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ENERGETIC VENTRICULAR BALANCE DURING CARDIAC RESYNCHRONIZATION THERAPY: NUMERICAL SIMULATION

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ABSTRACT
Cardiac Resynchronization Therapy (CRT), realised using biventricular pacemaker is used to treat patients with in systolic heart failure (HF) and with prolonged QRS. The goal of CRT is to eliminate or reduce the electromechanical dyssynchrony processes often responsible of cardiac remodelling. The aim of this work is to study the effects of CRT on the energetic left ventricular variables as external work, the pressure-volume area and the potential energy. In order to study the effects produced by CRT on energetic left ventricular balance it was used the numerical model of the cardiovascular system (CARDIOSIM©), able to reproduce the effects induced by biventricular pacemaker (BPM).
Starting from literature data, the haemodynamic conditions of a group of patients, representative of the most common disease etiologies of heart failure, were simulated before and after CRT treatment.
The trend of the energetic left ventricular variables was studied for each patient in order to evaluate the effects produced by the CRT.
The obtained results shown that the software simulator can predict the dynamics of energetic left ventricular balance in patients affected by HF and treated with cardiac resynchronization therapy.

KEY WORDS
Cardiovascular system, numerical simulation, heart failure, energetic variables.

1. Introduction

The Cardiac Resynchronization Therapy (CRT) was proposed in the mid 90s as a possible treatment for patients with end-stage heart failure (HF). In this pathological condition the left ventricle mechanics is depressed, uncoordinated and it presents a prolonged QRS time duration.

The following guidelines indications for CRT are proposed by ACC / AHA / NASPE (CRT, 2002) [1], by the ESC (failure chronic heart, 2005) [2] and ACC / AHA (failure chronic heart, 2005) [3]:

• The CRT is indicated for patients in sinus rhythm with advanced heart failure (NYHA class III-IV), left ventricular systolic dysfunction (ejection fraction EF ≤ 35%) LV telediastolic diameter ≥ 55 mm and QRS duration ≥ 130 ms (IIA) [1].

• The CRT can be applied in patients with reduced ejection fraction and ventricular dyssynchrony (QRS duration ≥ 120 ms) who remain symptomatic (NYHA III-IV) after medical therapy induced to improve the symptoms (IA), reduce hospitalizations (IA) and mortality (IB) [2]

• The CRT should be considered in patients with EF ≤ 35%, sinus rhythm, NYHA functional class III-IV and ventricular dyssynchrony (QRS ≥ 120 ms) [3].

The goal of CRT is to eliminate or reduce the electromechanical dyssynchrony processes often responsible of cardiac remodelling.

The aim of this work was to study the effects of CRT on the energetic left ventricular variables as external mechanical work (EW), the pressure-volume area (PVA) and the elastic potential energy (PE) [4,5]. These variables describe from energetic point of view the energetic balance of the ventricle. In order to study the ventricular energetic balance before and during CRT treatment it was used the numerical simulator of the cardiovascular system (CARDIOSIM©) [6,7]. In this software simulator the atrio-ventricular activity is related to ECG signal. The cardiovascular simulator is also able to reproduce the *interventricular* and/or *intraventricular* dyssynchrony. The ventricular interaction (or "*ventricular interdependence*") is implemented through the interventricular septum [4,8]. The concept of "*ventricular interdependence*" considers the properties of one ventricle to be a function of the properties of the contralateral ventricle.

Starting from literature data [9], the haemodynamic conditions of a group of patients, were simulated before and within seven days and within six months since CRT treatment. In order to place on the pressure-volume plane the left ventricular cardiac loop, the literature data [9] were used to set the software parameters to reproduce the end-systolic and end-diastolic left ventricular volume and the mean (AoP) aortic pressure. In this way, for each patient, the simulator can calculate and predict the trend of the EW, the PVA and the PE.

