CHAPTER 2

Numerical Models of the Cardiovascular System: Interaction Between the Septum and the Left (Right) Ventricular and Atrial Free Wall

Beatrice De Lazzari[1], Bernhard Quatember[2], Khosrow Mottaghy[3], Claudio De Lazzari[4,5]

Author Affiliation:

[1] "Roma Tre" University, Department of Engineering, Rome, Italy

[2] Univ.-Klinik für Radiologie, Innsbruck Medical University, Austria

[3] Institute of Physiology, Aachen University Hospital, RWTH Aachen University, Aachen, Germany

[4] National Institute for Cardiovascular Research (I.N.R.C.), Bologna, Italy

[5] National Research Council, Institute of Clinical Physiology UOS of Rome, Italy

Email: *claudio.delazzari@ifc.cnr.it*

Abstract

Introduction: Mathematical modelling of the cardiovascular system (CVS) can help understand the complex interactions between both ventricles and the septum. Variable elastance models are helpful to describe the behaviour of the left (right) ventricular free wall, the atria and the septa in order to reproduce their interactions. The relation between atrial and ventricular mechanical properties and the ECG signal allows the analysis of the effects produced by different ECG delays on haemodynamic parameters. Ventricular interactions play a key role in cardiac mechanics and can be affected by conditions such as symptomatic heart failure secondary to systolic dysfunction or ischaemic dilated cardiomyopathy. Cardiac Resynchronisation Therapy (CRT) is an interventional procedure that may have a potential beneficial effect on the clinical status of selected heart failure patients when acting on the duration of the QRS complex in the ECG signal.
Methods: This chapter describes the equations used and implemented in CARDIOSIM©, which is the software simulator of the CVS developed to reproduce the behaviour of the left and right ventricular free wall, left and right atria and septum. The equations are based on variable elastance models which are suitable to reproduce atrial and ventricular interactions. Literature data was used in different simulation settings in the context of CRT intervention in a patient with ischaemic dilated cardiomyopathy.
Conclusions: A numerical heart model implemented in CARDIOSIM© can reproduce the interaction between the septum, the left (right) ventricle and the left (right) atrium in order to evaluate the effects of CRT. The outcome of the simulations gives a haemodynamic profile in accordance with literature data.

Keywords. Cardiovascular System; Numerical Model; Cardiac Resynchronization Therapy; Coronary Blood Flow; ECG; Haemodynamic; Ventricular delays; Heart Failure.

2.1 Introduction

Ventricular remodelling in heart failure patients may lead to atrio-ventricular node or bundle branch dysfunction. As a consequence, inter-ventricular and/or intra-ventricular conduction delays (dyssynchrony) cause further progression of heart failure with symptomatic deterioration. Many patients in advanced heart failure (HF) may have already developed significant intra-ventricular or inter-ventricular conduction delays (IVCD) affecting the synchronous beating of the ventricles with reduced pump efficiency [1,2]. Ventricular dyssynchrony may cause a number of deleterious effects on cardiac function such as reduced diastolic filling time, weakened contractility, severe mitral regurgitation and regional wall motion abnormalities.

Cardiac Resynchronization Therapy (CRT) is an interventional procedure aimed at the reduction of the QRS complex duration in the ECG signal with potential for symptomatic relief [3-5]. Prolonged CRT may improve systolic function and diastolic filling time with restoration of a certain degree of cardiac autonomic control and reversal of adverse remodelling.

Essentially, there are two types of ventricular interactions. The first is the so called "in series" interaction where the outlet of one ventricle is connected to the inlet of the other ventricle through the systemic/pulmonary circulation. The second is the so called “direct” interaction where the septal wall is shared by the left and the right ventricle contained by the pericardium. The contribution of each type of interaction is difficult to measure [6].

The development of a numerical model of the cardiovascular system (CVS) may be a helpful tool to understand the complex interactions between the left and the right ventricular free wall, the atria and the septa. CARDIOSIM© is the numerical simulator of the cardiovascular system used for this purpose and described in this chapter [7,8]. The different circulatory compartments are represented with a lumped parameter model; the ventricular, atrial and septal function is implemented using a variable elastance model [9-11]. The simulator can reproduce coronary blood flow (CBF)-systemic aortic pressure (AoP) loops [12] in relation to different ECG time intervals, intra-ventricular and inter-ventricular delays.

