CHAPTER 13
ELECTROMECHANICAL MODELING APPLIED TO CARDIAC RESYNCHRONIZATION THERAPY

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INTRODUCTION

■ OVERVIEW

Heart failure is a major cause of morbidity and mortality, contributing significantly to global health expenditure. Heart failure patients often exhibit contractile dyssynchrony, which diminishes cardiac systolic function. Cardiac resynchronization therapy (CRT), a relatively new treatment modality that employs biventricular (bi-V) pacing to recoordinate the contraction of the heart, is a valuable therapeutic option for such patients. CRT has been shown to improve heart failure symptoms and reduce hospitalization, yet approximately 30% of patients fail to respond to the therapy. In the current environment, which emphasizes reducing health care costs and optimizing therapy, robust diagnostic approaches to identify patients who would and would not benefit from CRT would have a dramatic personal, medical, and economic impact on the lives of many Americans.

The poor predictive ability of current approaches to identify potential responders to CRT reflects the incomplete understanding of the complex pathophysiologic and electromechanical factors that underlie mechanical dyssynchrony. The goal of this chapter is to present the development, from magnetic resonance imaging (MRI) and diffusion tensor (DT) MRI scans, of individualized three-dimensional (3D) image-based multiscale computational models of ventricular electromechanics that incorporate the deleterious structural, mechanical, and electrophysiologic remodeling associated with dyssynchronous heart failure (DHF), from the level of the protein to that of the intact heart. We then demonstrate how this powerful predictive modeling approach could be used to provide mechanistic insight into heart failure contractile dyssynchrony and to possibly determine the optimal CRT strategy.

The development of a predictive model of ventricular electromechanics in the setting of DHF overcomes the inability of current experimental techniques to simultaneously record the 3D electrical and mechanical activity of the heart with high spatiotemporal resolution and thus to provide an understanding of dyssynchrony and CRT effectiveness. The new basic-science insights into the electromechanical behavior that can be acquired with this modeling approach will hopefully lead to rational optimization of CRT delivery and to improvements in the selection criteria for potential CRT candidates.

■ DYSSYNCHRONOUS HEART FAILURE

Heart failure is a major cardiovascular disease affecting 5 million people in the United States alone and is associated with high morbidity and mortality rates. The syndrome is characterized by impaired pump function due to the deleterious remodeling of the ventricles, from the organ down to the molecular level, which significantly alters the electrical and mechanical behavior of the heart. High-resolution MRI and DTMRI scans have shown that in DHF, there is a substantial remodeling of ventricular geometry and structure. At the organ level, the ventricles become dilated, and wall thickness is reduced. At the tissue level, laminar sheet angle is altered, and the transmural gradient in fiber orientation is increased. Because chamber geometry and sheet structure are major determinants of left ventricular (LV) mechanics, the mechanical deformation of the failing heart is markedly different. Furthermore, altered heart geometry and fiber and sheet orientations directly affect 3D electrical propagation in the failing heart.

Heart failure is also characterized by remodeling of the electrophysiologic and mechanical properties at the cellular and subcellular levels. Studies have shown that the gap junctional protein connexin 43 (Cx43) is redistributed from the intercalated disk to the lateral myocyte borders and that the amount of hypophosphorylated Cx43 is increased, leading to reduced conduction velocity in heart failure. There is a considerable downregulation of the membrane potassium channels carrying the I[K] and I_{Ks} currents and of the intracellular sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase (SERCA) pump and upregulation of the Na–Ca exchanger (NCX). Remodeled ionic currents and Ca^{2+} handling result in altered Ca^{2+} transients, which, in turn, impair active tension development by the myofilaments in the cell. Finally, differential expression of collagen isoforms and altered ratio of titin...
(an intrasarcomeric protein that modulates myofilament passive tension) isoforms result in increased myocardial stiffness.

