Relationship Between Regional Shortening and Asynchronous Electrical Activation in a Three-Dimensional Model of Ventricular Electromechanics

TARAS P. USYK, PH.D., and ANDREW D. MCCULLOCH, PH.D.

From the Department of Bioengineering, The Whitaker Institute for Biomedical Engineering, University of California, San Diego, La Jolla, California, USA

Three-Dimensional Ventricular Electromechanics. Introduction: Asynchronous electrical activation can cause abnormalities in perfusion and pump function. An electromechanical model was used to investigate the mechanical effects of altered cardiac activation sequence.

Methods and Results: We used an anatomically detailed three-dimensional computational model of the canine ventricular walls to investigate the relationship between regional electrical activation and the timing of fiber shortening during normal and ventricular paced beats. By including a simplified Purkinje fiber network and anisotropic impulse conduction in the model, computed electrical activation sequences were consistent with experimentally observed patterns. Asynchronous time courses of regional strains during beats stimulated from the left or right ventricular epicardium showed good agreement with published experimental measurements in dogs using magnetic resonance imaging tagging methods. When electrical depolarization in the model was coupled to the onset of local contractile tension development by a constant time delay of 8 msec, the mean delay from depolarization to the onset of systolic fiber shortening was 14 msec. However, the delay between the onset of fiber tension and initial shortening varied significantly; it was as late as 60 msec in some regions but was also as early as −50 msec (i.e., 42 msec before depolarization) in other regions, particularly the interventricular septum during free-wall pacing.

Conclusion: The large variation in delay times was attributable to several factors, including local anatomic variations, the location of the site relative to the activation wavefront, and regional end-diastolic strain. Therefore, we conclude that these factors, which are intrinsic to three-dimensional ventricular function, make the regional sequence of fiber shortening an unreliable surrogate for regional depolarization or electromechanical activation in the intact ventricles. (J Cardiovasc Electrophysiol, Vol. 14, pp. S196-S202, October 2003, Suppl.)

cardiac electromechanics, pacing, conduction abnormalities, finite element method

Introduction

Asynchronous electrical activation, induced by an ectopic focus or ventricular pacing, can cause abnormalities in perfusion and pump function and, when chronic, can lead to asymmetric ventricular hypertrophy. These may all be directly or indirectly related to heterogeneity in regional workload and shortening.

Assessing the magnitudes of regional myocardial work requires knowledge of regional myofiber stress and strain. Whereas some variables, such as regional strains and epicardial activation patterns, have been measured in the intact heart, practical experimental methods for mapping threedimensional distributions of other important variables such as stress, strain energy, or transmembrane potential still are not available.

Ectopic activation can adversely affect ventricular function by decreasing stroke volume, contractility, end-diastolic volume, and the synchrony of shortening. Conversely, by optimizing the sequence of electrical activation, pump function can be significantly improved in the failing heart. The pattern and timing of myocyte stretch and contraction affect the electrical properties of the myocytes. Therefore, it is important to understand the relationship between the spatiotemporal pattern of ventricular electrical activation and the regional distribution and sequence of mechanical strain.

To investigate the mechanical effects of altered cardiac activation sequence, some investigators have mapped ventricular electrical activity and regional contraction simultaneously in experimental animals. Wyman et al. mapped bipolar electrograms on the epicardium in anesthetized dogs and registered the activation patterns with the sequence of local midwall fiber shortening measured in the same preparations by magnetic resonance imaging tagging during ventricular pacing. These measurements showed a significant linear correlation between electrical depolarization time and the timing of the onset of regional fiber shortening. However, the extent to which the variability observed in this relation was due to measurement error or the effects of unknown systematic factors such as regional anatomy and stress distributions remains unknown. We used an anatomically detailed three-dimensional model of canine ventricular electromechanics to test the hypothesis that there is a 1:1 relationship between the timing of electrical activation and the onset of fiber shortening. We assumed a constant time delay of 8.4 msec between regional
electrical activation and the onset of systolic fiber tensor development. In spite of this assumption, the model predicted significant variations in the computed delay time between electromechanical activation and shortening onset times. In some regions, shortening was delayed by up to 60 msec after electrical activation, whereas in others it actually preceded depolarization by as much as 50 msec. The model was used to investigate the mechanisms of these variations.

**Methods**

We used a three-dimensional model of canine left ventricular (LV) and right ventricular (RV) anatomy with detailed Purkinje fiber network, myofiber, and sheet architecture that was developed from measurements in the canine heart. Pressure boundary conditions were specified as a nonlinear, orthotropic, and nearly incompressible degrees of freedom.

