Biocybernetics and Biomedical Engineering
2010, Volume 30, Number 1, pp. 3–15

Biventricular Pacemaker Synchronization: A Numerical Cardiocirculatory Model Application to Reproduce *In Vivo* Data

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Cardiac Resynchronization Therapy (CRT) seems to be the most encouraging treatment to limit the damages of ventricular remodelling in patients with moderate-severe cardiac insufficiency. Mathematical modelling of the cardiovascular system is a tool potentially useful to understand how the Biventricular Pacemaker (BPM) must be synchronised during CRT. In this work a computer simulator reproduces clinical data measured, on different patients affected by asynchronous ventricular contraction, before and after CRT. Three patients, affected by asynchronous ventricular contraction, were monitored before and after biventricular stimulation through CRT. Measured and simulated data were compared. Results show that the software simulator can well reproduce in vivo data. Besides, simulated results from BPM together with drug therapy are in accordance with literature data. Numerical modelling could be a useful tool to optimize the BPM synchronization.

K e y w o r d s: circulatory system, hemodynamics, coronary circulation, left ventricle, computer simulation

1. Introduction

In recent decades, despite improvements in survival, there has been a gradual increase in hospitalizations for heart failure (HF). It is evaluated that about five million

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Received 02 March 2009; accepted 23 September 2009

people had an heart failure only in the U.S.A. and that about ten million people are affected by chronic disease in Europe [1]. In Italy, in the last ten years, an important increase of hospitalizations, caused by HF, has been observed, opening new horizons in diagnosis and in therapy of the cardiac insufficiency.

Cardiac Resynchronization Therapy (CRT) seems to be the most encouraging treatment to limit the damages of ventricular remodelling in patients with moderate-severe cardiac insufficiency [1, 2].

CRT is responsible for the "reverse remodelling" which consists of a gradual reduction of left ventricular dilation (negative ventricular remodelling) [3, 4].

Assumptions about mechanisms of the "reverse remodelling" are the reduction of: 1) regional wall stress, 2) myocardial oxygen consumption, 3) sympathetic tone, 4) progression of mitral regurgitation [5].

A lot of patients with left ventricular failure present an intra-ventricular conduction delay due to asynchronous ventricular contraction. This fact worsens the ventricular performance by increasing regional wall-stress and dilation. Biventricular pacing works exactly on these problems [6, 7].

Biventricular stimulation through CRT can produce an improvement of the index dP/dt (that gives information on ventricular contractility) of the left ventricle, the ejection fraction and the cardiac index, while it reduces wall stress and filling pressure of the left ventricle [7].

The morpho-functional remodelling of the left ventricle can be studied by echocardiography, evaluating several parameters such as: 1) end-diastolic and end-systolic diameters, 2) end-diastolic and end-systolic volumes, 3) the indexes of global systolic function. These parameters are the reference for many studies on resynchronization therapy efficiency [3, 4].

Conventional biventricular pacing has three leads: the first one placed in the right atrium, the second one in the right ventricle and the last one in a vein on the surface of the left ventricle. However, it is not clear if this solution can completely guarantee inter-ventricular and atrio-ventricular synchronization also considering that synchronization must be specific for each patient. In fact, assuming that pacemaker is correctly placed, each patient presents different clinical responses like modest improvement in exercise tolerance, in quality of life, in congestive heart failure severity reduction, in echo measures and in neurohormones.

The aim of this work was to reproduce, using a numerical simulator of the cardiovascular system, the pathological conditions of three different patients undergoing CRT with biventricular pacemaker. They have been analyzed with echocardiography before the implantation and 15 days since CRT. For each patient, CRT produced by Biventricular Pacemaker (BPM) was studied and reproduced using the simulator. In this way in vivo clinical and simulated data have been presented and compared.

Computer simulation is a valid approach to study the effects of ventricular resynchronization. In this work it has been used the software package CARDIOSIM© that is a numerical model of the cardiovascular system [8]. This software enables

to simulate different pathological conditions due to different degrees of pathophysiological impairment together with their effect on cardiovascular function. The model has been modified to reproduce the effects of ventricular synchronization.

