Efficient preloading of the ventricles by a properly timed atrial contraction underlies stroke work improvement in the acute response to cardiac resynchronization therapy

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BACKGROUND The acute response to cardiac resynchronization therapy (CRT) has been shown to be due to 3 mechanisms: resynchronization of ventricular contraction, efficient preloading of the ventricles by a properly timed atrial contraction, and mitral regurgitation reduction. However, the contribution of each of the 3 mechanisms to the acute response to CRT, specifically stroke work improvement, has not been quantified.

OBJECTIVE To use a magnetic resonance image-based anatomically accurate 3-dimensional model of failing canine ventricular electromechanics to quantify the contribution of each of the 3 mechanisms to stroke work improvement and identify the predominant mechanisms.

METHODS An MRI-based electromechanical model of the failing canine ventricles assembled previously by our group was further developed and modified. Three different protocols were used to dissect the contribution of each of the 3 mechanisms to stroke work improvement.

RESULTS Resynchronization of ventricular contraction did not lead to a significant stroke work improvement. Efficient preloading of the ventricles by a properly timed atrial contraction was the predominant mechanism underlying stroke work improvement. Stroke work improvement peaked at an intermediate atrioventricular delay, as it allowed ventricular filling by atrial contraction to occur at a low diastolic left ventricular pressure but also provided adequate time for ventricular filling before ventricular contraction. Reduction of mitral regurgitation by CRT led to stroke work worsening instead of improvement.

CONCLUSION Efficient preloading of the ventricles by a properly timed atrial contraction is responsible for a significant stroke work improvement in the acute CRT response.

KEYWORDS Heart failure; Cardiac resynchronization therapy; Dyssynchronous heart failure; Left bundle branch block; Stroke work

ABBREVIATIONS **AV** = atrioventricular; **CRT** = cardiac resynchronization therapy; **DHF** = dyssynchronous heart failure; **LA** = left atrium; **LBBB** = left bundle branch block; **LRd** = Luo-Rudy dynamic; **LV** = left ventricle/ventricular; **MRI** = magnetic resonance image; **RA** = right atrium; **RV** = right ventricle/ventricular

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Introduction

Heart failure is a major cause of morbidity and mortality,[1] contributing significantly to global health expenditure. A large number of patients with heart failure exhibit a left bundle branch block (LBBB) type of electrical activation. In such patients, the left ventricle (LV) is activated through the septum from the right ventricle (RV), resulting in a delayed onset of LV contraction relative to that of the RV.[2] Cardiac resynchronization therapy (CRT), which uses biventricular pacing to recoordinate the contraction of the heart, has been demonstrated to be a valuable therapeutic option for such patients.[3] Even though CRT has been shown to improve heart failure symptoms and reduce hospitalization for most of the patients, one third of them fail to benefit from the therapy,[3] reflecting an incomplete understanding of the mechanisms underlying the response to CRT. Gaining a better understanding of these mechanisms will help optimize the delivery of CRT so that the benefit of the therapy is extended to a larger patient population.

CRT typically involves implantation of 3 leads: 1 into the right atrium (RA) and 2 in the RV and LV, respectively. The 2 ventricular electrodes provide stimuli simultaneously to elicit a synchronous contraction. The optimization of the pacing time interval between activating the RA and the subsequent activation of both ventricles (atrioventricular [AV] delay) has been shown to additionally improve the

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acute hemodynamic response of the heart.[4] Heart failure patients often exhibit mitral regurgitation as a result of ventricular dilation and increased chamber sphericity.[5] CRT has also been shown to acutely reduce mitral regurgitation severity in the dyssynchronous failing (dyssynchronous heart failure [DHF]) ventricles[5–7] by increasing the transmitral pressure gradient (the systolic LV-left atrium [LA] pressure difference)[5] and diminishing the dyssynchrony of papillary muscle contraction.[6,7] Overall, the acute response of the DHF ventricles to CRT is thus believed to be due to 3 main mechanisms: resynchronization of ventricular contraction, efficient preloading of the ventricles by a properly timed atrial contraction, and reduced mitral regurgitation.[8]

The acute response to CRT is manifested by an augmentation in stroke work.[9] However, the contribution of each of the 3 mechanisms to stroke work improvement during the acute response to CRT has not been quantified and therefore the predominant mechanism underlying this improvement has not been identified. Currently, it is difficult to isolate and quantify the contribution of each of the 3 mechanisms to CRT-induced stroke work increase through experimental methods.[10,11] Therefore, a computational approach was undertaken in this study. A magnetic resonance image (MRI)-based electromechanical model of the DHF ventricles was developed to determine the contribution of each of the 3 proposed mechanisms to CRT-induced acute stroke work augmentation and to identify the predominant mechanism.

