Published in final edited form as:

J Electrocardiol. 2014 ; 47(4): 486–490. doi:10.1016/j.jelectrocard.2014.02.005.

Acute Myocardial Ischemia: Cellular Mechanisms Underlying ST Segment Elevation

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Abstract

The electrocardiogram (ECG) is an essential tool for the diagnosis of acute myocardial ischemia in the emergency department, as well as for that of an evolving acute myocardial infarction (AMI). Changes in the surface ECG in leads whose positive poles face the ischemic region are known to be related to injury currents flowing across the boundaries between the ischemic and the surrounding normal myocardium. Although experimental studies have also shown an endocardium to epicardium differential sensitivity to the effect of acute ischemia, the important contribution of this transmural heterogeneous response to the changes observed in the surface ECG are less appreciated by the clinical cardiologist. This review briefly discusses our current knowledge regarding the electrophysiology of the ischemic myocardium focusing primarily on the electrophysiologic changes underlying the ECG alterations observed at the onset of a transmural AMI.

Keywords

Acute Myocardial Ischemia; ST segment; Transmural Conduction

Introduction

Using direct-coupled extracellular amplifiers, Samson and Scher(1) were the first to provide evidence that, following ligation of a coronary artery in the dog heart “in situ”, an electrode placed on the ischemic region will record both, T-Q depression and S-T segment elevation. From these local (extracellular) electrograms (EGs) in combination with simultaneous intracellular action potentials (AP) recorded from the heart surface, the authors demonstrated that T-Q depression (a downward shift in the diastolic isoelectric line) is the result of a “diastolic” injury current flowing from the partially depolarized ischemic region (-) to the normally polarized zone (+). Conversely, they showed that S-T segment elevation

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Disclosures: None.

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(an upward shift in the systolic isoelectric line) is the result of a “systolic” current of injury flowing from the normal zone (-) to the “abbreviated”, ischemic APs (+).

In later studies performed in the isolated pig heart by Kléber et al.,(2) it was confirmed that depolarization of the ischemic myocardium is associated with T-Q depression. Most importantly, it was demonstrated that, in addition to AP shortening, the ischemic cells undergo loss of AP amplitude and delayed activation.(2) In that, in the pig heart, regional ischemia results in consistently uniform transmural changes (and therefore absence of transmural gradients), their recordings of extracellular potentials with multiple electrodes allowed them to quantify the direction and magnitude of the ‘uncontaminated’ tangential extracellular currents on the epicardial surface (i.e., injury currents parallel to the ventricular wall), which explained the ST and TQ ischemic changes. Nevertheless, as highlighted below, additional experimental evidence also indicate that the extracellular currents underlying the ischemic ECG changes are not only directed parallel (tangential) *but also* perpendicular (i.e., transmurally) to the surface of the heart.

Electrocardiogram of an Early Acute Myocardial Infarction and Associated Transmural Electrical Changes

The electrocardiogram (ECG) changes attending a transmural myocardial ischemia caused by coronary artery spasm (Prinzmetal's angina; Figure 1A) as well as those occurring in the hyperacute phase of a developing acute myocardial infarction (AMI at its onset; Figure 1B) typically reveal -in leads whose positive poles are facing the ischemic region- a massive ST segment elevation in which the limits of the QRS complex and the T wave are frequently undefinable. This ECG pattern is referred to as “giant R wave” configuration, “tombstone” morphology or “monophasic QRS-ST complex”.(3, 4)

Experimentally, following an abrupt occlusion of the left circumflex coronary artery in the canine heart “in situ”, it was shown that the time course of the developing giant R wave during regional, acute transmural ischemia, correlates with a dramatic increase in transmural conduction time as assessed between the activation time of endocardial (Endo) and epicardial (Epi) electrograms.(5) A slow conduction across the ischemic ventricular wall following ligation of the left anterior descending coronary artery was also demonstrated in a study in which multiple intramural sites were simultaneously recorded between Endo and Epi.(6)