Because of the combined effects of chamber, contractile, and electrophysiologic remodeling, the ability of the LV to efficiently pump blood is severely compromised in heart failure patients. Furthermore, a subset of these patients exhibits abnormal electrical conduction that delays activation of one portion of the ventricle relative to another (intraventricular conduction delay due to left bundle branch block [LBBB]). This results in contractile dyssynchrony (ie, DHF), which further diminishes cardiac systolic function and energetic efficiency.

■ CARDIAC RESYNCHRONIZATION THERAPY

CRT is an established therapy for DHF patients. CRT typically employs bi-V pacing, with an endocardial right ventricular (RV) pacing lead and an epicardial LV pacing lead, to recoordinate contraction. CRT has been shown to acutely and chronically improve systolic function of the heart and to reverse the detrimental remodeling associated with heart failure. Clinical trials of CRT have consistently demonstrated improvement in heart failure symptoms, exercise tolerance, and quality of life and a reduction in recurrent hospitalizations.

Although CRT reduces morbidity and mortality, approximately 30% of patients fail to respond to the therapy. This reflects the poor predictive capability of current approaches to identify potential responders to CRT. The QRS duration (QRS >150 ms), which is widely used in clinical trials as a basic component of the inclusion criteria for CRT, does not provide an indication of the degree of mechanical dyssynchrony. Indeed, patients with long QRS duration may not exhibit mechanical dyssynchrony, and those with short QRS complexes may present with significant dyssynchrony in contraction. Measurements of mechanical dyssynchrony by Doppler echocardiography reveal only local dyssynchrony, whereas the complex deformations in DHF are global. In recent clinical trials, Doppler echocardiography demonstrated lack of repeatability and low predictive value. The poor predictive capability of the above measures indicates an incomplete understanding of the electromechanical behavior in DHF.

The presence of myocardial infarction is an additional reason for lack of response to CRT. Placement of a pacing electrode at or near the infarct scar may result in ineffective pacing and, thus, failure of resynchronization. Because infarction modulates electromechanical interactions, it also alters the mechanism of CRT. Bleeker et al documented that patients with transmural posterolateral scar have a much lower response rate to CRT than those without scar (14% vs 81%, respectively). Increased scar volume has been found to result in unfavorable response to CRT. Infarct location and scar transmurality are considered important yet unknown factors that affect the relationship between electrical activation and contraction and contribute to diminished CRT efficacy.

Finally, the location of LV pacing has been shown to play an important role in CRT efficacy. Currently, LV pacing lead is implanted in a tributary of the coronary sinus, as in epicardial bi-V pacing. However, for a small class of patients unsuitable for transvenous bi-V, a transeptal approach has been developed that allows endocardial bi-V pacing. Recent studies have brought to light the potential proarrhythmic effect of epicardial bi-V pacing, resulting from the reversal of the direction of electrical propagation in the LV. Furthermore, new findings indicate that endocardial bi-V pacing might be associated with improved resynchronization in canine models and humans.

A comprehensive characterization of the spatiotemporal electromechanical interactions in the DHF heart is paramount to any improvement in the selection criteria for viable CRT candidates and is fundamental to the effort toward improving CRT efficacy. The development of a multiscale model of ventricular electromechanics offers a powerful methodology to unravel the mechanisms by which the deleterious structural, mechanical, and electrophysiologic remodeling in DHF, from the scale of the protein to the intact organ, causes discord between electrical activation and mechanical contraction of the heart. This unique and novel tool overcomes the limitations of previous approaches to elucidating cardiac electromechanical interactions and provides insights that cannot be obtained by experiment alone.