The resulting 48-element tricubic Hermite mesh had 1,200 degrees of freedom and was used as the computational domain for simulating passive inflation and active contraction of the LV and RV. The model for electrical impulse propagation was based on the same anatomic mesh but required additional refinement to 768 tricubic elements and 19,200 degrees of freedom.

In the present analysis, the resting myocardium was modeled as a nonlinear, orthotropic, and nearly incompressible material. Pressure boundary conditions were specified on the LV and RV endocardial surfaces during filling.

Nonlinear membrane ionic kinetics were modeled using the two-variable modified FitzHugh-Nagumo equations, and impulse propagation was modeled using a monodomain formulation. The contribution of the Purkinje fiber network to ventricular conduction was modeled by adding an extra diagonal diffusion tensor, representing conductivity along the Purkinje fibers on the luminal surfaces of the endocardial elements. The ECG was calculated by summing up all the transmembrane potential gradients weighted by the distance from the area of initial activation. Electrical activation time was defined as the instant when transmembrane potential reached the value of $-40$ mV, and it was used to initiate regional systolic tension development following a constant delay of 8.4 msec. This latter time (electrical activation time plus 8.4 msec) we refer to as **contractile activation time**.

The model of active contraction computed regional stress as the sum of the passive three-dimensional stress tensor derived from a nonlinear orthotropic strain energy function and the active stress as a function of peak intracellular calcium and sarcomere length with transverse active stress components. A Windkessel model for arterial impedance was coupled to ventricular pressure and volume to compute the hemodynamic boundary conditions. Ventricular cavity volume constraints were imposed during the isovolumic phases. The details of the formulation and solution of the electromechanical model were described in detail previously for the case of normal activation stimulated from the base of the septum.

Following the definition of “mechanical activation time” used by Wyman et al., we determined **shortening onset time** in the model as the time of peak positive fiber strain, that is, the instant during systole that local fiber length first started to decrease. **Activation-shortening delay** then was computed as the difference between contractile activation time and shortening onset time at each point in the model. A negative delay means that the region began to shorten before the myofilaments at that site had begun to develop systolic tension.

**Results**

The calculation of the model of passive and active mechanics required 125 Mb of main memory and ran for approximately 20 minutes and 6 hours, respectively, on a single processor of a Silicon Graphics Origin 2100. The model of electrical propagation required 2.8 Gb of main memory and ran for approximately 72 hours on this platform.

All three-dimensional passive strain components (calculated with an orthotropic constitutive law) at the basal and apical regions were within 1 SD of measurements in anesthetized dogs, as shown earlier by Usyk et al. Diastolic displacements were smaller near the base, where the model was constrained.

Normal activation was modeled by stimulating the model at the base of the septum. With this His-bundle pacing, activation started on the left septal surface. In general, activation proceeded from left to right and in an apical-basal direction, as shown in Figure 1. Wavefront progress around the cavity was much more rapid than the spread toward the epicardium. The latest activation was seen in posterobasal areas of the LV and RV. These results are consistent with experimental recording from human hearts and dog hearts.

In the model of LV pacing, a wave of electrical activation emanated from the pacing site and traveled around the heart in both directions until it converged at the opposite wall. The model of RV pacing also showed a wave of propagation.

**Figure 1.** A: Model results for pacing from the His bundle. B: ECG activity computed in the model of normal ventricles.
starting near the pacing site and moving to the opposite free wall. For basal LV pacing, the total electrical activation time was 107 msec, and for RV basal pacing it was 122 msec.

In the ECG calculated from the three-dimensional model of normal rhythm (Fig. 1), there is no P wave and the T wave is inverted. Repolarization proceeded in the same sequence as depolarization because the ionic current parameters and action potential duration were spatially homogeneous. However, the mechanical solutions in this model only depended on depolarization times.

Using the model to investigate the mechanical effects of different ectopic beats, we compared stress and strain time courses at the LV lateral wall, mid-septal wall, and RV wall sites (Fig. 2). Significant differences in strains and stresses were found for all investigated regions. Peak fiber stress was lowest at the pacing site, highest in areas remote from the pacing site, and significantly higher during ectopic than normal beats.

Using the model to investigate the mechanical effects of pacing from the LV free wall, close agreement was obtained with spatiotemporal distributions of three-dimensional strain observed experimentally in dogs by Wyman et al.\(^3\) using tagged magnetic resonance imaging (Fig. 3). Similar agreement was seen for the model of RV pacing.

