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In vivo human demonstration of phase 2 reentry

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The presence of a prominent notch in the action potential of ventricular epicardium but not endocardium gives rise to a transmural voltage gradient during ventricular activation that manifests as a late delta wave following the QRS or what is commonly referred to as a *J wave*[1] or *Osborn wave*. The J wave and elevated J point have been described in the ECG of animals and humans for more than five decades, since Osborn's observation in the early 1950s.[2] In humans, the appearance of a prominent J wave on the ECG is considered pathognomonic of hypothermia,[3-6] hypercalcemia,[7,8] or sudden death syndromes, including idiopathic ventricular fibrillation (VF),[9] ischemia/reperfusion-induced VF,[10] and the Brugada syndrome.[11] A distinct J wave is commonly observed in the ECG of some animal species, including baboons and dogs, under baseline conditions and is greatly amplified under hypothermic conditions.[12-14] An elevated J point is commonly encountered in humans and some animal species under normal conditions.

A transmural gradient in the contribution of the transient outward current (I_{to}) is responsible for the transmural gradient in the magnitude of phase 1 and action potential notch, which in turn inscribes the J-wave or J-point elevation in the ECG.[1,15-18]

The presence of a prominent I_{to}-mediated notch predisposes canine ventricular epicardium to all-or-none repolarization and phase 2 reentry. Under pathophysiologic conditions (e.g., ischemia, metabolic inhibition, genetic defects in *SCN5A)* and with some pharmacologic interventions (e.g., I_{Na} or I_{Ca} blockers or $I_{K\text{-}ATP}$ activators), canine ventricular epicardium exhibits an accentuation of the notch leading to loss of the action potential dome secondary to a rebalancing of currents flowing at the end of phase 1 of the action potential. The dome fails to develop when the outward currents (principally I_{to}) overwhelm the inward currents (chiefly I_{Ca}), resulting in a remarkable (40–70%) abbreviation of the action potential. Loss of the action potential dome is seldom homogeneous. The action potential dome usually is abolished at some epicardial sites but not others, causing a marked dispersion of repolarization within the epicardium. Conduction of the action potential dome from sites at which it is maintained to sites at which it is abolished can cause local reexcitation of the preparation. This mechanism, termed *phase 2 reentry*, produces closely coupled extrasystolic beats capable of initiating circus movement reentry.[19] It is termed phase 2 reentry because phase 2 (dome) of the action potential reenters to reexcite the myocardium.

Electrical heterogeneity has been shown to give rise to phase 2 reentry in canine epicardium exposed to (1) K^+ channel openers such as pinacidil[20]; (2) sodium channel blockers such as flecainide[21]; (3) combined sodium and calcium channel block, as with terfenadine[22]; (4) increased $[Ca^{2+}]_o$[23]; (5) metabolic inhibition[15]; and (6) ischemic conditions.[10,19] Block of I_{to} restores the action potential dome, thus restoring electrical homogeneity and abolishing reentrant activity in all cases.

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Accentuation of the epicardial action potential notch and/or loss of the action potential dome can appear in the ECG as an elevated J point, accentuated J wave, or ST-segment elevation, all manifestations of the pronounced transmural voltage gradient.

In this issue of *Heart Rhythm*, Thomsen et al[24] provide for the first time evidence supporting the hypothesis that a phase 2 reentrant mechanism underlies arrhythmic activity arising from the right ventricle, often the right ventricular outflow tract. The authors demonstrate J-point elevation, ST-segment elevation, and T-wave changes in the sinus beat preceding ventricular extrasystoles and/or nonsustained ventricular tachycardia in 15 of the 18 patients (83%) studied. Although indirect, the evidence is compatible with phase 2 reentry as the mechanism responsible for ventricular extrasystoles and nonsustained ventricular tachycardia in man, a mechanism previously described only in experimental models.

The mean coupling interval of the extrasystoles ranged from 300 to 505 ms, with half of the patients showing relatively long coupling intervals of 400 ms or longer. Although phase 2 reentrant beats are expected to manifest relatively short coupling intervals in the ECG, the initial phase 2 reentry often is buried and therefore concealed in the T wave of the preceding sinus beat.[22] Under these conditions, only the second beat (first epicardial or intramural circus movement reentrant beat) is clearly discernible in the ECG, accounting for the longer apparent coupling interval for the phase 2 reentrant beat.[22]

These characteristics of the J wave and ST segment have been linked to idiopathic ventricular fibrillation and the Brugada syndrome.[25-28] The Brugada syndrome is characterized by ST-segment elevation (or exaggerated J wave) in the right precordial leads, leads V_1 to V_3 (unrelated to ischemia, electrolyte abnormalities, or structural heart disease), normal QT interval, and a high incidence of sudden cardiac death due to ventricular tachycardia or VF.[25]

In experimental models of the Brugada syndrome, loss of the epicardial action potential dome is caused by an outward shift in the balance of currents active during the early phases of the action potential, principally I_{to} and I_{Ca}. Autonomic neurotransmitters such as acetylcholine facilitate loss of the action potential dome[29] by suppressing I_{Ca} and/or augmenting potassium current. Beta-adrenergic agonists restore the dome by augmenting I_{Ca}. Sodium channel blockers also facilitate loss of the canine right ventricular action potential dome via a negative shift in the voltage at which phase 1 begins.[21,30] These findings are consistent with clinical reports of accentuation of ST-segment elevation in patients with Brugada syndrome following vagal maneuvers or administration of class I antiarrhythmic agents and of normalization of the ST-segment elevation following beta-adrenergic agents.[1,31] The appearance of ST-segment elevation only in the right precordial leads in Brugada patients is consistent with the finding that loss of the action potential dome is encountered much more commonly in right vs left canine ventricular epicardium.[15,32] The Brugada syndrome is a right ventricular disease because I_{to} density is intrinsically much greater in right vs left ventricular epicardium.[33] This observation is consistent with the finding by Thomsen et al that arrhythmic activity associated with J-point or ST-segment elevation generally arises from the right ventricle.

Because a prominent I_{to} is pivotal to this arrhythmogenic mechanism, agents that inhibit I_{to}, including quinidine, are effective in restoring the action potential dome, thus restoring electrical homogeneity and aborting all arrhythmic activity in experimental models of the Brugada syndrome[34] and in the clinic.[35-37] Future studies might be directed at examining the effectiveness of quinidine or more specific I_{to} blockers, as they become available, on the extrasystolic activity characterized by Thomsen et al as a further test of the hypothesis that phase 2 reentry underlies this activity and as an alternative approach to therapy.

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