In Silico Evaluation of New Approaches in Cardiac Resynchronization Therapy

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Abstract

Cardiac resynchronization therapy (CRT) is a widely used technique in the clinical setting to solve desynchronization problems in ventricular contraction. Among the different CRT approaches, the most widespread is biventricular pacing (BiVP), however, other newer approaches are beginning to be used, such as His optimized CRT (HOT-CRT) or left bundle branch area pacing (LBBAP).

In silico cardiac models allow assessing the effectiveness of different approaches of CRT in a non-invasive way, becoming a powerful tool to guide clinicians. Thus, the aim of this study was to evaluate in silico the effectiveness of HOT-CRT and LBBAP.

To do so, a biventricular model was used in which different pathologies were modelled and both CRT approaches (HOT-CRT and LBBAP) were analyzed. Multiple parameters have been considered when evaluating the effectiveness of each therapy, such as QRS duration (QRSd), time until 90% of ventricular activation (t90) or the time until 90% of QRS area is reached (a90).

Results showed that both therapies were found to be effective and superior to BiVP, significantly reducing QRSd, a90 and t90 values with respect to the pathological initial values.

1. Introduction

Heart failure (HF) is a common cardiovascular disease in which the heart muscle is unable to pump enough blood to meet the body's requirements. Often, heart failure is accompanied by alterations in the cardiac conduction system (CCS) such as left bundle branch block (LBBB) or right bundle branch block (RBBB), although other abnormalities in the CCS beyond the His branches are also found, here defined as left ventricular conduction delay (LVd). These concomitant pathologies in the CCS block or slow the normal propagation of the physiological stimulus causing an asynchronous ventricular contraction and further reducing the left ventricular ejection fraction (LVEF), a parameter usually evaluated when diagnosing HF.

Cardiac resynchronization therapy (CRT) is a well-known technique in the clinical setting that stands out for being the only one that doesn't use chemicals for treating ventricular desynchrony. This way, CRT attempts to correct ventricular contraction desynchrony by means of electrical stimuli applied in certain regions of the heart that replace or coordinate with the physiological stimulus from the sinoatrial node to achieve a simultaneous activation of both ventricles and improve cardiac output.

Usually, CRT is delivered in the form of biventricular pacing (BiVP) which is considered the gold standard. This approach consists in applying two external stimuli in the ventricular myocardium, one in the right ventricle (RV) apex and the other in the left ventricle (LV) free wall epicardium. However, with the development of medical technology other approaches are beginning to be used. This is the case of His optimized CRT (HOT-CRT) which considers the His bundle region instead of the RV apex as a stimulation point or the left bundle branch area pacing (LBBAP) which only considers one stimulus at that specific location.

In this regard, in silico cardiac models are a powerful tool that allows to predict and understand the outcomes of each therapy approach without risk for the patient. This study aimed to evaluate in silico the effectiveness of HOT-CRT and LBBAP compared with BiVP.

2. Methods

2.1. Biventricular 3D model

The biventricular in silico model used in this study was previously developed by our group [1]. Briefly, this is a 3D patient-specific biventricular model obtained from cardiac delayed enhanced magnetic resonance imaging (DE-MRI). First, the DE-MRI stack was segmented carefully in order to obtain a surface model of the ventricles and then a volume meshing was applied to the surface model giving as a result a hexahedra-based volume mesh comprised of 4 million nodes and 3.71

million elements with an average edge length of 380 µm.

The model also includes a Purkinje system (PS) network formed by linear elements and generated based on a stochastic grown method [2]. The network starts at His level and divides into right and left bundle branches that further divide into several subdivisions until myocardial tissue is reached through Purkinje-Myocardial junctions (PMJs).

2.2. Electrophysiological models

At cellular level, a modified version of the O'Hara model [1,3] was employed to describe the electrical behaviour of the human ventricular myocyte, whilst the model of Stewart et al. [4] was used for Purkinje cells.

At tissue level, the electrical propagation was described by the monodomain model. Although it is a simplification of the bidomain model, it worked well for the purpose of the study.

2.3. Pathological models

Two cases of study have been considered. The first one is a patient with RBBB, HF and LVd conditions (RBBB+HF+LVd). The other case suffers from LBBB and HF (LBBB+HF). To model both kinds of blocks (RBBB and LBBB), the conductivity of two linear elements in the PS model was set to zero in the right and left branches, respectively. On the other hand, HF and LVd conditions were reproduced by reducing the conductivity in all the myocardium and the left portion of the PS respectively. In HF, the overall conductivity was set to 50% of its basal value, in accordance with the reduction found in connexin43 protein [5], while in LVd, the conductivity was further reduced until the simulated ECG showed a pattern analogue to those found in the clinical practice [6].