Using the methods of Wyman et al.\(^3\) to calculate shortening onset time (termed “mechanical activation time” by those authors) from fiber strains in the model, we found that the latest shortening onset time was 135 msec during LV (basal) pacing and 130 msec during RV (apical) pacing. This is consistent with the experimental data,\(^3\) which showed mean shortening onset time for 90% activation of 130.2 ± 9.8 msec for LV basal pacing and 121.3 ± 17.9 msec for RV apical pacing.

External fiber work, calculated from fiber stretch-stress relationship at the early and late activated regions during LV and RV pacing, was very small (or even negative) at the pacing

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**Figure 2.** Comparison of fiber stress and strain time courses at the left ventricular (LV) lateral wall, mid-septal wall, and right ventricular (RV) wall during normal and ectopic beats. The time of the onset of LV ejection is also shown for normal and ectopic beats.
site and increased up to twice that of normal values in regions remote from the site of pacing.

Average normalized passive fiber stress just prior to electrical activation \( (T_{ff}/T_{ff}\text{(end diastole)}) \) was slightly higher in the areas of late activation (1.25) and lower in the areas of early activation (0.92) for all three pacing models. Similarly, regions of higher average presystolic fiber stress tended to have a longer activation-shortening delay (27, 20, and 7 msec for normal activation, LV pacing, and RV pacing, respectively), whereas lower mean stresses were found in regions with negative delays (−3, −7, and −25 msec for normal activation, LV pacing, and RV pacing, respectively); however, the correlation between these variables was weak. As expected, there was a strong correlation between the time of peak passive fiber stress and shortening onset time (Fig. 4), independent of distance from the pacing site. This reflects the fact that regardless of whether initial fiber shortening reflects passive unloading or active fiber tension development, the result is to reduce passive fiber strain and thus decrease passive stress.

During ectopic beats, three different temporal patterns were observed. There were prestretched regions, early shortening, and minimal shortening. Using the methods of Wyman et al.\(^3\) to define shortening onset time in different regions of the ventricular walls, we found a significant (\(P = 0.08\)) but weak (\(r^2 = 0.69\)) correlation between contractile activation time and shortening onset time for normal activation and ventricular pacing (Fig. 5). However, even in the absence of experimental noise, the delay between the onset of shortening

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**Figure 3.** Systolic fiber strains referred to the end-diastolic state at basal and apical sites during left ventricular pacing. Model results and experimental magnetic resonance imaging (MRI) data are compared for four different regions (septum, anterior, lateral, and posterior).

**Figure 4.** Relationship between the time of peak passive fiber stress and the time of onset of shortening. Both peaks occur at almost the same time and are not dependent on distance to the pacing site.

**Figure 5.** Shortening onset time versus corresponding electrical activation time. Solid line shows contractile activation time defined in the model as a constant delay after electrical activation. LV = left ventricular; RV = right ventricular.
and contractile activation showed a significant variation for all pacing sites, including regions of negative delay, where shortening began before contractile activation.

Figure 6 shows color maps of electrical activation time for all three pacing conditions. The first column represents contractile activation time, which is simply a constant delay following the electrical activation time; the second column represents shortening onset time; and third column represents the activation-shortening delay, which is the difference between the first two maps. Whereas the LV contractile activation maps showed a steady and consistent propagation of activation, RV contractile activation maps showed a more complex pattern of activation, especially around the septum. Those observations also are consistent with experimental reports. Figures 7 and 8 show how activation-shortening delay varies with anatomic location and distance from the pacing site.

Discussion

A three-dimensional computational model of ventricular electromechanics was developed to study the role of electrical propagation on mechanical activation during the cardiac cycle. The model showed good agreement with experimental data in end-diastolic and end-systolic strain and showed realistic time courses of strain during normal electrical activation and ventricular pacing. The results also demonstrate a significant role of the Purkinje fiber system during normal and ectopic beats on the contractile activation sequence, as expected. Owing to the significant computational and memory requirements, the electrophysiologic model was simplified in this study. In order to model more realistic electrical activation patterns, it will be desirable to use more detailed models of ionic currents, their spatial heterogeneity, and Purkinje fiber anatomy, which will require significantly higher spatial and temporal refinement in the computations.

