# Cellular Basis for ST-Segment Changes Observed During Ischemia

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**Abstract:** This study probes the cellular basis for ischemia-induced ST-segment elevation with the isolated arterially perfused canine ventricular wedge preparation. Transmembrane action potentials (AP) from epicardial (Epi) and endocardial (Endo) regions, a pseudo-electrocardiogram (ECG), and 5 intramural unipolar electrograms were simultaneously recorded at a basic cycle length of 800 or 2,000 ms. Global ischemia was induced by an abrupt interruption of coronary flow for 30 minutes. Under control conditions, the ST segment was isoelectric because of the absence of voltage gradients at the level of AP plateau among the cells spanning the ventricular wall. Global ischemia could cause an all-or-none repolarization at the end of phase 1 of the AP in Epi but not Endo leading to ST-segment elevation and extrasystolic activity secondary to phase 2 re-entry. In the majority of preparations, global ischemia resulted in a progressive increase in transmural conduction time after 25 to 30 minutes of interruption of flow caused by a step delay of impulse transmission in the midmyocardium. The ECG assumed a "tombstone" configuration. Correlation of the APs and ECG activity revealed that the apparent severe ST-segment elevation encountered under these conditions is actually a markedly prolonged R wave. In control, Endo repolarized after Epi yielding upright T waves in the ECG. After 30 minutes of ischemia Epi repolarized after Endo causing reversal of repolarization gradients and T-wave inversion. The ischemia-induced electrophysiologic changes returned to nearly control values within 5 minutes of reperfusion. Our results indicate that 2 distinctly different mechanisms involving 1) loss of the epicardial action potential dome and 2) markedly delayed transmural conduction underlie the apparent ST-segment elevation encountered during acute ischemia. **Key words:** Ischemia, ST-segment elevation, T-wave inversion.

The electrocardiogram (ECG) has long been recognized as an important tool for the diagnosis and localization of acute myocardial ischemia and infarction. Under these conditions, changes in the surface ECG are thought to be related to changes in the resting potential, action potential morphology, action potential duration, and conduction characteristics of the injured myocardial region (1–3). Current concepts regarding the pathophysiological mechanisms underlying myocardial ischemia-induced changes in the ECG derive principally from theoretical models since attempts to record action potentials form discrete transmural sites of the ischemic myocardium *in vivo* have generally been limited to the epicardial surface (4–6).

The present study attempts to overcome this

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limitation by assessing the cellular basis for the electrocardiographic changes attending ischemia in the isolated canine ventricular wedge preparation.

## Materials and Methods

Adult male mongrel dogs weighing 20 to 25 kg were anticoagulated with heparin and anesthetized with sodium pentobarbital (30-35 mg/kg, intravenously). The chest was opened via a left thoracotomy, the heart excised, placed in Tyrode's solution and transported to a dissection tray. Transmural right ventricular wedges with dimensions of approximately 9 mm × 25 mm × 10 mm were dissected from the mid-to-basal region of the right ventricular wall and a descending branch of the right coronary artery was cannulated to deliver the perfusate (Tyrode's solution). The composition of the Tyrode's solution was (in mmol/L): NaCl 129, KCl 4, NaH2PO4 0.9, NaHCO3 20, CaCl2 1.8, MgSO4 0.5, and D-glucose 5.5; pH=7.4.

Transmembrane action potentials were simultaneously recorded from epicardial (EPI) and endocardial (Endo) regions using floating microelectrodes. A transmural pseudo-ECG was recorded with 2 K-Agar electrodes (1.1 mm, internal diameter) placed at approximately 1 cm from the epicardial (+) and endocardial (-) surfaces of the preparation and along the same axis as the transmembrane recordings. Five intramural unipolar electrograms (EGs) were recorded by using stainless-steel wires (120 $\mu$m diameter) Teflon insulated except at their tips (~2 mm). The EGs' wires were introduced half way into the wedge through the cut surface.

Ventricular wedges were allowed to equilibrate in the chamber for 2 to 3 hours while paced at a basic cycle length of 800 ms or 2,000 ms with silver bipolar electrodes applied to the endocardial surface. Perfusion pressure was maintained at 40 to 50 mm Hg. The temperature was maintained at 36.5-37 $^{o}$C. Isometric contractile force was continuously recorded together with the electrical activity by fixing one end of the preparation to the bottom of the chamber and attaching the other to a force-displacement transducer by means of a 4-arm hook.

Global ischemia was induced by interruption of coronary perfusion for a period of 30 minutes. The solution level was kept 1 to 2 mm above the tissue surface during the entire protocol.