2.4. Stimulation protocols

To reproduce the different CRT approaches in our model, several stimulation protocols have been applied to the myocardium and PS. First, to emulate BiVP, two external stimuli were applied simultaneously in the RV apex and LV free wall epicardium. In the case of HOT-CRT, the RV apex stimulus was replaced by a stimulus in the right portion of the His bundle right after the block site. Finally, in the LBBAP approach, only one stimulus was applied in the area of the left bundle branch near the bifurcation into its corresponding fascicles and capturing both, the PS and the surrounding myocardium simultaneously. The stimuli applied were of 900 µA/µF intensity and 2 ms long.

Moreover, two values for atrioventricular delay (AVD) were tested in order to achieve the best coordination of the external stimuli with the physiological stimulus (which in our model starts right after the atrioventricular node) which has been proven to improve the results [7]. These AVDs were: 195 and 210 ms.

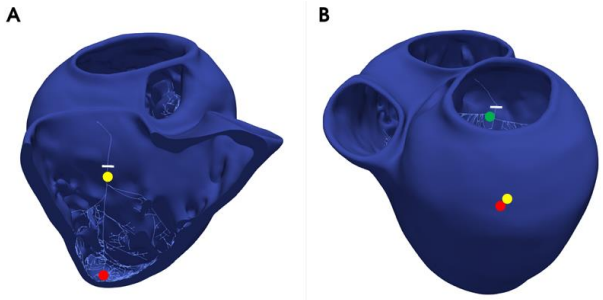

Figure 1. Block sites and stimulation points in the right ventricle endocardium (A) and the left ventricle (B). White lines indicate conduction block sites (RBBB and LBBB) and coloured dots indicate the stimulation spots for BiVP (red), HOT-CRT (yellow) and LBBAP (green).

2.5. 3D simulations

To run the simulations, ELVIRA software was used [8]. ELVIRA is a FEM solver specifically developed for solving the anisotropic reaction-diffusion equation of the monodomain model in cardiac electrophysiology. The conjugate gradient method with an integration time step of 0.02 ms was used for the numerical solutions.

2.6. ECG simulation

To reproduce the surface ECG signal, we used a torso model previously developed by our group [1,9] in which the biventricular model was fitted. This way, from the transmembrane potentials previously computed at the organ level using ELVIRA we computed the extracellular potentials through the torso model using an approximation of the bidomain model described in Keller et al. [10]. Then, using MATLAB scripts, the precordial ECG leads were computed by extracting the potential in those locations of the torso model where the electrodes are commonly placed to acquire the surface ECG in clinical practice.

2.7. Measurements

When evaluating the effectiveness of each therapy, several measurements were taken. First, QRS duration (QRSd) was measured from the simulated ECG. QRSd value is highly used in the clinical setting to evaluate CRT performance. Nonetheless, in previous studies [1], other parameters partially correlated with QRSd have been found to be good predictors of CRT efficacy. These are the time until 90% of ventricular activation (t90) and the time in which 90% of QRS area is reached (a90).

Matlab algorithms were implemented to plot de ECG signal and obtain these values.

3. Results

3.1. HOT-CRT

In RBBB+HF+LVd conditions, HOT-CRT produced a faster RV activation compared to the initial pathological conditions as well as an earlier LV lateral wall activation (figure 2).

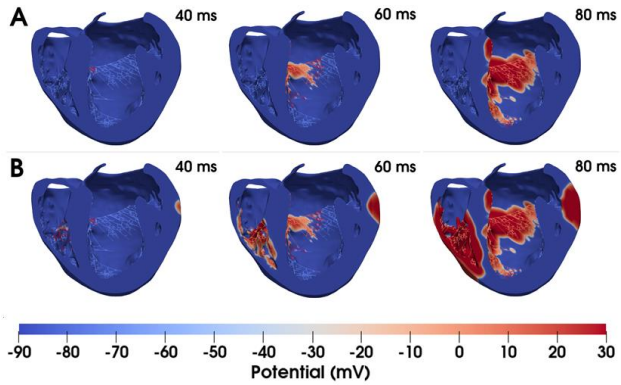

Figure 2. Electrical propagation in RBBB+HF+LVd conditions (A) and after HOT-CRT (B).