Studies in canine hearts have shown that earliest electrical activity during normal activation occurs in a central area on the left septal surface. Those experiments showed that the septal vector is directed from left to right and from apex to base. Consistent with these observations, the model showed early activation of the septum progressing primarily from left to right (Fig. 1).

The model shows that after about 20 msec, the normal activation front moved around the ventricular cavity. This movement around the cavity was much more rapid than the spread toward the epicardium. Earliest LV epicardial activation during normal conduction occurred 30 msec after stimulation. The latest part of the LV wall to be activated was the posterobasal area, also in agreement with experimental observations. Early epicardial breakthrough occurred 20 to 25 msec after activation of the His bundle. Excitation spread rapidly from the His bundle to the right and left bundle branches and significantly slower through the rest of the myocardial tissue. The numerical results were similar to experimental findings, showing LV depolarization...
occurring within 40 to 55 msec. Complete depolarization of the septum during normal activation occurred within 20 msec,16 and the depolarization wave crossed the wall from endocardium to epicardium within about 15 to 18 msec.21

Some experimental studies have shown another early activation site in the posterior paraseptal area at about one third of the distance from apex to base.15 These results were not seen in the model and may be due to a paucity of detail on Purkinje fiber network structure in the model at the RV septum.

Computed strains showed that the tissue shortened rapidly in the early activated regions, and shortening was preceded by prestretching (Fig. 3). This prestretching was a result of passive stretching of the late-activated regions in response to contraction of the tissue activated earlier. Contraction in the prestretched regions did not begin until a delay of about 40 msec after the earliest activation time. Three basic temporal patterns were observed during pacing: prestretched regions, early shortening, and relatively no shortening. Prestretch is defined as lengthening that takes place after normal diastole due to contraction of other parts of the wall. Those results also show that in early-activated regions, the tissue stretched during ejection (after rapid shortening during isovolumic contraction), consistent with the experimental measurements of Waldman and Covell.22

A limitation of the model is our assumption of a constant delay between electrical and contractile activation. However, even with this assumption, we found significant variation between contractile activation time and shortening onset time. The magnitudes of the computed activation-shortening delays were large compared with the electromechanical activation delay. Any variability in electromechanical activation delays is likely to be far smaller than the large variation seen in the activation-shortening delay. Using results of the model study, we investigated which factors influence the variability in the
relation between electrical activation time and shortening onset time. It is clear from Figure 6 that activation-shortening delay varies with anatomic region and distance from the pacing site, and that the time of onset of shortening does not predict true “contractile activation time” reliably. Because these differences were observed in a numerical model, they cannot be attributed to experimental noise or random errors.

Figure 6 shows that, overall, shortening in the model was more likely to begin after the onset of contractile activation, but it also can occur before. RV pacing has significantly higher proportion of regions where shortening began before contractile activation. Areas where shortening began before contractile activation were often found at the septal wall. During ventricular pacing, this may reflect unloading of the septum before activation by activation of the free walls. During LV pacing, the areas where shortening began before contractile activation were found mostly on the LV free wall and during RV pacing on the RV free wall. Thus, activation-shortening delay tended to increase from early-activated sites to late-activated sites.

Another mechanism by which shortening could occur before activation is by unloading of the endocardium by activation of epicardial layers during epicardial pacing and conversely by unloading of epicardial segments when underlying endocardial regions are activated first. Activation-shortening delays segregated by transmural location (Fig. 8) were shorter and more often negative in epicardial segments than endocardial fibers, especially during His-bundle pacing that resulted in activation proceeding from endocardium to epicardium in almost all regions. Even during epicardial pacing, the greatest mass of the myocardium was activated in this direction, except near the pacing site.

Just prior to mechanical activation, we found that average fiber stress was slightly higher in the areas of late activation and lower in the areas of early activation for all three pacing models. Similarly, higher average fiber stresses were found in the areas with positive activation—shortening delays, although correlations were weak compared with the relationship between the timing of peak passive fiber stress and the onset of shortening. Therefore, it is the effect of the activation pattern on regional stress distributions rather than simply on local myofilament activation that determines timing of fiber shortening.

Conclusion

Although a constant delay between electrical excitation and contractile activation is able to reproduce many of the features of regional mechanics during pacing, the model showed that the timing of the onset of shortening is not a very accurate predictor for true contractile activation, with activation-shortening delay varying from ~50 to +60 msec. This large variation in delay times was attributable to several factors, including local anatomic variations, the location of the site relative to the activation wavefront, and the regional end-diastolic strain and stress.

References