## Results

Interruption of the coronary perfusion led to a rapid and dramatic loss of contractility (data not shown). Peak force decreased to ~2.6 ± 0.6 % of control after 30 of flow interruption. Figure 1 shows an example of the electrophysiologic changes observed. Each panel shows (from top to bottom) simultaneous recordings of transmembrane action potentials from endocardium (Endo) and epicardium (Epi) and the ECG recorded along the same transmural axis. Figure 1A shows recordings obtained under control conditions (left) and after 25 minutes of ischemia produced by interruption of coronary perfusion. Endo and Epi action potentials abbreviate during exposure to ischemia and return to nearly control values after 5 minutes of reperfusion. The figure graphically illustrates the essential role of ischemia-induced transmural conduction slowing in the generation of an apparent ST-segment elevation and inverted T wave. Correlation of action potential and ECG activity reveals that the apparent severe ST-segment elevation encountered under these conditions is because of delayed transmural conduction of the impulse causing a marked prolongation of the R wave. The ischemia-induced increase in transmural (Endo to Epi) conduction time (CT), measured as the time interval between the minimum derivatives ($V_{min}$) of the QRS of the Endo and Epi unipolar recordings, reached 180.3 ± 57.3 % of control after 30 min of interruption of flow (n= 5).

In preparations displaying a prominent action potential notch another characteristics behavior was observed in response to ischemia. Figure 1B shows an example of ischemia-induced loss of the epicardial action potential dome and ST-segment elevation. Under baseline conditions (control), the electrocardiographic ST segment is isoelectric due to the absence of voltage gradients at the level of action potential plateau between the endocardial and epicardial regions. Twelve minutes after interruption of the coronary flow (at a time when conduction was not greatly affected) the epicardial action potential displayed an all-or-none repolarization at the end of phase 1, but not in endocardium (Fig 1D). Under these conditions, the manifestation of extrasystolic activity of epicardial origin was consistent with phase 2-re-entry (data not shown).

Figure 2A shows wedge data and a clinical example of ischemia-induced apparent ST-segment elevation and T-wave alternans. The tombstone morphology and T-wave alternans described by Childers (7) (Fig 2B) during coronary spasm is

