Towards a Personalized and Dynamic CRT-D

A Computational Cardiovascular Model Dedicated to Therapy Optimization

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Keywords
Cardiac resynchronization therapy, cardiovascular modeling, lumped parameter models, AV and VV optimization

Summary
Background: In spite of cardiac resynchronization therapy (CRT) benefits, 25–30% of patients are still non responders. One of the possible reasons could be the non optimal atrioventricular (AV) and interventricular (VV) intervals settings. Our aim was to exploit a numerical model of cardiovascular system for AV and VV intervals optimization in CRT.

Methods: A numerical model of the cardiovascular system CRT-dedicated was previously developed. Echocardiographic parameters, Systemic aortic pressure and ECG were collected in 20 consecutive patients before and after CRT. Patient data were simulated by the model that was used to optimize and set into the device the intervals at the baseline and at the follow up. The optimal AV and VV intervals were chosen to optimize the simulated selected variable/s on the base of both echocardiographic and electrocardiographic parameters.

Results: Intervals were different for each patient and in most cases, they changed at follow up. The model can well reproduce clinical data as verified with Bland Altman analysis and T-test (p > 0.05). Left ventricular remodeling was 38.7% and left ventricular ejection fraction increasing was 11% against the 15% and 6% reported in literature, respectively.

Conclusions: The developed numerical model could reproduce patients conditions at the baseline and at the follow up including the CRT effects. The model could be used to optimize AV and VV intervals at the baseline and at the follow up realizing a personalized and dynamic CRT. A patient tailored CRT could improve patients outcome in comparison to literature data.

1. Introduction
Cardiac Resynchronization Therapy (CRT) is an efficacious therapeutic strategy for non pharmacological treatment of patients affected by chronic heart failure with a wide QRS, low ejection fraction (<35%) and ventricular dysynchrony [1]. CRT is realized implanting a three catheters pacemaker/defibrillator. The first and the second catheter are implanted through the subclavian (or cefalic) vein into the right atrium and ventricle, respectively. The time interval that occurs between the impulse released by the first and the second catheter is the atrioventricular delay (AV). The third catheter is implanted into a branch of the coronary sinus on the left ventricular (LV) free wall. The time interval that occurs between the impulse released by the second and the third catheter is the interventricular delay (VV). Several studies evidenced that CRT determines an improvement in cardiac pumping efficiency, synchronizing heart chamber contraction, improving LV filling and inducing, as a long term effect, a LV reverse remodeling.

Despite CRT benefits, a percentage of 25–30% of non responders still remains [1].

Some unresolved issues, in fact, are still present as:
- the identification criteria to select CRT patients (guidelines, in facts, evolve constantly) [1, 2],
- the criteria to discriminate responders from non responders [1–3],
- the effect of LV catheter positions [4],
- the effect of biventricular pacemaker/defibrillator (BIV) programming, in particular, for the paced AV and VV intervals [1, 5–7].

The optimization of the AV and VV intervals is a relevant issue that can influence the improvement of patient conditions. These intervals are set on the base of [5–10]:
- statistical analysis on cardiac output or cardiac contractility (dP/dt) measured invasively in the acute phase during the BIV implantation,
- QRS duration in the ECG signal in order to decrease its duration,
- echocardiographic parameters.

It should be considered that the BIV programming effects in the acute phase are strongly different from long term effects. Moreover, it is now evident that even if the...
QRS duration is a selected criterion for patients undergoing CRT and also an end point of the therapy; it is not always well related to mechanical dyssynchrony and LV reverse remodeling. Otherwise, also the end point for the echocardiographic optimization is not completely well identified [3]. AV and VV interval settings could be performed automatically by the use of an algorithm or empirically (QRS and Echo). Automatic algorithms proposed by companies are:

- QuickOpt® of the St.Jude Medical™, where the AV is set to maximize ventricular filling and allow for proper timing of mitral valve closure, while the ventricular sense, right ventricular pace, and the LV pace tests are used to calculate VV to time the pacing stimuli so that the resultant ventricular contractions meet near the ventricular septum [10, 11].
- LIVIAN™ algorithm of the Boston Scientific™ is implemented for the VV optimization together with the SmartDelay™ for the AV optimization. The parameter chosen for the optimization by LIVIAN™ is the LV dP/dt, while the SmartDelay™ is aimed at optimizing ventricular filling and mitral valve closure [12].

Basing on these considerations and considering the different cardiocirculatory and ventricular conditions of each patient and the consequent large number of parameters that affects the problem, a numerical model could be useful to analyze and optimize CRT effects, introducing a quantitative approach based on both echocardiographic and electrocardiographic parameters.