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2. Materials and Methods

2.1 Numerical simulator

The software simulator of the cardiovascular system CARDIOSIM(C) [6,7] is able to reproduce, by haemodynamic point of view, physiopathological circulatory phenomena. The simulator has a modular structure that includes (Figure 1): the systemic (pulmonary) arterial section modelled by a modified windkessel with a characteristic resistance Rcs (Rcp), a inertance Ls (Lp), a compliance Cas (Cap) and a variable related to ECG signal [9,11]. Also ventricles are described by variable elastance models reproducing the Starling's law of the heart [4,8,11].

The left time-varying ventricular elastance *elv(t)* is described as a function of the left ventricular systolic elastance *Elvs*, the left ventricular diastolic elastance *Elvd* and the left activation function *alv(t)*:

$$elv(t) = Elvd + \frac{Elvs - Elvd}{2} \cdot alv(t) \qquad (1)$$

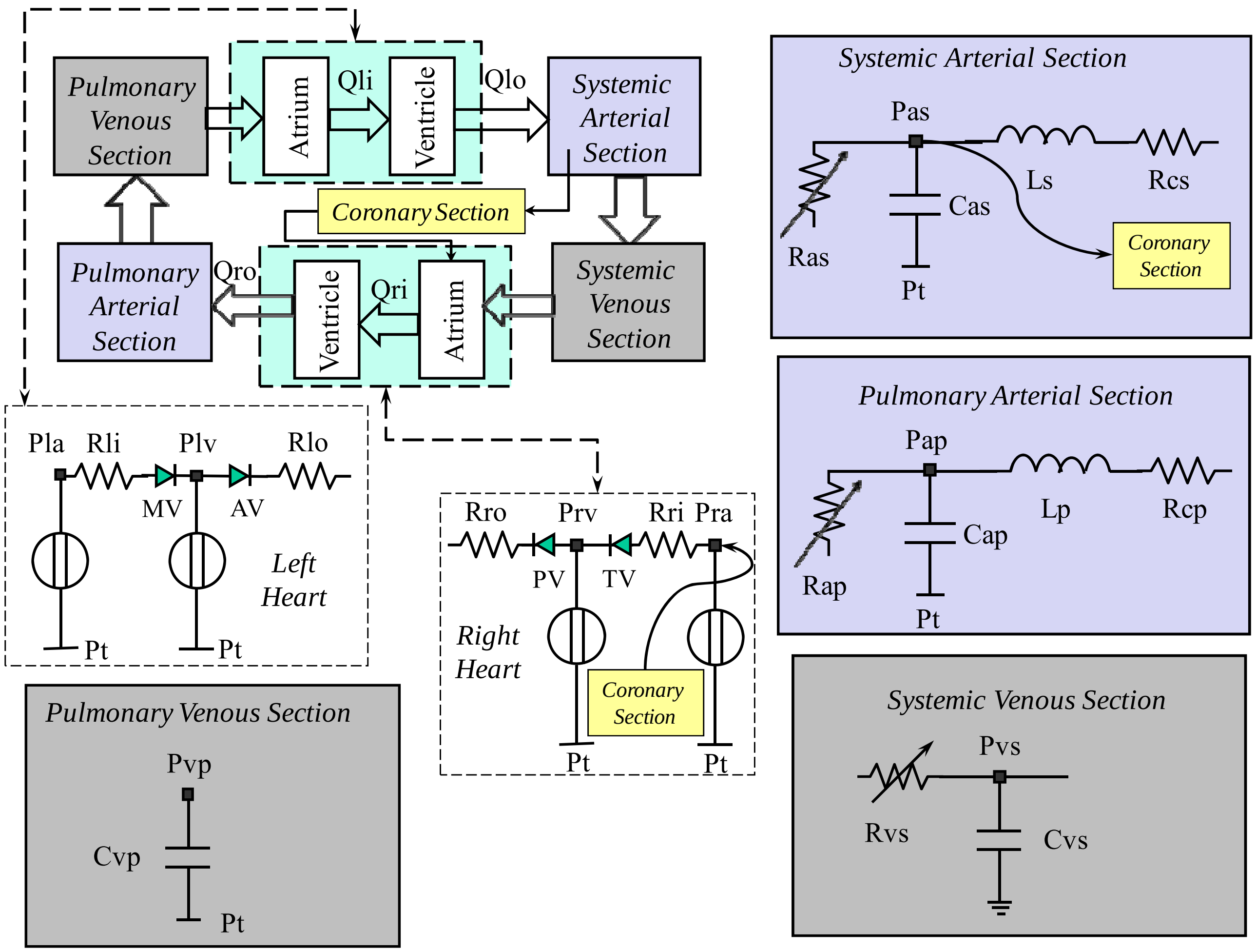

Figure 1. Electric analogue of the cardiovascular system

peripheral resistance Ras (Rap); the systemic venous section modelled by a compliance Cvs and the variable resistance Rvs [10]; the pulmonary venous section modelled by a simple compliance Cvp [10]; the coronary section [7];the left and the right heart.

Heart valves are modelled using a diode with a series resistance (Figure 1) assuming the unidirectional way of the blood flow.

The behaviour of both atria is described by variable elastance models and their mechanical properties are

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

T is the duration of the ECG signal (heart period), T_{TE} is the end of ventricular systole and T_T is the T-wave peak time.
The instantaneous left ventricular pressure is described by:

$$Plv(t) = elv(t)\cdot(Vlv(t) - Vlo) \Rightarrow Vlv(t) = \left(\frac{Plv(t)}{elv(t)}\right) + Vlo \quad (3)$$

Vlo is the rest volume of the left ventricle and *Vlv(t)* (*Plv(t)*) is the instantaneous left ventricular volume (pressure).
