Review Article

J Wave Syndromes

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Introduction

The J wave is a deflection with a dome or hump morphology immediately following the QRS complex on the body surface ECG. Also referred to as the Osborn wave because of Osborn's landmark description in the early 1950s,[1] the J wave has been observed in humans under physiological and pathophysiological conditions. Since Yan and Antzelevitch published a landmark study a decade ago in which the underlying ionic and cellular mechanisms of the J wave were elucidated,[2] our understanding of the clinical significance of the J wave has been greatly enhanced. An increasing number of evidence indicate that the J wave, mediated by the transient outward current (I_{to}), is a unique ECG marker of several clinical syndromes including the Brugada syndrome, idiopathic ventricular fibrillation (or sudden nocturnal death syndrome) and early repolarization syndrome. The ionic and cellular basis of the J wave plays an important role in sudden cardiac death associated with the Brugada syndrome, idiopathic ventricular fibrillation and, perhaps, acute ST segment elevation myocardial infraction. Therefore, these clinical entities or syndromes may be better referred to as I_{to}-mediated ***J wave syndromes***.[3-5] This review attempts to summarize our state of knowledge of the J wave and its basic and clinical significance.

Ionic and Cellular Basis of J wave

In the late 1980's, Antzelevitch and his colleagues proposed a difference in repolarization phases 1 and 2 of the action potential between the ventricular epicardium and endocardium as the basis for the ECG J wave.[6,7] The ventricular epicardium commonly displays action potentials with a prominent I_{to} mediated notch (spike and dome). A prominent I_{to}-mediated action potential notch in the ventricular epicardium but not endocardium may produce a transmural voltage gradient during early ventricular repolarization that could register as a J wave or J point elevation on the ECG. Direct evidence in support of this hypothesis was obtained in the arterially-perfused canine ventricular wedge preparation by Yan and Antzelevitch in 1996.[2] As shown in Figure 1, when activation starts from the endocardium and spreads transmurally to the epicardium, a distinct J wave coincident with the epicardial action potential notch is seen on the ECG. Conversely, if activation starts from the epicardium and travels to the endocardium, the J wave disappears from the ECG because it is buried

within the QRS complex. Therefore, factors that influence I_{to} kinetics and the ventricular activation sequence can modify the J wave on the ECG. For example, acceleration of heart rate reduces I_{to} as the consequence of its slow recovery from inactivation, resulting in a decrease in the J wave size.[8] This property of the J wave is particularly useful in distinguishing it from the terminal part of a notched QRS complex. Since a notched QRS is the consequence of altered ventricular activation, an increase in heart rate may amplify its terminal size. Similarly, some sodium channel blockers that possess additional I_{to} inhibition, such as quinidine and disopyromide, reduce the J wave size and normalize ST segment elevation.[9,10] However, they would be not expected to have an effect on the terminal part of a notched QRS.

ST Segment Elevation

The ST segment is the portion of the ECG that bridges the QRS complex and the T wave. Normally, the ST segment stays at same level as the T-P segment. Two changes in the ST segment are considered as clinically important: (1) the ST segment displacement; and (2) a change in the ST segment morphology. ST segment elevation is another ECG feature of the J wave syndromes. Exploring the intrinsic linkage between the J wave and ST segment elevation may increase our understanding of the mechanisms responsible for arrhythmogenesis associated with ST elevation.

The classic concept for ST segment elevation is the so-called “injury current” theory, explained as a current flow from injured myocardium, where the cells are partially depolarized, to the uninjured.[11] In animal experiments, however, the injury current measured by using a direct-current coupled amplifier, causes a TP (or TQ) segment depression rather than ST segment elevation.[12,13] In clinical practice, however, the ECG signals are inputted to an ECG recorder with a high-pass filter in order to avoid direct current drift. Under this condition, the TP depression is transformed to apparent “ST segment elevation” (Figure 2A).

A number of clinical observations also indicate that an “injury current” due to a difference in the resting membrane potentials between the injured and uninjured myocardial tissues is not the primary mechanism for ST segment elevation. In the early repolarization syndrome, idiopathic ventricular fibrillation and the Brugada syndrome, no “injured zone” is identified. There is also some doubt as to

whether the “injury current” plays a primary role in ST segment elevation during early acute myocardial ischemia.[5] It is commonly observed during coronary artery angioplasty that distinctive ST segment elevation occurs within tens of seconds after interruption of coronary perfusion. Within this brief period of myocardial ischemia, extracellular potassium accumulation is minimal and exhibits no significant effect on the resting membrane potentials.[13]

Because the ST segment corresponds temporally to the action potential plateau phase, the difference in the plateau potentials within the ventricles may produce ***true*** ST segment elevation. As illustrated in Figure 2B, the depression or loss of the action potential dome in the epicardium but not endocardium may result in a transmural voltage gradient during repolarization that can manifest as ST segment elevation. Because the epicardium, particularly in the right ventricle, has a large I_{to}-mediated action potential spike and dome, the epicardial action potential dome predisposes to partial or complete loss in response to an increase in outward currents (like $I_{K\text{-}ATP}$ current) or a decrease in inward currents (such as I_{Na})., leading to ST segment elevation. It is widely accepted that depression or loss of the action potential dome in the epicardium but not endocardium underlies ST segment elevation in the early repolarization syndrome, the Brugada syndrome and idiopathic ventricular fibrillation.[9,14,15] This mechanism may also contribute importantly to ST segment elevation during early acute myocardial ischemia.[5] Recently, we analyzed the ECG data of 382 consecutive patients, among which 57 were females, who were admitted to our hospital with acute ST segment elevation myocardial infarction over the past 4 years. Interestingly, male patients presented with more significant ST segment elevation than females. This may be explained by the fact that males have a much larger I_{to} than females.[14]