A dramatic slowing in transmural conduction is also revealed in isolated canine ventricular wedge preparations subjected to 0-flow ischemia.(7),(8) These preparations allow a temporal correlation between APs, intramyocardial EGs and a transmural pseudo-ECG. Recordings of Endo and Epi APs from these isolated preparations expose the contribution of “transmural electrophysiologic gradients” (Figure 1C): A major step delay in impulse transmission across the ventricular wall results in a tombstone ECG configuration. Figure 1D shows an example of this phenomenon. Five intramural unipolar EGs were positioned transmurally (Endo, M3, M2, M1 and Epi). Shown are 2 consecutive beats at a basic cycle length of 800 msec. The dots and arrows indicate the activation time at each intramural site. In the first grouping, conduction proceeds promptly from endocardium to the deep

subendocardium and is observed to undergo a major step delay (87 msec) in the midmyocardium before resuming in epicardium. In the second grouping, the impulse is blocked in the midmyocardium (M2-M1), leading to failure of activation of the epicardium and loss of the negative T wave. Of note, as shown in Figure 1C and D, the negative T wave is the consequence of a dramatic delay in Epi activation causing its repolarization to outlast that of the Endo AP response.

The experimental observations derived from transmural ischemia performed “in vivo”, from the canine ventricular wedge preparations undergoing global ischemia as well as from isolated ventricular Endo and Epi tissues exposed to simulated ischemic conditions strongly suggest that transmural conduction slowing and a greater depression of the Epi AP response importantly contribute to the typical ECG changes encountered at the onset of a transmural AMI.

Basis for the Transmural Heterogeneous Response to Ischemia

Universal Metabolic and Electrophysiological Changes

The metabolic dysfunction attending the onset of an AMI, including depletion of ATP and accumulation of lactic acid, are associated with interstitial accumulation of K⁺ (owing at least in part, to opening of ATP-sensitive K channels (I_{K-ATP})), catecholamines and lipid metabolites.(9) Intracellular acidification activates the Na⁺/H⁺ exchanger resulting in H⁺ extrusion in exchange for Na⁺ entry, which in turn results in calcium overload by means of activation of the Na⁺/Ca⁺⁺ exchanger. The consequent electrophysiological changes include depolarization, Na⁺ channel inactivation (causing a reduction in peak I_{Na}) and slow conduction. Abbreviation of the ischemic APs are a consequence of a decreased slow inward calcium current (I_{Ca}) and, more importantly, activation of the I_{K-ATP} .(10, 11) Ultimately, however, these universal metabolic and electrophysiologic changes translate into disparate responses in AP and conduction characteristics of the ischemic myocardium across the ventricular wall. For in depth reviews on biochemical and electrophysiological ischemic changes, please see Carmeliet(12) and Janse(13))

Epi vs. Endo peak I_{Na} availability at depolarized potentials

At the onset of ischemia, a small depolarization in combination with unchanged threshold potential can lead to a transient, early increase in excitability. However, further depolarization leading to inactivation of the fast sodium channels (peak I_{Na}) invariably results in reduced excitability. In that the reduction of excitability is more severe in the epicardial region(12, 14) the consequent development of a systolic transmural gradient is expected to contribute to the ST elevation attending ischemia as detailed below.

In experiments performed in isolated canine ventricular Endo and Epi tissue-slices exposed to high extracellular potassium, a component of ischemia, a greater depression of the Epi AP response is apparent, particularly when the depolarized membrane potentials reaches values approximating -65 mV, as shown in Figure 2A.(15) At a resting membrane potential of -66 mV, V_{max} is shown to decrease to $51.1 \pm 5.3\%$ of control in Endo but to $26.8 \pm 9.6\%$ of control in Epi (Figure 2B). This study demonstrated differences in the inactivation characteristics of I_{Na} in the two cell types. In fact, steady-state inactivation in Epi was

shown to display a half-inactivation voltage 8 mV more negative than Endo.(15) As a consequence, when the magnitude of I_{Na} is measured at depolarized membrane potentials (Figure 2C and 2D; holding potential -70 mV) a significant reduction in I_{Na} in Epi cells is apparent when compared to Endo cells. These data suggest that transmural differences in sodium channel availability, particularly at depolarized potentials, contribute to the greater electrical depression of Epi. As a result, transmural gradients in AP amplitude, repolarization time, excitability and conduction are expected to contribute to the ECG changes attending an early AMI.