In order to simulate the intra-ventricular dyssynchrony a model of the ventricular interaction is implemented through the inter-ventricular behaviour of the septum [4,8]. Using a time-varying elastance model to reproduce the behaviour of the septum, it is possible describes the instantaneous left (right) ventricular pressure as fellow:

$$\begin{cases} Plv(t) = \dfrac{e_{SPT}(t)\cdot elv(t)}{e_{SPT}(t)+elv(t)}\cdot(Vlv(t)-Vlo) + \dfrac{elv(t)}{e_{SPT}(t)+elv(t)}\cdot Prv(t) \\ Prv(t) = \dfrac{e_{SPT}(t)\cdot erv(t)}{e_{SPT}(t)+erv(t)}\cdot(Vrv(t)-Vro) + \dfrac{erv(t)}{e_{SPT}(t)+erv(t)}\cdot Plv(t) \end{cases} \quad (4)$$

$e_{SPT}(t)$ is the time-varying septum elastance, *erv(t)* is the right time-varying ventricular elastance, *Vrv(t)* (*Prv(t)*) is the instantaneous right ventricular volume (pressure) and *Vro* is the rest volume of the right ventricle.
In this way the pressure of the left (right) ventricular chamber is described as a function of its elastance, of the pressure and the elastance of the right (left) ventricular chamber.

2.2 Energetic left ventricular variables

In the pressure-volume plane the left ventricular loop is represented as in Figure 2.
The total external mechanical work (EW) represents the area within the pressure-volume loop. PE is the elastic potential energy stored in the ventricular wall at end systole. The pressure volume area (PVA) consists of EW performed during systole and PE presumed to be stored in the myocardium at end systole [4,5].

2.3 Experimental setup

Staring from literature data [9], the conditions of the patients were reproduced by setting model parameters as reported below:
• in order to obtain the measured systolic (BP_S) and diastolic (BP_D) systemic arterial pressure [9], the peripheral resistance was automatically calculated;
• starting from Ras, BP_S, BP_D and the time constant, the aortic compliance was estimated;
• left ventricular systolic (diastolic) elastance was set in order to place the left ventricular loop in the pressure-volume plane, knowing the measured end systolic volume (ESV) and end diastolic volume (EDV). To place the left ventricular loop, it has also been assumed that the left ventricular end systolic pressure (Pes) can be approximated with mean aortic pressure value [4,5,9];

