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The renin-angiotensin system regulates transmural electrical remodeling in response to mechanical load

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Contents

1. Introduction: The history of the T-wave and transmural heterogeneity

Initial studies first documenting electrical activity in the heart defined two electrical events, which we now know correlate with excitation and repolarization (Burdon-Sanderson and Page, 1880, 1883). If excitation occurs at a particular site and repolarization also starts at the same site, then given the opposite polarity of the currents flowing, the wave of excitation (the QRS complex) should evince an opposite polarity to that of repolarization (the T-wave). Indeed in these initial studies of Burden-Sanderson and Page using the frog heart, the QRS complex was of opposite polarity to the T-wave. However with the recording of the initial large animal and human EKGs (Waller, 1887; Mines, 1913; Bayliss and Starling, 1892; Einthoven, 1913), the QRS complex had the same polarity as the T-wave, implying that the spread of depolarization was in the opposite direction to the spread of repolarization. This could only occur if the action potential was shorter where repolarization was initiated than where excitation began. This conclusion is further supported by the additional conduction time from the excitation point to that where repolarization began. Thus, more than half a century prior to the first microelectrode recordings (Ling and Gerard, 1949), it was clear that there was a difference in the electrical activity of the endocardial base where the action potential was initiated in the ventricle and the epicardial apex where the wave of repolarization began. The questions became 1) how was this electrical "heterogeneity" generated, and 2) for what purpose?

2. Multiple types of heterogeneity exist within the ventricular wall

Following the discovery of the microelectrode (Ling and Gerard, 1949), it became possible to record action potentials from a single cell within a section of cardiac tissue. The first detailed characterization of all these different results was presented in the text by Hoffman and Cranefield (1960). However, recording from cardiac myocytes within a tissue did not allow separation of differences in ion currents due to differing electrical properties from those due to differences in anatomy (like restricted extracellular spaces where

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ion concentrations could change during electrical activity). Indeed one explanation of the differences in transmural electrical activity proposed differences in extracellular anatomy in the EPI and ENDO allowing for different changes in driving force. The authors' argument was that the differences in APD disappeared with a sufficient period of quiescence (Cohen et al., 1976). However with the advent of the patch clamp technique (Hamill et al., 1981) and dissociation protocols to permit the study of individual mammalian cardiac myocytes (Isenberg and Klockner, 1982), it was possible to record action potentials from individual heart cells. From these studies it was clear that some of the EPI, ENDO differences were due to the gating and ion transport properties of individual ion currents. There seemed to be two types of heterogeneity. One that existed transmurally and could be responsible for the surprising polarity of the T-wave (Noble and Cohen, 1978), and others that differed specifically in the midmyocardium, whose isolated myocytes had longer action potential durations (APDs) than those close to either surface (Isenberg and Klockner, 1982). The first current discovered to be distributed transmurally was the transient outward potassium current I_{to}, which was larger in EPI than in ENDO (Furukawa et al., 1990; Liu et al., 1993; Clark et al., 1993; Nabauer et al., 1996; Brahmajothi et al., 1999). Since i_{to} is an outward current, which contributes to repolarization, the larger it is, the shorter the expected APD (Dong et al., 2010). Since it is larger in EPI than ENDO, it alone should make the EPI APD shorter than that in ENDO. Other currents like the persistent Na current I_{NaP} are largest in the midmyocardium (Zygmont et al., 2001). Since I_{NaP} is an inward current, it should contribute to making the APD of midmyocardial (M) cells

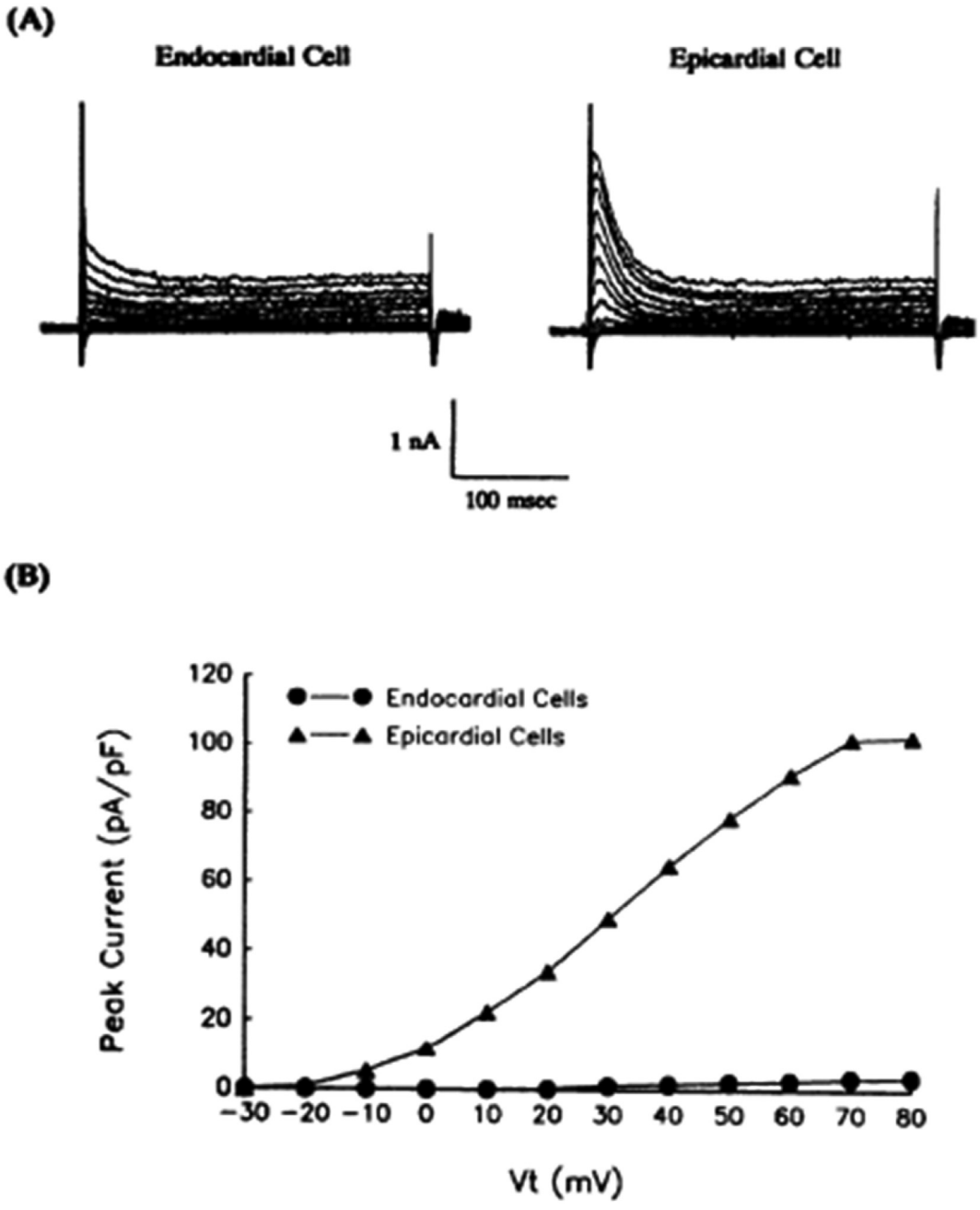

Fig. 1. Comparison of transient outward current in feline ventricular ENDO and EPI myocytes (Furukawa et al., 1990).