Atrioventricular Delay Optimization in Cardiac Resynchronization Therapy Assessed by a Computer Model

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Abstract

A lumped-parameter model of the cardiovascular system is applied in this work to the analysis of the characteristics of mitral flow profiles, for different atrio-ventricular pacing configurations, in the context of cardiac resynchronization therapy (CRT). Primarily, a sensitivity analysis is performed on the main model parameters, so as to discern their influence on mitral flow. Parameter identification is then applied to reproduce pulsed-wave Doppler profiles of the mitral inflow acquired from three patients during post-operative CRT optimization sessions. The model is able to reproduce patient-specific morphological variations on mitral inflow profiles for different AVD values, providing relative mean squared errors reading 0.031, 0.068 and 0.076 for the three patients.

1. Introduction

Cardiac resynchronization therapy (CRT) is the therapy of choice for patients suffering from heart failure (HF), meeting specific criteria [1]. Clinical studies have shown that patient response to CRT is highly dependent on the pacing configuration, namely the atrioventricular (AVD) and interventricular (VVD) delays, with the former being the most sensitive parameter. Research in this field is currently geared towards individualization of AVD and VVD, in order to optimize the patient response. Different echocardiographic indicators have been proposed to optimize CRT delivery and, maximizing left ventricular filling is widely regarded one of the main optimization targets to achieve, with respect to AVD selection.

In a previous work, we have proposed a lumped-parameter model that was able to reproduce variations of systolic blood pressure due to AVD and VVD modifications [2]. In this paper, we adapt and complete this model to focus on the analysis of mitral inflow during AVD optimization. After briefly describing the model, a sensitivity analysis of the main model parameters is presented. Finally, a parameter identification stage is applied on data acquired from three patients undergoing CRT optimization.

2. Model description

The system model proposed in this paper is composed of three components representing: i) the cardiac electrical activity, ii) the cardiac mechanical activity and the circulation and iii) a bi-ventricular pacemaker (CRT-P).

The model of the cardiac electrical activity is based on previous work [3] and has been adapted to our purpose. It is made of nine generalized automata, representing the sinoatrial node (SAN), atrioventricular node (AVN), upper and lower bundle of His ($UH\&LH$) and left and right bundle branches (LBB and RBB) and the four cardiac chambers, left and right atria (LA and RA) and left and right ventricles (LV and RV). The model has four inputs; the baseline heart rate (HR), which is fed directly to the SAN and three stimulation inputs coming from the pacemaker ($Stim.A$, $Stim.RV$ and $Stim.LV$) simulating the three pacing leads used in CRT. After a certain electro-mechanical delay, controlled by the *Upstroke Activation Period* parameter (UAP), each myocardial automaton sends an activation signal which is fed to the corresponding chamber of the mechanical model and eventually sent to the pacemaker model for the sensing function. Parameters of this model can be identified so as to reproduce a left bundle branch block, as observed in patients selected for CRT [3].

The CRT pacemaker sub-model reproduces the function of a CRT-P in DDD mode, that is, it is able to i) stimulate the LA and both ventricles at specific instants, ii) sense the spontaneous activity from each chamber and iii) inhibit atrial and/or ventricular pacing when a spontaneous activity is sensed, while a lone atrial sense will trigger the stimulation of RV and LV after a delay controlled by the two CRT-P parameters (AVD and VVD).

Finally, the mechanical and circulatory models are composed of a simplified description of the mechanical proper-

ties of the heart, including the mechanical function of the four cardiac chambers, and a circulatory model, based on a Winkessel formalism. The mechanical function of atria and ventricles are described by elastic chambers. One cycle of the atrial elastance is given by:

$$E_a(t) = E_{a,max}\left[e_a(t) + \frac{E_{a,min}}{E_{a,max}}\right], \quad (1)$$

with $e(t)$ being a Gaussian driver function, defined by [4]:

$$e_a(t) = exp\left[-B_a.\left(\frac{HR}{HRR}\right)^2.\left(t - \frac{C_a.HRR}{HR}\right)^2\right] \quad (2)$$

where $B_a = 84.375\ s^{-2}$ controls the rise and $C_a = 0.32\ s$ the peak position of the atrial driver function; $HRR = 60$ bpm is the resting heart rate and HR is the instantaneous heart rate.

