Prediction of Cardiac Resynchronization Therapy Response by Means of 3D Trajectory Assessment of the Coronary Sinus Lead

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Abstract

Cardiac resynchronization therapy (CRT) is an effective treatment for chronic symptomatic systolic heart failure with cardiac dyssynchrony, but about one-third of patients do not respond favorably to the therapy. We tested the hypothesis that changes in the movements of coronary sinus (CS) electrode tip during the cardiac cycle, induced by the start of biventricular pacing could be related to resynchronization process and predictive of CRT response. In 13 CHF patients submitted to CRT implant, a previously validated method for CS lead tracking throughout cardiac cycles in 3D was applied, before (t_{-1}) and immediately after (t_0) the turn-on of biventricular pacing. The variations in several parameters describing CS lead's 3D trajectory at t_0 with respect to t_{-1} were compared between echo responder and non-responder patients. Preliminary data showed a significantly more circular and smooth trajectory as an immediate result of the CRT turning-on in the echo-responder group. Therefore, 3D trajectories could describe features of resynchronization start-up in CRT recipients and could help to understand the reasons of therapy failure in non-responder patients.

1. Introduction

In the large population of patients with drug-refractory heart failure, chronic symptomatic systolic heart failure and cardiac dyssynchrony, cardiac resynchronization therapy (CRT) has shown impressive results [1]. The benefits of CRT include improvements in left ventricular (LV) haemodynamic, reduction of LV volumes and dyssynchrony, as well as improvements in clinical symptoms [2]. Several studies demonstrated that CRT lowers mortality [3] and improves both exercise tolerance and quality of life [4]. These benefits depend on LV "reverse remodelling", which consists of an improvement of systolic function and of a reduction of LV volumes [5].

However, about one-third of patients do not respond to CRTs, and up to 40-50% of cases do not demonstrate any improvement in LV function on echocardiography [4,6].

The reasons of failure are still unclear and may be related to various factors determining electrical and mechanical features of biventricular pacing and could be a turning point towards different kinds of accomplishment of CRT. Among these factors we hypothesize coronary sinus (CS) lead-vein-myocardium interactions both at implant and in the long-term, such as a suboptimal or non-continuous stimulation, an unsuitable or unstable location in the CS branch, and an ill-defined incapacity to change myocardial mechanics. Very little information exists about this issue.

In this study, we evaluated the acute effects of biventricular pacing at implant applying a recently validated new method based on standard chest fluoroscopy imaging for reconstructing the electrode tip three-dimensional trajectory throughout cardiac cycles [7]. We investigated the hypothesis that acute modifications of the CS lead tip trajectory induced by CRT may offer clues about the underlying resynchronization process. Therefore, studying the CS lead trajectory before and immediately after the turning-on of biventricular pacing at the implant could make it possible to derive prognostic information about long-term responses to CRT.

2. Methods

2.1. Data analysis

To evaluate the CS lead dynamic position and movements we processed the x-ray fluoroscopy sequences acquired immediately before (t_{-1}) and just after (t_0) the turning-on of biventricular pacing.

A previously developed and validated method for automated CS lead tracking based on region matching techniques was applied (figure 1) [7] to obtain the two trajectories at t_{-1} and t_0.

These CS lead's trajectories were analysed by computing several parameters describing their shape and 3D position.

For each trajectory, the extracted parameters were:

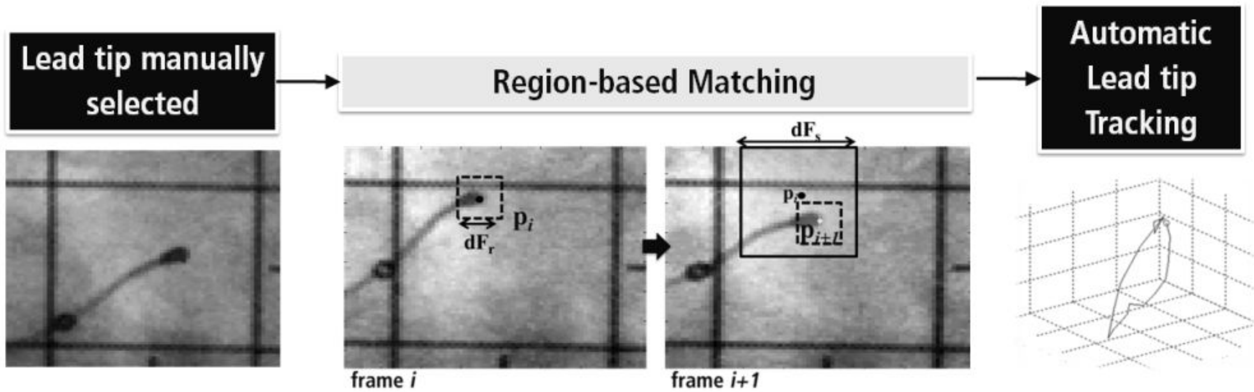

Figure 1. Schematic flowchart of the previously developed and validated method for automated CS lead tracking based on region matching techniques (see [7] for details).