The aim of this work is to exploit a numerical model of the cardiovascular system for optimizing and setting in the implanted device the AV and VV intervals in relation to echocardiographic and electrocardiographic parameters chosen by clinicians for the specific patient conditions to guarantee a dynamic and personalized CRT.

2. Materials and Methods

2.1 The Numerical Model of the Cardiovascular System

A lumped parameter computational model of the cardiovascular system able to reproduce the main pathophysiological events in terms of pressure, volume and flow [13, 14] was updated in order to develop a CRT-dedicated application.

The numerical model, implemented in LabView™ 7.1, describes the whole cardiocirculatory system. It has a flexible modular structure (Fig. 1) composed of the following sections:

- The left heart (left ventricle and atrium);
- The systemic circulation (arterial and venous);
- The right heart (right ventricle and atrium);
- The pulmonary circulation (arterial and venous);
- The coronary circulation;
- The interventricular septum.

Fig. 1 Electrical analogue of the cardiocirculatory model. Each circulatory section is represented by a resistance, a compliance and an inductance. Resistance, Inertance and compliance values are reported in Table 1. Atria and ventricles are represented as a pressure generator (Pla, Pra, Prv, Plv), whereas valves are represented as diode series resistances. Qli (Qlo) is the left ventricular input (output) flow, while Qri (Qro) is the right ventricular input (output) flow. Pas (Pap) represents the systemic (pulmonary) pressure, while Pvs (Pvp) represents the systemic (pulmonary) venous pressure. Pt is the intrathoracic pressure that is assumed to be zero.
Each section of the peripheral circulation is represented by a Windkessel model [6,13]. For each section of the circulatory model (Fig.1), the input flow is transmitted from the previous block, while the output flow and the generated pressure are calculated and transmitted to the next block as it is described by the following equations:

\[ Q_{in} = Q_{Ci} + Q_{out} \]

\[ P_{i-1} - P_i = L_i \frac{dQ_i}{dt} + Q_0 R_i \]

\[ Q_{Ci} = C_i \frac{dP_i}{dt} \]

\[ Q_{out} = Q_{out(i+1)} \]

\[ Q_{out(i+1)} = \frac{(P_i - P_{i+1})}{R_{i+1}} \]

\[ C_i, L_i, R_i \] are respectively the capacitive, inertial and resistive elements of the considered section. \( P_{i-1} \) is the pressure of the previous section, \( P_{i+1} \) is the pressure of the next section and \( R_{i+1} \) is the resistive element of the next section. \( P_i \) is evaluated from the third equation, while \( Q_{in} \) is calculated from the second one. An additional equation, applied to the systemic venous compliance, takes into account the mass conservation law. Equations are solved by Euler’s methods.

The default values of the lumped elements are given in Table 1. The model architecture guarantees the necessary flexibility for an easy adaptation of the model to different and specific clinical and research applications. The model of the heart was updated to study the AV and VV intervals optimization in CRT [15]. The heart is divided into atrial, ventricular and septal sections. Each of them is represented by a variable elastance model reproducing Starling’s law [13, 17]. Functional relationships describing variable elastance model are reported below:

\[ e_i(t) = E_{Di} \frac{E_{0i} - E_{Di}}{2} e(t) \]

\[ P_j(t) = e_i(t)(V_i(t) - V_0) \]

where \( e_i(t) \) is the time varying elastance of the generic heart section, \( E_{Di} \) (\( E_{0i} \)) is the diastolic (systolic) elastance of the generic heart section, \( e_i(t) \) is the activation function of the generic heart section, \( P_j(t) \)

\( V_i(t) \) is the instantaneous pressure (volume) of the generic heart section and \( V_0 \) is the rest volume of the generic heart section.

The mechanical activity of each heart section is related to its electrical activity, represented by the ECG signal, by the activation function.

In particular:

- the activation function of atria \( (aa(t)) \) depends on the ending time \( (T_{PB}) \) and the beginning time \( (T_{PF}) \) of the P wave of the ECG signal [17],

\[ a(t) = \begin{cases} 
0 & 0 \leq t \leq T_{PB} \\
\frac{1 - \cos \left( \frac{t - T_{PB}}{T_{PE} - T_{PB}} \right)}{2\pi} & T_{PB} < t \leq T_{PF} \\
0 & T_{PF} < t \leq T 
\end{cases} \]

- the activation functions of left \( (alv(t)) \) and right \( (arv(t)) \) ventricles depend on the peak time \( (T_T) \) and the ending time of the T wave of the ECG signal [17].

