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Cardiac resynchronization results in aortic blood flow-associated changes in the arterial load components: basal biomechanical conditions determine the load changes

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***Abstract*- The cardiac resynchronization therapy (CRT) effects on the arterial load components, the mechanisms (i.e. haemodynamic changes-dependence) involved in the load reduction and the factors (i.e. basal load conditions) associated with the load changes after CRT, are to be evaluated. Aims: a) to analyze the potential changes in the arterial load components (peripheral resistances, arterial compliance and impedance) associated with the CRT, b) to determine if the load components changes are associated with variations in haemodynamic variables (pressure, heart rate or blood flow), c) to analyze the relationship between the load components basal state and their changes after CRT. To fulfill these aims cardiac and arterial structural and mechanical parameters were non-invasively evaluated in 8 heart failure patients, pre- and post-CRT (23±8 days). The main results were that short-term after CRT: 1) there were changes in the static and dynamic determinants of the arterial load; 2) the changes in the load components were not associated with heart rate or pressure variations, but with blood flow changes, and 3) the load components basal levels and their changes after CRT were associated.**

I. Introduction

Cardiac resynchronization therapy (CRT) has shown to be an effective treatment for a subgroup of heart failure patients. The main working mechanism of the CRT would be optimizing the left ventricle (LV) mechanical activation pattern and improving its intrinsic functional capability [1]. In addition, taking into account that the LV (pump) and the vascular system (external load) work coupled, it would be expected CRT-associated vascular changes that could contribute to explain the therapy benefits. About this, it was recently shown that, in the long-term, CRT is associated with a reduction in the net arterial load, evaluated by means of the effective arterial elastance (E_a) [2], [3]. However, it is noteworthy that E_a depends on haemodynamic variables and is not a measure of a specific arterial property. In fact, it is an integrative index that takes into account steady and pulsatile load components [4]. Hence, an adequate evaluation of the CRT effects on the arterial load requires considering the effects on its individual components (systemic resistances, SVR; arterial compliance, AC; and aortic characteristic impedance, Zc). *However, as we recently discussed, the CRT effects on the different arterial load components and the mechanisms (i.e. haemodynamic changes-dependence) involved in the load after CRT are to be evaluated* [5].

High basal ventricle-arterial uncoupling levels have shown to be associated with a major probability of response to CRT (evaluated using the quality-of-life score or the LV end systolic volume) [3]. *However, the relationship between the basal (pre-CRT) load components condition, and their potential changes after CRT remains to be analyzed.*

In this context, this work aims were: *a) to analyze the potential changes in the arterial load individual components (peripheral resistances, aortic compliance and characteristic impedance) associated with the CRT, b) to determine if the changes in the load components were associated with variations in the main haemodynamic variables (blood pressure, heart rate and/or blood flow), c) to analyze the relationship between the basal (pre-CRT) conditions of arterial load components and their changes after CRT.* Our hypothesis was that CRT could result in changes in the arterial load static and dynamic components by means of blood flow-related mechanisms, and that the CRT-associated changes in the arterial load would be related with the basal levels of the arterial load determinants.

To comprehend the mechanics that contribute to the CRT effects on the cardiovascular system could be useful to identify parameters to be used in the patient selection and/or in the post-CRT evaluation, as well as to understand why some patients do not respond to CRT despite of they fulfill the standard therapy criteria for selection.

II. Materials and Methods

A. Subjects and study protocol

The study protocol was approved by the ethics committee and the participants gave informed consent. Eight consecutive patients (60±5 years; 5 men) with New York Heart Association (NYHA) functional class III or IV despite

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optimized medical treatment, echocardiographic LV ejection fraction <35% (22±3%, range 16-24%) and QRS duration >120 ms (135±17 ms), scheduled for implantation of a CRT device were included. The subjects were submitted to cardiac and aortic echographic evaluation, performed by a trained physician, before and after (23±8 days) CRT.

B. *Pacemaker implantation*

The right atrial and ventricular leads were positioned conventionally. The LV lead was inserted transvenously via subclavian route. A coronary sinus venogram was obtained. Next, the LV pacing lead was inserted via the coronary sinus using a guiding catheter and positioned in a vein as close as possible to the region of major delay. Leads and CRT device (St. Jude Frontier II; Medtronic INSYNC III and Biotronik Selox SR and Kronos LV) implantation was successful in all patients without major complications [Figure 1].