2. Materials and Methods

In the U.O.C. of Cardiology of the University "la Sapienza", three patients undergoing CRT with BPM have been studied. They have been evaluated by echocardiography before the implantation and 15 days since CRT.

The implant occurred in patients by installing:

- an electrode on the lateral epicardial wall of left ventricle (left ventricular stimulator),
- an electrode on the septal endocardial wall of right ventricle (right ventricular stimulator),
- an electrode on the endocardial wall of the right atrium (right atrium stimulator).

The three electrodes were connected to BPM which was placed into a left subclavicular subcutaneous pocket previously prepared.

The electric catheters were driven with the Seldinger technique from venous system (left subclavian vein) to the right heart cavity (right atrium and right ventricle) and through the coronary sinus and the great cardiac vein to the epicardium of left ventricle.

Once the electro-catheters were positioned, the measures of sensing and of stimulation threshold were performed; when the measures were considered satisfactory, the electrocatheters were tied. The whole procedure was performed under fluoroscopic control, using low levels of ionizing radiations.

At the end of the surgical procedure a final device programming and echocardiographic control were performed.

All patients were processed to echocardiographic study collecting hemodynamic parameters of left ventricular function such as: left ventricular end systolic volume (LVes), left ventricular end diastolic volume (LVed), shortening fraction (FS) and ejection fraction (EF), QRS complex of ECG duration (TDI), pulmonary venous flow velocity (PVFV) and cardiac output (CO). Also systolic aortic pressure [AoP(S)] and diastolic aortic pressure [AoP(D)] were measured. All clinical data before CRT are reported in Table 1 together with age, weight (W) and heart rate (HR).

Table 2 shows the clinical data 15 days since BPM implantation.

The measured data, in both pathological and assisted conditions (by BPM), were reproduced using CARDIOSIM©, which is a software simulator of the human cardiovascular system [8]. This numerical simulator reproduces the most important circulatory phenomena, in terms of pressure and volume relationship. It has a modular structure including the left and the right heart, the systemic arterial (pulmonary)

Table 1. Clinical data before CRT

	Age [yo]	W [Kg]	HR [bpm]	LVes [cm^3]	LVed [cm^3]	AoP(S) [mmHg]	AoP(D) [mmHg]	FS	EF	TDI [ms]	PVFV [ms]	CO [l/m]
P #1	86	65	97	133.1	170	110	85	22%	22%	140	26	3.6
P #2	79	72	98	135.9	176	117	95	24%	23%	135	27	3.9
P #3	62	80	100	144.0	183	140	110	19%	21%	160	29	3.8

Table 2. Clinical data after 15 days from CRT

	Age [yo]	W [Kg]	HR [bpm]	LVd [cm]	LVed [cm^3]	AoP(S) [mmHg]	AoP(D) [mmHg]	FS	EF	TDI [ms]	PVFV [ms]	CO [l/m]
P #2	86	65	89	64	160	125	100	24%	27%	96	23	3.8
P #2	79	72	88	62	170	124	98	32%	27%	94	21	4.0
P #3	62	80	85	69	160	150	120	19%	30%	90	29	4.0

section, the systemic (pulmonary) venous section and the coronary section (Fig. 1). Entire circulation is described by a lumped parameter model. The systemic arterial (pulmonary) section is modelled using a modified windkessel represented by the characteristic resistance *Rcs* (*Rcp*), the inertance Ls (*Lp*) and the compliance Cas (*Cap*) with a variable peripheral resistance *Ras* (*Rap*). The compliance *Cvs* and the variable resistance *Rvs* are able to reproduce the systemic venous section [9, 10]. The simple compliance *Cvp* permits to simulate the behaviour of the pulmonary venous circulation [9, 10]. The heart valves connecting the left atrium to the ventricle (mitral valve