### Table 1: Physiological value of models parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Symbols</th>
<th>Physiological Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic systemic resistance</td>
<td>( R_{cs} )</td>
<td>66 g · cm(^{-4}) · s(^{-1})</td>
</tr>
<tr>
<td>Characteristic pulmonary resistance</td>
<td>( R_{cp} )</td>
<td>3 g · cm(^{-4}) · s(^{-1})</td>
</tr>
<tr>
<td>Systemic Inertance</td>
<td>( L_s )</td>
<td>0.0000736 mmHg · cm(^{-3}) · s(^{-2})</td>
</tr>
<tr>
<td>Pulmonary Inertance</td>
<td>( L_p )</td>
<td>0.000035 mmHg · cm(^{-3}) · s(^{-2})</td>
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<td>Arterial systemic compliance</td>
<td>( C_{as} )</td>
<td>3.47 cm(^3) · mmHg(^{-1})</td>
</tr>
<tr>
<td>Pulmonary arterial compliance</td>
<td>( C_{ap} )</td>
<td>4 cm(^3) · mmHg(^{-1})</td>
</tr>
<tr>
<td>Variable peripheral resistance</td>
<td>( R_{as} )</td>
<td>1054 g · cm(^{-4}) · s(^{-1})</td>
</tr>
<tr>
<td>Variable pulmonary compliance</td>
<td>( R_{ap} )</td>
<td>100 g · cm(^{-4}) · s(^{-1})</td>
</tr>
<tr>
<td>Systemic venous compliance</td>
<td>( C_{vs} )</td>
<td>84 cm(^3) · mmHg(^{-1})</td>
</tr>
<tr>
<td>Pulmonary venous compliance</td>
<td>( C_{vp} )</td>
<td>5 cm(^3) · mmHg(^{-1})</td>
</tr>
<tr>
<td>Systemic venous resistance</td>
<td>( R_{vs} )</td>
<td>80 g · cm(^{-4}) · s(^{-1})</td>
</tr>
<tr>
<td>Pulmonary venous resistance</td>
<td>( R_{vp} )</td>
<td>1 g · cm(^{-4}) · s(^{-1})</td>
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<tr>
<td>Mitral valve resistance</td>
<td>( R_{li} )</td>
<td>4 g · cm(^{-4}) · s(^{-1})</td>
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<tr>
<td>Aortic valve resistance</td>
<td>( R_{lo} )</td>
<td>10 g · cm(^{-4}) · s(^{-1})</td>
</tr>
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<td>Tricuspid valve resistance</td>
<td>( R_{ri} )</td>
<td>7 g · cm(^{-4}) · s(^{-1})</td>
</tr>
<tr>
<td>Pulmonary valve resistance</td>
<td>( R_{ro} )</td>
<td>3 g · cm(^{-4}) · s(^{-1})</td>
</tr>
<tr>
<td>Left ventricular systolic elastance</td>
<td>( E_{ls} )</td>
<td>2.5 mmHg · ml(^{-1})</td>
</tr>
<tr>
<td>Left ventricular diastolic elastance</td>
<td>( E_{ld} )</td>
<td>0.1 mmHg · ml(^{-1})</td>
</tr>
<tr>
<td>Right ventricular systolic elastance</td>
<td>( E_{rs} )</td>
<td>1.15 mmHg · ml(^{-1})</td>
</tr>
<tr>
<td>Right ventricular diastolic elastance</td>
<td>( E_{rd} )</td>
<td>0.1 mmHg · ml(^{-1})</td>
</tr>
<tr>
<td>Atrial systolic elastance</td>
<td>( E_{as} )</td>
<td>0.25 mmHg · ml(^{-1})</td>
</tr>
<tr>
<td>Atrial diastolic elastance</td>
<td>( E_{ad} )</td>
<td>0.1 mmHg · ml(^{-1})</td>
</tr>
<tr>
<td>Septum systolic elastance</td>
<td>( E_{ss} )</td>
<td>3 mmHg · ml(^{-1})</td>
</tr>
<tr>
<td>Septum diastolic elastance</td>
<td>( E_{sd} )</td>
<td>2 mmHg · ml(^{-1})</td>
</tr>
</tbody>
</table>
Time delay parameters were inserted into the left ($t_{LV}$) and right ($t_{RV}$) ventricular activation functions to simulate the interventricular delay ($|t_{LV} - t_{RV}|$) that represents the time interval that occurs between the right and the LV contraction. Moreover, introducing the activation function of the interventricular septum, it is possible to modify the time delay parameters inserted into the activation functions of the ventricles, to reproduce also the intraventricular dys synchrony. The intraventricular delay is the time interval that occurs between the interventricular septum and ventricular free wall contractions. The interventricular septum was modeled as a membrane that separates the two ventricles [16, 17]. In this way, it is possible to model the interventricular effect that is described by the variation of ventricular volumes due to the deviation of septum position [17]. A more detailed description of the model is reported in [13–17].