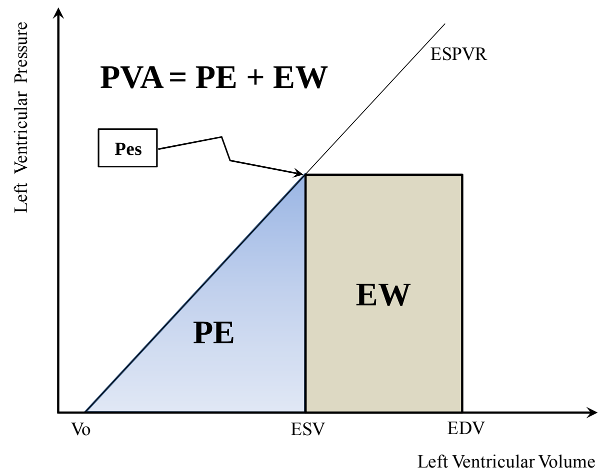

Figure 2. Schematic representation of the cardiac loop on the pressure-volume plane. ESPVR is the End Systolic Pressure Volume Relationship line. Pes (ESV) is the left ventricular end systolic pressure (volume). Vo and EDV are respectively the rest volume the end diastolic volume.

• septum systolic (diastolic) elastance was calculated starting from systolic (diastolic) septum thickness [9];
• heart rate (HR), QT, PQ, and QRS times were set as the measured value [9];
• inter-ventricular and intra-ventricular delay were set as the data measured [9].
Table 1 shows the data used to set the software simulator in order to reproduce the patient conditions before, within 7 days and within 6 months CRT treatment.

3. Results

Table 2 shows the results obtained by software simulator before, within 7 days and within 6 months CRT treatment. From Suga and Sagawa studies [4,5] it is possible to define the external work as:

$$EW = Pes\cdot(EDV - ESV) \quad (5)$$

where *Pes* can be approximated with the mean aortic pressure [4,5].
Starting from this approximation it is possible estimate the EW value from the data reported in Table 1. Figure 3 shows the trend of the normalized EW evaluated in patients before CRT treatment. In the chart the “calculated” EW values were obtained as previously described using the data presented in Table 1.

Table 1. Data used to set the software simulator in order to reproduce the patient conditions before CRT respectively, within 7 days and within 6 months. (FA indicates atrial fibrillation).

PZ	HR [beats/min]	BP_S [mmHg]	BP_D [mmHg]	AoP [mmHg]	ESV (EDV) [ml]	Inter-ventricular Delay [ms]	Intra-ventricular Delay [ms]	QRS [ms]	QT [ms]	PQ [ms]
	Before CRT									
#1	76	90	60	70	192 (213)	20	70	180	340	180
#2	75	110	60	77	139 (201)	28	50	140	420	220
#3	68	110	70	83	105 (160)	50	60	150	410	180
#4	80	130	85	100	110 (170)	45	60	150	420	FA
#5	70	100	70	80	78 (105)	37	67	120	400	180
#6	64	110	80	90	115(160)	30	50	140	410	160
#7	65	100	60	73	144 (186)	37	50	140	400	160
	Within 7 days since CRT									
#1	75	94	62	73	167 (204)	20	25	120	370	160
#2	75	100	60	73	153 (225)	3	20	180	400	200
#3	66	100	60	73	95 (160)	25	25	130	420	180
#4	75	120	80	93	94 (150)	30	20	130	420	FA
#5	70	100	60	73	52 (80)	10	12	120	400	180
#6	68	123	75	91	105 (155)	14	20	130	400	160
#7	70	105	60	75	127 (177)	20	32	130	410	160
	Within 6 months since CRT									
#1	75	95	60	72	130 (169)	20	20	120	370	160
#2	75	110	70	83	145 (215)	10	20	160	420	180
#3	64	100	60	73	86 (153)	20	25	140	420	180
#4	70	110	70	83	90 (150)	25	20	130	430	FA
#5	80	100	60	73	46 (85)	0	6	120	420	180
#6	70	120	75	90	94 (154)	9	20	130	410	160
#7	70	110	70	83	120 (171)	9	20	130	410	160

Table 2. Simulated data.