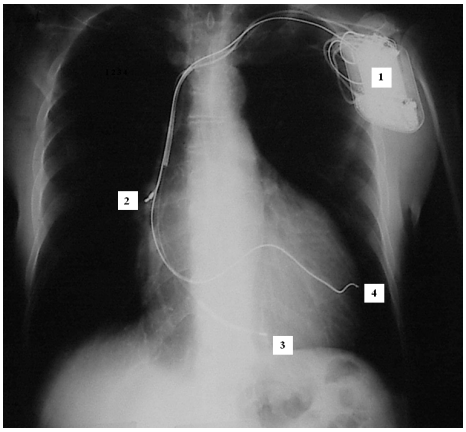

Fig 1. Thoracic radiographic image obtained from a patient in which the pacemaker (1) and the three leads (2, 3 and 4) are visualized.

C. *Structural and functional cardiovascular evaluation*

Standard structural and functional echocardiographic data were quantified and mechanical dissynchrony was evaluated following the American Society of Echocardiography (ASE) expert consensus statements [6].

Aortic biomechanical behavior was characterized analyzing the diameter and flow recordings, and the derived central aortic pressure. To evaluate the diameter the ascending aorta was visualized longitudinally by high resolution B-Mode ultrasound (Hewlett-Packard, Sonos 5500, Andover, MA, USA). Video sequences (10 s) were recorded and analyzed off-line using an automated step-by-step algorithm applied to each digitalized image [7]. The aortic flow waveform (5 beats) was obtained using continuous Doppler. An ensemble average was constructed for the diameter and flow signals. The aortic pressure waveform and systolic and diastolic values were obtained by calibration of the diameter waveform, applying Vermeersch *et al.* [8] method. The method assumes an exponential relationship between pressure and diameter: $p(t) = p_d \exp\left[\alpha\left(\frac{A(t)}{Ad} - 1\right)\right]$ (Eq. 1), $A(t) = \frac{\pi d^2(t)}{4}$ (Eq. 2), $\alpha = \frac{Ad\ In\left(\frac{Ps}{Pd}\right)}{As - Ad}$ (Eq. 3), where p(t), d(t) and A(t) are the pressure, diameter and arterial cross-section waveform as a function of time, Pd and Ps are end diastolic and systolic pressures, Ad and As are end diastolic and systolic arterial cross-section areas, and α the pressure-independent wall stiffness coefficient [8].

Arterial (E_a) and ventricular end systolic (E_{ES}) elastances were calculated: $E_a = \frac{ESP}{SV}$ (Eq. 4), $E_{ES} = \frac{ESP}{(ESV - Vo)}$ (Eq. 5), where ESP is the aortic end systolic pressure, SV is the stroke volume, ESV the LV end systolic volume, and Vo is the LV end-systolic pressure-volume relationship x-axis intercept (assumed negligible compared with ESV) [9].

D. *Arterial load determinants*

The ascending aorta local properties were quantified in terms of the Zc and the cross-sectional AC [10]. The Zc was calculated in the early systole from the instantaneous ratio of the pressure and flow upstroke above end-diastolic levels (time domain method) [10]. The AC was calculated as: $AC = \frac{(SD - DD)}{(cSBP - cDBP)}$. (Eq. 6), where, SD and DD are the systolic and diastolic aorta internal diameters, respectively. The SVR was quantified as [10]: $SVR = \frac{MBP}{CO}$ (Eq. 7), where MBP and CO are the mean pressure and cardiac output.

E. *Statistical analysis*

Data obtained pre- and post-CRT were compared using Student t-test. Linear regression analysis was used to determine association between: a) changes in pressure, heart rate or blood flow, and those in E_A components, and b) changes in haemodynamic and load components, as a function of their basal levels. A $P<0.05$ indicated significant statistical differences.

III. RESULTS

After CRT there were beneficial changes in the structural and functional cardiac parameters. There were no changes in blood pressure or heart rate after CRT [Table I]. CRT determined changes in the arterial load determinants: SVR and Zc reduction and AC increase [Table II].

Figure 2 shows the relationships between percentual changes in aortic peak flow and those in arterial load components. The higher the blood flow increase, the higher the SVR and Zc reduction and the AC increase.

Figure 3 shows the relationship between the basal biomechanical conditions and the biomechanical changes after CRT. Note that a worst pre-CRT basal level (i.e. higher SVR or Zc, or lesser AC) was associated with a higher CRT-associated change in the corresponding load determinant.

Table I. Haemodynamic and cardiac parameters.

