Ventricular-arterial coupling in patients with heart failure treated with cardiac resynchronization therapy: may we predict the long-term clinical response?

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Objective To evaluate the effects of cardiac resynchronization therapy (CRT) on ventricular-arterial coupling (VAC) in patients with refractory congestive heart failure (HF), left bundle branch block, and sinus rhythm.

Background The ratio between arterial elastance (Ea) and left ventricular end-systolic elastance (Ees), the so-called VAC, defines the efficiency of the myocardium in pumping blood.

Methods Seventy-eight patients were studied with echocardiography before CRT, and 1 year later. End-systolic elastance was calculated according to the method of Chen. Arterial elastance (ratio of the systolic pressure to the stroke volume), end-systolic volume (ESV), and quality of life (QoL) (Minnesota Living with Heart Failure Questionnaire) were assessed at the baseline and after 1 year. Patients with a reduction >15% of ESV or a decrease >33% in QoL score were considered responders to CRT.

Results QRS duration and interventricular delay were significantly reduced with CRT compared with baseline (156 ± 2 vs. 195 ± 3 ms, P < 0.001; and 25 ± 2 vs. 55 ± 3 ms, P < 0.001, respectively). Arterial elastance/Ees decreased significantly on CRT (2.47 ± 1.48 vs. 1.41 ± 0.87, P < 0.0001). The lowering of Ea/Ees was congruent to a decrease in intraventricular delay (83.1 ± 55.7 vs. 28.4 ± 49.5 ms, P < 0.0001) and an increase in ejection fraction (26 ± 6.3 vs. 36.9 ± 8.0%, P < 0.0001). Responders to CRT were 74 and 71% of the overall patient population, considering as endpoint QoL or ESV, respectively. The analysis of VAC showed a baseline cut-off value of 2, above which 88% and 69% of patients responded to CRT, considering as endpoint QoL or ESV, respectively.

Conclusions The non-invasive assessment of VAC may be proposed as an immediate, easy, and optimal tool for quantifying the effect of CRT in patients with HF.

Introduction

The myocardial pump function and the performance of the entire cardiovascular system are determined by preload, afterload, and contractility.1 The best clinical measure of preload is the end-diastolic volume of the heart. From a clinical point of view, afterload can be estimated by measuring arterial blood pressure. In contrast, contractility is the most difficult parameter to estimate in clinical practice, since this would require invasive measurements of left ventricular (LV) pressure–volume (PV) loops.

Left ventricular-arterial coupling (VAC) describes the ratio between arterial elastance (Ea) and ventricular end-systolic elastance (Ees). The mathematical ratio between these two elastances, the so-called VAC, defines the efficiency of the myocardium in pumping blood through the arteries, which is the desired result of heart contraction. From a mechanical point of view, the net flow and pressure output of a pump depend on three interacting factors: the intrinsic properties, such as power and stroke capacity, the mass or inertia of the fluid to be ejected, and the capacitance—the resistance and inertial properties of the system receiving the ejected material.2 In the cardiovascular system, the left ventricle is obviously the pump, the blood is the fluid, and the arteries constitute the system receiving the ejected blood. As blood viscosity is the only constant factor in this energy transfer, the best performance of the cardiovascular system is determined by the best fit...
between the factors characterizing the ventricles and the arteries. The intrinsic properties of the myocardium are strictly related to the end-systolic and -diastolic elastances, which is the consequence of maximal and minimal chamber stiffness. The blood per se determines the inertial load, depending on the mass in the myocardium at the end of the diastole. The arterial load depends on the dimensions of the proximal vessels, the mean vascular resistance, and the pulsatile components related to compliance and wave reflections. The result of the complex interactions among these factors is expressed by the relationship between Ees and Ea, which describes the mechanical pumping function. As the standard methods of evaluating Ees formerly involved invasive techniques, the assessment of VAC was not feasible in clinical practice. Efforts have been made to assess VAC non-invasively, and a method has recently been developed and validated to estimate LV Ees in humans from non-invasive arm-cuff blood pressure, echo-Doppler echocardiography, and ECG, thus making VAC assessment feasible in clinical practice (see Appendix).