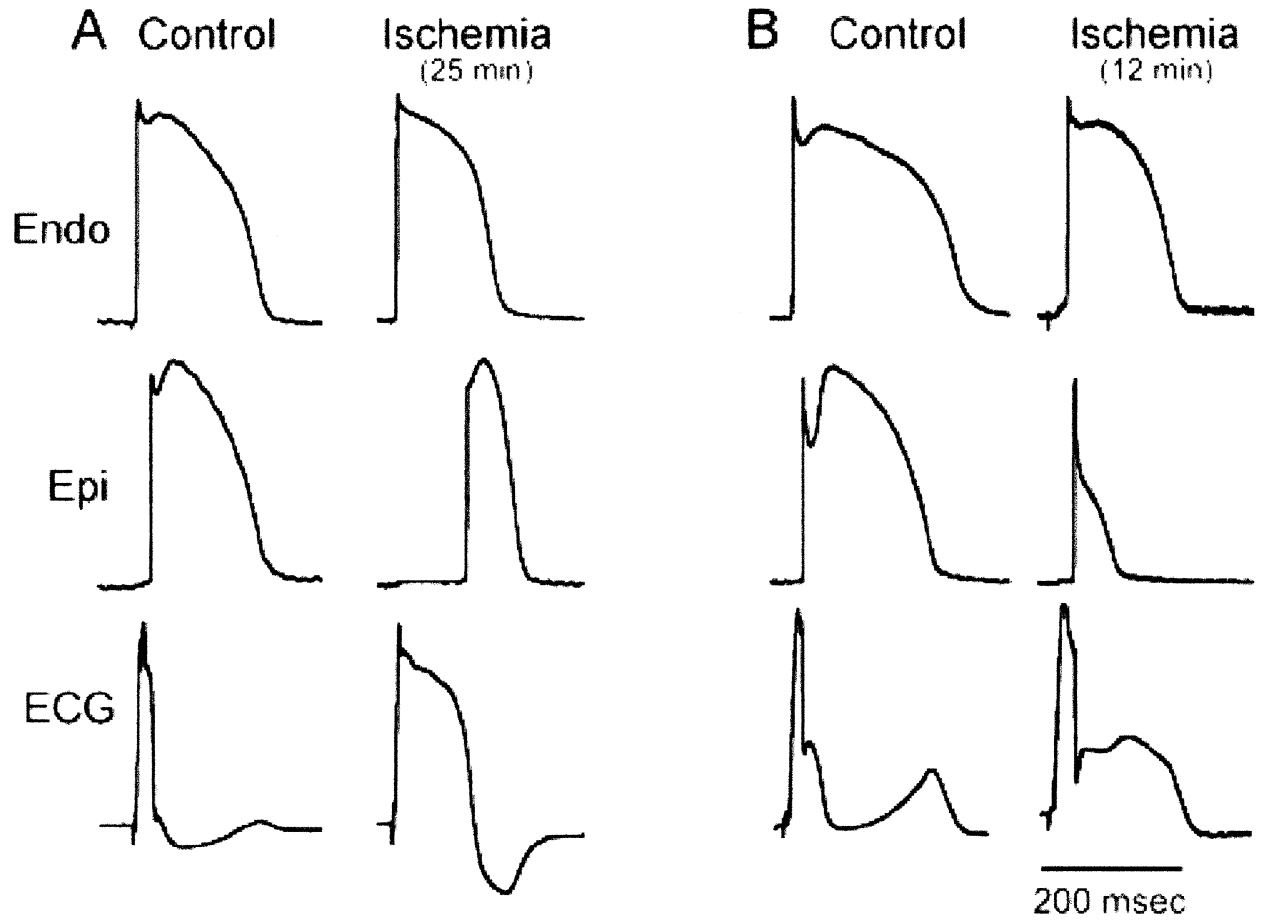


**Fig. 1.** Electrophysiologic effect of ischemia in the ventricular wedge model. Results are from 2 different preparations. Each panel shows (from top to bottom) simultaneous recordings of transmembrane action potentials from endocardium (Endo) and epicardium (Epi) and the ECG recorded across the bath along the same axis. (A) Recordings obtained under control conditions and after 25 minutes of ischemia. (B) Recordings obtained under control conditions and after 12 minutes of ischemia. BCL= 800 ms. Two distinctly different mechanisms involving 1) markedly delayed transmural conduction and 2) loss of the epicardial action potential dome underlie the apparent ST-segment elevation encountered during acute ischemia.

mimicked by ischemia in the wedge and shown to be caused by alternation of slow transmural conduction and conduction block. Figure 2C shows total normalization of the ECG after reperfusion.

## Discussion

ST-segment displacement and T-wave inversion are common ECG manifestations of transmural myocardial infarction in leads facing the injury (8). Although the mechanisms responsible for such changes have not been experimentally identified, several theoretical models have predicted their correlation with changes in action potential morphology (1,3).

Our data suggest that ischemia-induced transmural conduction delay plays a key role in the development of an apparent ST-segment elevation and T-wave inversion. Moreover, the data indicate that the apparent ST-segment elevation is actually a prolonged R wave that develops secondary to marked delays of impulse conduction across the right ventricular wall.

When a prominent transient outward current is present, reflected by a prominent notch in right ventricular action potential, ischemia can lead to a true ST-segment elevation secondary to loss of the epicardial action potential dome. Loss of the dome in epicardium but not endocardium leads to the development of a transmural voltage gradient that manifests on the ECG as an ST-segment elevation.