	Pre-CRT	Post-CRT	
Heart rate [beats/min]	63 ± 6	67 ± 6	
Cardiac output [l/min]	3.0 ± 0.9	5.1 ± 1.3	*
Aortic peak blood flow [ml/s]	609 ± 14	750 ± 31	*
Mean aortic diameter [mm]	28.6 ± 1.5	29.4 ± 1.6	*
Peripheral SBP [mmHg]	116 ± 10	106 ± 9	
Peripheral DBP [mmHg]	68 ± 6	62 ± 6	
Peripheral PP [mmHg]	48 ± 7	45 ± 4	
Central SBP [mmHg]	99 ± 10	94 ± 9	
Central PP [mmHg]	30 ± 9	33 ± 6	
LV end diastolic volume [ml]	232 ± 55	202 ± 52	*
LV end systolic volume [ml]	184 ± 47	127 ± 45	*
LV ejection fraction [%]	22.0 ± 3.2	36.8 ± 11.0	*
Inter-ventricular septum [mm]	9.2 ± 0.7	8.7 ± 1.7	
LV posterior wall [mm]	8.4 ± 1.5	8.3 ± 1.5	
Left atrium [cm^2]	30.2 ± 7.5	25.3 ± 10.3	
LV end systolic elastance [mmHg/ml]	0.60 ± 0.17	0.83 ± 0.25	

MV±SD. SBP, DBP, PP: systolic, diastolic and pulse blood pressure, respectively. LV: left ventricle. CRT: cardiac resynchronization therapy.
*$p < 0.05$ with respect to Pre-CRT condition.

Table II. Arterial elastance and arterial load determinants.

	Pre-CRT	Post-CRT	
Ea [mmHg/ml]	2.43 ± 0.97	1.52 ± 0.77	*
SVR [mmHg.min/s]	32.3 ± 14.5	15.34 ± 6.36	*
Aortic compliance [10^{-1} mm/mmHg]	1.33 ± 0.18	1.56 ± 0.16	*
Aortic Zc [mmHg/ml]	1.61 ± 0.20	1.43 ± 0.14	*

MV±SD. Ea: arterial elastance. SVR: systemic vascular resistances. Zc: characteristic impedance. CRT: cardiac resynchronization therapy.
*$p < 0.05$ with respect to Pre-CRT condition.

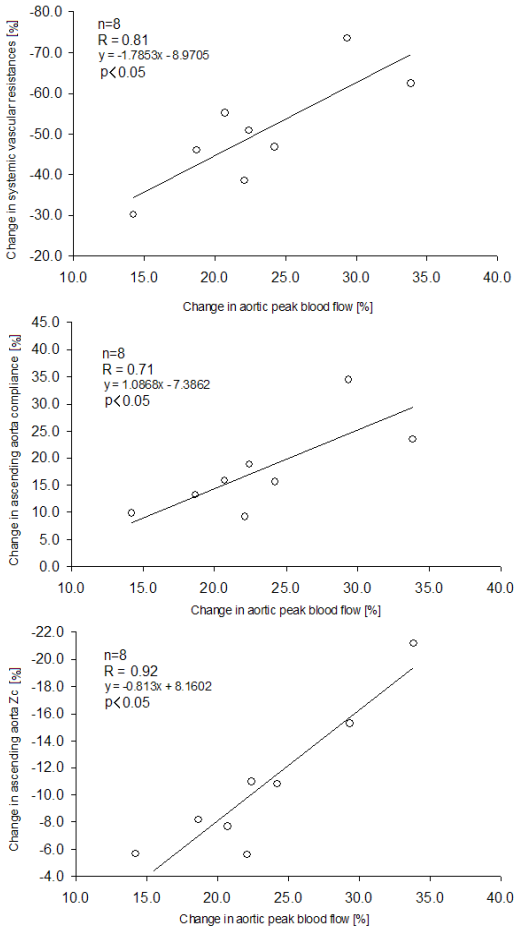

Fig 2. Relationship between CRT-associated changes in aortic blood flow and changes in the arterial load determinants.

