Phase 2 Reentry as a Trigger to Initiate Ventricular Fibrillation During Early Acute Myocardial Ischemia

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**Background**—Phase 2 reentry caused by heterogeneous loss of the transient outward potassium current (I_{to})—mediated epicardial action potential (AP) dome can produce a closely coupled R-on-T extrasystole leading to ventricular fibrillation (VF) under conditions of ST-segment elevation unrelated to ischemia. The present study examined the role of phase 2 reentry in the initiation of VF during early myocardial ischemia.

**Methods and Results**—Regional myocardial ischemia was produced in an isolated, arterially perfused canine right ventricular wedge preparation. Transmembrane APs from 2 epicardial sites at each side of the ischemic border were simultaneously recorded together with measurements of extracellular potassium concentration ([K^{+}]_o) and a transmural ECG. Loss of the I_{to}-mediated epicardial AP dome in the ischemic zone but not in the perfused tissue resulted in phase 2 reentry and associated R-on-T extrasystoles capable of initiating VF in 7 of 15 preparations during the first 3 to 9 minutes of myocardial ischemia, with marked ST-segment elevation and [K^{+}]_o accumulation. The I_{to} and phase 1 magnitude of epicardium contributed importantly to the onset of VF. Phase 1 magnitude and I_{to} density at +30 mV in the group with phase 2 reentry–related R-on-T extrasystoles were 32.2±1.3 mV and 30.3±0.5 pA/pF (n=7), respectively, significantly greater than those (24.0±1.8 mV and 23.2±1.0 pA/pF) in the group without the extrasystoles (n=8, P<0.01).

**Conclusions**—Acute regional myocardial ischemia results in markedly heterogeneous loss of I_{to}-mediated epicardial AP domes across the ischemic border, leading to phase 2 reentry. Phase 2 reentry can in turn produce an R-on-T extrasystole capable of initiating VF. (*Circulation.* 2004;110:1036-1041.)

*Key Words:* ischemia ■ arrhythmia ■ electrocardiography

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Each year, about 1 million people in the United States have acute myocardial infarction (AMI), of whom approximately 20% to 25% die suddenly as the result of the development of ventricular fibrillation (VF) at an early stage of the event. Animal studies have shown that VF during the first 2 to 10 minutes (phase 1a) of acute ST-segment–elevation myocardial ischemia often emerges from tissue bordering the ischemic zone.1–3 However, cellular mechanisms underlying the first initiating beat capable of triggering VF, which invariably manifests as a closely coupled R-on-T extrasystole in the setting of ST-segment elevation on the ECG, is poorly understood.

Interestingly, the initiation of VF by an R-on-T extrasystole can be observed under conditions of ST-segment elevation unrelated to acute myocardial ischemia—for example, the Brugada syndrome or idiopathic VF.4,5 Our previous study has demonstrated that phase 2 reentry, a local reexcitation caused by heterogeneous loss of the transient outward potassium current (I_{to})—mediated epicardial action potential (AP) dome and its transmural propagation can manifest as a closely coupled R-on-T extrasystole capable of initiating VF in the Brugada syndrome.6 The similarities between the ECG manifestations of the Brugada syndrome and those of acute myocardial ischemia indicate that the fundamental mechanism responsible for ST-segment elevation and the initiation of VF may be similar, although the pathogeneses differ.6,7 However, a direct demonstration of this mechanism in the intact wall of the ventricles during acute ST-segment–elevation myocardial ischemia has been lacking. The present study tested this hypothesis in an in vitro ischemic model consisting of an isolated, arterially perfused canine right ventricular wedge preparation in which epicardium exhibited a prominent I_{to}-mediated AP dome.