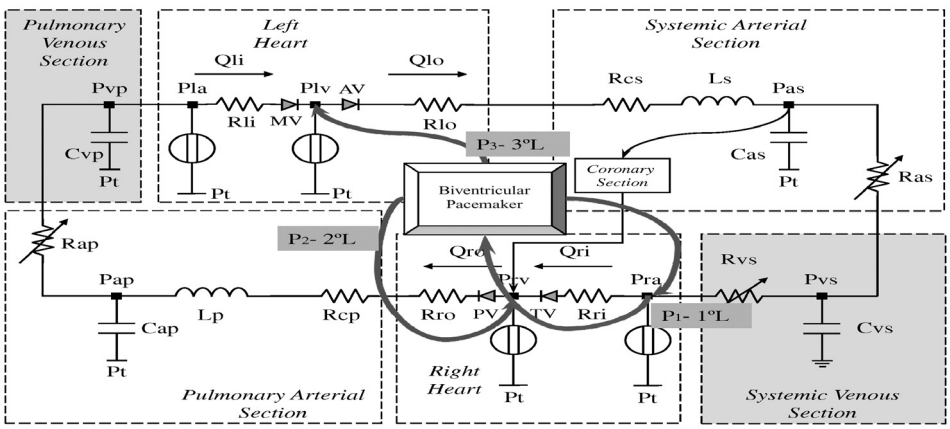


Fig. 1. Electric analogue of the numerical simulator. The legend describing variable and parameters is reported in Table 3. Biventricular pacemaker is connected by three leads. Generally, the first (1ºL) gives an impulse (P_1) in the right atrium; the second (2ºL) gives an impulse (P_2) in the right ventricle; the third (3ºL) gives an impulse (P_3) in the left ventricle

– MV), the right atrium to the ventricle (tricuspid valve – TV), the left ventricle to the aorta (aortic valve – AV) and the right ventricle to the pulmonary artery (pulmonary valve – PV), are assumed as unidirectional ideal valves. Table 3 presents the legend of parameters and variables used in the numerical simulator (Fig. 1).

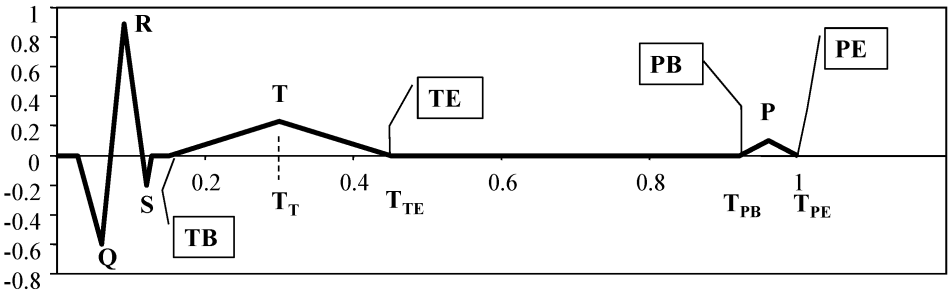
Table 3. Legend of parameters and variables used in CARDIOSIM©

	Resistance [mmHg·cm^{-3}·sec]	Compliance [cm^3·mmHg^{-1}]	Inertance [mmHg·cm^{-3}·sec^2]	Pressure [mmHg]	Flow [l·min^{-1}]
LEFT (RIGHT) HEART					
Left input (output) valve	Rli (Rlo)				
Right input (output) valve	Rri (Rro)				
Left (right) atrium				Pla (Pra)	
Left input (output) flow					Qli (Qlo)
Right input (output) flow					Qri (Qro)
Left (right) ventricle				Plv (Prv)	
SYSTEMIC SECTION					
Systemic arterial section	Rcs, Ras	Cas	Ls	Pas	
Systemic venous section	Rvs	Cvs		Pvs	
PULMONARY SECTION					
Pulmonary arterial section	Rcp, Rap	Cap	Lp	Pap	
Pulmonary venous section	Rvp	Cvp		Pvp	
Mean Thoracic Pressure				Pt	

In order to simulate the effects and the temporizations of BPM it was necessary to synchronize the simulator with the ECG signal. For this reason CARDIOSIM© was updated describing in different way the ventricular and atrial characteristics relating them with the ECG times. The behaviour of the ventricle (atrium) is described by variable elastance models [8, 9, 11, 12] reproducing the Starling's law of the heart. The left time-varying ventricular elastance $elv(t)$ is a function of the left ventricular systolic elastance ($Elvs$), left ventricular diastolic elastance ($Elvd$) and left activation function $alv(t)$:

$$elv(t) = Elvd + \frac{Elvs - Elvd}{2} alv(t)\,. \tag{1}$$

The ECG signal was schematically reproduced (Fig. 2) to synchronize the contraction and the relaxation phases of the ventricle (atrium). In Figure 2 the period ($T_T - T_{TE}$) represents the ventricular ejection time (in which the ventricular volume decreases) even if ventricular systole starts at the end of QRS complex [the period ($T_{PB} - T_{PE}$)