Phase 2 Reentry and R-on-T Extrasystole

While loss of the I_{to}-mediated action potential dome in the epicardium but not in the endocardium generates a significant voltage gradient across the ventricular wall that manifests as ST segment elevation, loss of the dome is often not uniform, i.e. loss of the dome at some sites but not others, and leads to marked dispersion repolarization on the epicardial surface (Figure 3). The epicardial action potential dome, which is similar to early afterdepolarization (EAD) under conditions

of delayed ventricular repolarization,[16] may propagate to the epicardial sites where the dome is completely lost and action potential duration markedly shortened, producing local re-excitation (i.e. so called phase 2 reentry). The extrasystole produced via phase 2 reentry occurs always on the down limb of the T wave (R-on-T phenomenon). This may in turn initiate polymorphic ventricular tachycardia (VT) or ventricular fibrillation (Figure 3).

The ionic mechanism for loss or depression of the epicardial action potential dome is due to an outward shift of currents due to either a decrease in inward currents (I_{Na} and I_{Ca}) or an increase in outward currents ($I_{K\text{-}ATP}$). This may lead to two different fates of the I_{to}-mediated action potential dome in the epicardium depending on the size of I_{to} and I_{to}-mediated phase 1 magnitude.[9,15,17] When I_{to} is prominent, as it is in the right ventricular epicardium,[9,15,18] an outward shift of currents can accentuate the I_{to}-mediated action potential notch in the epicardium to a more negative potential. The L-type calcium current ($I_{Ca,L}$) then fails to activate, and the action potential dome fails to develop, leading to an ***all-or-none*** repolarization at the end of phase 1. All-or-none repolarization, i.e. ***complete*** loss of the action potential dome, results in marked abbreviation of action potentials and phase 2 reentry if heterogeneous loss of the dome occurs (Figure 3).[9,18,19] In contrast, when I_{to} is weak as seen in the left ventricular epicardium, an outward shift of currents may cause only depression (partial loss) of the dome and therefore a minimal change in action potential duration so that phase 2 reentry is unlikely to occur.

Therefore, we can summarize the ionic, cellular mechanisms and ECG features underlying ST segment elevation and arrhythmogenesis associated with a J wave as follows (Figure 4).

(1) I_{to}-mediated spike and dome in the epicardium but not the endocardium registers as a J wave on the ECG;

(2) Prominent spike and dome predisposes the epicardium to complete loss of its dome, leading to a significant increase in transmural dispersion of repolarization that manifests as ST segment elevation in the ECG and serves as a functional reentrant substrate for the development of polymorphic VT and VF;

(3) Because of its relatively slow recovery from inactivation, I_{to} is more prominent during bradycardia, and so are J wave and ST segment elevation;

(4) Heterogeneous loss of the epicardial action potential dome can cause local re-excitation via phase 2 reentry, producing an R-on-T extrasystole that functions as a trigger capable of initiating polymorphic VT and VF.

Clinical syndromes or Diseases that are Associated with the J Wave (J Wave Syndromes)

The clinical and ECG features of the J wave syndromes are summarized in the Table 1.

The Brugada syndrome

The Brugada syndrome is a clinical entity described by the Brugada brothers.[20] It manifests clinically as recurrent syncope and sudden cardiac death from ventricular fibrillation.[20,21] Although observed worldwide, it is more common in young to middle-aged Asian males. The ECG features of the Brugada patient includes an accentuated J wave imitating incomplete right branch bundle block (RBBB) and ST segment elevation in the right precordial leads (V_1-V_3) in the absence of myocardial ischemia and electrolyte disturbance.[20,21]

As one of J wave syndromes, the Brugada syndrome exhibits its ECG characteristics and clinical outcomes dictated by the ionic and cellular mechanism for the J wave. It has been shown that ST segment elevation in the Brugada patients is significantly influenced by heart rate and autonomic tone [22] and its coved morphology, which represents heterogeneous loss of the epicardial action potential dome, is associated with a higher incidence of sudden cardiac death. Quinidine, an antiarrhythmic drug that has an inhibitory effect on I_{to}, normalizes the ST segment and reduces sudden cardiac death in the Brugada patients.[23]

The early repolarization syndrome

The early repolarization syndrome is characterized by a distinct J wave or J point elevation, concave upward ST segment elevation defined predominantly in the left precordial leads V_4-V_6, with a broad and upright T wave. The early repolarization syndrome is considered as a “benign” ECG

phenomenon that is more commonly seen in young healthy men and athletes.[15] Interest in this well-known syndrome has recently been rekindled because of its electrocardiographic similarity to the highly arrhythmogenic Brugada syndrome and idiopathic ventricular fibrillation.[4,15,24]

The underlying mechanism for ST segment elevation in the early repolarization syndrome is principally similar to that for ST elevation in the Brugada syndrome. As shown in Figure 5, pinacidil, a potassium channel opener, leads to partial loss of the I_{to}-mediated action potential dome in the canine left ventricular epicardium and results in ST segment elevation. As discussed in the previous section, partial loss of the epicardial action potential dome in the left ventricle is the consequence of a smaller I_{to} and I_{to}-mediated phase 1 magnitude.[9] Because only mild to moderate action potential shortening occurs when the dome is partially lost, phase 2 reentry may not occur. However, the early repolarization syndrome may not always be benign and is potentially associated with sudden cardiac death.[25,26] Similar to other clinical entities in the J wave syndromes, the heart rate and autonomic tone also modify not only the J wave size but also the ST segment elevation in the early repolarization syndrome.[27]

Idiopathic ventricular fibrillation

This syndrome has many other names such as sudden unexpected death syndrome, sudden nocturnal death syndrome and sudden arrhythmia death syndrome. It has been especially reported in Southeast Asian and Pacific Rim countries and has remained a mystery in etiology for many decades.