■ PREVIOUS ATTEMPTS TO MODEL CARDIAC ELECTROMECHANICS AND CRT

In the last decade, simulation research in cardiac electrophysiology has made important steps forward in linking models of myocyte action potential to geometrical models of cardiac tissue and the entire organ (see review by Tice). Although integrative multiscale models of organ behavior that incorporate detailed biophysical models of the myocyte cellular and subcellular processes are not yet commonplace, they have nonetheless made major contributions to obtaining insight into electrical excitation and the mechanisms of arrhythmogenesis and defibrillation in the normal and, in some cases, the diseased heart. Similarly, finite element continuum models incorporating anatomy, structure, and passive mechanics have been developed, and recently, attempts have been made to couple them to biophysical models of cellular active tension. The development of models of these two major physical processes in the heart has occurred largely independently. However, in the last few years, coupled models of cardiac electromechanics, in which contraction is triggered by the electrical event, have also been assembled. All of these models incorporate major simplifications in the representations of membrane dynamics, triggering process for contraction, cellular active tension, and tissue/organ geometry and structure. In addition, with very few exceptions, these models represent electromechanical activity in the normal heart. Simplifications limit the models’ predictive capabilities, particularly their utility in simulating the acute effects of CRT. Indeed, models addressing CRT include those representing bi-V pacing in the normal heart without accounting for cardiac mechanics or simulating mechanics with a simple two-element rheologic model. Even the most sophisticated models of CRT use phenomenologic representations of membrane dynamics that do not incorporate remodeling in heart failure.

The multiscale electromechanical model of DHF presented here is a major step forward in representing the detailed
electromechanical interactions in the remodeled heart, from the protein to the organ level, overcoming limitations of previous model developments. Furthermore, we incorporate, for the first time, individualized image-based organ and structure in the models, thus ensuring that the mechanistic insights that can be obtained with the model are directly applicable to the clinical setting and the clinical CRT procedure.

**IMAGE-BASED ELECTROMECHANICAL MODEL OF THE HEART**

- **IMAGE-BASED RECONSTRUCTION OF THE GEOMETRY AND STRUCTURE OF DHF HEARTS**

Figure 13–1 illustrates the pipeline for assembling image-based models of the heart by showing the processing of an example image slice. It is important to note that the models generated in this way will retain fine structural details, such as endocardial trabeculations and papillary muscles, provided that such structural details are resolved by the ex vivo imaging method. Further details on the processing pipeline can be found in our recent publications.

**Suspension Medium Removal**

The ex vivo structural MRI is processed to label and “remove” voxels corresponding to cavity content and surrounding medium. First, the image edges are detected, and the myocardial boundary of the heart is extracted using a region-growing algorithm. The surrounding medium is removed by assigning the background intensity to all voxels in the medium. The result is an image of the myocardium (step 1 in Fig. 13–1). In step 2, the myocardium is separated from the large coronary arteries.

**Separation of Ventricles From Atria**

In each slice, ventricular tissue is labeled by fitting a closed spline curve through spline points placed around the ventricles and along the atrioventricular border. All voxels that belong to tissue inside the curve are marked as ventricular (step 3 in Fig. 13–1). Ventricles and atria are then separated.

**Infarct Segmentation**

Often patients with DHF also have myocardial infarction. Therefore, we included in our model reconstruction pipeline the capability to segment the zone of infarct. From the DTMRI, a 3D fractional anisotropy (FA) image is constructed. FA is a measure of the directional diffusivity of water. Based on the difference in FA values, the infarct region is separated from the normal myocardium. Next, the infarct region is subdivided into two areas, an inexcitable scar and a peri-infarct region, which is assumed to contain excitable and contracting but pathologically remodeled tissue, by thresholding the structural MRI based on voxel intensity values (step 4).

