**Supplemental Materials**

***Supplemental Methods***

*Overview of the MRI-based electromechanical model of the DHF ventricles*

The ventricular geometry and the three-dimensional arrangement of ventricular myofibers were constructed from high-resolution MR and diffusion tensor (DT) MR images of DHF canine ventricles. The original experimental studies in which the imaging data have been acquired have been previously published.[1](#_ENREF_1), [2](#_ENREF_2) The heart failure animal model in these experimental studies[1](#_ENREF_1), [2](#_ENREF_2) was that of a tachycardia pacing-induced heart failure. The imaging data has since been publicly available (<http://gforge.icm.jhu.edu/gf/project/dtmri_data_sets>). Our electromechanical model consisted of coupled electrical and mechanical components, and a representation of the circulatory system. In the model of the circulatory system, parts (e.g. pulmonic veins) of the system were lumped together and thus compliances were averaged and resistances summed over these parts, as described in.[3](#_ENREF_3) The electrical component of the model involved standard methods of wave propagation in the tissue.[4](#_ENREF_4) The ventricular mechanics component was based on the continuum mechanics equations,[5-7](#_ENREF_5) which treated the myocardium as a continuous medium. The myocardium deformed differently in different directions and it was assumed to be of nearly-incompressible material.[5-7](#_ENREF_5)

To minimize computational effort, 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 Rice et al. myofilament model[8](#_ENREF_8) in the mechanics component of the model, was initiated at the Gauss points of each mechanical mesh element. The electrical component of the ventricular electromechanical model has been extensively described in our previous studies.[9](#_ENREF_9) [10](#_ENREF_10)

*Myofilament model*

The Rice et al. myofilament model,[8](#_ENREF_8) as modified in our previous publication,[9](#_ENREF_9) was employed in this study. For this study, the myofilament model was further modified so that it could reproduce (Fig. S1) the experimentally determined relationship between ATP consumption and stress-strain area (the area under the stress-strain curve)[11](#_ENREF_11) and the relationship between ATP consumption and tension at different temperatures.[12](#_ENREF_12) The modifications were implemented by setting the values of the crossbridge detachment rate constant to the permissive conformation state of the regulatory protein, of the scaling constant for the effects of strain on negative shortening velocities, and of the rate constant for Ca binding in the myofilament model to 140s-1,1 and 30μM-1s-1, respectively. The value of the scaling factor for tension in the myofilament model was adjusted to 1230 so that ejection fraction, LV peak pressure, and maximal rise in LV pressure matched values observed experimentally in failing canine ventricles.[13](#_ENREF_13)

*Simulating LBBB activation and CRT in the canine ventricles*

To simulate LBBB activation of the canine ventricles, the RV endocardial surface was stimulated 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.[14](#_ENREF_14) A pacing cycle length of 500ms was used, consistent with the pacing rate in DHF canine ventricles in CRT experimental studies.[13](#_ENREF_13) LBBB was simulated with an atrioventricular (AV) delay of 140ms; this AV delay has been measured in the DHF canine ventricles.[13](#_ENREF_13) AV delay in the model of LBBB activation was defined as the time interval from the onset of atrial contraction until the start of electrical activation in the ventricles; atrial contraction was represented in the model of the circulatory system using a time-varying elastance model.[5](#_ENREF_5), [9](#_ENREF_9)

In each CRT simulation, an AV delay of 70ms was implemented, consistent with the AV delay used in canine CRT protocols.[13](#_ENREF_13) CRT AV delay was defined as the time interval from the onset of atrial contraction until the start of biventricular pacing.

*Calculating the degree of heterogeneity in ATP consumption throughout the LV*

The degree of heterogeneity in ATP consumption throughout the LV was determined by calculating ATP consumption per myosin head (ATP\_c) at every Gauss point in the LV mechanical mesh and at every millisecond of the pacing cycle (500ms in duration, from end-diastole of a given cardiac cycle to that of the next). ATP\_c calculation involved multiplying the crossbridge detachment rate by the single-overlap fraction of the thick filament and the probability that the crossbridge is in the post-rotated force-generating state in the myofilament model. At each Gauss point in the LV mechanical mesh, ATP\_c values calculated at each time instant (every millisecond) of the pacing cycle were then added up to obtain the total ATP\_c, ATP\_cT (i.e. ATP\_c over one pacing cycle) at that point**.** ATP\_cT thus represented the number of ATP molecules consumed by a single myosin head over one pacing cycle**.**

(1)

where gxbT is the crossbridge detachment rate;

XBPostR is the probability that the crossbridge is in the post-rotated force-generating state;

SOVFthick(x) is the single-overlap function for the thick filament;

x is the sarcomere length; and

is the total ATP\_c over one pacing cycle at each Gauss point. , and are the local coordinates in Gaussian quadrature and they range from 0 to 1.