**Methods**

**Ischemic Model Including an Arterially Perfused Canine Right Ventricular Wedge**

The Institutional Animal Care and Use Committee of the Lankenau Institute for Medical Research approved the study protocol for the use of dogs. The preparation of an isolated, arterially perfused ventricular wedge and the characterization of its viability and electrical stability have been detailed in previous studies.6,8 Briefly,
Arterially Perfused Canine Right Ventricular Wedge

![Diagram of a transmural wedge preparation dissected from canine right ventricular free wall and cannulated through a coronary artery and perfused with Tyrode’s solution buffered with 95% O₂ and 5% CO₂ (36±0.3°C, Figure 1). The preparation was then suspended in an artificial atmosphere. The preparation is perfused with Tyrode’s solution buffered with 95% O₂ and 5% CO₂. A transmural ECG signal was recorded with the use of a Student’s t test for paired and unpaired data. The χ² test was used for the comparison between 2 groups for event incidences. Data are presented as mean±SEM. In the present study, 2 or 3 wedge preparations could be obtained from a single canine right ventricle. In 21 of 24 dogs, the available wedge preparations from each dog were used for different types of experiments described above. In 3 of 24 dogs, 2 identical experiments in terms of experimental design were performed in the wedge preparations isolated from the same canine right ventricle. For these 3 dogs, the data obtained from 2 identical experiments in a single dog were then averaged and treated as those obtained from a single experiment. Therefore, the number (n) in this study represents the number of dogs that were used.

Results

ST-Segment Elevation and Phase 2 Reentry in Acute Myocardial Ischemia

During normal perfusion, right ventricular epicardium displayed prominent \( I_{\text{Ca}} \)-mediated AP dome, as reported previously (Figure 2, Control). Phase 1 magnitude was 27.8±1.0 mV at a BCL of 2000 ms in a total of 24 dogs during normal perfusion. There was no significant difference in preischemic phase 1 magnitude between the wedge preparations with subsequent global myocardial ischemia (27.6±1.4 mV, n=10) and those with subsequent regional myocardial ischemia (28.0±1.3 mV, n=15, P>0.05).

Six minutes after the interruption of perfusion flow to the entire wedge preparation (acute global myocardial ischemia), complete loss of \( I_{\text{Ca}} \)-mediated epicardial AP dome occurred in all dogs (n=10), leading to prominent ST-segment elevation (Figure 2). At the same time, \([K^+]) increased from 4.2±0.2 to 8.1±0.3 mmol/L (n=7). Phase 2 reentry and resultant VF were observed only in 1 of 10 dogs during 10 minutes of acute global myocardial ischemia.

On the other hand, acute regional myocardial ischemia was associated with complete loss of \( I_{\text{Ca}} \)-mediated epicardial AP dome within the ischemic zone but not in the perfused side, leading to a marked difference in epicardial repolarization across the ischemic border (Figure 3A). As demonstrated in Figure 4, the difference in repolarization time on epicardial surface between Epi and Epi sites, particularly at AP phase 2 (ie, APD₂₀, Figure 4B), was significantly greater during
Effect of \( I_w \) Density and Phase 1 Magnitude on Phase 2 Reentry and VF During Acute Myocardial Ischemia

Prominent \( I_w \)-mediated epicardial AP dome during normal perfusion was associated with a high incidence of phase 2 reentry and VF during myocardial ischemia, as shown in Figure 3. Phase 1 magnitude and \( I_w \) density at +30 mV in the group with ischemia-induced R-on-T extrastyles and VF were 32.2±1.3 mV and 30.3±0.5 \( \mu \)A/pF (n=7), respectively, significantly greater than those (24.0±1.8 mV and 23.2±1.0 \( \mu \)A/pF) in the group without the extrastyles (n=8, \( P<0.01 \)). At a dose of 2 mmol/L, 4-AP reduced phase 1 magnitude from baseline 29.4±1.4 to 8.9±1.0 mV (n=6, \( P<0.01 \)). No phase 2 reentry or resultant VF was observed in the presence of 4-AP during 10 minutes of acute regional myocardial ischemia.