**Mesh Generation**

Next, a finite element tetrahedral mesh is generated from the segmented MRI for the solution of the electrical component of the model. The mesh requirements are based on the spatiotemporal characteristics of wave propagation in the heart; it has been shown that a spatial resolution of approximately 250 µm is appropriate for electrophysiologic finite element models of the heart. A novel approach was recently published by our team for image-based mesh generation. The electrical meshes of the heart used in the preliminary studies were generated using this methodology. Step 5 in Fig. 13–1 shows the mesh for the example slice, whereas Fig. 13–2A presents the electrical mesh of the entire canine heart. The meshing technique is automatic and produces boundary-fitted, locally refined, and smooth conformal meshes (see Fig. 13–2A, inset). The local adaptation of the resolution, as shown in Fig. 13–1 (step 5), significantly reduces the number of elements in the mesh without compromising geometric detail. Note that we typically generate electrical meshes of the heart that incorporate both ventricles and atria.
FIGURE 13–2. Computational meshes. A. Electrical mesh (mesh detail in inset). B. Mechanical mesh generation; numbers denote the various surfaces used in the mesh generation.

However, the electrical problem is effectively solved only on the ventricular portion of the mesh because atria and ventricles are electrically isolated.

The mechanical mesh consists of hexahedral elements with Hermite basis. This choice of finite elements maintains continuity of strain and is appropriate for maintaining incompressibility constraints. The mechanical mesh is also generated from the segmented images and based on the electrical mesh to ensure exact match in geometries; for mechanical mesh generation, we use only the segmented ventricles. The methodology to construct image-based mechanical meshes has been recently developed by our team. The mesh is constructed from a sheet with a thickness of two elements that is “wrapped around” the segmented ventricles as shown in Fig. 13–2B. Note that current mechanical meshing procedures introduce an artificial hole in the LV apex; the meshing procedure described here avoids this artifact.

**Fiber and Sheet Mapping**

Fiber and laminar sheet organization underlie the orthotropic electrical conductivities of the tissue and the tissue mechanical properties. We recently developed a methodology to interpolate DTs from the DTMRI data onto the elements in both meshes, thus mapping the fiber and laminar sheet organization onto the meshes (ie, defining the orthotropic properties of the myocardium for the solution of the electrical and mechanical problems). To incorporate fiber and laminar sheet architecture in the model, tensors and tensor gradients were defined at each node of the finite element mesh and interpolated within the finite elements using Hermite interpolation. The eigenvectors of the tensors in the interpolated mesh were found using the least-squares method in a metric space of tensors, was similar to that of angle fitting.

For positive definite symmetric matrices, these operations become:

\[
A_1 \odot A_2 = A_1 A_2
\]

\[
k \odot A = A^k = (UDU^T)^k = UD^k U^T = U \begin{bmatrix} \lambda_1^k & 0 & 0 \\ 0 & \lambda_2^k & 0 \\ 0 & 0 & \lambda_3^k \end{bmatrix} U^T
\]

where \( U \) is an orthogonal matrix and \( D \) is a diagonal matrix of eigenvalues \( \lambda_1, \lambda_2, \) and \( \lambda_3 \). Using the operations in Equations 13-1 and 13-2, the Hermite interpolation is defined as:

\[
A = \prod A_i^{\Psi_i}
\]

where \( \Psi_i \) are the Hermite basis functions described in Nielsen et al, and \( A_i \) are the tensors and tensor gradients with respect to the arc lengths assigned to the nodes of each finite element.

The method for tensor fitting to the DTMRI data, which uses the least-squares method in a metric space of tensors, was similar to that of angle fitting. The tensors and the tensor gradients at the nodes of the mesh were determined using the least-squares method by minimizing the sum of the squared distances between the DT from the DTMRI data and the tensors from the interpolated tensor field. The log-Euclidean metric applied in the least-squares method was as follows:

\[
d(A_i, A_j) = (\text{Trace}[\ln (A_i) - \ln (A_j)]^2)^{1/2}
\]

To remove artifacts that appear when voxels of MRIs represent both ventricular tissue and surrounding media at the epicardial and endocardial surfaces, the approximated tensor field was regularized. Regularization of the tensor field using the log-Euclidean metric in Equation 13–4 was performed by introducing a penalty term \( \text{Reg}(s) \) to the least-squares method; the latter was derived from the norm of the tensor field gradient:

\[
\text{Reg}(s) = \frac{n}{V} \int s^2 dV
\]

\[
s^2 = \sum \text{Trace} \left[ \sum \frac{\partial \Psi_i}{\partial x_j} \ln (A_i) \right]_j^2
\]
of each myocyte initiates the release of calcium (Ca) from the intracellular Ca stores, followed by binding of Ca to troponin C and cross-bridge cycling, which forms the basis for contractile protein movement and development of active tension in the cell, ultimately resulting in contraction of the ventricles.