- its length (l) and its 3D surface area (A);
- the mean curvature (K_m);
- the three singular vectors highlighting the three principal directions of the trajectory and the corresponding singular values (S_1,S_2,S_3);
- the ratio between the two main singular values S_1/S_2;
- the trajectory eccentricity computed as: $$ecc = \frac{\sqrt{S_1^2+S_2^2}}{S_1};$$
- the circularity index computed as: $$csi = \frac{4\pi A}{l^2};$$
- the three rotation angles (α, β, γ) of the coordinate system given by the three singular vectors.

The changes of these parameters at t_0 with respect to t_{-1} were also computed.

In addition, we calculated the:

- Euclidean distance between the trajectory barycentre at t_0 and t_{-1} (d).

Patients were classified as echo-responder (R) or non-responders (NR), based on echocardiographic examinations at 6±3 months follow-up. All the parameters, describing the 3D position of CS lead and its trajectory throughout the cardiac cycle at t_{-1} and t_0, were compared between R and NR by applying the Mann-Whitney U test.

1.2. Patients

For enrolment into this single-center prospective study, consecutive patients with New York Heart Association (NYHA) functional class III or IV heart failure despite optimal medical therapy, echocardiographic LV ejection fraction (EF) <35%, and QRS duration >120 ms, in a stable hemodynamic situation, who were scheduled for implantation of a CRT device, were evaluated.

In addition, inclusion criteria, to be verified just at the x-rays data acquisition, were: stable hemodynamic state with no changes in BP; stable heart rate between 60 and 80 beats per minute with no more than 1 premature beat (either supra- or ventricular) every sequence of at least 5 regular beats; stable respiratory rate not exceeding 20 breaths per minute. Before CRT implantation, all patients underwent clinical status evaluation as well as transthoracic echocardiography.

Following these indications, 13 consecutive patients (12 men, age: 72±8 years, EF: 30±4 %, end systolic volume (ESV): 166±43 ml, NYHA: 3.0±0.5) were enrolled.

The protocol was approved by the Area Vasta Romagna ethics committee, and all patients gave informed consent.

At 6±3 months follow-up, patients underwent an examination including echocardiography to evaluate CRT response.

2. Results

At follow-up, considering an absolute increase of 5 points in EF and a relative decrease of 15% in ESV as cutoff indices of echo-response, 6 patients were echo-responders (R) (6 males, age: 72±7 years, ΔEF%: 15±6.5, ΔESV%: -37±28, ΔNYHA: -1.7±0.5), 7 were not (NR) (6 males, 71±10 years, ΔEF%: -0.7±6, ΔESV%: 26±33, ΔNYHA: -0.7±0.5).

Two typical examples of the computed trajectories at t_0 and t_{-1} in one R and one NR, are shown in figure 2.

All the results obtained in the two groups of patients are summarized in table 1.

No significant difference was found in the trajectory parameters comparing all the values at t_0 with respect to t_{-1}.

On the contrary, several significant differences were found between the two groups when comparing the variation of each parameter (median value [25%-75%]) from t_{-1} to t_0. In particular, the variations of the ratio between the two main axes of the trajectories ($p<0.001$),

Table 1. Computed CS lead trajectory parameters (median [25%-75%] in the responders (R) and non-responders (NR) patients.

	l (mm)	A (mm^2)	K_m	S_1/S_2	ecc	csi	α (°)	β (°)	γ (°)	d (mm)
R										
t_{-1}	6.6 [6.2-7.8]$^{\Delta}$	1.3 [0.7-1.6]	0.65 [0.64-0.67]$^{\Delta}$	4.1 [3.5-5.6]$^{\Delta}$	0.97 [0.96-0.98]$^{\Delta}$	0.33 [0.22-0.38]	96 [53-128]$^{\diamond}$	116 [105-140]$^{\diamond}$	83 [49-128]	
t_0	6.0 [4.3-8.2]$^{\Delta}$	1.4 [0.9-3.7]	0.55 [0.45-0.59]$^{\S\Delta}$	1.6 [1.4-2.2]$^{\S\Delta}$	0.80 [0.72-0.88]$^{\S\Delta}$	0.39 [0.21-0.56]§	126 [54-144]	97 [94-114]	57 [37-118]	
diff	-0.6 [-1.7-0.01]	0.2 [0-2.2]	-0.12 [-0.2-0.06]*	-2.4 [-3.4 - -1.7] *	-0.18 [-0.23 - -0.09]*	0.09 [-0.17 – 0.28]	9 [-3 - 28]*	-10 [-48 - 8]*	-17 [-31 - 11]	3.0 [1.8-5.6]
NR										
t_{-1}	6.0 [4.3-9.1]	1.0 [0.5-2.7]	0.60 [0.57-0.64]	3.8 [3.0-4.0]	0.96 [0.94-0.97]	0.31 [0.38-0.33]$^{\sim}$	133 [128-145]$^{\diamond}$	80 [55-89]$^{\diamond\sim}$	57 [38-82]	
t_0	4.4 [4.3-6.9]	1.2 [0.4-3.9]	0.64 [0.55-0.69]§	4.2 [2.8-7.7]§	0.97 [0.93-0.99]§	0.18 [0.10-0.26]$^{\S\sim}$	108 [51-137]	93 [84-109]$^{\sim}$	65 [39-141]	
diff	-0.2 [-2.0-0.01]	-0.1 [-0.2-1.2]	0.05 [-0.06-0.09]*	0.47 [-0.23-3.24]*	0.01 [0-0.05]*	-0.08 [-0.24 - -0.05]	-20 [-78 - -8]*	23 [-3 - 44]*	-8 [-19 - 98]	4.0 [2.2-7.5]