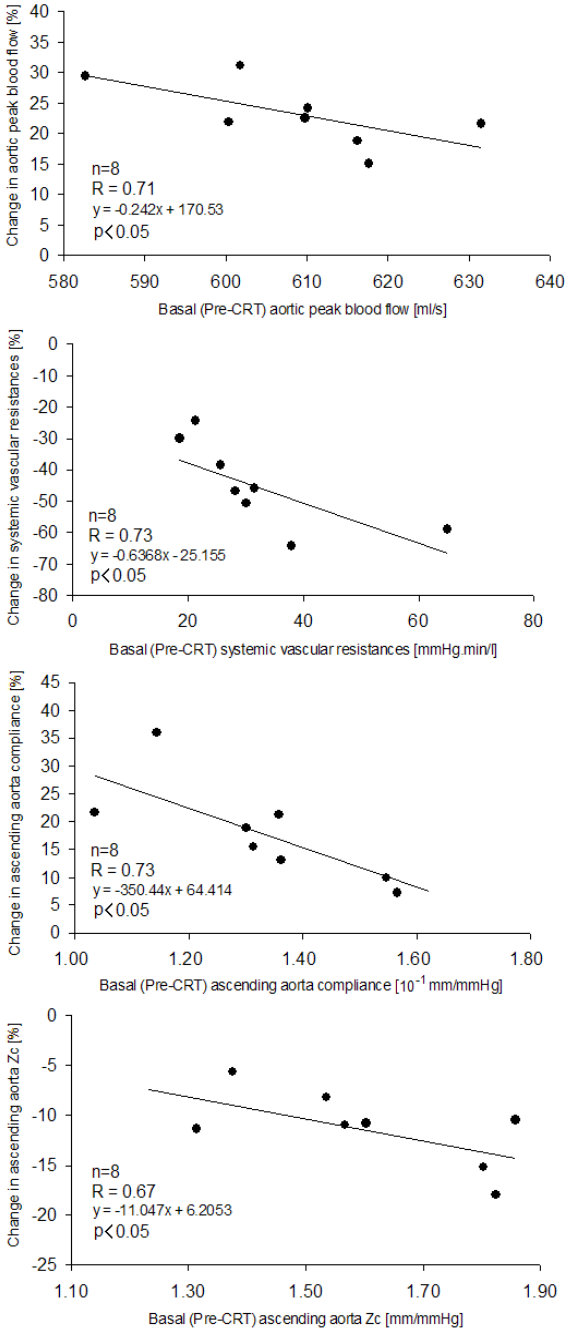

Fig 3. Relationship between CRT-associated changes in the arterial load determinants and their basal (pre-CRT) levels.

IV. DISCUSSION

This work main findings were:

a) Short-term after CRT there were changes in the static and dynamic determinants of the net arterial load.

b) The changes in the arterial load determinants were not associated with heart rate or blood pressure variations (isobaric and isofrequency conditions), but with aortic blood flow changes.

c) The basal biomechanical conditions and their changes after CRT were associated. The worse the basal conditions the major their changes (improvement).

An adequate evaluation and interpretation of the net arterial load (and it changes) requires analyzing, separately its individual components [4] [9]. In this work, to analyze the individual components contribution to the net arterial load, it was deconstructed. To this end, the vascular system biomechanical and functional behavior was modeled as a three-element Windkessel model, consisting in proximal impedance to pulsatile flow (aortic Zc) upstream to SVR and AC arranged in parallel [10].

After a mean time of 23 days, in addition to the expected cardiac beneficial effects, CRT resulted in al reduction in the SVR and in the aortic Zc and stiffness [Table II]. The combined effects of CRT on arterial load determinants are of particular importance in a disease in which an increase in the arterial system conduit and buffering functions, may contribute to improve regional and/or global blood flow. Even more, considering that in heart failure the net arterial load is frequently elevated, which *per se* represents a detrimental factor for the failing heart.

Our work was not designed to investigate the bio-molecular mechanisms explaining the geometrical (i.e. aortic diameter increase) [Table 1] and biomechanical findings (i.e. Zc reduction) [Table 2], but our results suggest that variations in the aortic blood flow (probably through smooth muscle tone modifications) could have contributed. First, the geometrical (i.e. aortic and peripheral dilatation) and biomechanical changes (isobaric arterial stiffness reduction) agree with a vascular smooth muscle relaxation pattern [11]. Second, the changes in the arterial load determinants were associated with the changes in aortic blood flow levels [Figure 2]. It is known that an increase in blood flow increases the shear stress exerted on the arterial wall endothelial layer, and consequently determines a flow-mediated smooth muscle relaxation, that would result in arterial dilatation and stiffness reduction. Related with this, it has been shown that the reestablishment or improvement of altered haemodynamic conditions could determine humoral changes (i.e. reduction in the activation of Rennin-Angiotensin system), part of a "virtuous circle" of beneficial changes in the cardiovascular biomechanics, that could modify the vascular tone, with or without dependence on the endothelium [12]. Even more, it is noteworthy that CRT has shown to improve the sympatho-vagal balance, with a reduction in peripheral sympathetic nerve activity and improvement in cardiac sympathetic activity [13]. These findings could contribute to the understanding of our results and add support to the proposed existence of changes in muscle tone on their basis.

Finally, our results showed that the CRT-associated changes in arterial load determinants could be associated with their basal (pre-CRT) state [Figure 3]. Then, those patients with worse biomechanical cardiovascular conditions would have a major improvement (major benefits) in the biomechanical parameters after CRT. This agrees with Zanon et al. [3] who found that those patients with worse ventricle-arterial coupling conditions would have a major probability to respond to CRT.

V. CONCLUSION

We found that CRT resulted in changes in the arterial load components, associated with aortic blood flow variations and basal load conditions. Then, pre and post CRT vascular biomechanical evaluation could contribute to the patients selection, to understand the CRT results in a particular patient and/or to guide therapeutic strategies/objectives in non-responders patients. Future large scale works would be necessary to add support to our findings.

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