Accordingly, the electrical component of the model (see Fig. 13–4, left) simulates the propagation of a wave of transmembrane potential by solving a reaction-diffusion partial differential equation (PDE) for the transmembrane potential on the electrical finite element mesh. This equation describes current flow through cardiac tissue, which has orthotropic passive electrical conductivities, the latter stemming from the cellular organization into fibers and laminar sheets. The current flow is driven by active processes of ionic exchange across myocyte membranes. These active electrical processes are represented by an ionic model of the myocyte membrane (see Fig. 13–4, left), where current flow through ion channels, pumps and exchangers in the myocyte membrane, and subcellular Ca cycling between cell compartments and buffers are represented by a set of ordinary differential equations (ODEs) and algebraic equations. Simultaneous solution of the PDE with the set of ionic model equations represents simulation of electrical wave propagation in the heart; a review of all the modeling details can be found in Plank et al.\textsuperscript{79}

The intracellular Ca released during the electrical activation couples the electrical and mechanical components (see Fig. 13–4). It serves as an input to the cell myofilament model representing the generation of active tension within each myocyte, in which a set of ODEs and algebraic equations describe Ca binding to troponin C, cooperativity between regulatory proteins, and cross-bridge cycling. Contraction of the ventricles arises from the active tension generated by the cardiac cells. Ventricular deformation is described by the equations of passive cardiac mechanics,\textsuperscript{81-88} with the myocardium being an orthotropic (due to fiber and sheet organization), hyperelastic, and nearly incompressible material with passive mechanical properties defined by an exponential strain energy function. Simultaneous solution of the myofilament model equations and those representing passive cardiac mechanics on the finite element mesh constitutes simulation of cardiac contraction. During contraction, the stretch ratio (ie, the ratio of myocyte length before and after deformation) and its time derivative affect myofilament dynamics, including length-dependent Ca sensitivity, providing a feedback loop.

where integration was performed over the volume of finite elements, \( n \) is the number of samples (tensors) in the DTMRI data set, \( V_t \) is the tissue volume of the ventricles, \( \gamma = 1.0 \) is the penalty factor, and \( \frac{\partial \Phi_i}{\partial \mathbf{x}} \) are the derivatives of the Hermite basis functions with respect to a fixed set of global coordinates, \( \mathbf{x} \).

Step 6 in Fig. 13–1 displays the fiber orientations for the example slice, whereas fiber and sheet organization in both meshes are shown in Fig. 13–3. It is important to note that our image-based reconstruction captures all the structural and geometrical remodeling in DHF. This approach is radically different from previous attempts at modeling heart failure,\textsuperscript{63,64} where the ventricles were enlarged to simply approximate the increased size of the heart without representing the structural remodeling (ie, that of fibers and laminar sheets) associated with heart failure.

## SIMULATING ELECTROMECHANICAL ACTIVITY IN THE NORMAL AND FAILING HEARTS

### Structure and Modules of the Multiscale Electromechanical Model

A schematic of the model is shown in Fig. 13–4. It is composed of two coupled parts, electrical and mechanical. Physiologically, as an electrical wave propagates through the heart, the depolarization of each myocyte initiates the release of calcium (Ca) from the intracellular Ca stores, followed by binding of Ca to troponin C and cross-bridge cycling, which forms the basis for contractile protein movement and development of active tension in the cell, ultimately resulting in contraction of the ventricles.