In the 1980s, the Center for Disease Control (CDC) received approximately 120 case reports of sudden cardiac death in Southeast Asian refugees in the USA.[28,29] These victims who had died during their sleep were young males without a history of any cardiac diseases, confirmed by autopsy. In 1984, Otto et al noticed that ST segment elevation in the inferior leads was present in three apparently healthy Southeast Asian male immigrants who survived ventricular fibrillation (VF).[30] In 2000, scientists from Yan's group reported a case of a previously healthy Asian male with recurrent episodes of VF who exhibited a prominent J wave and ST segment elevation in the inferior leads II, III and aVF. He firstly pointed out that this syndrome is closely associated with the Brugada syndrome.[8]

Like the Brugada and the early repolarization syndromes, bradycardia accentuates ST segment elevation, whereas tachycardia tends to normalize the ST segment. In the idiopathic ventricular fibrillation syndrome, VF occurs often at midnight or in the early morning hours when the heart rate is slower and, perhaps, the parasympathetic tone is increased.[8,26]

From the mechanistic point of view, the Brugada syndrome, the early repolarization syndrome and idiopathic ventricular fibrillation are different sides of the same coin because the ionic, cellular and, probably, genetic basis's are identical. This is strongly supported by the fact that the ECG features of these two or even three clinical entities can be seen in the same individual or the same family.[26,31-33] It has been shown that the SCN5A mutation is associated with ST segment elevation in the right precordial as well as the inferior leads.[34,35] The only difference among these clinical entities is the difference in I_{to} density and associated J wave size (Table 1). This is better demonstrated from a case reported by Qi et al.[26] A Chinese man was admitted with cardiac arrest and recurrent ventricular fibrillation. He ruled out for myocardial infarction, and cardiac examination and laboratory tests, including echocardiogram and cardiac catheterization, were normal. As shown in Figure 6, prominent J waves and ST segment elevation were seen across almost all ECG leads. Based on the current diagnostic criteria and understanding, this case does not belong to any of these entities: the Brugada syndrome, idiopathic VF and the early repolarization syndrome. Interestingly, saddleback-type ST segment elevation in precordial leads of V_2 to V_3 (solid arrows), which is thought to be less arrhythmogenic,[17] was coupled with R-on-T extrasystoles which were likely via phase 2 reentry (open arrows). After the extrasystoles, a longer pause resulted in coved ST segment elevation (dashed arrows). This indicates that extrasystoles may not necessarily originate from the right ventricle. In other words, the ECG data do not support the diagnosis of the Brugada syndrome. In fact, ST segment elevation was more profound in the left precordial leads, indicating that the R-on-T extrasystoles may originate from the left ventricle.

Arrhythmogenesis during Early Acute Myocardial Ischemia: Does it Share the Same Mechanism as in the J Wave Syndromes?

Sudden cardiac death (SCD) accounts for more than 60% of all cardiac deaths, with annual deaths in excess of 400,000 in the USA.[36] The majority of SCD occur in the setting of coronary artery disease. Interestingly, there are a number of similarities in ECG and clinical features between acute myocardial ischemia and the J wave syndromes.[9,17] On the ECG alone, ST segment elevation and polymorphic VT and VF are virtually indistinguishable between acute myocardial ischemia and idiopathic VF or the Brugada syndrome.[8,30] Sodium channel blockers, which are currently used to unmask the concealed form of the Brugada syndrome, produce marked ST segment elevation simulating acute inferior myocardial ischemia.[37] Women with coronary heart disease have only a quarter of the risk for sudden cardiac death as men.[38] As discussed in the previous section, clinical data from our hospital have demonstrated that females also exhibited less prominent ST segment elevation during acute myocardial infarction. All of these indicate that the fundamental mechanisms responsible for ST segment elevation and the initiation of VF are similar between acute myocardial ischemia and the J wave syndromes.[8,9] A recent study has provided direct and solid evidence that R-on-T extrasystoles capable of initiating VF can develop via the mechanism of phase 2 reentry during the early acute myocardial ischemia(Figure 7).[5]

It is therefore not surprising that the incidence of primary VF is higher in patients with acute inferior MI who have right ventricle involvement (8.4%) than those without (2.7%), or anterior MI (5.0%)[39] This is because I_{to} in the epicardium is much more prominent in the right ventricle vs. the left.[40] Another clinical observation that favors the important implication of I_{to} in arrhythmogenesis of coronary heart disease is a sex-related difference in sudden cardiac death. In men and women with coronary heart disease, the incidence of sudden death in men was significantly higher than that in women.[38,41] This may be due, in part, to a more prominent I_{to} in males versus females, which has been thought to be responsible for the predominance of the Brugada syndrome or idiopathic VF in men.[14]

Summary

Advancement and progress in modern laboratory technologies, including electrophysiological study and genetic analysis, have permitted in-depth research into many clinical mysteries related to

sudden cardiac death, among which the J wave is one typical example. ST segment elevation and arrhythmogenesis associated with the J wave now have plausible ionic and cellular explanations. Our enhanced understanding of the J wave syndromes is expanding our interest in exploring the mechanisms underlying sudden cardiac death in the setting of coronary diease, the number one killer of Americans.