Epi vs. Endo AP morphology, late I_{Na} and I_{to}

Acidosis, another component of ischemia, was shown to significantly reduce Endo and Epi peak I_{Na} equally and thus may contribute to the characteristic depressed excitability of the ischemic myocardium. Similarly, late I_{Na} was also shown to be reduced to the same extent in Endo and Epi cells.(16) However, using AP voltage-clamp techniques, acidosis was shown to produce a greater reduction in late I_{Na} when an Epi waveform is applied as compared with an Endo waveform applied to the same cell. Thus, a greater reduction of late- I_{Na} in cells displaying spike and dome configuration may contribute to the greater Epi depression attending an early transmural AMI.(16) This notwithstanding, ischemia has been shown to increase late I_{Na} .(17-19)

We have previously demonstrated that the presence of a prominent transient outward current (I_{to})-mediated spike and dome morphology in Epi accounts, at least in part, for the differential response to ischemia secondary to the loss of the dome portion of its AP.(20-25) An outward shift in the balance of currents active at the end of the Epi phase 1 repolarization, caused largely by a decrease in peak I_{Na} and I_{Ca} and by an increase in potassium currents (mainly I_{K-ATP}), can lead to loss of the Epi AP dome in the early stages of AMI and thus contribute to the development of ST segment elevation secondary to the development of transmural systolic gradients (Figure 3A and 3B). Of note, studies performed in the cat have shown a greater Epi sensitivity to I_{K-ATP} activation(26, 27) and a more recent study reported transmural heterogeneity in the expression of I_{K-ATP} in rabbits. (28)

The phenomenon of the loss of dome in the setting of ischemia occurs more readily at slow rates and in right ventricular Epi tissues (owing to a greater availability of I_{to})(29) and as long as the membrane potentials are only slightly depolarized as shown in Figure 3 (loss of the dome throughout epicardium). Loss of the AP dome at some Epi sites but not others can give rise to phase 2 reentry thus generating closely coupled extrasystoles capable of precipitating ventricular tachycardia or fibrillation (VT/VF).(21-25) Further depolarization and depression of V_{max} would eventually lead to a lack of spike and dome configuration (absence of phase 1; Figure 2).

The transmural heterogeneity observed under the conditions depicted in Figure 3 (loss of the dome throughout epicardium) may lead to greater ST segment elevation. Although phase 2 reentry within the ischemic region is unlikely to occur under these conditions, the accentuated transmural dispersion of repolarization and refractoriness can lead to phase 2 reentry secondary to the propagation of the dome from the surrounding normal myocardium,

across the border zone, as previously demonstrated.(30) The extrasystoles generated in this manner led to the development of VT/VF. Thus, the presence of a pre-existing prominent I_{to} -mediated spike and dome configuration, relatively slow rates, and the severity of membrane depolarization associated with the extent of interstitial potassium accumulation all contribute to the electrocardiographic and arrhythmic manifestations of acute MI.

Nevertheless, under ischemic conditions, the characteristic heterogeneities in excitability, refractoriness and conduction can precipitate ectopic excitation through arrhythmia mechanisms other than phase 2 reentry including abnormal automaticity, early and delayed afterdepolarizations (EADs and DADs), currents of injury and reentry.(12, 31, 32)

It is noteworthy that in experimental ischemia involving the left ventricle exclusively, the amplitude of the TQ depression and ST segment elevation has been shown to transiently decrease after the first 10-15 minutes of coronary occlusion at the time APs may partly regain amplitude and resting membrane potential.(2) These transient electrophysiologic changes have been ascribed to extracellular potassium flowing from the ischemic to the normal zone,(33) as well as to reuptake of potassium into the cells.(34) The decline in the amplitude of the TQ depression and ST segment may also be secondary to electrical uncoupling of ischemic cells(2) which develops rapidly after 10-15 min of interruption of the coronary flow.(35)

Summary

The ECG changes attending the first 10-15 minutes of acute transmural myocardial ischemia in leads whose positive poles face the ischemic region include ST segment elevation and inverted T waves. The extracellular currents underlying these ischemic ECG changes are proposed to be directed parallel as well as perpendicular (i.e., transmurally) to the surface of the heart. Experimental studies strongly suggest a number of electrophysiologic mechanisms to be responsible at one time or another or concurrently. These include: 1) Diastolic and systolic currents of injury; 2) Transmural conduction delay and intramural conduction block; 3) Greater depression of the Epi AP amplitude; and 4) Loss of the Epi AP dome.