MANN WHITNEY U TEST: $^{\diamond}p<0.05$ at t_{-1} R vs NR; $^{\S}p<0.05$ at t_0 R vs NR; $^{*}p<0.01$ diff R vs diff NR; $^{\Delta}p<0.05$ R at t_{-1} vs t_0; $^{\sim}p<0.05$ NR at t_{-1} vs t_0;

their per cent difference (R: 57.5%±11% vs NR: -25.2%±44.7%; $p<0.001$), the changes in the eccentricity ($p<0.001$) and in the mean curvature ($p<0.008$) resulted statistically different between the two groups. It is worth to note that no significant differences were found in the same trajectory parameters between R and NR groups at t_{-1}. The differences consistently indicate a more circular and smooth trajectory as an acute effect of the CRT turning-on in the R group, which is absent in the NR group.

The changes of two angles α and β at t_0 and t_{-1} were also found statistically different.

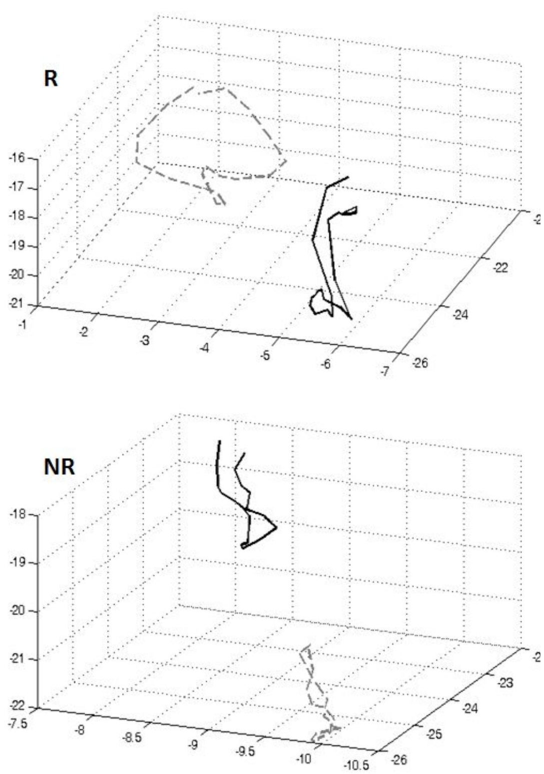

Figure 2. Examples of trajectories obtained in an echo-responder patient (R, top panel) and in a non-responder patient (NR, bottom panel) at t_{-1} (black solid line) and t_0 (gray dotted line).

3. Discussion and conclusions

To our knowledge, this is the first study using the new method for CS lead tip trajectory reconstruction to assess the correlation between acute trajectory modifications induced by CRT and the response to treatment. The striking result of our preliminar analysis is that some of the trajectory parameters computed at the implant have a predictive value on the mid-term CRT-induced cardiac remodelling.

Course and magnitude of tip trajectory geometry changes immediately brought about by biventricular pace were widely different between R and NR and were correlated to the chronic reverse remodelling. Metrics describing tip trajectory pointed towards a smoother, more circular and more regular geometry in the R group, while either no variations or an increase in irregularity and complexity occurred in trajectories belonging to NR patients.

It is worth noting that CS lead tip three-dimensional trajectory in patients who would be chronic responders to CRT in the mid-term was at once extensively and quite uniformly modified by biventricular pacing at its start-up and that response to CRT was categorized with regards only to the occurrence and entity of reverse remodelling as assessed by the simplest and most used echocardiographic LV metrics (ESV and EF).

Further investigation is required to confirm these results in a larger population, and to better understand the meaning of the significant difference of the parameters α and β between the R and NR groups.

Preliminary data showed a more circular and smooth trajectory as an immediate result of the CRT turning-on in the echo-responder group. Therefore, 3D trajectories could describe features of resynchronization start-up in CRT recipients and could help to understand the reasons of therapy failure in non-responder patients.

Acknowledgements

We would like to thank Giorgio Bevilacqua, Davide Morelli and Cinzia Rubboli, technicians at the Electrophysiology Lab, Ravenna Hospital, for image acquisition.

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