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EDITORIAL COMMENT

Regional Left Ventricular Electric and Mechanical Activation and Relaxation*

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There has recently been a strong clinical interest in assessing synchronization of myocardial function in heart failure patients. There are still a number of unresolved issues that relate to intra- as well as interventricular synchronization, and there is need for better insights into the mechanisms that control regional timing of myocardial contraction and relaxation. The study by Sengupta et al. (1) in this issue of the *Journal* puts focus on the physiology of electromechanical activation and relaxation of the intact ventricle.

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Most studies of left ventricular (LV) activation have measured timing of either electric (2,3) or mechanical events (4). Prinzen et al. (5) measured both electric and mechanical activation of the LV, but measurements were limited to the epicardial surface. In the study of Sengupta et al. (1), measurements were done simultaneously in the subendocardium and subepicardium of regional electric events (depolarization and repolarization) and onset of regional mechanical shortening and lengthening in the anterior wall of the porcine LV. The researchers found that the apical level is activated before the basal level and that the subendocardium is activated before the subepicardium. However, the delay between depolarization and onset of mechanical shortening is longer in the basal region than in the apical region. The mechanical relaxation sequence showed no clear pattern and no clear relation to repolarization.

The measured propagation of electric activation is in agreement with previous studies (2), and also Prinzen et al. (5) measured an increased delay between electric and mechanical activation in late-activated regions. However, the mechanism behind the increased delay is yet to be determined. From a physiologic viewpoint, it makes sense that the base contracts after the apical part, as a reverse pattern would squeeze the blood in the direction of the apex away from the aortic valve.

Assessment of regional myocardial function in relation to fiber orientation is challenging because of the complex architecture of myocardial fibers. In the subendocardium, the fibers have an approximately longitudinal orientation, with an angle of about 80° with respect to the circumferential direction. The angle decreases toward the midwall, where the fibers are oriented in the circumferential direction (0°), and decreases further to an oblique orientation of about −60° in the subepicardium (Fig. 1). This fiber orientation appears to be essentially similar in humans (6,7) and other mammalian species, including dogs and pigs (8,9). The present study (1) assesses deformation in longitudinal and circumferential directions. It is only in the subendocardium, however, that the myofiber orientation is in approximate alignment with one of the measured directions, i.e. the longitudinal direction, and the subendocardium therefore is the only wall layer in which electric events may be directly compared with onset of myofiber shortening and lengthening. In the subendocardium, the onset of longitudinal shortening follows the sequence of electric activation from apex to base. In the subepicardium, the fibers are oriented at an angle both to the longitudinal and circumferential directions, and it is therefore difficult to interpret measured deformation in these two directions in relation to electric events. Tethering effects from shortening of the circumferential fibers in the midwall and the longitudinal fibers in the subendocardium may blur the relationship further.

As demonstrated by Sengupta et al. (1), differences in timing of contraction exist not only between segments, but also between longitudinal and circumferential shortening within the same segment. These differences reflect earlier electric activation of subendocardial fibers, with predominantly longitudinal orientation, than of midwall and subepicardial fibers with more circumferential orientation. Theoretically, abnormalities in endocardial to epicardial activation may disturb the fine coordination of shortening and lengthening of myocardial fibers that normally occurs with different orientation. It remains to be determined, however, whether delay in endocardial to epicardial activation is of significance for ventricular function and, more importantly, whether abnormalities in endo- to epicardial activation may contribute to LV dysfunction in heart failure. Investigation of these principles in humans is now possible through magnetic resonance tagging (10), tissue Doppler echocardiography (11), and the more recent modality of speckle tracking echocardiography (12). A recent study by Helm et al. (13) that used three-dimensional magnetic resonance tagging showed that longitudinal strains were less sensitive than circumferential strains as markers of dyssynchrony, suggesting that it may be important to take fiber orientation into account when assessing LV function.

In addition to a direct negative effect on stroke volume, dyssynchrony may cause abnormal myocardial stresses that may lead to local hypertrophy and remodeling. This effect was suggested by Prinzen et al. (14), who showed that relatively small temporal differences in electric activation were associated with increased shortening in late activated areas owing to abnormal fiber stretch before contraction.

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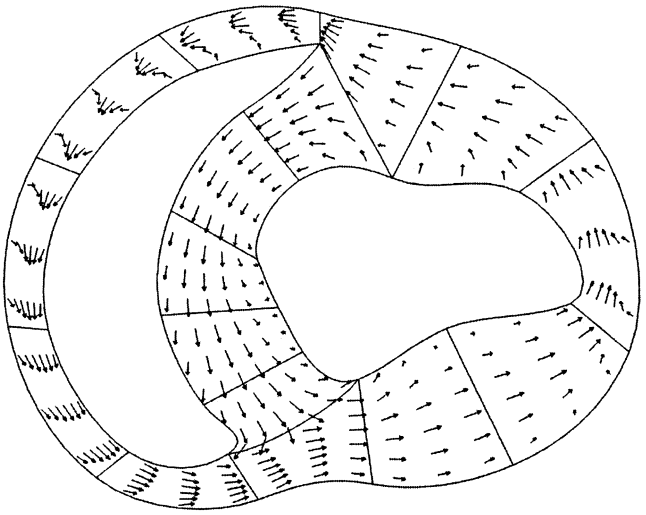

Figure 1. Measured fiber directions in a pig heart. Fiber direction vectors are projected onto a two-dimensional cross-section viewed from base toward apex. All fibers are drawn as vectors with the same length, so the more longitudinally aligned fibers, particularly in the subendocardium, have a smaller projection onto this plane than the circumferentially aligned midwall fibers. (The apparent inward orientation of some of the subepicardial and subendocardial fibers reflects the taper of the wall, out of the plane of this projection, and does *not* indicate a nonzero imbrication angle.) Reprinted from reference 9 with permission.

This in turn leads to increased local work and might be a stimulus to regional hypertrophy. The latter notion is supported by the study of Spragg et al. (15), who used a canine model of dyssynchrony that demonstrated modulation of myocardial protein expression in late-activated locations with increased hemodynamic load. It remains to be studied, however, whether moderate disturbances of intraventricular conduction in humans can modulate regional wall stress and gene expression.

The study of Sengupta et al. (1) provides many interesting measurements and results that raise new questions. Some of their findings, however, may be model dependent and may not reflect human physiology. In addition, we should be careful about extrapolating measurements from a small region to the whole wall, as both electric activity and mechanical deformation may be more heterogeneous. Their study, however, puts focus on the important relationship between regional electric and mechanical activation and relaxation. We expect that future studies with newer cardiac functional imaging modalities will provide us with a better understanding of the electromechanical coupling in the in vivo heart.

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