Compared to BiVP, HOT-CRT managed to reduce QRSd from 158 ms (pathological initial value) to 154 ms. On the contrary, BiVP further increased the QRSd initial value up to 169 ms. Regarding a90, both therapies reduced slightly the initial value: 123 vs 122 ms in the case of BiVP and 123 vs 119 ms when HOT-CRT was applied. Finally, t90 was significantly reduced with both approaches: 133 vs 117 ms when simulating BiVP and 133 vs 118 in HOT-CRT (table 1).

Moreover, when the AVD was changed from 195 to 210 ms, all the aforementioned values slightly improved.

3.2. LBBAP

In LBBB+HF conditions, LBBAP gave as a result an earlier activation of the LV septum, thus producing a more synchronous activation of both ventricles (figure 3).

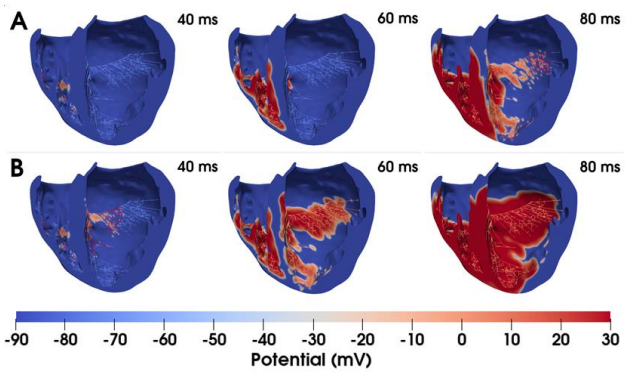

Figure 3. Electrical propagation in LBBB+HF conditions (A) and after LBBAP (B).

Compared to BiVP, both therapies reduced QRSd, a90 and t90 with respect to the initial pathological values.

Specifically, BiVP reduced QRSd from 166 to 156 ms, a90 from 123 to 114 ms and t90 from 134 to 115 ms. On the other hand, LBBAP manages to reduce QRSd, a90 and t90 initial values to 142, 104 and 108 ms, respectively.

When AVD was changed from 195 to 210 ms, the results worsened in the case of LBBAP while in BiVP the trend was not clear.

Table 1. Measured values. Red boxes indicate the initial pathological values in each case of study and green boxes show the CRT approach and AVD in which the greatest reduction is achieved.

				QRSd (ms)	a90 (ms)	t90 (ms)
Case study	Healthy	-	-	95	72	77
	RBBB+HF+LVd	Initial value	-	158	123	133
		After BiVP	AVD195ms	169	122	117
			AVD210ms	164	118	115
		After HOT-CRT	AVD195ms	154	119	118
			AVD210ms	151	114	114
	LBBB+HF	Initial value	-	166	123	134
		After BiVP	AVD195ms	156	114	115
			AVD210ms	151	113	120
		After LBBAP	AVD195ms	142	104	108
			AVD210ms	146	113	121

4. Discussion

In view of the results, both novel approaches (HOT-CRT and LBBAP) outperformed the standard procedure (BiVP) in the cases where they have been tested.

In HOT-CRT (applied in RBBB+HF+LVd conditions) this can be explained because of the early recruitment of the right bundle branch through the hisian stimulus which coordinates with the physiological stimulus descending from the left bundle branch and gives, as a result, a faster and more synchronous ventricular activation. This fact results in a QRSd reduction as in the clinical studies found in the bibliography [11,12], but also, in the other measured values (a90 and t90).

On the other hand, under LBBB+HF conditions, LBBAP also performs better than BiVP, which is in agreement with several clinical studies [13]. However, in this case, this is due to an early LV septum activation (including the Purkinje system) which again, in coordination with the physiological stimulus that in this case propagates through the right bundle branch, produces a faster and synchronous activation.

Last but not least, the use of two different AVDs demonstrated the dependence of the results on the coordination degree of the external stimuli applied and the physiological stimulus descending from the AV node, thus highlighting the importance of this parameter in CRT optimization.

5. Conclusion

Through this study, the utility of in silico models to understand, evaluate and optimize different CRT approaches has been clearly demonstrated, which could help clinicians in the clinical setting to plan the procedure and reduce the risk for the patient.

Acknowledgements

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