Methods

MRI-based electromechanical model of the DHF canine ventricles

To achieve the goals of this study, we used an MRI-based electromechanical model of the DHF canine ventricles (Figure 1) developed previously by our group.[12] The model and the advancements implemented in it for the present research are described briefly below. The ventricular geometry and fiber-sheet architecture of the model were constructed from high-resolution MR and diffusion tensor MR images of DHF canine ventricles. The model consisted of coupled electrical and mechanical components and a lumped-parameter representation of the circulatory system. A mathematical description of the electrical component of the model involved the use of the monodomain representation of cardiac tissue; the ventricular mechanics component was based on the continuum mechanics equations, with the myocardium assumed to be an orthotropic, hyperelastic, nearly incompressible material.[13–15]

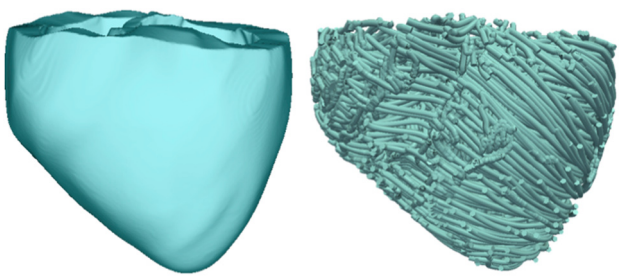

Figure 1 Geometry (left) and fiber orientation (right) of the dyssynchronous heart failure canine ventricular model.

For computational tractability, the electrical and mechanical components of the electromechanical model were weakly coupled. The local electrical activation times calculated from the electrical component of the model determined the instants when the Ca transient, which served as an input into the myofilament model of Rice et al[16] in the mechanics component of the model, was initiated at the Gaussian points of each mechanical mesh element. The electrical component of the ventricular electromechanical model used the Luo-Rudy dynamic (LRd) model[17] to represent membrane kinetics; generic mammalian membrane kinetics models, such as LRd, are often used in whole-heart electromechanical models.[18,19] The LRd model is considered to be of medium-to-low complexity and is thus a reasonable trade-off in large-scale electromechanical simulations.

The formulation of the Ca transient in the myofilament model was modified to reflect abnormal Ca handling associated with DHF[20] (see details in Appendix 1A in the Online Supplemental Material). Furthermore, the values of the scaling factor for tension, of the cross-bridge attachment rate constant to the first strongly bound state, and of the scaling factor for all cross-bridge cycling rates were adjusted to represent behavior in the canine ventricles; these were set to 205, 5000 s^{-1}, and 0.4, respectively, so that ejection fraction, LV peak pressure, and maximal rise in LV pressure matched values observed experimentally in failing canine ventricles.[21] In addition, the elastance of the atria in the lumped-parameter model of the circulatory system[22] was increased fourfold so that atrial contraction accounted for 10% of ventricular filling, as reported for the failing canine ventricles.[23] Mitral regurgitation was represented in the model of the circulatory system by allowing for backward flow from the LV to the LA when LV pressure was higher than LA pressure (see the Appendix 1B in the Online Supplemental Material).

To simulate LBBB activation of the canine ventricles, the RV endocardial surface of the ventricles was stimulated at a basic pacing cycle length of 500 ms[21] at discrete locations as if the electrical activation was emanating from the activation of the corresponding branch of the Purkinje network; the locations and timings were based on experimental findings.[24] LBBB was simulated with an AV delay of 140 ms, as recorded in DHF canine ventricles.[21]

CRT simulation

The model of the DHF ventricles described above was subjected to CRT. RA pacing was represented by the onset of atrial contraction via initiating the activation function for atrial elastance in the model of the circulatory system; at a certain AV delay, the ventricles were paced simultaneously from the RV apex and the LV lateral wall.