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It is important to note that our electromechanical model is generic and uses any cardiac mesh (idealized-geometry or image-based); its modular structure allows for the use of ionic and myofilament models of any species. Here, we use the DHF canine heart geometry and implement ionic and myofilament models specific to the failing canine myocyte.

**Choice of Species-Specific Ionic and Myofilament Models**

We use the canine ionic model by Fox et al, suitable for organ-level simulations, which we modify to include an equation for Ca buffering by troponin C. For the myofilament model, we use the Rice et al comprehensive yet tractable model of cell mechanics. However, it was developed for the rabbit cell; thus, we modify it to incorporate protein kinetics specific to the canine.

**Modifications in the Ionic and Myofilament Models to Represent Remodeling in Heart Failure at the Cellular Level**

Based on canine-specific heart failure remodeling data from the literature, we implement the following additional changes in the canine ionic models: K channels carrying I_{Ks} and I_{Kr} are downregulated by 66% and 32%, respectively; SERCA pump is downregulated by 62%; and NCX is upregulated by 75%. These alterations in ionic currents result in an altered shape of the canine action potential in heart failure, as shown in Fig. 13–6A, as well as in a Ca transient with reduced magnitude and increased duration, as validated with experimental data. Because the Ca transient serves as an input to the myofilament model, the profile of the active tension developed by the failing myocyte is different from that in the normal cell; it exhibits a reduced peak amplitude and a longer twitch duration (Fig. 13–6B), consistent with experimental findings.

**Electrical and Mechanical Tissue Properties in Heart Failure**

Experimental data have shown lateralization and hypophosphorylation of Cx43 in heart failure. Cx43 controls the passage of current from one cell to the next; accordingly, we decrease the values of the electrical conductivities in the tissue by 30%. To account for the heart failure changes in the tissue mechanical properties, the passive stiffness constant of the exponential strain energy function is increased by 500%, representing altered expression ratios of titin and collagen isoforms.

**Implementing Sinus Rhythm, LBBB, and bi-V Pacing**

To represent activity corresponding to sinus rhythm, the model ventricles are activated at discrete locations along the endocardial
To determine the 3D distribution of electromechanical delay (EMD), the local time difference between myocyte depolarization and onset of myofiber shortening is evaluated throughout the ventricles. Myocyte depolarization is defined as the instant at which the transmembrane potential exceeds 0 mV. Onset of shortening is defined as the instant when local myofiber shortening reaches 10% of its maximal value.

**RESULTS OF SIMULATIONS**

**THE NORMAL CANINE VENTRICLES**

Using the normal canine geometry, several cardiac cycles were simulated during sinus rhythm to demonstrate the feasibility of using the model assembly pipeline to generate ventricular models of electromechanics and simulate electromechanical activity. Figure 13–7 shows the ventricles and laminar sheets near the endocardium in two stages of the cardiac cycle: end-diastole (Fig. 13–7A) and end-systole (Fig. 13–7B).

Temporal traces of transmural strain, active tension from the cardiac myofilament models, and pressure-volume relationships and torsion deformations of the ventricles during contractions are shown in Fig.13–8. The simulated fiber strain (Fig. 13–8A),
which was obtained from the mid-base of the ventricles at locations in the endocardium, midwall, and epicardium, demonstrated prestretching of myofibers during the isovolumic phase of contraction, which agrees with previous experimental findings. The model also reproduces the experimentally observed larger amplitude of shortening at the midwall as compared with myocardial layers located closer to the wall surfaces.

In addition to transmural strain, the model provides information about the transmural stress distribution, which is difficult to obtain experimentally. Figure 13–8B shows the active tension at the same transmural locations as in Fig. 13–8A. Maximum tension developed by myofibers at the midwall is less than that at the endocardium and epicardium due to the faster shortening during the ejection phase. The magnitude of the tension at the endocardium is the largest among the different layers due to the larger end-diastolic strain (with respect to the undeformed, stress-free reference state of the ventricles). The model also provides information about global variables of ventricular contraction such as ventricular pressure and volume. Pressure-volume loops for the LV and RV are shown in Fig. 13–8C.

