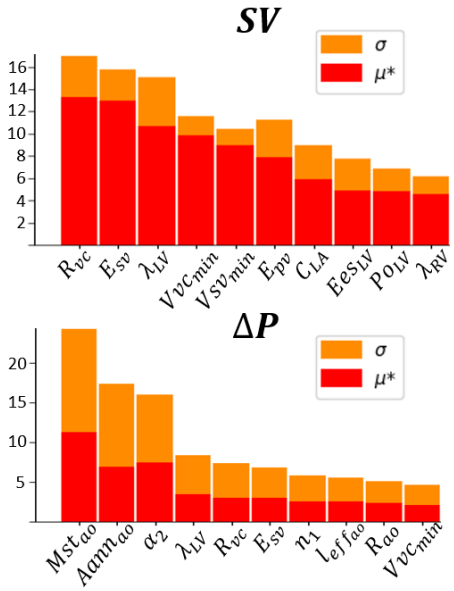

Figure 3: 10 most influential parameters from Stroke Volume (SV) and ΔP sensitivity analyses

2.4. Parameter identification

Based on the results of the sensitivity analyses, a set of parameters is selected for patient-specific model identification. This identification was implemented with an evolutionary algorithm (EA) [14]. This type of algorithm consists of making evolve a population of set of parameter values X in order to minimizing a fitness function f by selecting, crossing and mutating the population through generations. The function f is defined in order to minimize the error between LV pressure P_{lv} and volume curves V_{lv}, systolic and diastolic arterial pressure ($P_{ao,sys}$ and $P_{ao,dias}$) from experimental measurements and simulated by the model:

$$f(X) = f_{P_{lv}}(X) + f_{V_{lv}}(X) + f_{P_{ao}}(X) \tag{5a}$$

$$f_{P_{lv}}(X) = \frac{1}{T_K} \sum_{t_k} |\frac{P_{lv}^{sim}(t_k) - P_{lv}^{exp}(t_k)}{P_{lv,sys}^{exp}}| \tag{5b}$$

$$f_{V_{lv}}(X) = \frac{1}{T_K} \sum_{t_k} |\frac{V_{lv}^{sim}(t_k) - V_{lv}^{exp}(t_k)}{V_{lv,max}^{exp}}| \tag{5c}$$

$$f_{P_{ao}}(X) = \frac{|P_{ao,sys}^{sim} - P_{ao,sys}^{exp}| + |P_{ao,dias}^{sim} - P_{ao,dias}^{exp}|}{2P_{ao,sys}^{exp}} \tag{5d}$$

where t_k corresponds to the time elapsed since the onset of the identification period and T_K is the duration of a cardiac cycle. The whole process was repeated 3 times to propose the best set of parameters for each patient.

3. Results and discussion

Concerning sensitivity analysis results (fig.3), the most influential parameters on SV are associated with LV systolic and diastolic properties. The resistance R_{vc}, the unstressed volumes Vvc_{min} and Vsv_{min} and the elastance E_{sv} (cf fig.2) are directly related to the systemic circulation as vena cava and systemic veins parameters. These circulatory parameters can modify the afterload conditions, whereas parameters such as E_{pv} is more likely associated with LV preload. Moreover, as the link between LV pressure and volume is almost direct (eq.1), λ_{LV} and $P_{0_{LV}}$ affiliated to the LV end-diastolic function and Ees_{LV}, to the end-systolic one, appear influential on SV.

The most influential parameters of ΔP were mainly related to the aortic valve sizes and the LV elastance, which underline the direct impact of the aortic narrowing of this pathology on the gradient pressure [12]. In fact, $l_{eff_{ao}}$ and $Aann_{ao}$ correspond to the aortic valve length and area, modulated by Mst_{ao} and used in the valve dynamics computations (eq.2, 3). In addition, parameter such as α_2, n_1 and λ_{LV} are used in the computation of LV pressure through the driving function and end-diastolic pressure. Modification of these parameters not only change the maximum value of the LV elastance but also its timing and pattern. The parameters with the highest sensitivities were selected for parameter identification.

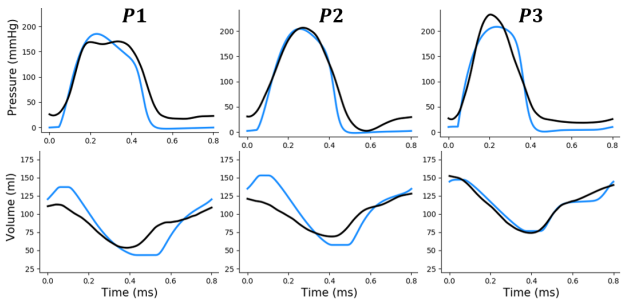

Figure 4: LV pressure and volume curves: i) simulated (blue) ii) experimental (black)

From the identification process we obtained patient-specific simulated LV pressure and volume curves. Figure 4 compares the simulated and experimental LV pressure and volume of the 3 AS patients.

A close match was observed between experimental and simulated pressure and volume curves. The global root mean square error (RMSE) for pressure and volume curves are respectively $21.8(\pm 1.8)$ mmHg and $14.8(\pm 9.4)$ ml.

The main contribution of this work concerns the proposal of the parameter identification procedure, applied to an integrated CVS model, able to reproduce LV pressure and volume simultaneously and specifically to each AS patient. The coupling of the CVS model, developed by our team, and adapted to AS patient with integrating heart valve model allows to simulate accurate patient specific myocardial function. Previous work [4, 15] demonstrate the ability to this model to estimate LV pressure with only non-invasive data. This work aims at go further by estimate LV pressure and volume simultaneously.

One of the main limitations of this work is the limited number of patients included. Further work is necessary in order to apply and validate this method on a higher number of patients. Moreover, for the purpose of the use of non-invasive data, parameters identify in this study must be fixed and a large data base will be needed.

4. Conclusion

The model-based approach shows promising results to reproduce accurate LV pressure and volume in AS case with close match between simulated and measured curves. Further works will focus on the estimation of patient-specific curves and the assessment of myocardial work indices from non-invasive data.

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