Acknowledgments

This study was supported by a Grant-in-Aid (10GRNT4210016) from the American Heart Association (Di Diego), by grant HL47678 from the NHLBI (Antzelevitch), and by the Masons of New, Florida, Massachusetts, Connecticut, Rhode Island, and Wisconsin.

We gratefully acknowledge the expert technical assistance of Judy Hefferon.

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Figure 1.

A: Clinical example of the tombstone morphology accompanied by T-wave alternans in the right precordial leads after vasospastic ischemia (modified from reference(3)). **B:** Clinical example of electrocardiogram (ECG) pattern in precordial leads reveals tall R waves merging with the markedly elevated ST segments in comparison with the ECG prior to an acute myocardial infarction (AMI) and the formation of monophasic QRS-ST complexes (modified from reference(4)). **C:** Recording from arterially perfused right ventricular wedge preparation after 25 minutes of ischemia. Shown are 2 consecutive beats at a BCL of 800 msec. Delayed transmural conduction gives rise to 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 (from reference(8)). **D:** Top five traces are electrograms recorded from 5 transmural sites across the wedge. The next two are action potential recordings obtained from the endocardial (Endo) and epicardial (Epi) surfaces and the bottom trace is the ECG recorded across the bath. The dots and arrows denote the activation time (V_{min}) at each site. The first grouping displays discontinuous conduction with an 87 msec delay of impulse transmission in the midmyocardium. The second grouping shows failure of epicardium to activate due to conduction block in the midmyocardium.

Figure 2.

Progressive electrophysiological changes following superfusion with Tyrode solution containing 12 mM [K]_o (BCL= 800 msec). **A:** Endocardial (Endo) and epicardial (Epi) action potentials (APs) recorded from isolated right ventricular tissue slices using the standard microelectrode technique. V_{max} traces are shown underneath the respective APs. Consecutive sets of recordings were obtained at 5-mV depolarization intervals between the resting membrane potentials (RMPs) of -86 and -66 mV. Right traces show 5 consecutive beats of Endo and Epi APs superimposed. **B:** V_{max} as a function of membrane depolarization in Endo and Epi. Values are means $\pm$ SE; $n = 9$ Endo and 14 Epi. * $P < 0.05$ vs. RMP of -86 mV. **C and D:** I-V relations for Epi and Endo cells showing a reduction in current as the holding potential (HP) is more depolarized; $n = 8$ cells from Epi and Endo. **E:** bar graph showing the maximum current available at different HPs from the two cell types. * $P < 0.05$. Modified from reference.(15)

Figure 3.

A: Electrophysiologic effect of ischemia in a ventricular wedge isolated from the right ventricle. Each panel shows (from top to bottom) simultaneous recordings of tension development (Contraction), transmembrane action potentials (APs) from endocardium and epicardium, and the electrocardiogram (ECG) recorded across the bath along the same axis. Recordings obtained under control conditions and after 12 minutes of ischemia. BCL= 800 msec. Loss of the epicardial (Epi) AP dome underlie the ST segment elevation encountered during acute ischemia. Modified from reference.(8) **B:** Loss of I_{to} -mediated Epi AP dome after onset of acute global myocardial ischemia gives rise to ST segment elevation in an arterially-perfused, right ventricular wedge preparation. Each panel shows transmembrane APs simultaneously recorded from one endocardial (Endo) and 2 Epi sites, together with a transmural ECG. Complete loss of AP dome in Epi was associated with marked ST segment elevation. BCL= 2000 msec. From Reference (30).