PZ	BP_S [mmHg]	BP_D [mmHg]	ESV [ml]	EDV [ml]	EW [Joule/beat]	PE [Joule/beat]	PVA [Joule/beat]
	Before CRT						
#1	90,7	58,3	190,58	213,217	0,062	0,549	0,611
#2	112	59	139,43	200,53	0,847	0,718	1,565
#3	110	71,7	104,2	159,63	0,648	0,52	1,168
#4	130,5	88	110,37	170,84	0,94	0,708	1,648
#5	99	72,2	78,59	106,11	0,225	0,342	0,567
#6	109,7	79,3	115,28	162.5	0,374	0,548	0,922
#7	100.4	62,8	144,19	186,08	0,214	0,459	0,673
	Within 7 days since CRT						
#1	92,8	62	164,31	205,57	0,394	0,732	1,126
#2	101,5	61,5	152,36	225,85	0,949	0,729	1,678
#3	101	61,8	95,95	162,96	0,645	0,4	1,045
#4	119,2	81,9	93,98	151,55	0,744	0,538	1,282
#5	101,9	61,7	51,42	80,88	0,208	0,188	0,396
#6	121,2	76,4	103.13	152.85	0,436	0,372	0,808
#7	102,2	64,4	127,05	177,27	0,47	0,54	1,01
	Within 6 months since CRT						
#1	91,4	60,9	129,96	171,20	0,374	0,566	0,94
#2	109,6	69,7	144,29	216,22	0,772	0,726	1,498
#3	101,4	61.6	85,90	153,3	0,66	0,357	1,017
#4	110	71,8	90,10	151,7	0,721	0,469	1,19
#5	102	61	45,97	85,15	0,393	0,19	0,583
#6	125,8	72,8	94.11	152.72	0,602	0,468	1,070
#7	111,3	72,3	120,86	171,23	0,539	0,578	1,117

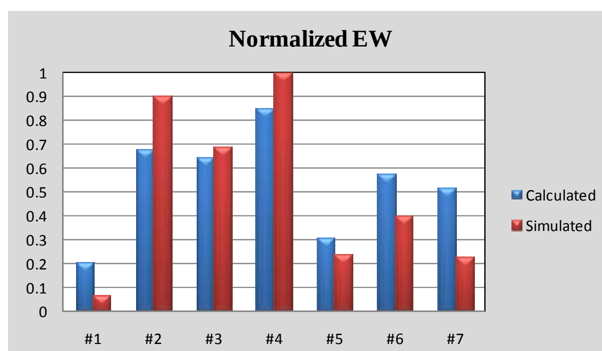

Figure 3. EW evaluated in patients before CRT treatment. Comparison between data obtained starting from Table 1 values (using approximated equation 5) and simulated values.

The simulated EW values were calculated by the simulator as the area within the pressure-volume loop. Figure 4 an 5 show the normalized EW in patients respectively within 7 days and within 6 months since CRT treatment.

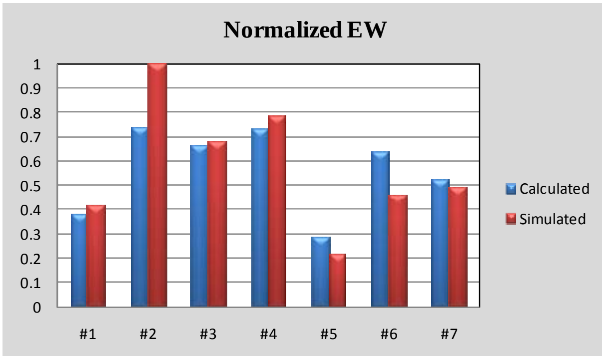

Figure 4. EW evaluated in patients within 7 days since CRT treatment. Comparison between data obtained starting from Table 1 values (using approximated equation 5) and simulated values.

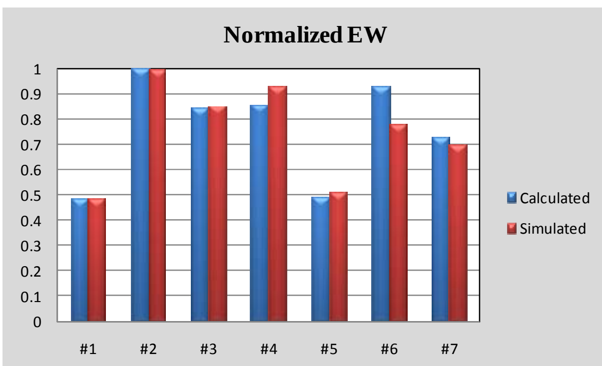

Figure 5. EW evaluated in patients within 6 months since CRT treatment. Comparison between data obtained starting from Table 1 values (using approximated equation 5) and simulated values.