$$\text{abv}(t) = \begin{cases} 1 - \cos \left( \frac{t - t_{LV}}{T_T} \right) \pi & 0 \leq t \leq T_T \\ 1 + \cos \left( \frac{t - t_{RV}}{T_{TE} - T_T} \right) \pi & T_T \leq t \leq T_{TE} \\ 0 & T_{TE} < t \leq T \end{cases}$$

$$\text{arr}(t) = \begin{cases} 1 - \cos \left( \frac{t - t_{RV}}{T_T} \right) \pi & 0 \leq t \leq T_T \\ 1 + \cos \left( \frac{t - t_{RV}}{T_{TE} - T_T} \right) \pi & T_T \leq t \leq T_{TE} \\ 0 & T_{TE} < t \leq T \end{cases}$$

Time delay parameters were inserted into the left ($t_{LV}$) and right ($t_{RV}$) ventricular activation functions to simulate the interventricular delay ($|t_{LV} - t_{RV}|$) that represents the time interval that occurs between the right and the LV contraction. Moreover, introducing the activation function of the interventricular septum, it is possible to modify the time delay parameters inserted into the activation functions of the ventricles, to reproduce also the intraventricular dys synchrony. The intraventricular delay is the time interval that occurs between the interventricular septum and ventricular free wall contractions. The interventricular septum was modeled as a membrane that separates the two ventricles [16, 17]. In this way, it is possible to model the interventricular effect that is described by the variation of ventricular volumes due to the deviation of septum position [17]. A more detailed description of the model is reported in [13–17].

2.2 The Numerical Model of the BIV

The effect of the BIV on cardiovascular system was simulated by virtual catheters representing the device as an electrical impulse generator, driving the heart chambers and septum contraction with fixed time intervals (AV and VV). This approach ensures that the BIV effect does not depend on the device characteristics, as these could vary, depending on the producer. In the version of the software used for this paper the effect of catheters position is not considered and each virtual catheter drives the whole heart chamber contraction where it is inserted. In particular, the effect of LV catheter position in the LV free wall (anterior, posterior, lateral wall) was not taken into account. Different LV catheter positions are shown in Figure 2. The first virtual catheter drives left and right atrial contractions, that are assumed to be synchronized. The second virtual catheter is modeled considering that it is placed on the right side of the interventricular septum, synchronizing septum and right ventricular free wall contraction. The third virtual lead is placed on the LV free wall and it drives the LV free wall contraction. The position of catheters is shown in Figure 2. When an AV interval is chosen, the model sets the duration of the

Fig. 2
Representation of CRT catheters positioning. In all figures, the first catheter is implanted in the right atrium (RA) and the second catheter is placed in the right ventricle (RV), while the left ventricular (LV) catheter is placed in an antero-lateral (AL) position in fig. b, in a lateral (LL) position in fig. c and in a postero-lateral (PL) position in fig. d. fig. a. is a schematic diagram that shows catheters positions in heart chambers.
PQ interval of the ECG signal equal to the chosen AV interval.

\[ AV = PQ = T_{QB} - T_{PB} \]

where \( T_{PB} \) drives the atrial chambers contraction, as described in the previous paragraph (aa(t)) and \( T_{ QB } \) is the beginning of the Q wave of the ECG signal and from this parameter the model can calculate \( T_T, T_{ TB} \) and \( T_q \) that drive septum and ventricular free walls contraction.

When a VV interval is set and it is established which ventricular contraction is pre-dated, the model calculates the corresponding value of the time delay parameters and inserts them into the activation function of both ventricular free walls:

\[ VV = |t_{LV} - t_{RV}| \]

The user can set AV and VV intervals manually or automatically. For this second option, the user can select the variable/s that the software should optimize calculating the AV and VV intervals. Some of the variables that can be optimized are the cardiac output (CO), LV end systolic and end diastolic volumes, LV external work (EW) and cardiac mechanical efficiency (CME).

Starting from the specific hemodynamic condition of each patient, the model can calculate the AV and VV intervals that correspond to the highest obtainable value for the chosen parameter (ex.: cardiac output, mechanical efficiency) or the lowest one (ex.: volumes). If more than one variable is chosen for the optimization, the model suggests the AV and VV intervals that provide the best combination for all variables to be optimized.

2.3 The Clinical Study

Twenty patients with standard indication for CRT [1] were enrolled in this pilot study. All patients were surgically treated by implanting a BIV. Catheters were implanted through the subclavian or cephalic veins into the right heart, while the third catheter was implanted into an antero-lateral or postero-lateral or lateral branch of the coronary sinus (Fig. 2).