T_T	Ventricular ejection starting
T_{TE}	Ventricular ejection ending
$T_T - T_{TE}$	Ventricular ejection time
T_{PB}	Atrial depolarization starting
T_{PE}	Atrial depolarization ending
$T_{PB} - T_{PE}$	Atrial depolarization time

Times	Value [s]
T_{PE}	0
T_Q	0.06
T_R	0.09
T_S	0.12
T_T	0.3
T_{TE}	0.45
T_{PB}	0.92
T_P	0.96
T	1

Fig. 2. Schematic representation of the electrocardiogram (ECG) signal. The period ($T_T - T_{TE}$) represents the ventricular ejection; the period ($T_{PB} - T_{PE}$) corresponds to the atrial depolarization time. The duration of the different periods are reported in the table

precedes the atrial systole]. The assigned values for HR = 60 of each period are presented in the lowest part of Fig. 2. In equation (1) the left activation function describes the contraction and the relaxation changes in the ventricular muscle:

$$alv(t) = \begin{cases} 1 - \cos\left(\dfrac{t}{T_T}\pi\right) & 0 \le t \le T_T \\ 1 + \cos\left(\dfrac{t - T_T}{T_{TE} - T_T}\pi\right) & T_T < t \le T_{TE} \\ 0 & T_{TE} < t \le T \end{cases} \tag{2}$$

where T_T is the T wave peak time in the ECG signal, T_{TE} is the T wave ending time in the ECG signal and T is heart period [13]. Changing T_T and T_{TE}, (Eq. 2) it is possible to determine when ventricular ejection starts and its duration. This permits to synchronize ventricular mechanics with the ECG signal. The right ventricular model is similar to that for the left side, except the values of parameters that are different. A contraction delay was inserted between left and right ventricles in order to simulate the inter-ventricular dyssynchrony.

The time-varying atrial elastance $ea(t)$ (for both atria) is also a function of the characteristic elastance during atrial systole (*Eas*), atrial diastole (*Ead*) and activation function $aa(t)$:

$$ea(t) = Ead + \frac{Eas - Ead}{2} aa(t) . \tag{3}$$

The activation function describes the contraction and the relaxation changes in the atrial muscle:

$$aa(t) = \begin{cases} 0 & 0 \le t \le T_{PB} \\ 1 - \cos\left(\dfrac{t - T_{PB}}{T_{PE} - T_{PB}} 2\pi \right) & T_{PB} < t \le T_{PE} \\ 0 & T_{PE} < t \le T \end{cases} \tag{4}$$

where T_{PB} is *P* wave beginning time in the ECG signal and T_{PE} is the *P* wave ending time in the ECG signal (Fig. 2). In equation (4) changing T_{PE} and T_{PB}, it is possible to determine when atrial active ejection starts. This permits to synchronize the atria mechanics with the ECG signal. Considering the equations (2) and (4), changing T_{PE}, T_{PB}, T_T and T_{TE}, it is possible to reproduce the atrio-ventricular contraction delay. BPM drives right atrium and both ventricular contractions. In the presented model BPM action was simulated changing T_{PE}, T_{PB}, T_T, T_{TE} and the inter-ventricular delay. The block diagram of the whole model, including BPM model, is reproduced in Fig. 1.