As for the ventricles, one can identify two main characteristics in their pressure-volume (PV) loops, namely the end systolic PV relationship (ESPVR) and the end diastolic PV relationship (EDPVR), which define respectively the upper and lower bounds of the loops. These two relationships can be written as $P_{es} = E_{es}(V - V_0)$ and $P_{ed} = P_0\left(e^{\lambda(V-V_0)} - 1\right)$ [5]. The former equation describes the linear relationship between end systolic pressure (P_{es}), volume (V), volume at zero pressure (V_0) and elastance (E_{es}), while the latter defines the non linear relationship between end diastolic pressure (P_{ed}) and volume (V). Here, P_0 defines the elastance of the ventricular walls during diastole and λ the curvature of the EDPVR. The pressure of anyone ventricle can finally be written in terms of these equations and its driver function ($e_v(t)$):

$$P_v(V,t) = e_v(t)P_{es} + (1 - e_v(t))P_{ed}. \quad (3)$$

Whereas the driver functions for the atria are symmetrical, in this paper we propose asymmetrical functions for the ventricles, defined as:

$$e_v(t) = \alpha t^4 e^{-\beta(t - T_p)} \text{ with } \alpha = \frac{1}{T_p^4} \text{ and } \beta = \frac{4}{T_p}. \quad (4)$$

where T_p represents the time at which the driver function peaks and it is made to vary inversely with the heart rate:

$$T_p = \frac{T_{p,ref}.HRR}{HR};$$

with $T_{p,ref} = 0.22\ s$. This single parameter controls the width and the rise/decay rates of the driver function. We have assumed that a longer rise implies a longer decay and vice-versa. It should be noted that, compared to the model we previously presented [2], we have here removed the fifth chamber representing the interventricular septum. Since we are focusing in this paper on AVD optimization, with synchronous ventricular pacing (VVD = 0), we believe it is not necessary to further complexify the model by adding a ventricular coupling.

The circulatory model is based on the Windkessel approach, such as in [4, 6], and has been described in a previous work [2]. Four diodes have been included to represent, in a simple way, the four cardiac valves, with resistance values of $0.01\ mmHg.s/ml$ in forward bias and $100\ mmHg.s/ml$ in reverse bias.

3. Simulation results

Fig. 1 shows examples of mitral flows obtained through the model with different parameter sets, so as to simulate a normal heart and cases of moderate (MHF) and severe heart failure (SHF) both undergoing CRT with simultaneous pacing at AVD = 120 ms. With respect to the normal heart, in both heart failure cases, it has been assumed that ventricular contractility is reduced (smaller value of $E_{es,lv}$), asynchronicity increased (higher value of $T_{p,ref,lv}$) and relaxation impaired (higher value of λ_{lv}). The main difference between the two HF cases resides in the ability of the left atria to compensate the loss in ventricular function; in the MHF case atrial contractility is higher that in the normal case whereas in SHF, the atrial function also is affected due to continuous atrial dilation. The signals displayed correspond to a stationary state reached by the model after an initial transient regime.

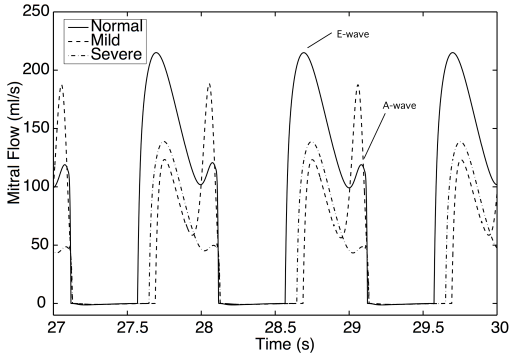

Figure 1. Simulated mitral inflows obtained from our model reproducing the case of a normal heart, moderate and severe heart failure.

The simulated mitral flow can be compared to the observed pulsed-wave Doppler (PWD) of mitral inflow with two components: the E-wave, corresponding to ventricular diastolic filling and an A-wave, due to atrial filling. In the case of the normal heart, the peak E-wave to A-wave ratio (EAR) equals 1.8 while the ratio of the mitral flow duration to RR-interval ($RMitRR$) reads 0.56. As for the MHF patient, with preserved atrial function, there is an inversion of the EAR which reads 0.66 whereas for SHF the left atrium being impaired, there is nearly no A-wave. The

EAR is equal to 1.8 similarly to the normal case but there is a consequent reduction in peak E-wave value; 215 vs 123 ml/s. Compared to the normal case, $RMitRR$ values are lower for the MHF and SHF cases (respectively 0.45 and 0.49).