All patients were analyzed before the implantation and 9 months after the implantation, collecting the following parameters:

1. Non invasive systolic (AoP(S)) and diastolic (AoP(D)) Aortic Pressure;
2. ECHO C/D Measurement (Siemens Acuson Sequoia 512):
   - The LV end systolic volume (LVes) and end diastolic volume (LVed) were measured with the Simpson method in four and two chambers. Also LV diameters in parasternal and in four chamber view were collected to evaluate LV dimensions.
   - The intraventricular and interventricular delays were evaluated recording the aortic and pulmonary ejection flows. The electromechanical delay of the left (right) ventricle LVED (RVED) was measured as the time interval between the onset of the QRS complex of the surface ECG signal (recorded by the lead ECG cable of the Acuson Sequoia 512, 50mm/s) and the onset of the aortic (pulmonary) flow obtained at the pulsed wave Doppler imaging. The interventricular delay was calculated as the difference between LVED and RVED [3].
   - Interventricular septum dimensions: end systolic/diastolic thickness in M-mode and septum length in four chamber apical view.
   - Valve diseases by measuring the velocity gradient and the anulus dimensions.

![Flow diagram of the simulation procedure](image-url)

Fig. 3 Flow diagram of the simulation procedure. Cas and Ras were adjusted until the measured value of AoP(S) (M_AoP(S)) was equal to the simulated value of AoP(S) (S_AoP(S)) and until the measured value of AoP(D) (M_AoP(D)) was equal to the simulated one (S_AoP(D)). Starting from the estimated value, Elvs and Ervs were empirically adjusted until the measured LVes (M_LVes) was equal to the simulated one (S_LVes). Ervd and Elvd were adjusted until the measured LVed (M_LVed) was equal to the simulated one (S_LVed).
● Diastolic Function by measuring the velocity of the E and the A waves [18].
● Estimation of the systolic arterial pulmonary pressure. In the presence of tricuspid regurgitation, the peak flow velocity of the transtricuspid jet was measured with the use of continuous-wave Doppler. Pressure gradient between the right ventricle and the right atrium was calculated by the use of the modified Bernoulli equation. The value was adjusted adding: 0–5 mmHg if no dilatation were observed in the right atrium, ventricle and in the inferior caval vein (subcostal view); 5–10 mmHg in the presence of light dilatation or 15 to 20 mmHg in the presence of severe dilatation of right atrium, ventricle and inferior caval vein. When no tricuspidal regurgitation can be assessed, the deceleration time on pulmonary valve is measured to evaluate the presence of pulmonary hypertension. [19]

Considering the limitations of the ECHO measurements that are operator-dependent, each measurement was repeated three times for each patient at each step of the study by the same operator in a double blinked way in order to reduce the measurement errors [3,20].

1. ECG (Mortara, ELI 250c) Measurement at 25mm/s, sampling rate of 40,000 samples per second per channel:
   ● Heart Rate (HR);
   ● PQ interval;
   ● QRS duration;
   ● QT interval.

In this paper, the results obtained at the longest analyzed follow up (9 months) are shown, even if patients were evaluated also 1, 3 and 6 months after BIV implantation. At the baseline and at each follow up, AV and VV intervals were programmed according to the newly developed algorithm. All proper informed consents compiled by patients were obtained. This study adheres to the principle of the declaration of Helsinki and it was approved by the ethical commission of the University of “Tor Vergata” (protocol number: 43.10–44.10).

2.4 Simulations

During each step of the study, the pathophysiological conditions of the patients were simulated by the numerical model and the model “in turn” calculates the AV and VV intervals for the specific patient in the specific pathophysiological condition in relation to the chosen variable/s.

Starting from the measured data, the simulations were performed feeding the
ECG parameters, the interventricular and the intraventricular delays into the model and calculating or estimating the mean aortic pressure (Pas), the peripheral arterial resistance (Ras) and compliance (Cas), the systolic and diastolic elastances of septum and ventricles.

\[
P_{\text{ras}} = \frac{\text{sys} \cdot A_{\text{P}S} + \text{dia} \cdot A_{\text{P}D}}{T}
\]

where sys and dia are the systolic and diastolic phase duration in the ECG, respectively.

Cas and Ras were set to reach the measured value of systolic, diastolic and mean aortic pressure [15].

LV systolic elastance (Elvs) was estimated as the ratio between the systolic aortic pressure and the LVes, while the rest volumes of the heart chambers were assumed to be zero. Interventricular septum elastances were estimated starting from the measured aortic pressure, the end systolic and end diastolic septum thickness and length. As an example, the end systolic septum elastance (Ess) is:

\[
\text{Ess} = \frac{\text{Pas} + A_{\text{P}S}}{2V_{\text{es}}}
\]

where V_{es} is the end systolic septum volume. Septum volumes were estimated considering it as a bulk whose dimensions can be measured by echocardiography. Starting from the estimated parameters values, all other mentioned parameters were set to place correctly the LV pressure-volume loop in the pressure-volume plane [15].