Both the pathological conditions and the clinical response of three patients have been simulated. To realize the simulation in pathological conditions (Table 1) and 15 days since CRT, model parameters have been set as shown in Table 4 and Table 5 respectively. During simulation, HR and TDI were set exactly as measured clinical data. The delay expressed by the TDI is due to left branch block. In the simulator, measured AoP(S), AoP(D), LVed and LVes were reproduced changing *Elvs*, *Ervs*, *Eas*, *Ras*, *Cas*, *Rvs*, *Cvs*, *Rap* and cardiac stiffness (*k*) empirically. *Elvs* and *k* are set in order to place the left ventricular work cycle in the pressure-volume plane reproducing measured LVes and LVed. An algorithm that adjust *Ras* (*Rap*) automatically maintaining the mean aortic pressure (mean pulmonary arterial pressure) constant, was already implemented in the software [9]. Knowing Ras, AoP(S), AoP(D) and the timing constant, it is possible to estimate *Cas*. The left ventricular end systolic pressure can be approximated with mean aortic pressure value [12]. This last parameter together with LVes and LVed permits to place the left ventricular loop in the pressure-volume plane. *Ervs*, *Eas*, *Rvs* and *Cvs* are set in order to simulate the venous pulmonary flow (*Qvp*) and the preload of the left heart.

For CRT simulation only cardiac parameters (*Elvs*, *Ervs*, *Eas* and *k*) are changed assuming that the biventricular stimulation acts on the whole heart. In fact, the

Table 4. Model parameter setting before CRT

	HR	Elvs	Ervs	k	Eas	TDI	Ras	Cas	Rvs	Cvs	Rap
P #1	97	0.82	0.6	1	0.25	60	2000	2.6	100	82.5	600
P #2	98	0.85	0.7	0.95	0.25	55	1950	2.7	90	83	500
P #3	100	0.95	0.6	0.97	0.25	80	2350	1.8	100	84	400

The left ventricular systolic elastance (*Elvs*), the right ventricular systolic elastance (*Ervs*) and the systolic atrial elastance (*Eas*) are expressed in [$mmHg \cdot cm^{-3}$]. The cardiac stiffness (*k*) is expressed in [$mmHg^{-1} \cdot cm^{3}$]. The rest of appropriate units is given in Table 3

Table 5. Model parameter setting after 15 days from CRT. Appropriate units are given in Tables 3 and 4

	HR	Elvs	Ervs	k	Eas	TDI	Ras	Cas	Rvs	Cvs	Rap
P #1	89	1.05	0.6	0.9	0.4	16	2000	2.6	100	82.5	625
P #2	88	1	0.7	0.85	0.35	14	1950	2.7	90	83	500
P #3	85	1.34	0.6	0.9	0.25	10	2350	1.8	100	84	400

improvement in circulatory parameters can be evaluated only after a period longer than 15 days.

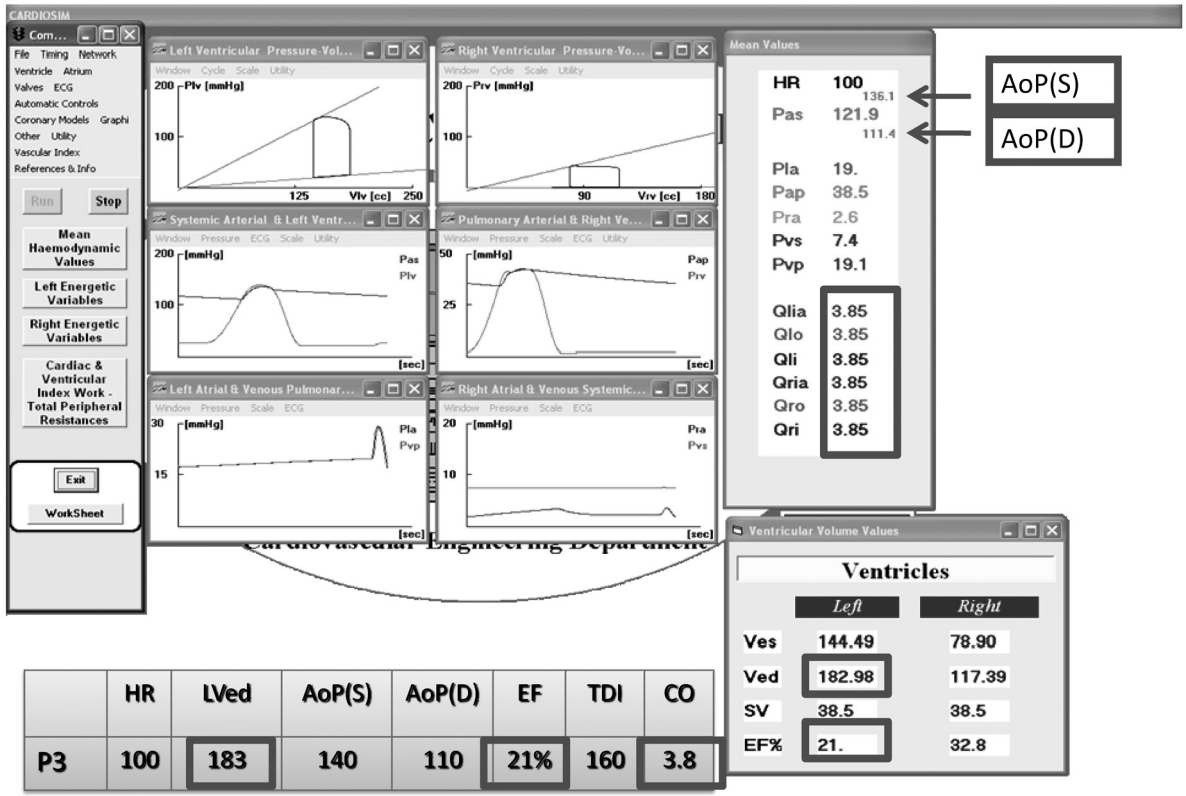
Using the cardiovascular simulator, it is possible to predict how the hemodynamic condition will improve treating simulated patients with vasodilator drugs. Drug therapy was simulated decreasing the systemic peripheral resistance (*Ras*) value.