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Table 1. J Wave Syndromes

	ERS	Idiopathic VF	Brugada Sydrome
Anatomic Location	Left anterolateral	infero-posterior	Right Ventricle
I_{to} Density in Epi	small	medium?	large
J Wave Amplitude	small	medium	large
ST Elevation	V4-V6,	II, III and aVf	V1-V3
Dynamic Change in ST Elevation	↑ in bradycardia ↑ by Na+ blockers ?	↑ in bradycardia ↑ by Na+ blockers	↑ in bradycardia ↑ by Na+ blockers
Sex Dominance	male	male	male
VF	?, likely no	yes	yes
Quinidine's Effect	?	normalizing ST and inhibiting VF	normalizing ST and inhibiting VF
Gene Mutation	?	SCN5A	SCN5A (20-30%)

ERS:early repolarization syndrome; ?: unknown; ↑: increase.

Figure Legends

Figure 1. Effect of ventricular activation sequence on the J wave on the ECG. **A.** When the wedge preparation is stimulated from the endocardial surface with epicardium activated last, a J wave on the ECG is temporally aligned with I_{to}-mediated epicardial action potential notch. **B.** When the preparation is paced from the epicardial surface with endocardium activated last, the epicardial action potential notch is coincident with the QRS, and a J wave is no longer observed (reprinted from ref.[2] with permission).

Figure 2. Mechanisms responsible for ST segment elevation. ***A:*** the concept of "injury current". "Injury" zone in the epicardium with a reduction in resting membrane potential produces an "injury current" during resting phase that should result in TQ depression instead of ST elevation. ***B:*** The concept of "loss of AP dome or plateau amplitude". A difference in action potential plateau amplitude generates a transmural voltage gradient that manifests as ST segment displacement. Reprinted from ref.[15] with permission.

Figure 3. The mechanism responsible for J wave related arrhythmogenesis. **A:** Polymorphic VT in a patient with the prominent J waves (reprinted from ref.[42] with permission). **B:** Polymorphic VT initiated by phase 2 reentry in a canine right ventricular wedge in the presence of 2.5 μmol/L of pinacidil. APs were simultaneously recorded from two epicardial sites (Epi_1 and Epi_2) and one Endo site. Loss of the AP dome in Epi_1 but not in Epi_2 led to phase 2 reentry capable of initiating polymorphic VT (modified from ref.[9] with permission).

Figure 4. Schematic diagram to demonstrate ionic and cellular mechanisms for the genesis of J wave, ST segment elevation and arrhythmogenesis in the J wave syndromes. Epi: epicardium; +: facilitating; -: inhibiting; ?: unknown.

Figure 5. Cellular basis for the early repolarization syndrome. ***Panel A:*** Surface ECG (lead V5) recorded from a 17-year-old healthy African American man. Note the presence of a small J wave and marked ST segment elevation. ***Panel B:*** Simultaneous recording of transmembrane action potentials

from epicardial (Epi) and endocardial (Endo) regions and a transmural ECG in an isolated arterially perfused canine left ventricular wedge. A J wave in the transmural ECG is present due to the action potential notch in the epicardium but not the endocardium. Perfusion of the preparation with pinacidil (2 μmol/L), an ATP-sensitive potassium channel opener, causes partial loss of the action potential dome in the epicardium, resulting in ST segment elevation in the ECG resembling the early repolarization syndrome. Reprinted from ref.[15] with permission.

Figure 6. Body surface ECG obtained from a 34-year-old Chinese man who survived from cardiac arrest. Prominent J waves and ST segment elevation were seen in almost all leads. Interestingly, saddleback-type ST segment elevation in precordial leads of V_2 to V_3 (solid arrows), which is thought to be less arrhythmogenic,[17], was coupled with R-on-T extrasystoles (open arrows). After the extrasystoles, a longer pause resulted in coved ST segment elevation (dashed arrows). This indicates that extrasystoles may not necessarily originate from the right ventricle. Reprinted from ref.[26] with permission.

Figure 7. Acute regional myocardial ischemia resulted in complete loss of prominent AP dome at Epi_2 within the ischemic zone but not at Epi_1 in the perfused side of the ischemic border, leading to propagation of the dome from Epi_1 to Epi_2 (phase 2 reentry). Phase 2 reentry and its transmural propagation manifested as a closely-coupled R-on-T extrasystole on the ECG that was able to initiate VF. BCL=2000 msec. **B.** I_{to} traces recorded at step voltages from –20 to +30 mV in canine right ventricular epicardial myocytes isolated from the same ventricle in which the ventricular wedge in **Panel A** was dissected. I-V relationships (right): Averaged I_{to} density (30.3 pA/pF) was normalized by cell membrane capacitance in 4 myocytes. Reprinted from ref.[15] with permission.