The simulation procedure is summarized in Figure 3. A detailed description of the simulation procedure is reported in [15]. Starting from the simulated condition, the BIV timing that optimizes the CO or/and LV reverse remodeling was evaluated to set the AV and VV intervals into the patients. The BIV optimization procedure is summarized in Figure 4. In Figure 4, as an example, the variable chosen for the optimization is the CO.

The model permits also to estimate the trend of some variables that are difficult to be measured, but that could be useful to evaluate better patient conditions as Elvs and CME.

### 2.5 Statistical Analysis

Continuous variables are expressed as mean value and standard deviation. In order to evaluate if the model can reproduce well the pathophysiological condition of patients, a paired T-student test evaluating the p-value was performed on the two groups of variables formed by simulated and measured data. Moreover, the Bland Altman analysis was performed to compare measured and simulated data to evaluate the bias and the limits of agreement between the two sets of measurement.

### 3. Results

Table 2 shows the average value and the standard deviation of measured and simulated LV end systolic and end diastolic volumes, the mean aortic pressure and the mean pulmonary pressure before CRT and after nine months (fu9). Data are expressed as mean and standard deviation value. Also the p-value is reported for each group of data to compare measured and simulated data. No statistically significant differences were evidenced between the two groups. Moreover, Table 2 shows the value of the bias and the limits of agreement obtained by the Bland Altman analysis. Both the bias and the limits of agreement values suggest that the model can well reproduce measured data without introducing clinically relevant errors. Figure 5 shows the normalized optimization curves for different AV intervals at the implantation, while Figure 6 shows the normalized optimization curves as a function of VV intervals with the best AV interval fixed at the baseline. A negative value of VV interval means that LV contraction is predated. The variable chosen for the optimization curves in Figures 5 and 6 is the cardiac output. The normalization (CO) is obtained dividing for each group, all values obtained changing the AV or VV interval during the simulation (CO) by the highest one (COmax):

\[
\text{CO} = \frac{\text{CO}}{\text{CO}_{\text{max}}}
\]

These figures show that the best AV and VV intervals and the optimization trend can be different for each patient. Some of the 20 patients show a similar trend, for this reason we identified four families of curves for CO as a function of AV and other four families of curves for the CO as a function of the VV. It can be deduced that some patients can have the same optimum values of AV and VV and also a similar optimization trend. Most of the patients have a short AV as the optimum value (Fig. 5a) and most of the patients have only one value of the AV that optimizes the CO (Fig. 5a, c). Some patients show a better response to CRT with longer AV (Fig. 5b) and present more than one AV interval that can optimize the CO (Fig. 5b, d). Most of the patients have an optimum VV interval around the synchronous contraction of the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measured</th>
<th>Simulated</th>
<th>p-value</th>
<th>Bias</th>
<th>Limits of agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVes_preBIV [ml]</td>
<td>207.20 ± 97.59</td>
<td>205.30 ± 99.14</td>
<td>0.95</td>
<td>1.90</td>
<td>4.81</td>
</tr>
<tr>
<td>LVes_fu9 [ml]</td>
<td>111.45 ± 44.85</td>
<td>109.75 ± 44.09</td>
<td>0.90</td>
<td>1.70</td>
<td>5.22</td>
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<tr>
<td>LVed_preBIV [ml]</td>
<td>264.40 ± 104.55</td>
<td>266.75 ± 104.49</td>
<td>0.94</td>
<td>–2.35</td>
<td>9.77</td>
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<td>LVed_fu9 [ml]</td>
<td>169.05 ± 56.86</td>
<td>176.50 ± 52.53</td>
<td>0.66</td>
<td>–7.45</td>
<td>16.43</td>
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<td>Pas_preBIV [mmHg]</td>
<td>89.08 ± 9.05</td>
<td>88.77 ± 8.54</td>
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<td>2.35</td>
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<tr>
<td>Pas_fu9 [mmHg]</td>
<td>88.90 ± 9.23</td>
<td>85.82 ± 9.48</td>
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<td>5.79</td>
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<td>Pap_preBIV [mmHg]</td>
<td>19.37 ± 7.82</td>
<td>21.85 ± 5.56</td>
<td>0.25</td>
<td>–2.48</td>
<td>7.38</td>
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<tr>
<td>Pap_fu9 [mmHg]</td>
<td>21.28 ± 6.80</td>
<td>24.13 ± 4.40</td>
<td>0.12</td>
<td>–2.85</td>
<td>7.72</td>
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</tbody>
</table>
left and right ventricles or \(-20\) ms (LV contraction predated from the right ventricular contraction), that is the most physiological value (Fig. 6b). Most of the patients show only one optimum value of the VV (Figs. 6a, b, c), while others patients have a range of optimization (Fig. 6d). Some patients need to predate consistently the LV contraction (Fig. 6a). Usually these patients show a greater interventricular dyssynchrony at the echocardiography.