**Aim of the study**

The aim of the study was to prospectively evaluate the long-term effects of cardiac resynchronization therapy (CRT) on VAC, in patients with refractory congestive heart failure (HF), left bundle branch block, and sinus rhythm.

**Methods**

The study had the approval of the Ethics Committee and informed consent to participate in the investigation was obtained from each patient before enrolment.

All patients underwent a clinical examination and echocardiographic evaluation before CRT and after 1 year of follow-up (FU). Echocardiography was performed by means of a commercially available imaging system (General Electric Vivid Five GE Medical System, Milwaukee, WI, USA) equipped with a 2.5–3.6 MHz probe, with the patient in the left lateral position. The LV volumes and ejection fraction were measured by the biplane Simpson’s method. Left ventricular Ees was calculated according to the method proposed by Chen et al. Arterial elastance was measured as the ratio of the systolic pressure to the stroke volume (SV). The latter was obtained by subtracting the LV end-systolic volume (ESV) from the LV end-diastolic volume. The cardiac output was calculated by multiplying the by the heart rate as measured during echocardiography. QRS duration was also collected. Quality of life (QoL) was assessed by the Minnesota Living with Heart Failure Questionnaire. In the first 20 patients, the inter-observer and intra-observer variability of EDV, ESV, EF, and SV was tested to evaluate reproducibility of the data. The inter-observer variability was <4.2% and the intra-observer variability <3.4%.

Each patient was kept at rest for at least half an hour before measuring any echo parameter.
Statistical analysis

All data are expressed as mean ± SD. An intra-patient analysis was performed, and the data were compared by means of paired Student’s t-test. A P-value of ≤0.05 was regarded as significant.

Results

Seventy-eight patients (61 male) entered the study. The mean age was 72 ± 9 years (range 44–88); 42% were affected by ischaemic cardiomyopathy. The mean NYHA class was 3.1 ± 0.6, the Minnesota quality life score was 62 ± 12, and the mean EF was 26 ± 7%. Ninety-five percent of patients were on treatment with ACE-inhibitors, 61% with β-blockers and 67% with spironolactone. At the end of the study, 94 and 63% of the patients were treated with ACE-inhibitors and beta-blockers, respectively.

All patients were successfully implanted with CRT devices, defibrillators (34 patients, 44%) or pacemakers depending on the indication. The target veins into which the LV lead was inserted were: basal posterior–lateral in 6 patients (8%), the indication. The target veins into which the LV lead was inserted were: basal posterior–lateral in 6 patients (8%), middle lateral in 45 (58%), and lateral-apical in 14 (18%).

The mean time of the procedure was 85 ± 34 min, of which 9 ± 10 min were required for LV lead positioning and 17 ± 12 min for fluoroscopy.

QRS duration and interventricular delay were significantly reduced with CRT: 195 ± 32 vs. 156 ± 17 ms, P < 0.001, and 55 ± 33 vs. 25 ± 19 ms, P < 0.001, respectively.

Table 1 summarizes the echo-Doppler parameters and indexes 1 year after CRT, in comparison with the baseline. On CRT, all values significantly improved.

According to the improvement of the QoL score, 74% of the overall patient population responded to CRT. According to the improvement of ESV, 71% of patients were classified as responders. The analysis of VAC showed a baseline cut-off value of 2, above which at least 88 and 69% of patients responded to CRT, considering as endpoint QoL or ESV, respectively (Figure 1A and B).

A subanalysis of ischaemic and non-ischaemic patients is showed in Figures 2 and 3. At least 75% of all non-ischaemic patients (Figure 2A) are responders to CRT independently of VAC and the percentage becomes very high when VAC ≤ 2. When the endpoint is ESV (Figure 2B) responders range around 50% if VAC ≤ 2, but they rise to 81 and 100% with higher values of VAC.

In the case of ischaemic patients, on average 75% responded to CRT when VAC was >2 (range 69–100%), according to the QoL criterion (Figure 3A). When ESV is the endpoint, responders are ~50% if VAC < 4, rising up to 100% when VAC > 4 (Figure 3B).