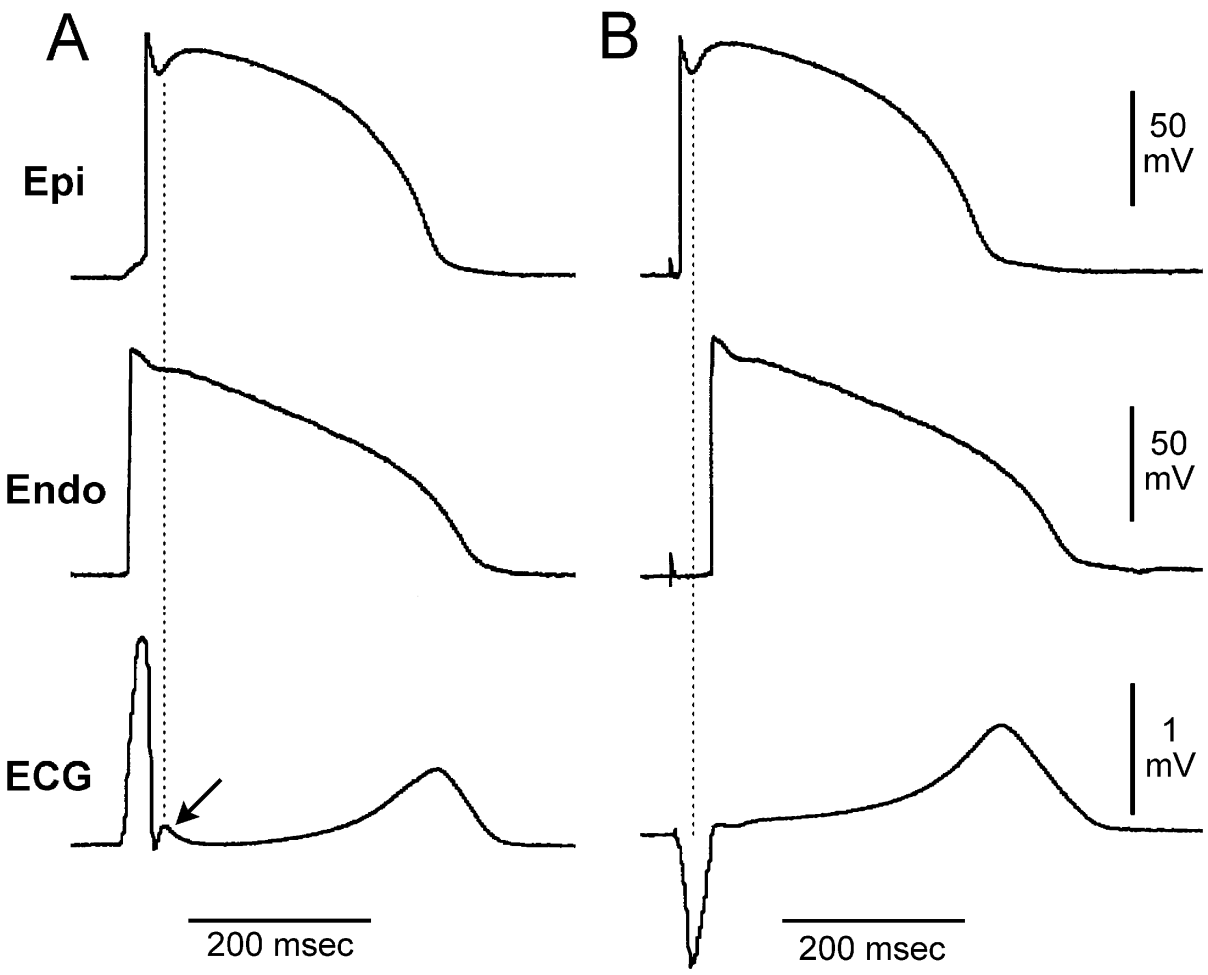


Figure 1

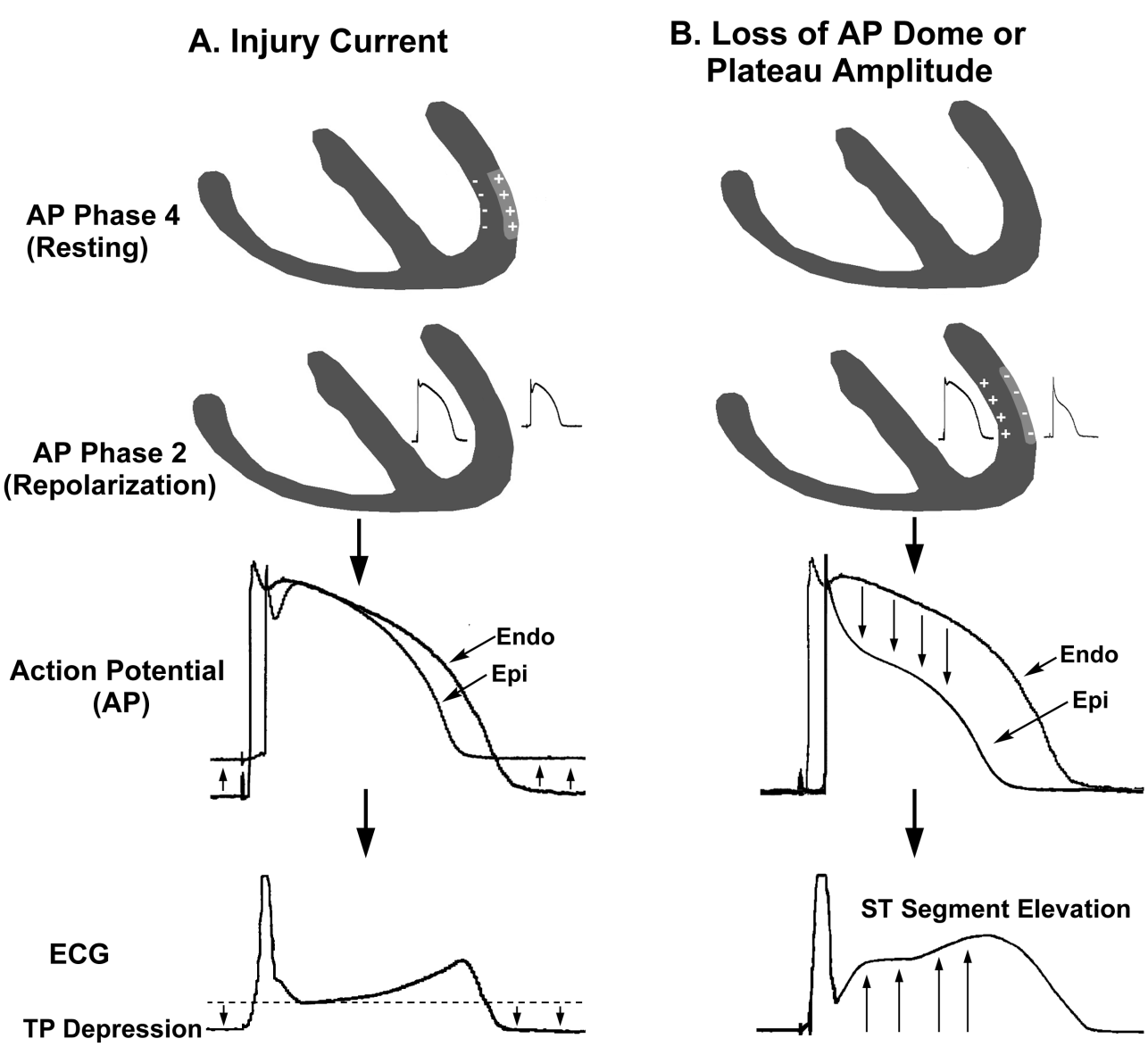
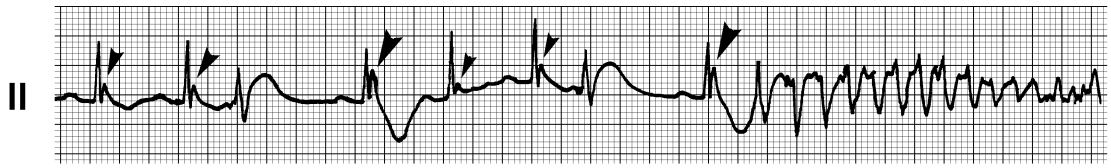