Finally, the most the change in CO depends on AV and VV intervals, the most the optimization procedure plays an important role in patients response and the model can estimate the trend of CO for each single patient. In Table 3 only the optimal AV and VV are reported for all patients. Table 3 shows the AV and VV intervals values calculated by the model and set into the patients at the implantation (PreBIV), nine months (fu9) after the implantation and the variable/s chosen for the optimization.

Nine months after BIV implantation, an average reduction of 97.75 ml (95.35 ml) in LV end systolic (diastolic) volume and an average improvement of 11% in EF were measured. An average increase of 0.57 mmHg/ml in Elvs and of 0.17 (+56%) in CME were estimated. Estimated variables trends follow the trend of measured variables as it can be deduced comparing LV reverse remodeling and the measured EF with estimated Elvs and CME, respectively (Fig. 7).

Figure 7 shows for each patient the CRT outcomes presenting measured and simulated parameters. In particular, the figure shows, comparing the preBIV and the fu9:

- the measured reduction of LVes and LVed,
- the estimated trend of Elvs,
- the measured improvement of EF,
- the estimated trend of CME.

Percentage changes (delta) are calculated as:

\[
\Delta \% = 100 \frac{xf - xi}{xi}
\]

where \(xf \) (\(xi \)) is the value of the variable at the fu9 (preBIV).

Then, a reverse remodeling is represented by a negative bar, while the improvement of Elvs, EF and CME is represented by a positive bar. For 17 patients the estimated

![Fig. 5 Optimization curves for the AV intervals at the BIV implantation. Graphs show the normalized cardiac output as a function of AV intervals.](image-url)
Elvs and CME trends are in accordance with LVes, LVed reduction and EF improvement.

4. Discussion

The model can reproduce well clinical data in pathological and follow-up conditions as expressed by the Bland Altman analysis and there are no statistically significant differences between the groups of measured and simulated variables as reported in Table 2. Moreover, the model permits to evaluate the trend of the variable/s chosen for the optimization as a function of AV and VV intervals as it is shown in Figures 5 and 6. From Figures 5 and 6 and Table 3, it is possible to deduce that BIV programming should be different and specific for each patient, in fact the shape of normalized CO is different for different patients. Moreover, at each follow up the variable/s to be optimized can be chosen and then the corresponding AV and VV intervals re-calculated. Using this numerical model, it is possible to select each time the best BIV programming to adapt the CRT to the patient in the specific hemodynamic condition, realizing a dynamic and personalized therapy. Finally, the model gives the possibility to estimate some variables starting from non invasive measurements. An example is reported in Figure 7, where together with measured trends of LVes, LVed and EF, the estimated trends of Elvs an CME are reported.

In Elvs estimation, the LV rest volume is assumed to be zero. This assumption can induce an underestimation of Elvs in the pathological condition and an over or underestimation of Elvs after CRT. However, the trend of Elvs is well estimated as it could be deduced comparing estimated Elvs trend and measured EF trend. The EF in fact is one important index used to evaluate LV systolic function. For each patient, it is possible to evidence both a decrease of LV volumes and an increase of heart contraction capability. In 17 cases, estimated data are in accordance with measured variables. Starting from the simulated pathological condition, the numerical model could permit to estimate in advance CRT effect, setting the AV and VV intervals. This feature could be helpful to select CRT candidates or to understand better which parameter/s is/are critical to

Fig. 6 Optimization curves for the VV intervals at the BIV implantation. Graphs show the normalized cardiac output as a function of VV. A negative value of VV means that LV contraction is predated.
Table 3 AV and VV intervals before the implantation (_preBIV) and at the 9 months follow up (fu9) together with the variables chosen for the optimization. LV→RV: left ventricular free wall contraction is predated from right ventricular free wall contraction. CO: cardiac output; LVes: left ventricular end systolic volume; L Ved: left ventricular end diastolic volume.