The model also reproduces well-known features of the ventricular contraction such as apical twisting. Figure 13–8D shows the anterior view of ventricles during contraction and demonstrates clearly twisting of the ventricular apex relative to the base. The angle of apical twist was roughly estimated to be 35° to 40°, which agrees with experimental data.

**THE FAILING CANINE VENTRICLES**

A better understanding of the 3D spatiotemporal interactions between electrical activation and mechanical contraction in the DHF heart will ultimately lead to significant improvements in the selection criteria for CRT candidates and to rational optimization of CRT delivery. The image-based electromechanical model developed here can be used to enhance this understanding. The capabilities of the model were demonstrated in the previous section; here, we illustrate, for the first time, the application of the model to understanding the mechanism and characteristics of electromechanical function in DHF. Specifically, the electromechanical model of the DHF canine ventricles was used here to obtain insight into the electromechanical activation sequence in the DHF heart and how it is altered in bi-V pacing. To do so, we examined the distribution of EMD during LBBB and following bi-V pacing.

**Figure 13–9.** Transmural maps in a short axis view of electrical activation time (A), onset of myofiber shortening time (B), and electromechanical delay (C) during left bundle branch block (LBBB; left) and following biventricular (bi-V) pacing (right). D. Plots of electrical activation times versus mechanical activation times for LBBB (top) and following bi-V pacing (bottom).
In LBBB, electrical and mechanical activations begin from the RV endocardium and propagate toward the LV lateral wall. Following bi-V pacing, the depolarization wave propagates from the pacing sites (the RV endocardial apex and the LV epicardial base) toward the LV anterior and posterior wall; in general, mechanical activation proceeds in the same direction.

The corresponding transmural maps of EMD are shown in Fig. 13–9C and demonstrate that the 3D distribution of EMD is heterogeneous for both LBBB and following bi-V pacing. In LBBB, EMD is longest at the late-depolarized lateral wall. Following bi-V pacing, EMD at the lateral wall was reduced and shorter than that at the anterior and posterior walls. Regression analysis of myofiber shortening onset times versus the electrical activation times is shown in Figure 13–9D. For both LBBB and bi-V, the slope of the regression lines was greater than 1, indicating that as depolarization occurred later, the onset of myofiber shortening was progressively more delayed; thus, regions that were depolarized later were characterized with a longer EMD.

Why would examining the distribution of EMD in the DHF heart be important to CRT? Previous studies have demonstrated that the LV pacing location is important for optimizing CRT response; however, it is unclear what criteria should be used to determine the optimal pacing location. The results presented in this section suggest that minimizing the regions with extended EMD may be the approach to optimizing CRT therapy.

### CONCLUSION

This chapter presents an overview of DHF, CRT, and the image-based electromechanical model developed in our lab that has demonstrated high hope for uncovering the mechanisms of electromechanical dyssynchrony, for optimization of CRT, and for possible personalized approach to the therapy. The chapter focuses, to a large extent, on the actual development of the electromechanical model and its features and, in particular, the fact that the model is developed from high-resolution MRI and DTMRI scans, allowing for an individualized approach to understanding cardiac electromechanical dysfunction. Such an image-based approach takes into account the structural remodeling of the individual failing heart and allows for seamless integration with other simulation tools such as mesh generation from segmented images and simulation of electrical and mechanical function, as presented here. The new electromechanical model presented here opens a new avenue for exploring cardiac electromechanical behavior and presents possibilities for translating the approach to patient-specific approaches to CRT optimization.

### REFERENCES


SECTION II: Foundations of Future Methods for Cardiovascular Multimodal Imaging