Interestingly, \( I_w \)-mediated epicardial phase 1 magnitude became significantly smaller during reperfusion after 10 minutes of global myocardial ischemia (Figure 5). Phase 1 magnitude was 27.5±1.6 mV in control perfusion and decreased to 22.9±1.5 mV during reperfusion after a brief episode of ischemia (n=8, \( P<0.01 \)). Attenuation of epicardial phase 1 magnitude was associated with a reduction in phase 2 reentry and associated R-on-T ectopic beats in subsequent regional ischemic insult (0/8, \( P<0.05 \)).

Discussion

Early ventricular arrhythmias during the first 30 minutes of myocardial ischemia occur in a biphasic temporal distribution, that is, phase 1a (“immediate”) and phase 1b (“delayed”). The phase 1a VF occurs during the first 2 to 10 minutes, with a peak incidence at 5 to 6 minutes after the acute interruption of coronary flow, when [K⁺]ᵢ approaches close to its plateau phase and ST-segment elevation becomes prominent.²³ The onset of VF is almost always initiated by a closely coupled R-on-T extrasystole under conditions of ST-segment elevation. The present study provides the first direct evidence that acute myocardial ischemia can lead to loss of \( I_w \)-mediated epicardial AP dome, contributing in part to the development of ST-segment elevation mechanistically similar to that observed in the Brugada syndrome.⁶⁻⁷ More importantly, heterogeneous loss of \( I_w \)-mediated epicardial AP dome across the ischemic border during regional myocardial ischemia facilitates the development of phase 2 reentry that manifests as a closely coupled R-on-T extrasystole on the ECG. The extrasystole in turn is capable of initiating VF.

An outward shift in the balance of currents active in AP phases 1 and 2 caused by a decrease in inward currents (principally \( I_{Na} \) and \( I_{Ca} \)) and/or an increase in outward currents (principally \( K^+ \) currents) predisposes to the loss of \( I_w \)-mediated epicardial AP dome.⁶⁻⁷,ⁱ⁵ Abrupt arrest of coronary flow to the myocardium deprives ventricular myocytes of O₂ and causes the cessation of delivery of metabolites, resulting in a cascade of pathophysiological events that are associated with a decrease in inward currents of \( I_{Na} \) and \( I_{Ca} \) and a significant increase in outward currents such as \( I_{KATP} \) and \( I_{KMA} \).¹⁴ Our data indicate that these ischemia-related changes in membrane currents can lead to the loss of AP dome in epicardium, in which \( I_w \) is prominent. Loss of \( I_w \)-mediated epicardial dome with relatively maintained plateau phase and AP duration in endocardium (Figure 2) can generate a transmural voltage gradient that leads to ST-segment elevation on the ECG. From a mechanistic viewpoint, this is similar to the early observations by Kléber et al.¹⁵: Loss of AP amplitude and AP shortening in the ischemic core is responsible for ST-segment elevation during systole. The so-called “injury current” caused by the difference in resting membrane potentials contributes to only a moderate TQ- (or TP)-segment depression when the ECG signal is input through DC coupling (ie, high-pass filter frequency=0 Hz).¹⁵ In clinical practice, the frequency for the high-pass filter in an ordinary ECG recorder is often set to the 0.1- to 0.5-Hz range to avoid direct current drift. Under this condition, the TP depression is transformed to apparent “ST-segment upward deviation” that contributes partially to the overall ST-segment elevation.⁷

On the other hand, complete loss of \( I_w \)-mediated epicardial AP dome occurs at some sites but not at others during
myocardial ischemia, resulting in a marked heterogeneity in ventricular repolarization on the epicardial surface. This is particularly exaggerated during regional myocardial ischemia, in which an ischemic border is created. Heterogeneous loss of $I_{\text{to}}$-mediated epicardial AP dome across the ischemic border facilitates the development of phase 2 reentry, that is, a local reexcitation secondary to the dome propagating from the sites where the dome is maintained to the other sites where the dome is completely lost. Phase 2 reentry on the epicardial surface adjacent to the ischemic border and, probably, its transmural propagation, likely is responsible for R-on-T extrasystoles on the ECG (Figure 3). This might explain why a trigger initiating phase 1a VF often originates from the perfused tissue bordering ischemic tissue.1–3,16