3. Results

Three patients were simulated starting from measured data before CRT and 15 days since BPM implantation using the modified model.

Figure 3 reproduces the simulation of the pathological condition of patient 3 (P#3). The table reported in Fig. 3 shows the measured data on P#3 in pathological condition (Table 1). The CO, the left ventricular end diastolic volume and the ejection fraction are evidenced both in the table and in the two rectangular windows produced by the software simulator. Figure 4 shows P#3 hemodynamic data simulation 15 days since BPM implantation. The table of Fig. 4 reports P#3 measured data after BPM implantation (Table 2).

Finally, Fig. 5 shows the improvement of hemodynamic condition of the three simulated patients comparing the values of different parameters (EF, CO, AoP(D) and AoP(S)) in the following cases: simulated pathological conditions (white columns), after BPM implantation (gray columns), after BPM and drug (D) therapy (black columns).



	HR	LVed	AoP(S)	AoP(D)	EF	TDI	CO
P3	100	183	140	110	21%	160	3.8

Fig. 3. Simulation of the pathological condition of P#3 obtained using CARDIOSIM©. The mean values of the different hemodynamic parameters in (produced by the software simulator) are reported in the right column . For the mean systemic arterial pressure (*Pas* shown by the software) the two labels AoP(S) (systolic arterial pressure) and AoP(D) (diastolic arterial pressure) are added. The left (right) upper window shows the left (right) ventricular cardiac loop. The left middle window shows the instantaneous left ventricular and systemic arterial pressure waveforms during the cardiac cycle. The right middle window shows the instantaneous right ventricular and pulmonary arterial pressure waveforms during the cardiac cycle. The left lower window shows both the instantaneous left atrial and pulmonary venous pressure waveforms during the cardiac cycle. Finally, the right lower window shows the instantaneous right atrial and systemic venous pressure waveforms during the cardiac cycle. *Qlia* (*Qria*) is the left (right) atrial input flow, *Ves* (*Ved*) is the end systolic (diastolic) volume and SV is the stroke volume