The outcome of the simulations has shown that CARDIOSIM© is a suitable environment to reproduce features observed in patients with idiopathic dilated cardiomyopathy and IVCD. In addition, the software can generate the haemodynamic conditions observed in a clinical setting following CRT simulation. Finally the numerical simulator can predict the trend of CBF-AoP slope, CBF-AoP area with minimum and maximum values of CBF waveform during the cardiac cycle in patients treated with CRT.

2.2 Methods

CARDIOSIM© can reproduce patho-physiological circulatory phenomena and simulate the effects of different mechanical assist devices in terms of haemodynamic and energetic parameters [13-15]. This software simulator has a modular structure that includes:

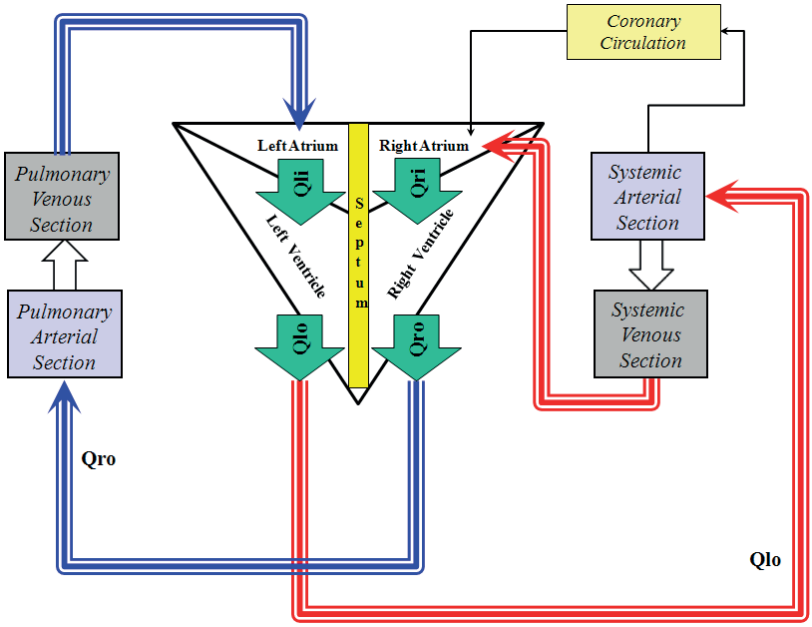


Fig. 1. General structure of the CARDIOSIM© software simulator. Qlo (Qro) and Qli (Qri) represent the left (right) ventricular output flow and the left (right) ventricular input flow respectively.

left (right) atrium and ventricle, pulmonary venous (arterial) section, systemic venous (arterial) section and coronary circulation (Fig.1). The systemic arterial section is modelled with a three-cell approach [8,12] implemented using a modified windkessel for each cell with resistance, inertance and compliance (Fig. 2). This representation emulates the behaviour of aortic, thoracic and abdominal tracts. Rcbs represents the variable peripheral arterial resistance. The pulmonary arterial section is modelled with a modified windkessel with a resistance Rap, an inertance Lap, a compliance Cap and a variable peripheral resistance Rcbp. The systemic venous section is modelled with the compliance Cvs and the variable resistances Rvs1 and Rvs2. Finally, the pulmonary venous section is modelled with the compliance Cvp and the resistances Rvp1 and

Rvp2 (Fig. 2). Each heart valve is modelled as a diode with a resistance (Fig.2), assuming the unidirectional way of the blood flow. Rli represents the resistance of mitral valve (MV); Rlo represents the resistance of aortic valve (AV); Rri represents the resistance of pulmonary valve (PV); Rro represents the resistance of tricuspid valve (TV). The coronary circulation is developed with a lumped parameter model [12].