Discussion

Our study, for the first time, evaluated the long-term effects of CRT on VAC in patients with HF and sinus rhythm. The main result is the positive effect that CRT has on VAC and, moreover, the potential of VAC for identifying patients responder to this therapy.

Ea/Ees ratio in normal subjects is generally between 0.7 and 1.0: the range of optimal function. In patients with congestive HF, this ratio typically rises to as high as 4.0, owing to the relative decline in ventricular contractile function (lower Ees) and concomitant rise in Ea. Such coupling is detrimental from the standpoint of ventricular performance and metabolic efficiency.

In their non-invasive analysis, Chen et al. demonstrated the feasibility of using a single PV point, timed at the onset of ejection (end of the isovolumic period). This method requires five accurately measured parameters obtained from non-invasive arm-cuff blood pressures, echo-Doppler, and the electrocardiogram. Correlations between measured and estimated VAC, both at rest and with acute contractility change(s), were generally good, and the reproducibility of measurements over time proved reasonable, making this method applicable in clinical practice.

The proposed method offers a new tool for a complete estimation of the cardiac network with regard to the final result of the heart: the efficiency of the mechanical pumping function. This method is relatively fast, requiring the evaluation of few parameters and is based on the standard parameters evaluated by echocardiography, plus blood pressure. Ventricular-arterial coupling is calculated immediately by means of a software formula, and the result is a single index that summarizes the mechanical efficiency of the myocardium in pumping blood.

Cardiac resynchronization therapy has recently been introduced to improve haemodynamics and symptoms in patients with advanced HF. Much of the information regarding the clinical benefits of CRT derives from clinical trials, which together demonstrate that CRT improves symptoms and exercise tolerance in medically treated patients with persistent, moderate-to-severe symptoms of HF, poor LV function, and intraventricular conduction delay. Nevertheless, the identification of responders to CRT is still matter of debate. The measurement of VAC

Table 1. The echo-Doppler parameters and indexes 1 year after CRT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before CRT_Baseline</th>
<th>CRT on_1 Year</th>
<th>P 1 Year vs. baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-diastolic volume index (mL/mq)</td>
<td>157.76 ± 47.88</td>
<td>139.90 ± 51.44</td>
<td>0.0002</td>
</tr>
<tr>
<td>End-systolic volume index (mL/mq)</td>
<td>118.21 ± 41.82</td>
<td>88.95 ± 40.43</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EF (%)</td>
<td>25.96 ± 6.30</td>
<td>38.15 ± 8.20</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke volume (mL/b)</td>
<td>49.71 ± 19.23</td>
<td>66.09 ± 19.37</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ea (mmHg/mL)</td>
<td>2.74 ± 1.11</td>
<td>2.02 ± 0.59</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ees (mmHg/mL/mq)</td>
<td>1.25 ± 0.47</td>
<td>1.97 ± 1.09</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ea/Ees</td>
<td>2.47 ± 1.48</td>
<td>1.31 ± 0.71</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Intrav.Delay (ms)</td>
<td>83.09 ± 55.72</td>
<td>23.00 ± 46.58</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>QoL score</td>
<td>58 ± 13</td>
<td>34 ± 8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
not only may allow to estimate the baseline condition and the improvement of the patient submitted to therapeutic actions, but it probably may be of help in the selection of responders. Of course, a larger scale, prospective and long-term trial should be designed for this purpose.

To define responders and non-responders, we assumed both a clinical criterion based on QoL and a functional parameter of remodelling based on ESV. This is in accordance with the objectives of standard clinical practice. Although different approaches have been proposed to select patients for CRT, there is no unifying definition of responders. Our proposal is not only coherent with clinical practice, but also coherent with the results of large-scale trials like MUSTIC and MIRACLE, which first validated CRT on the basis of clinical response. In these two trials, CRT failed to improve clinical status in up to 30% of patients, with a corresponding success rate of 70%. Similarly, we obtained a 74% response with the QoL criterion and 71% with ESV. When ESV

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**Overall Patient Population**

**Figure 1** Patients responding to CRT in the overall population, as a function of the basal value of VAC: a cut-off value of 2 may identify 88% of responders to CRT as evaluated through the QoL and 69% of responders as defined through ESV.