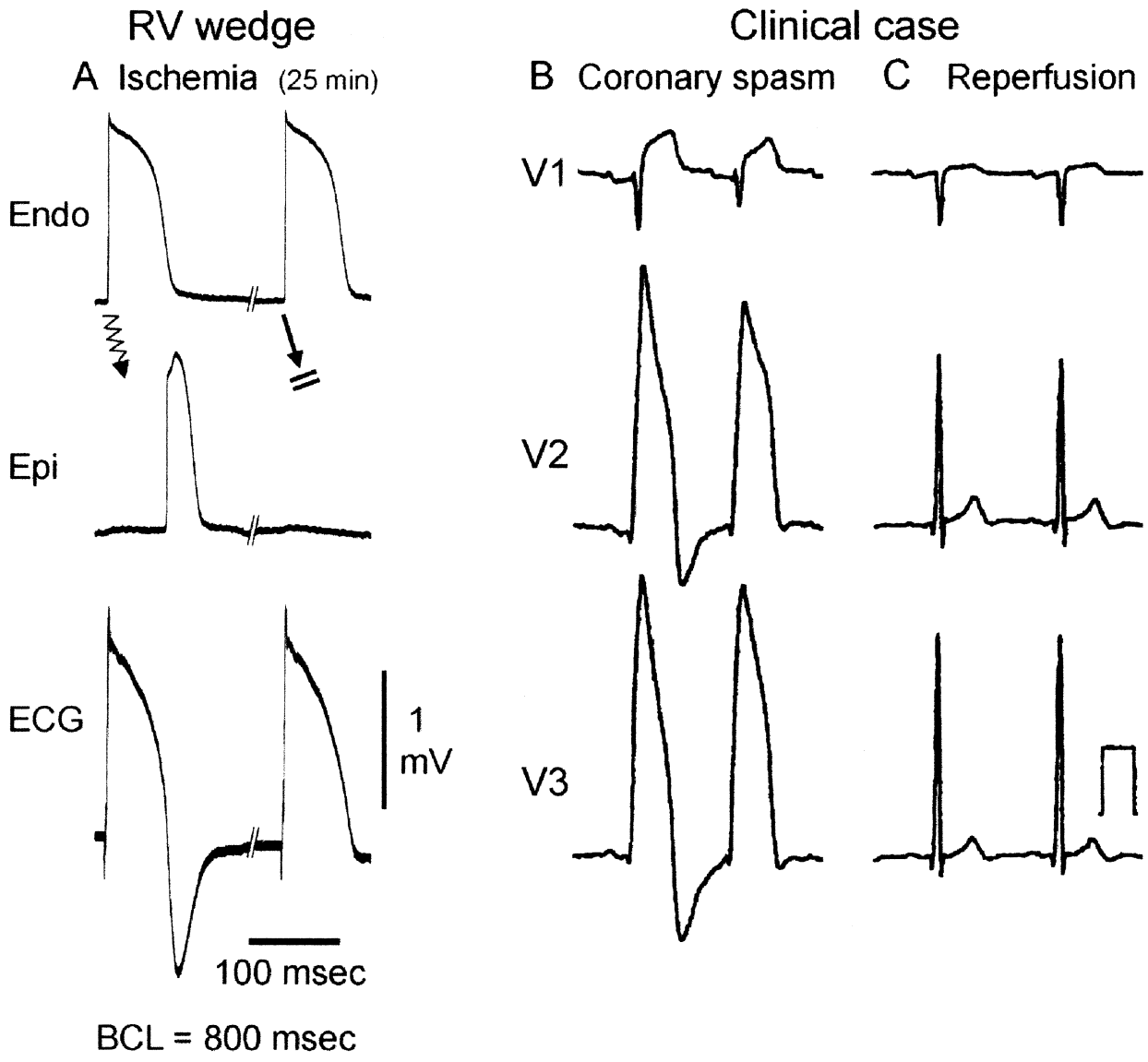


**Fig. 2.** Ischemia-induced tombstone morphology accompanied by T-wave alternans. (A) Recording from arterially perfused right ventricular wedge preparation after 25 minutes of ischemia. Shown are 2 consecutive beats at a BCL of 800 ms. Delayed transmural conduction gives rise to an apparent ST-segment elevation (tombstone morphology) and negative T wave. In the following beat, intramural conduction block leads to manifestation of a wide QRS, but disappearance of the T wave. (B) Clinical example of the tombstone effect and T-wave alternans appearing in the right precordial leads after vasospastic ischemia (C) Normalization of the ECG after spontaneous reperfusion [B and C are reprinted with permission (7)].

These results are analogous to those observed in models of the Brugada syndrome, in which sodium channel inhibition leads to a conduction disease phenotype (wide QRS complex) when $I_{to}$ is relatively weak and to the Brugada syndrome phenotype (ST segment elevation) when $I_{to}$ is prominent (9). The latter occurs more typically in males, whereas the former is more common in females (10,11). The Brugada phenotype is most readily produced in the RV wedge preparation using combined sodium and calcium channel block. Inhibition of these 2 inward currents also characterizes acute ischemia.

In parallel studies, ST-segment secondary to loss of the epicardial action potential dome occurs more readily and apparent ST-segment elevation or R-wave prolongation is less likely to occur during exposure to metabolic toxins during normal perfusion of the wedge. The contrast with ischemia caused by interruption of coronary flow may be

explained by the lack of accumulation of metabolites and extracellular potassium. Accumulation of $[K^+]_o$ would be expected to depolarize the myocardium, thus inactivating sodium channels and slowing conduction. In addition, the elevation of $[K^+]_o$ would be expected to reduce $I_{to}$ via a diminution of the chemical gradient for the current. Both of these factors would favor QRS prolongation versus true ST-segment elevation when coronary flow is obstructed.

In summary, 30 minutes of interruption of the coronary flow in the arterially perfused ventricular wedge preparation leads to electrocardiographic alterations that reasonably reproduce the patterns of acute myocardial ischemia in humans. Our data indicate that 2 distinctly different mechanisms involving 1) loss of the epicardial action potential dome and 2) markedly delayed transmural conduction underlie the apparent ST-segment elevation encountered during acute ischemia.

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