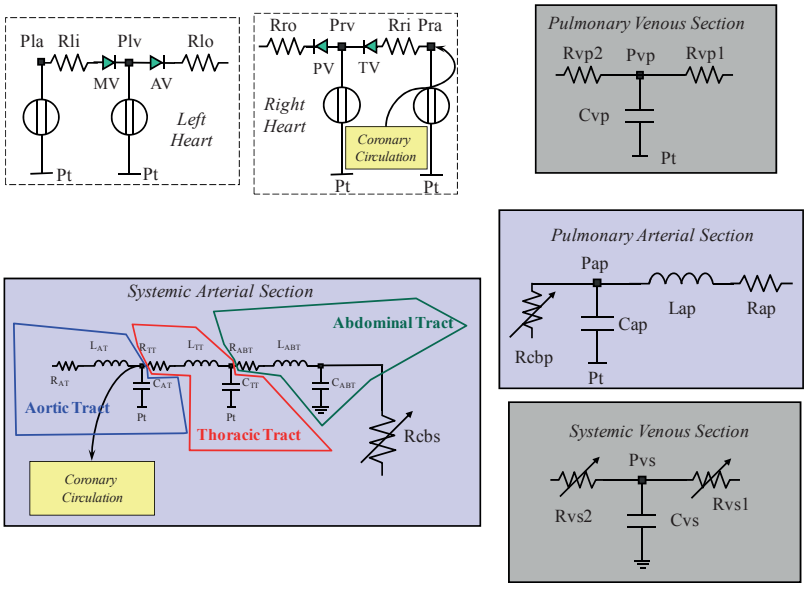


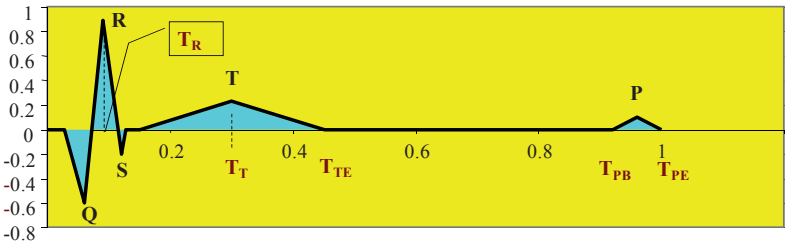
Fig. 2. Schematic representation of the different circulatory districts described using lumped parameter models. In the systemic arterial section R_{AT} (L_{AT}) is the aortic resistance (inertance) and C_{AT} is the aortic compliance. R_{TT} (L_{TT}) is the thoracic resistance (inertance) and C_{TT} is the thoracic compliance. R_{ABT} (L_{ABT}) is the abdominal resistance (inertance) and C_{ABT} is the abdominal compliance. Pt represents the mean intrathoracic pressure. The behaviour of the ventricles, the atria and the septa is reproduced with variable elastance models.

2.2.1 Atrial Numerical Modelling

A variable elastance model describes the behaviour of the left and right atrium in CARDIOSIM© [10,16] while their mechanical properties are related to the ECG signal (Fig. 3).

The left/right atrial time-varying elastance *ela(t)*/*era(t)* is based on the electromechanical interaction by synchronizing the different phases of the atrial cycle with the ECG signal. The left/right atrial time-varying elastance *ela(t)*/*era(t)* is a function of the left/right atrial systolic elastance (*Elas*/*Eras*), left/right atrial diastolic elastance (*Elad*/*Erad*) and left/right atrial activation function *ala(t)*/*ara(t)*:

$$ela(t) = Elad + \frac{Elas - Elad}{2} ala(t) \qquad era(t) = Erad + \frac{Eras - Erad}{2} ara(t) \qquad (1)$$



T_R	R wave peak time
T_T	T wave peak time [Ventricular ejection starting]
T_{TE}	Ventricular systole ending
T_T-T_{TE}	Ventricular systole duration
T_{PB}	Atrial depolarization starting
T_{PE}	Atrial depolarization ending
T_{PB}-T_{PE}	Atrial depolarization duration

Fig. 3. Schematic representation of the ECG signal.