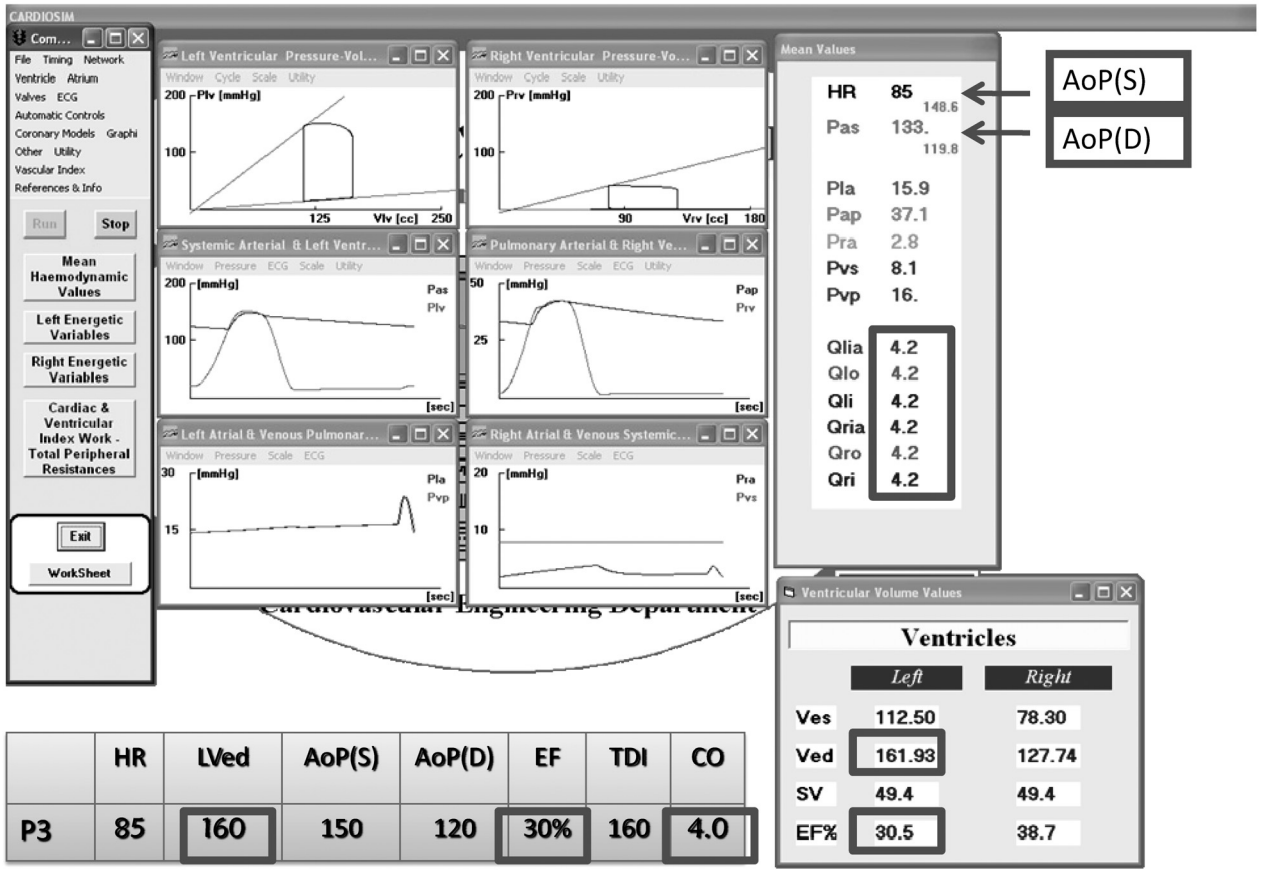


Fig. 4. P#3 hemodynamic data simulation 15 days since BPM implantation. The mean values of the different hemodynamic parameters (produced by the software simulator) are reported in the right column