**Non-Ischaemic Patients**

**Figure 2** Patients responding to CRT in the non-ischaemic group, as a function of the basal value of VAC: a cut-off value of 1.5 may identify 89% of responders to CRT as evaluated through the QoL and a cut-off value of 2 may identify 81% of responders defined through ESV.

**Ischaemic Patients**

**Figure 3** Patients responding to CRT in the ischaemic group, as a function of the basal value of VAC: a cut-off value of 2 may identify 69% of patients responders to CRT as evaluated through the QoL and a cut-off value of 4 may identify 100% of responders defined through ESV. Responders range to ~50% when VAC < 4, if ESV is considered the endpoint.
is considered the reference parameter to evaluate responders, fewer patients reach the cut-off value of 15% improvement. This may suggest that some HF patients can be clinically responders even if there is no cardiac remodelling as evaluated through ESV.

Differences are also evident between ischaemic and non-ischaemic patients. Probably, ischaemic patients have non-homogeneous myocardial tissue, and pacing may result in a different effectiveness in each patient. Non-ischaemic patients have a dilated, but homogeneous tissue and we may expect a higher and more reproducible effectiveness of pacing for resynchronization of the LV wall.

The recently published study of Steendijk et al. shows improved VAC and improved mechanical efficiency with CRT: these haemodynamic findings are consistent with the observed improvements in clinical and functional status. Our study for the first time showed the long-term improvements of VAC with CRT. In addition, we underlined the potential of this parameter to select responders to this electrical therapy and to assess the cardiac performance over the time. It could be undertaken in any institution without additional costs and time, since echocardiography must be performed in each patient before and after implantation of a CRT device.

Echocardiography plays an evolving and important role in the care of HF patients treated with biventricular pacing, or CRT. However, no ideal approach has yet been found so we advise that the dyssynchrony reporting should not include a recommendation whether a patient should undergo CRT, as this should be a clinical decision on a case-by-case basis for these borderline or challenging cases. Therefore, we think that VAC itself may represent a reliable index of the complex effects of pumping blood.

Study limitations
We only used non-invasive methods to estimate all cardiovascular parameters used in the study.

Conclusions
Cardiac resynchronization therapy increases Ees, which is a main determinant of LV systolic performance, reduces Ea, and improves VAC. The improvement in VAC may suggest an improved mechanical efficiency of the myocardium in pumping blood.

The selection of responders to CRT on the basis of the basal value of VAC is promising, but it should be further investigated in a prospective, large-scale, and long-term trial.

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Conflict of interest: In connection with the submitted article, there are no financial associations that might pose a conflict of interest.

Appendix
The formula proposed and validated by Chen for the estimation of Ees is reported below:

\[ Ees = \frac{[Pd - (ENd \times Ps \times 0.9)] / [SV \times End]}{C0} \]

where Pd is the brachial diastolic pressure, Ps the brachial systolic pressure, SV the stroke volume, and ENd the predicted normalized LV elastance at the onset of ejection. The estimate is described by the following formula:

\[ ENd = 0.0275 - 0.165 \times EF + 0.3656 \times (Pd / Pes) + 0.515 \times ENd(\text{avg}) \]

where Pes = Ps \times 0.9 and EF is the basal ejection fraction.

\[ ENd(\text{avg}) = \frac{0.35695 - 7.2266 \times TNd + 74.249 \times TNd^2 - 307.39 \times TNd^3}{-684.54 \times TNd^4 - 856.92 \times TNd^5 + 571.95 \times TNd^6 - 159.1 \times TNd^7} \]

where TNd was determined by the ratio of pre-ejection period (R-wave - flow-onset) to total systolic period (R-wave – end-flow), with the time at onset and termination of flow defined non-invasively from the aortic-Doppler waveform.

Once these formulas are implemented on an automatic algorithm, the determination of non-invasive parameters like Ps, Pd, SV, EF, and TNd allows the immediate calculation.

References