According to the ECG schematization shown in Fig.3, atrial systole corresponds to the period (T_{PB}-T_{PE}) and the activation function describing the contraction and the relaxation phases is written as follows:

$$ala(t) = ara(t) = \begin{cases} 0 & 0 \le t \le T_{PB} \\ 1 + \cos\left(\frac{t - T_{PB}}{T_{PE} - T_{PB}} 2\pi\right) & T_{PB} < t \le T_{PE} \\ 0 & T_{PE} < t \le T \end{cases} \qquad (2)$$

where T is the duration of the ECG signal (heart period). Using Eqs.1 and 2, the instantaneous left/right atrial pressure (as a function of left/right atrial time-varying elastance *ela(t)/era(t)* and instantaneous left/right atrial free wall volume $V^*la(t)/V^*ra(t)$) can be described by the following equation:

$$Pla(t) = P_0 la + ela(t) \cdot (V^* la(t) - V_0 la) \qquad Pra(t) = P_0 ra + era(t) \cdot (V^* ra(t) - V_0 ra) \qquad (3)$$

where P_0la, P_0ra, V_0la and V_0ra are constants.
This atrial representation combined with the ventricular model and related with the ECG signal is used to simulate the atrio-ventricular delay that occurs in atrio-ventricular block and atrial fibrillation.

2.2.2 Ventricular Numerical Modelling

A variable elastance model also describes the left and right ventricular function in CARDIOSIM© [9,11,16].
The left/right ventricular time-varying elastance *elv(t)*/*erv(t)* is described as a function of the left/right ventricular systolic elastance *Elvs*/*Ervs*, the left/right ventricular diastolic elastance *Elvd*/*Ervd* and the left/right activation function *alv(t)*/*arv(t)*:

$$elv(t) = Elvd + \frac{Elvs - Elvd}{2} alv(t) \qquad erv(t) = Ervd + \frac{Ervs - Ervd}{2} arv(t) \tag{4}$$

According to ECG schematization (Fig.3), the left/right activation function describing the left/right ventricular phases can be written as follows:

$$alv(t) = arv(t) = \begin{cases} 1 - \cos\left(\frac{t}{T_T}\pi\right) & 0 \le t \le T_T \\ 1 + \cos\left(\frac{t - T_T}{T_{TE} - T_T}\pi\right) & T_T < t \le T_{TE} \\ 0 & T_{TE} < t \le T \end{cases} \tag{5}$$

where T_{TE} is the end of ventricular systole and T_T is the T-wave peak time.
Therefore, the instantaneous left/right ventricular pressure is:

$$\begin{aligned} Plv(t) = elv(t) \cdot (V^*lv(t) - Vlo) \quad &\Rightarrow \quad V^*lv(t) = \left(\frac{Plv(t)}{elv(t)}\right) + Vlo \\ Prv(t) = erv(t) \cdot (V^*rv(t) - Vro) \quad &\Rightarrow \quad V^*rv(t) = \left(\frac{Prv(t)}{erv(t)}\right) + Vro \end{aligned} \tag{6}$$

where $V^*lv(t)/V^*rv(t)$ is the instantaneous left/right ventricular free wall volume and *Vlo*/*Vro* is the rest volume of the left/right ventricle.
The above equations are used to simulate inter-ventricular dyssynchrony. A model of ventricular interaction (or "ventricular interdependence") was implemented through the inter-ventricular septum to simulate intra-ventricular dyssynchrony as well [9,11].

2.2.3 Interventricular Septum Numerical Modelling

The concept of ventricular interdependence considers the properties of one ventricle to be a function of the properties of the contra-lateral ventricle. The time-varying elastance concept is used to model the behaviour of the inter-ventricular septum:

$$e_{ventrSPT}(t) = Ed_{ventrSPT} + \frac{Es_{ventrSPT} - Ed_{ventrSPT}}{2} a_{ventrSPT}(t) \tag{7}$$

where $Ed_{ventrSPT}$ is the inter-ventricular septum diastolic elastance, $Es_{ventrSPT}$ is the inter-ventricular septum systolic elastance and $a_{ventrSPT}(t)$ is the activation function described according to the ECG schematization (Fig.3) as follows:

$$a_{ventrSPT}(t) = \begin{cases} 1 - \cos\left(\frac{t}{T_R}\pi\right) & 0 \le t \le T_R \\ 1 + \cos\left(\frac{t - T_R}{T_{TE} - T_R}\pi\right) & T_R < t \le T_{TE} \\ 0 & T_{TE} < t \le T \end{cases} \tag{8}$$