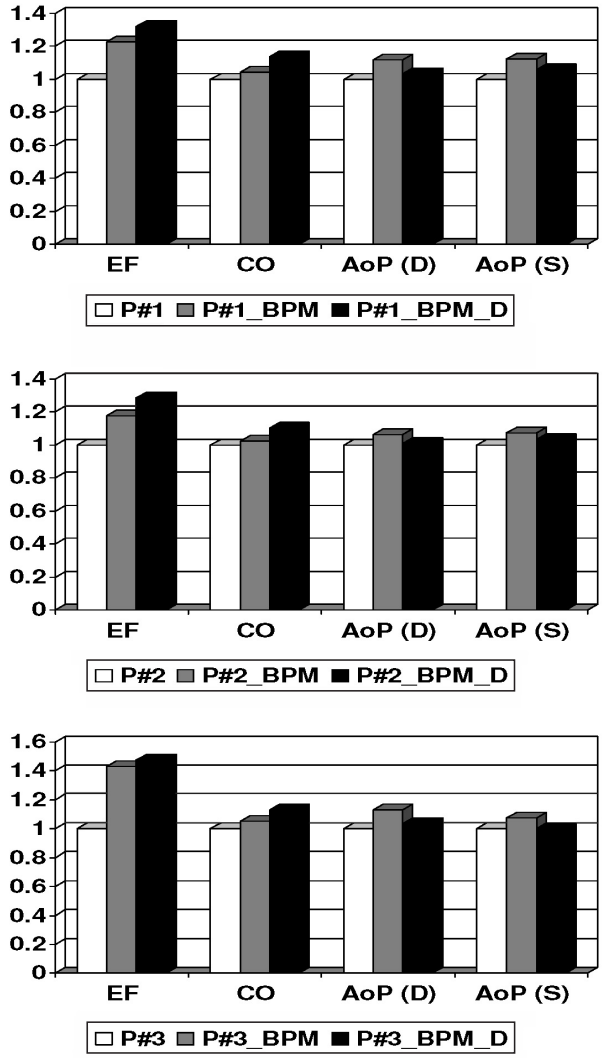


Fig. 5. Results of the three simulated patients comparing the values of different parameters [EF, CO, AoP(D) and AoP(S)]. White columns represent the simulated pathological conditions. Gray columns represent the simulated results obtained after BPM implantation. Black columns represent the simulated results after BPM and drug (D) therapy. Simulated values are normalized to pathological values

4. Discussion

The modified software can well reproduce in vivo measured data as shown in Figs 3 and 4. Figure 3 shows the results obtained simulating the pathological condition of P#3. According to literature data about moderate and severe HF, a high value of the

left ventricular end diastolic volume, low values of EF and CO can be observed [14]. The model can well reproduce the pathological conditions from hemodynamic point of view and also from electrical point of view changing the QRS complex duration (TDI) in the ECG signal. This delay is applied only to the left ventricle in order to simulate a left branch block. In Figure 4 the hemodynamic condition of P#3, 15 days since CRT is shown. Also in this case clinical data are reproduced by the software. After cardiac resynchronization therapy with the biventricular pacemaker, a decrease of delay in left ventricular contraction expressed by TDI can be observed in clinical data. This effect was simulated changing BPM synchronization and QRS complex duration in the ECG signal. The software can simulate the cardiac resynchronization therapy using biventricular pacemaker with three leads setting the times in which they must release the impulses in heart chambers. 15 days since CRT, clinical data show that the left ventricular end diastolic volume decreases while the EF and CO increase. Generally, in patients treated with BPM, the cardiac output increases of about 7–15%. This result can be obtained also from the simulation as it is shown in Figs 3 and 4.

In Figure 5 some simulated data are shown. White and gray columns are derived starting from in vivo data, while black columns are obtained simulating vasodilator therapy. In fact this drug therapy is often used together with BPM by clinicians to improve hemodynamic conditions. In all three cases a progressive increase of EF and CO can be observed according to literature data. In the upper panel first patient's data are shown, in the middle and in lower panels second and third patients's data are shown, respectively.

5. Conclusions

The aim of the presented work is to develop a numerical model able to simulate moderate and severe HF and the cardiac resynchronization therapy using BPM. In fact, assuming that the leads of BPM are correctly placed, the synchronization must be specific for each patient. Results presented in this paper show that the software simulator can well reproduce in vivo data. Besides, results simulated in the case of BPM together with drug therapy are in accordance with literature data. For these reasons, numerical model can be a useful tool to support medical decision in order to understand the appropriate therapy for each patient. In particular, numerical model could be a useful tool to optimize BPM synchronization. Model could also be useful to understand the trend of some parameters, as ventricular elastance and stiffness, which are difficult to be measured and useful to estimate.

Further investigations will be devoted also to the analysis of the relations among hemodynamic variables trend, TDI and QRS complex duration.

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