Mechanisms Underlying ST Segment Elevation
A. Injury Current
B. Loss of AP Dome or Plateau Amplitude
AP Phase 4 (Resting)
AP Phase 2 (Repolarization)
Action Potential (AP)
Endo
Epi
Endo
Epi
ECG
TP Depression
ST Segment Elevation

Figure 2

A. J wave and Associated Ventricular Tachycardia in a Patient



B. Phase 2 Reentry and Ventricualr Tachycardia in a Canine Ventricular Preparation

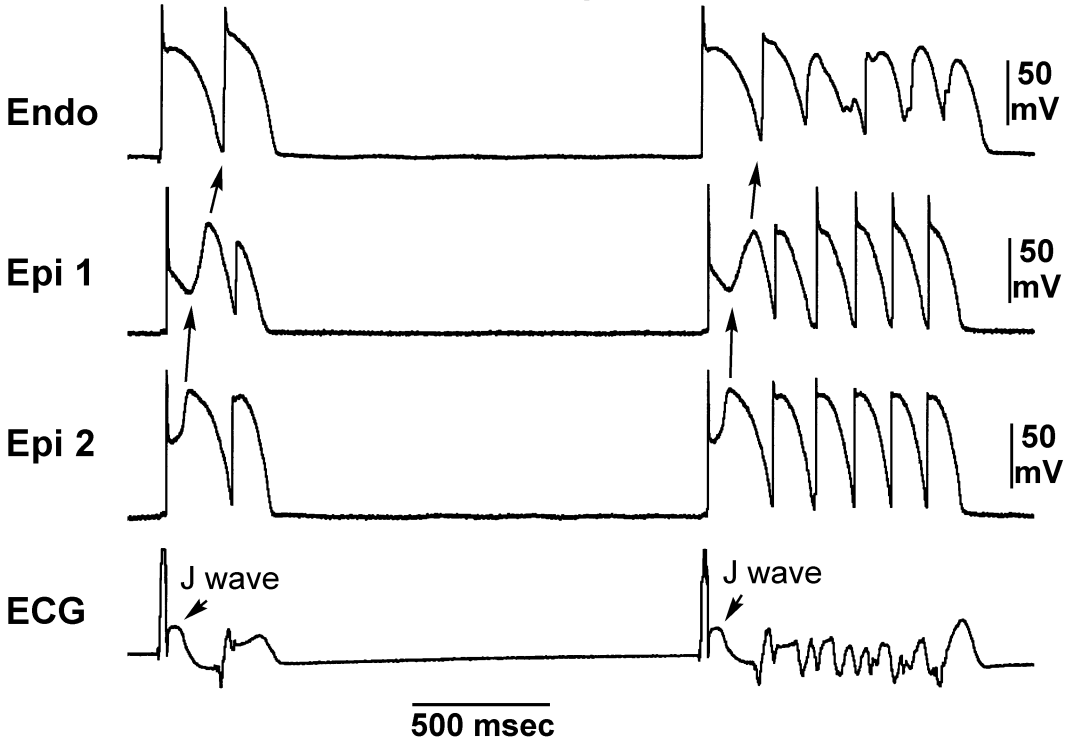


Figure 3

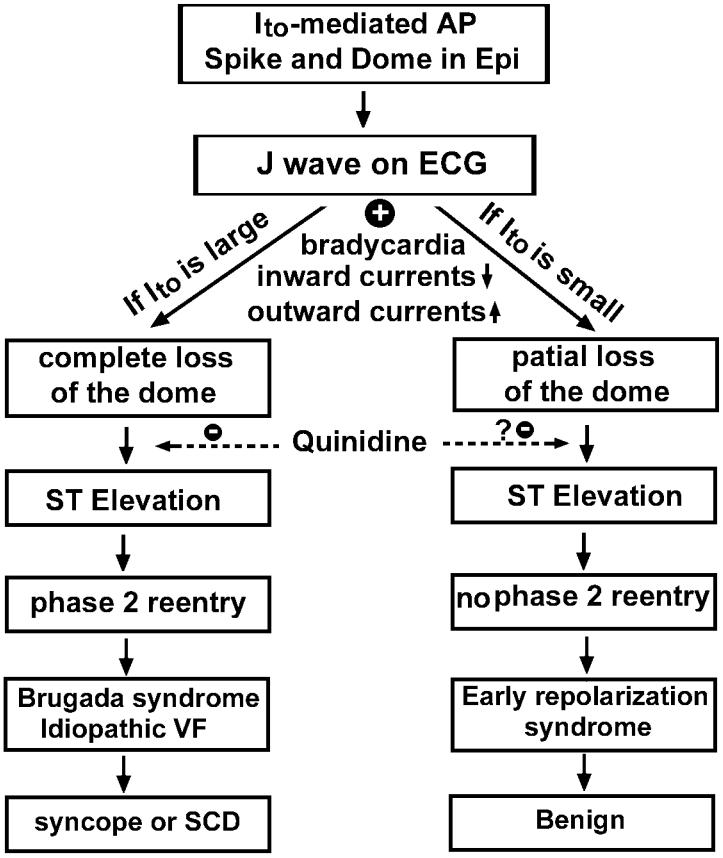
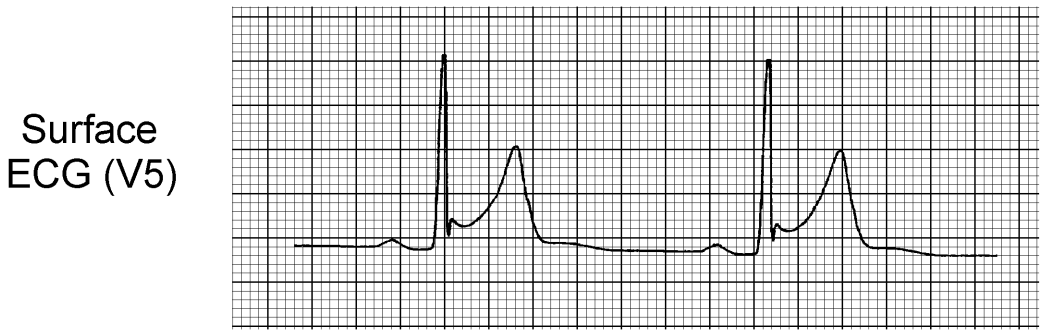

Ito-mediated AP
Spike and Dome in Epi
J wave on ECG
If Ito is large
bradycardia
inward currents
outward currents
If Ito is small
complete loss
of the dome
patial loss
of the dome
Quinidine
?
ST Elevation
ST Elevation
phase 2 reentry
no phase 2 reentry
Brugada syndrome
Idiopathic VF
Early repolarization
syndrome
syncope or SCD
Benign