T_{TE} is ventricular systole ending and T_R corresponds to the R-wave peak time.
When the instantaneous left and right ventricular pressures are different ($Plv(t) \neq Prv(t)$), the instantaneous inter-ventricular septum volume ($V_{ventrSPT}(t)$) becomes the volume of shift of the inter-ventricular septum from the neutral position toward the left/right ventricular lumen [9,11]:

$$V_{ventrSPT}(t) = \frac{Plv(t) - Prv(t)}{e_{ventrSPT}(t)} \tag{9}$$

The instantaneous left/right ventricular volume $Vlv(t)/Vrv(t)$ can be described by:

$$\begin{cases} Vlv(t) = V^*lv(t) + V_{ventrSPT}(t) \\ Vrv(t) = V^*rv(t) - V_{ventrSPT}(t) \end{cases} \tag{10}$$

Starting from Eq.10, substituting $V^*lv(t)/V^*rv(t)$ with Eq.6 and $V_{ventrSPT}(t)$ with Eq.9, results:

$$Vlv(t)=\left[\frac{Plv(t)}{elv(t)}+Vlo\right]+\frac{Plv(t)-Prv(t)}{e_{ventrSPT}(t)}$$
$$Vrv(t)=\left[\frac{Prv(t)}{erv(t)}+Vro\right]-\frac{Plv(t)-Prv(t)}{e_{ventrSPT}(t)} \quad (11)$$

From Eq. 11 the instantaneous left/right ventricular pressure becomes [17]:

$$\begin{cases} Plv(t)=\dfrac{e_{ventrSPT}(t)\cdot elv(t)}{e_{ventrSPT}(t)+elv(t)}\cdot(Vlv(t)-Vlo)+\dfrac{elv(t)}{e_{ventrSPT}(t)+elv(t)}\cdot Prv(t) \\ Prv(t)=\dfrac{e_{ventrSPT}(t)\cdot erv(t)}{e_{ventrSPT}(t)+erv(t)}\cdot(Vrv(t)-Vro)+\dfrac{erv(t)}{e_{ventrSPT}(t)+erv(t)}\cdot Plv(t) \end{cases} \quad (12)$$

This numerical model is used to simulate the interactions between the two ventricular chambers.

2.2.4 Interatrial Septum Numerical Modelling

Again, a time-varying elastance model describes the behaviour of the inter-atrial septum in CARDIOSIM©. The concept of atrial interdependence considers the properties of one atrium to be a function of the properties of the contra-lateral one. The behaviour of the inter-atrial septum is described by:

$$e_{atriaSPT}(t)=Ed_{atriaSPT}+\frac{Es_{atriaSPT}-Ed_{atriaSPT}}{2}a_{atriaSPT}(t) \quad (13)$$

where $Ed_{atriaSPT}$ is the inter-atrial septum diastolic elastance, $Es_{atriaSPT}$ is the inter-atrial septum systolic elastance and $a_{atriaSPT}(t)$ is the activation function. According to the ECG schematization (Fig.3), it follows:

$$a_{atriaSPT}(t)=\begin{cases} 0 & 0\le t\le T_{PB} \\ 1+\cos\left(\dfrac{t-T_{PB}}{T_{PE}-T_{PB}}2\pi\right) & T_{PB}<t\le T_{PE} \\ 0 & T_{PE}<t\le T \end{cases} \quad (14)$$

T_{PB} and T_{PE} are the onset and the end of the P wave of the ECG signal, respectively. When the instantaneous left and right atrial pressures are different ($Pla(t)\neq Pra(t)$), the instantaneous inter-atrial septum volume ($V_{atriaSPT}(t)$) becomes the volume of shift of the inter-atrial septum from the neutral position towards the left/right atrial lumen:

$$V_{atriaSPT}(t) = \frac{Pla(t) - Pra(t)}{e_{atriaSPT}(t)} \tag{15}$$

The instantaneous left/right atrial volume *Vla(t)/Vra(t)* is described by:

$$\begin{cases} Vla(t) = V^{*}la(t) + V_{atriaSPT}(t) \\ Vra(t) = V^{*}ra(t) - V_{atriaSPT}(t) \end{cases} \tag{16}$$