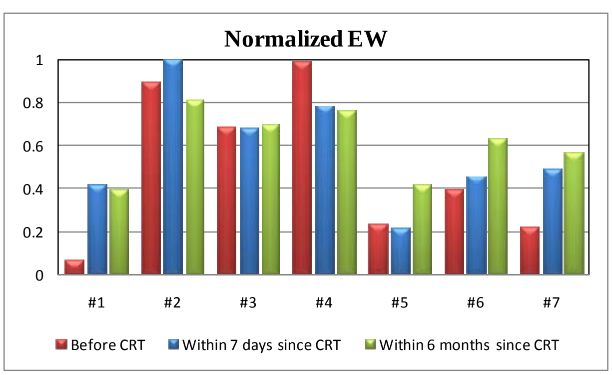

Figure 6. Normalized EW evolution before CRT, within 7 days since CRT and within 6 months since CRT.

In order to evaluate the evolution of EW, PE and PVA before CRT, within 7 days since CRT and within 6 months since CRT [12], for each patient, different simulations were done using as input parameters of the software the data reported in Table 1. Results, reported in Table 2, have been normalized and are shown in Figure 6, 7 and 8.

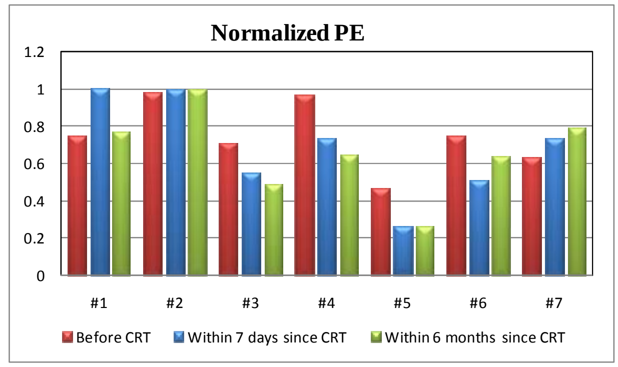

Figure 7. Normalized PE evolution before CRT, within 7 days since CRT and within 6 months since CRT.

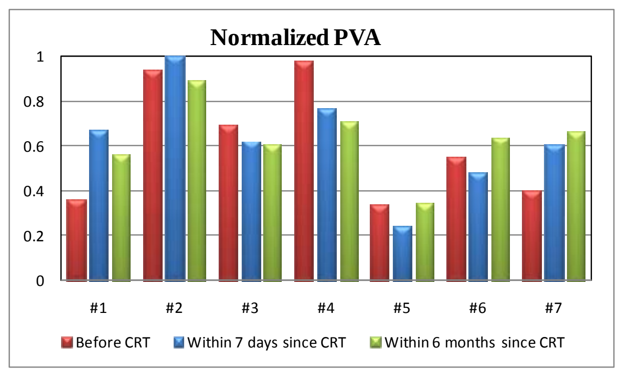

Figure 8. Normalized PVA evolution before CRT, within 7 days since CRT and within 6 months since CRT.

4. Conclusion

The data presented showed that the software simulator of the cardiovascular system, permits to reproduce the haemodynamic parameters in different cardiocirculatory conditions. By comparing the simulated data BP_S, BP_D, ESV and EDV (Table 2) with the corresponding measured data (Table 1), it is possible to observe as the software simulator can reproduce the patient conditions in different situations. Finally Figure 3,4 and 5 show as calculated EW data (in approximated way) can be compared with the corresponding data elaborated by the simulator.

The study suggests that tracking of the energetic balance of the left ventricle and its optimization might be important for the management of the cardiac resynchronization therapy [13,14].

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