Modifications of the AVD value lead to changes in the mitral flow profile. Figure 2, shows such modifications for the MHF case. The superposed signals are centered around LV stimulations, whereas the other vertical lines correspond to the various atrial stimulations. It can be observed that, at low AVD values, the simulated A-wave is truncated by the sooner ventricular contraction, leading to a faster increase in intraventricular pressure, closing the mitral valve. At higher AVD values, there is a fusion of the E and A-waves. This response has been described in the literature and is one of the basis of AVD optimization.

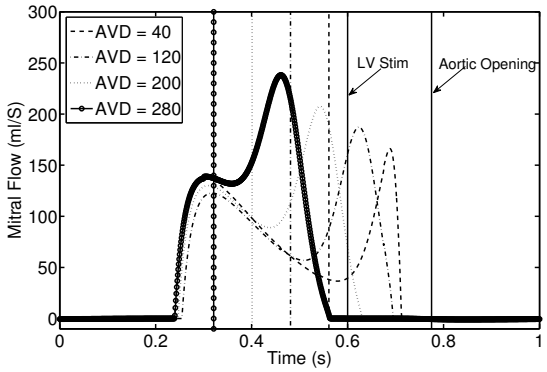

Figure 2. Simulated mitral flow profiles for a CRT patient with MHF for AVD ranging from 40 ms to 280 ms, at a fixed HR = 60 bpm.

4. Sensitivity analysis and parameter identification

To carry out the sensitivity analysis, we have followed the method proposed by Morris [7]. Briefly, for k model parameters, whose effects are to be investigated, a k-dimensional p-level grid whose boundaries are given by the upper and lower limits of the model parameters is defined. The elementary effect of the i^{th} parameter with respect to a certain model output y is given by:

$$\Delta_i(\mathbf{x}) = [y(x_1, x_2, ..., x_{i-1}, x_i + \delta, x_{i+1}, ..., x_k) - y(\mathbf{x})]/\delta, \quad (5)$$

Running the model a certain number of times with the rule that two consecutive simulations have one and only one parameter being different, yields a number of elementary effects due to each parameter and these can be computed to give for each output of interest a mean elementary effect with respect to each model parameter as well as its standard deviation. Higher mean values tend to imply greater effects of the model parameter on the output considered while high standard deviation values could mean either non linear variations of the output with the parameter or that there is a strong interaction between the different parameters.

We have assumed that the mitral flow pattern is mainly dependent on the left atrial ($E_{la,max}, E_{la,min}, C_{la}$ and B_{la}) and ventricular ($E_{es,lv}, \lambda_{lv}, P_{0,lv}, T_{p,lv}, UAP_{lv}$ and $UAP_{sensing}$) parameters. Morris analyses have been carried out on the following output variables: maximum E and A-waves (E_{max} and A_{max}), mitral flow duration (MFD) and mitral flow time integral ($MFTI$). The most sensitive parameters for E_{max} (figure 3), MFD and $MFTI$ were, in order, λ_{lv}, $T_{p,lv}$ and $E_{es,lv}$, whereas, for A_{max}, the most sensitive was $E_{la,min}$. $UAP_{sensing}$ and UAP_{lv} were consistently the least sensitive parameters.

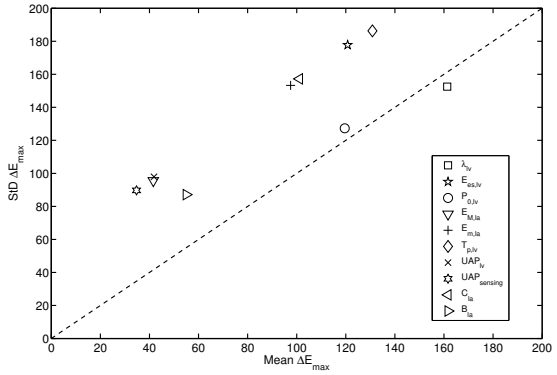

Figure 3. Results of Morris sensitivity analysis carried out on maximum E-wave.