From Eq.3 can be derived:

$$V^{*}la(t) = \left[\frac{Pla(t) - P_0 la}{ela(t)}\right] + V_0 la \qquad V^{*}ra(t) = \left[\frac{Pra(t) - P_0 ra}{era(t)}\right] + V_0 ra \tag{17}$$

Starting from Eq.16, substituting $V^{*}la(t)/V^{*}ra(t)$ with Eq.17 and $V_{atriaSPT}(t)$ with Eq.15, results:

$$\begin{cases} Pla(t) = \frac{e_{atriaSPT}(t)\cdot ela(t)}{e_{atriaSPT}(t)+ela(t)}\cdot(Vla(t)-V_0 la)+\frac{ela(t)}{e_{atriaSPT}(t)+ela(t)}\cdot Pra(t)+\frac{e_{atriaSPT}(t)}{e_{atriaSPT}(t)+ela(t)}\cdot P_0 la \\ Pra(t) = \frac{e_{atriaSPT}(t)\cdot era(t)}{e_{atriaSPT}(t)+era(t)}\cdot(Vra(t)-V_0 ra)+\frac{era(t)}{e_{atriaSPT}(t)+era(t)}\cdot Pla(t)+\frac{e_{atriaSPT}(t)}{e_{atriaSPT}(t)+era(t)}\cdot P_0 ra \end{cases} \tag{18}$$

This numerical model is used to simulate the interactions between the two atrial chambers.

2.2.5 Coronary Numerical Modelling

In CARDIOSIM©, the coronary network is developed with a lumped parameter representation based on the intra-myocardial pump concept [18,19]. The coronary model consists of three parallel sections representing the endocardial, the middle and the epicardial layers of the left ventricular wall. Each parallel layer is modelled in the same way using RC elements. The equations describing the coronary numerical modelling are reported in [20].

2.3 Simulations Before and After CRT

Simulations based on clinical data from patients with dilated cardiomyopathy requiring CRT have been collected in this section [21].
The screen output in Fig. 4 shows a table with data obtained from patients with dilated cardiomyopathy [21].

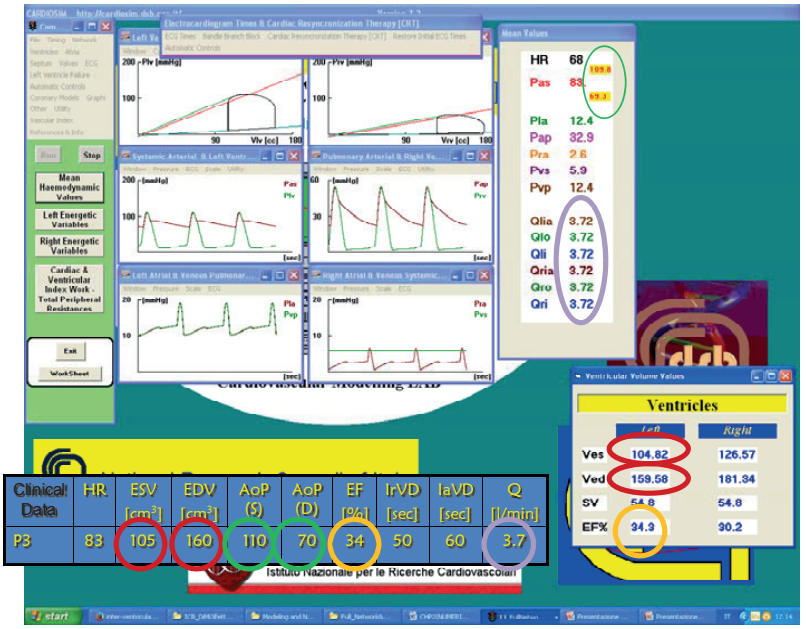


Fig. 4. Screen output produced by CARDIOSIM© software simulator. In the table the clinical literature data [21] for pathological patient conditions are reported. HR is the heart rate [beat/min]; ESV (EDV) is the left end-systolic (end-diastolic) ventricular volume [cm^3]; AoP(S) (AoP(D)) is the systolic (diastolic) aortic pressure [mmHg]; EF[%] is the left ventricular ejection fraction; IrVD (IaVD) is the left inter-ventricular (intra-ventricular) delay [ms]. Q is the cardiac output [l/min]. In the right column for Pas (aortic pressure) mean, systolic and diastolic values are reported.