Figure 4

A. Early Repolarization Syndrome in a Healthy Young man



B. Canine Ventricular Action Potentials and ECG

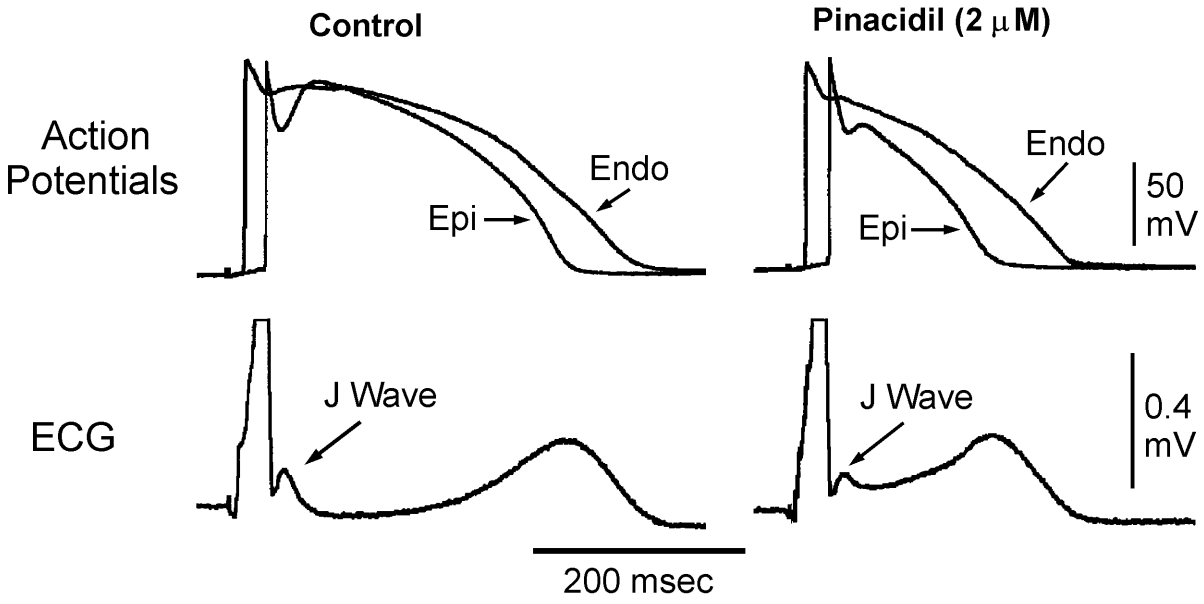


Figure 5

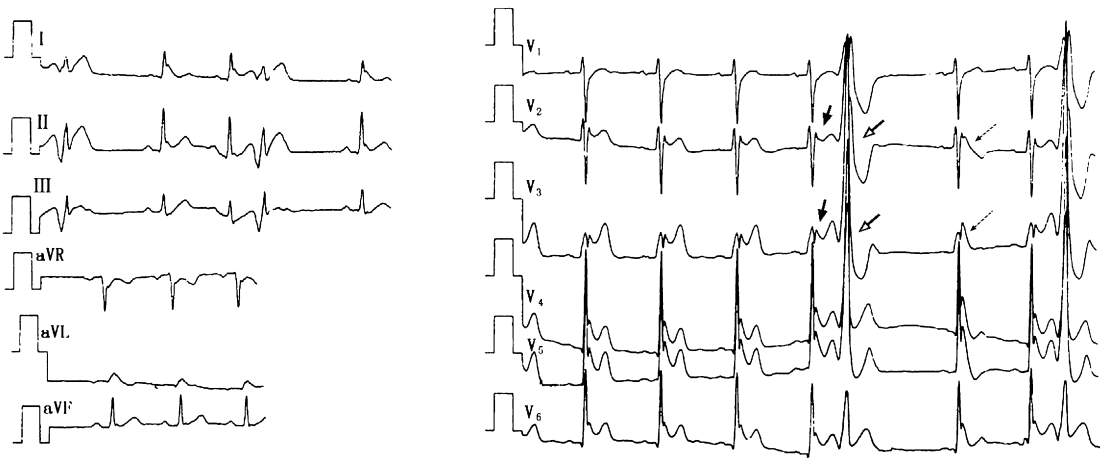


Figure 6

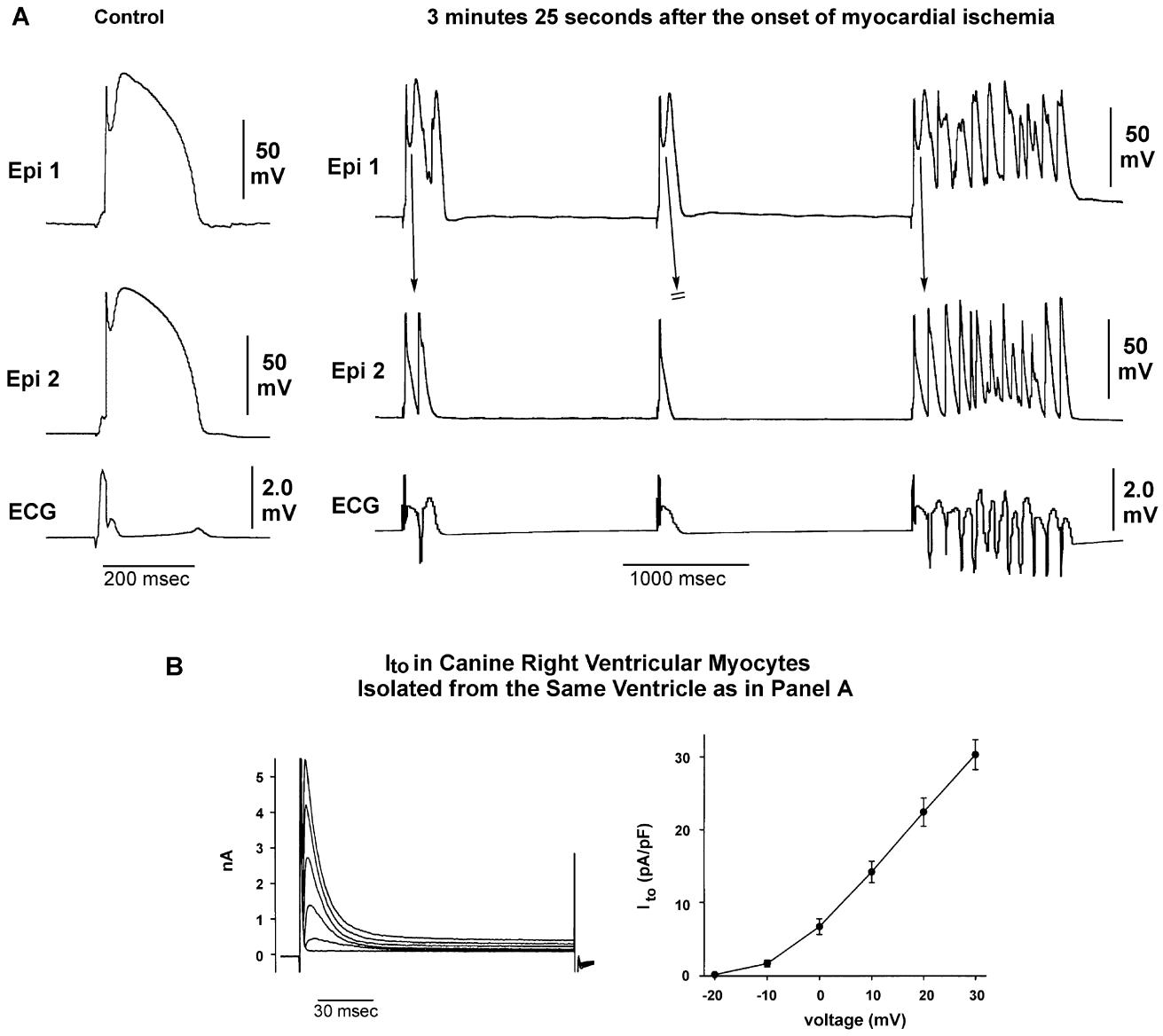

A
Control
3 minutes 25 seconds after the onset of myocardial ischemia
Epi 1
50 mV
Epi 2
50 mV
ECG
2.0 mV
200 msec
1000 msec
B
Ito in Canine Right Ventricular Myocytes
Isolated from the Same Ventricle as in Panel A
nA
30 msec
Ito (pA/pF)
voltage (mV)

Figure 7