<table>
<thead>
<tr>
<th><em>AV</em> [ms]</th>
<th><em>VV</em> [ms]</th>
<th>Optimized Variables</th>
</tr>
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<tbody>
<tr>
<td>100</td>
<td>10 LV→RV</td>
<td>CO, LVes</td>
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<tr>
<td>200</td>
<td>40 LV→RV</td>
<td>L Ved</td>
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<td>CO</td>
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<td>80 LV→RV</td>
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let the patient be a responder to the therapy. It should be considered that, even if a more detailed representation and characterization of the circulatory sections could be useful, for this specific study, the heart parameters play the major role. In this work, the heart is represented by a lumped parameter model, where the mechanical activity is related to ECG signal as it is a representation of heart electrical activity. To realize the coupling between electrical and mechanical heart activity, the activation functions of septum and ventricular free walls depend on QRS duration, while left branch block was simulated considering also a contraction delay between septum and left ventricular free wall starting from echocardiographic measurement. Finally, a mechanical delay can be inserted between the left and right ventricular free walls. The pre-ejection aortic and pulmonary times permit to evaluate the electromechanical delay considering both QRS duration and the mechanical activation of the ventricles. A more reliable representation of the electro-mechanical coupling could be given by a three-dimensional model, where both electrical and mechanical signal propagation can be represented. However, it should be considered that this kind of models are time consuming and that they need more data to personalize CRT, that are often not available (as for example the magnetic resonance images to reconstruct heart anatomy, that is costly and that cannot be performed in some patients). Moreover, one aim of this work was to provide a tool that could be used daily and during clinical practice (both for the selection of CRT candidates and during the ambulatory follow up) without altering significantly the clinical protocol for CRT patients evaluation and without introducing invasive, costly or wasteful measurements. Finally, a lumped parameter model can well reproduce the comprehensive pathophysiological conditions of a patient in terms of pressure, volume and flow in different circulatory sections and considering also the arterioventricular coupling. This can give a realistic idea of the haemodynamic improvement of a patient undergoing CRT. CRT in fact permits to synchronize heart chambers contraction, that can be well simulated by a 3D model, but the main outcome are the
haemodynamic (and clinical) benefits as this kind of patients are affected by chronic heart failure (and then a low cardiac output syndrome). This fact can be better represented with a comprehensive lumped parameter model.

Considering the LV reverse remodeling, a percentage of non responders of 10% was observed in the studied population. This percentage of non responders is significantly lower than the one reported in literature (25–30%) [8]. Moreover, the average LV reverse remodeling obtained in the studied population is 38.7%, significantly higher than the average value proposed by literature (about 15%) [1, 19]. Even if the number of patients is rather small, these results suggest that a personalized and dynamic CRT could improve patients’ response to the therapy.

It should be said that, this paper shows the preliminary results of a pilot study aimed at evaluating the clinical, echocardiographic and electrocardiographic outcomes every three months (till the 24th month). Preliminary data suggest that the changing in optimal AV and VV is more frequent in the first year of treatment, when the pathophysiological conditions of patients change more due to CRT. Usually the highest improvements (especially in terms of LV reverse remodeling) were observed at the follow up of 6, 9 and 12 months.

Some of our next studies on CRT will be focused on:
- the comparison in a clinical prospective and randomized study between a group of patients programmed with the developed algorithm and a group of patients programmed by standard software. Preliminary data collected during this prospective and randomized trial show that patients programmed at each follow up using the newly developed model improve their condition faster and more than the others (in particular, in terms of LV reverse remodeling) and that a personalized and dynamic CRT based on both echocardiographic and electrocardiographic parameters allows to prolong in time CRT benefits.
- The effect of BIV on peripheral circulation,
- the effect of BIV on LV diastolic function [18],
- the effect of the LV catheter position.

With reference to the last point, starting from the pathological condition of a patient and selecting the variable/s that should be optimized, the same numerical model improved by dividing the LV free wall into three parts with three variable elastance models, could be used to predict the best left catheter position (antero-lateral, lateral or postero-lateral wall of the left ventricle) and calculate the best timing for each position. It would be particularly interesting to understand better the effect of the LV catheter position, also considering the evolution of the technology that is going into the direction to obtain a multi-configuration and multipolar stimulation [4]. Moreover, introducing this representation of the LV free wall, the intraventricular dysynchrony could be better simulated as the model can reproduce the spatio-temporal distribution of the electrical signal between the different parts of the LV free walls and not only between septum and a...
LV free wall represented by one element only. This mentioned partialized model will provide a representation that is closer to three-dimensional model, but with all the advantages of lumped parameter models.

The developed and validated model can be a useful tool to:

- support clinicians in patients selection simulating in advance the CRT effect,
- optimize and personalize AV and VV intervals on the base of both echocardiographic and electrocardiographic parameters avoiding empirical procedures,
- optimize (future step) LV catheter position.

These three points are all necessary to guarantee a tailored therapy and to decrease the rate of non responders, especially in the field of electrophysiology where engineering tools could be very useful to support clinical practice and innovation [4, 7, 10, 11, 14, 15, 21, 22].

References