The left (right) upper window in Fig. 4 shows the left (right) ventricular pressure-volume loop. The mean values (calculated during the cardiac cycle) of the left atrial pressure (Pla), pulmonary arterial pressure (Pap), right atrial pressure (Pra), systemic venous pressure (Pvs) and the pulmonary venous pressure (Pvp) are listed in the right

column. HR is the heart rate and Pas consists of systolic, diastolic and mean aortic pressure. Qli (Qlo) is the left ventricular input (output) flow, Qri (Qro) is the right ventricular input (output) flow and Qlia (Qria) is the left (right) atrial input flow. The end-systolic (Ves) and the end diastolic (Ved) ventricular volume, the stroke volume (SV) and the ejection fraction (EF%) are recorded in the "Ventricles" window. The “Command” column is placed on the left side in Fig. 4.

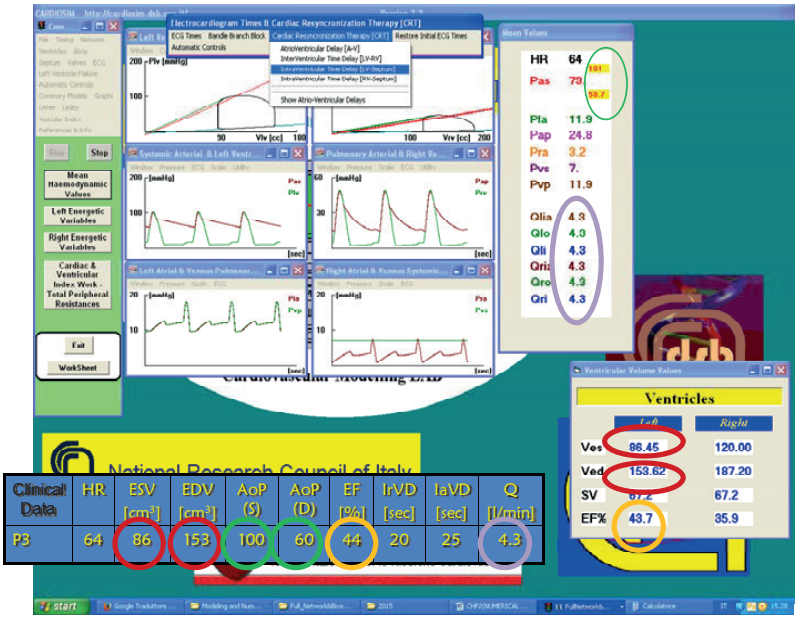


Fig. 5. Screen output produced by CARDIOSIM©. In the table the clinical literature data [21] for assisted patient conditions are reported. The assistance was performed by CRT.

Fig. 5 shows the screen output produced by the software cardiovascular simulator when cardiac resynchronization therapy was applied. The simulation was undertaken in a patient who underwent CRT six months earlier where literature data was initially considered [21]. Data is listed in the table of Fig. 5. The mean aortic pressure, the heart rate, the left inter-ventricular and intra-ventricular delays were the input software data. The software automatically adjusts the variable peripheral arterial resistance (Rcbs), the left end-systolic pressure-volume relationship and the arterial compliances in order to approximate the measured cardiac output, the left ventricular end-systolic (end-diastolic) volume, the systolic and diastolic aortic pressure and the ejection fraction.

2.4 Conclusion

The numerical heart model implemented in CARDIOSIM© can emulate the interaction between the septum, the left (right) ventricle and the left (right) atrium in order to evaluate the effects of CRT. The software simulator can reproduce the diseased status of heart failure patients with significant intra-ventricular or inter-ventricular conduction delays requiring CRT. When a simulation set up is applied, the haemodynamic parameters obtained are realistic and in accordance with literature data.
In addition, the software simulator can be used to evaluate cardiac contractility before and after CRT over a period of time.
Given the scarce availability of data obtained in a non-invasive manner and considering the limitations and invasiveness of thermo-dilution techniques, the use of a numerical simulator has the potential to overcome these difficulties and improve our understanding of the effects of CRT in heart failure patients.

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