For the DHF ventricles and each CRT simulation (corresponding to each of the 34 LV pacing sites), we calculated the ATP\_cT heterogeneity index (ATPCTHI), a single value, defined as the dispersion of the ATP\_cT across all Gauss points (from the average ATP\_cT over all Gauss points) in the LV mechanical mesh.

(2)

(3)

where J is the determinant of the Jacobian of the transformation matrix from local coordinates to global coordinates;

Wi, Wj and Wk are the weights of the Gauss points in , and directions; and

ATPCTHI is the ATP\_cT heterogeneity index (ATPCTHI).

Finally, we determined the improvement in ATPCTHI induced by CRT from the given LV pacing site. Improvement in ATPCTHI was defined as the percentage decrease in ATPCTHI as a result of CRT relative to its value in the DHF ventricles.

(4)

*Calculating stroke work improvement*

For the DHF ventricles and each CRT simulation (corresponding to each of the 34 LV pacing sites), stroke work was calculated by integrating the area within the pressure-volume loop, as we have done in our previous publication.[9](#_ENREF_9) Stroke work improvement for the given pacing site was defined as the percentage increase of stroke work as a result of CRT relative to that in the DHF ventricles.

***Supplemental Results and Discussion****: Stroke work improvement in the acute response to CRT*

As presented in the main text, stroke work improvement was determined for each of the CRT simulations (34 epicardial LV pacing sites and 3 endocardial LV). Almost all of the epicardial pacing sites (33 out of 34) led to significant (≥ 33%) stroke work improvement, as seen in Fig. 3B and discussed in the main text. The slow decrease reflected the fact that our model of CRT was tuned to achieve maximum stroke work improvement i.e. significant stroke work improvement was reached by pacing from a broad area of the LV lateral wall. This tune up was achieved here by setting the AV delay to 70ms, which is the value shown to lead to a significant stroke work improvement in the canine DHF model.[9](#_ENREF_9) Indeed, our previous work[9](#_ENREF_9) and a recent experimental study[15](#_ENREF_15) have demonstrated that AV delay optimization was a very important contributor to stroke work improvement following CRT.

The epicardial LV pacing site that resulted in maximal stroke work improvement is marked by the black triangle in Fig. 3B. It increased stroke work from 135.7 kPa\*mL in the DHF ventricles to 191.3 kPa\*mL, as documented by the pressure-volume loops in Fig. S2. Since the AV delay was 140ms in the DHF ventricles and the pacing cycle length was 500ms (see Supplementary Methods), atrial contraction occurred when LV was in the process of relaxation and therefore ventricular filling started before the complete relaxation of the LV. Consequently, the pressure at the end of isovolumic relaxation ended up being higher than the end-diastolic pressure. Such pressure-volume relationship has been observed in DHF hearts, such as in Patient 4 and 5 in Dekker et al.[16](#_ENREF_16) The latter study clearly indicates that there is large interindividual variability in the morphology of pressure-volume loops in CRT clinical studies.[16](#_ENREF_16) Future studies are needed to gain a thorough understanding of the hemodynamics in the DHF ventricles prior to and after CRT therapy.

Consistent with findings in our previous research,[9](#_ENREF_9) the end-diastolic volume in CRT was higher than that in the DHF ventricles, as seen in Fig. S2. When the AV delay was shortened from 140ms in the DHF ventricles to 70ms in CRT, atrial contraction occurred when LV was at a more relaxed state and LV pressure was lower. As a result, in CRT, the pressure against which LV filling by atrial contraction occurred was lower than in the DHF ventricles and LV preloading became more efficient. Consequently, LV end-diastolic volume was larger in CRT and a stronger LV contraction resulted according to Starling’s Law.

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Figure S1: The myofilament model reproduces experimentally determined relationship between ATP consumption and stress-strain area and the relationship between ATP consumption and tension at different temperatures.

Figure S2: Pressure-volume loops for the DHF ventricles and the ventricles following CRT from the LV site that resulted in maximal stroke work improvement.