The final step on the analysis of the proposed model is based on the identification of the main model parameters to reproduce observed data from patients undergoing CRT. Three HF patients without mitral regurgitation passed an echographic examination for a post-operative CRT optimization session, evaluating different AVD values, ranging from 80 to 190 ms. A complete standard transthoracic ultrasound examination was performed for each configuration. The audio output of a *GE VIVID 7* scanner was connected to a data acquisition system and the raw mitral inflow audio signal was recorded at a sampling frequency of 10 kHz for at least three consecutive cardiac cycles showing the same ECG morphology. A three way ECG was simultaneously recorded at a sampling frequency of 1 kHz. For each AVD configuration, the audio signal was processed by a short-term Fourier transform and from the obtained spectrogram, the contour for each cycle was extracted using a threshold-based algorithm. The average contour was generated and correlated to each cycle-contour so as to eliminate eventual outlying cycles. Those remaining cycles are finally used to generate an average mitral inflow from which the average mitral flow envelope

is determined. The extracted averaged contours for 3 patients and for each pacing configuration have been used for patient-specific parameter identification.

For this task, an evolutionary algorithm has been used, as described in [3]. The error function is defined as the relative mean squared error ($rMSE$) computed between the observed mitral flow contours and normalized model-generated mitral flows. The normalization is carried out patient-wise and with respect to the maximum value of the extracted contours, for all AVD configurations tested. The identified parameters are divided into two groups: $E_{la,max}$, $E_{la,min}$, C_{la}, B_{la} and $P_{0,lv}$ are assumed to be constant for all $AVDs$ while $E_{es,lv}, \lambda_{lv}, T_{p,lv}$ and UAP_{lv} are allowed to vary with AVD around a central value ($\pm 20\%$). Results obtained for patients 1 and 2 are presented in figure 4 and the rMSEs give respectively for patients 1-3: 0.031, 0.068 and 0.076.

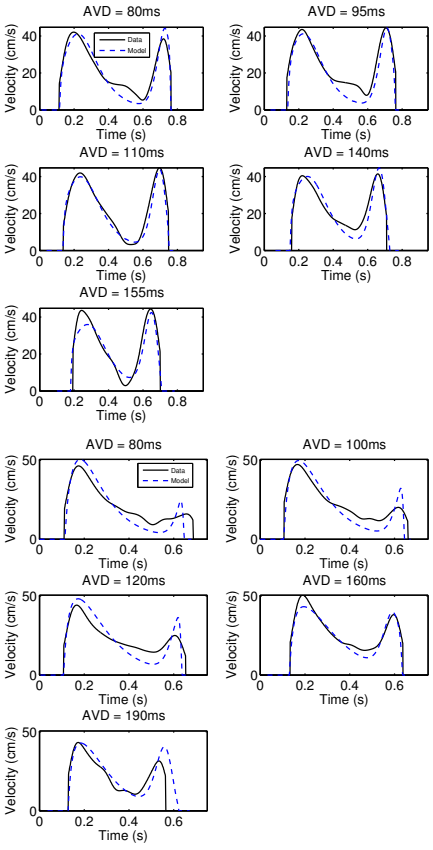

Figure 4. Observed (continuous line) and simulated (segmented line) mitral flow profiles at different AVD for patients 1 (top) and 2 (bottom).

5. Conclusion

This paper proposed a lumped-parameter model representing the cardiac electrical and mechanical activities, the circulation and a simplified CRT-P. The sensitivity analysis of this model underlines the significant role of the diastolic properties of the failing heart, as well as the importance of the atrial activity and preload modulation, which are often underestimated when applying modeling methods to the analysis of CRT. The model can produce different patterns of mitral flows with changes in AVD values. Parameter identification results show coherent variations when reproducing real data from three HF patients. In this sense, this model may be useful, during post-operative optimization phases, to reduce the number of AVD-VVD combinations tested and to provide, via the identified parameters, new quantitative estimators of the patient's response. Current work is directed to the improvement of some components of the proposed model, by selectively adjusting their spatial resolutions, in order to better represent valve dynamics and regional ventricular heterogeneity.

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