Additionally, loss of epicardial AP dome may also generate a transmural repolarization gradient that manifests as ST-segment elevation on the ECG (Figure 2), which may serve as a reentrant substrate for the maintenance of VF.6

The physiological and pathophysiological significance of a prominent $I_{\text{to}}$ has been long recognized.6,7,13,17,18 Similar to observations under other pathophysiological conditions,6,7,13 a prominent preexisting $I_{\text{to}}$ is essential to the development of phase 2 reentry during early myocardial ischemia. Because $I_{\text{to}}$ in epicardium is much more prominent in the right ventricle than in the left,7 one may expect that the incidence of primary VF in humans would be higher in the MI location involving or having a border with right ventricle. Conflicting observations have been reported, however.19–22

In the Grupo Italiano per lo Studio della Streptochinasi nell’Infarto miocardico (GISSI) trial (11 712 patients), the incidence of VF caused by...
AMI in the posteroinferior wall, in which the right ventricle may be more likely to be involved, was significantly higher than that in anterolateral area (3.7% versus 2.5%). This was further supported by the Thrombolysis In Myocardial Infarction II data (2546 patients). In contrast, Gheeraert et al recently reported that acute anterior MI caused by occlusion of the left coronary artery was associated with greater risk of primary VF compared with the right coronary artery, according to angiographic findings of 72 patients who survived out-of-hospital VF. In a more recent clinical trial (Collaborative Organization for RheothRx Evaluation [CORE] trial, with 2100 patients), the incidence of primary VF was higher in patients with acute inferior MI who had right ventricular involvement (8.4%) than in those with inferior MI without right ventricular involvement (2.7%) or anterior MI (5.0%). Despite a higher incidence of VF, the patients with inferior MI who had right ventricular involvement showed lower peak creatine kinase level, smaller infarct size, and greater left ventricular ejection fraction compared with patients with anterior MI. Another clinical observation that favors the important implication of Ito in arrhythmogenesis of coronary heart disease is the sex-related difference in sudden cardiac death. In men and women who had coronary heart disease, the incidence of sudden death in men was significantly higher than that in women. In the Myocardial Infarction Triage Registry study, for example, the hazard ratio for sudden cardiac death was 0.78 in women compared with men. This is probably in part due to a more prominent Ito in men versus women, which has been thought to be responsible for the predominance of the Brugada syndrome or idiopathic VF in men.

Another interesting phenomenon in the present study is that a brief episode of ischemia, that is, ischemic preconditioning, reduces Ito-mediated epicardial phase 1 magnitude and arrhythmogenesis during subsequent myocardial ischemia. It is well known that ischemic preconditioning exhibits a powerful cardioprotective effect. Ito may play an important role in ischemic preconditioning.

**Limitations of the Study**

The relative contribution of “injury current” caused by a regional difference in the resting membrane potentials could
not be determined in the present study. This was largely because of the difficulty in simultaneously obtaining resting membrane potentials in both epicardium and endocardium. The measurement of TP depression, which may serve as a surrogate of the injury current,7 was also technically limited because of direct current drift. This probably was due to our experimental setup, in which the small ventricular wedge preparations were suspended in the tissue chamber with a high flow of N2 and CO2 gases for preventing O2 contamination. The fact that prominent ST elevation coincides with the loss of Iclo-mediated epicardial AP dome indicates that the difference in AP plateau phase between epicardium and endocardium plays an important role in ST-segment elevation during early acute myocardial ischemia.

In this study, the wedge preparations were paced at a BCL of 2000 ms. Therefore, the effect of a faster pacing rate on the onset of VF in our experimental model is unknown. However, it has been recognized that the development of VF during acute myocardial ischemia in humans as well as animals is often preceded by bradycardia or a pause.26,27 This is consistent with the properties of Iclo such that bradycardia or pause exaggerates the Iclo-mediated epicardial AP dome and facilitates the development of phase 2 reentry.6,7,13,17

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