The electrocardiogram (ECG) is widely used in clinical practice to detect cardiac arrhythmias, conduction disturbances, myocardial ischemia, electrolyte or metabolic disturbances, structural changes of the myocardium, and drug effects. However, the correlation between cellular events and the various components on the surface ECG is not well established, despite the fact that ECG recording has been used in clinical practice for over a century (1). The ECG waveforms are known to depend on the properties of transmembrane action potentials (APs) of atrial and ventricular myocytes, the spread of excitation, and the characteristics of the volume conductor. Among them, transmembrane AP as an electromotive generator clearly plays a central role. Therefore, the ECG recording of a normal cardiac cycle is composed of two basic processes: depolarization and repolarization. Ventricular depolarization (activation) is depicted by the QRS complex, whereas ventricular repolarization is defined by the interval from the beginning of the QRS complex to the end of the T- or U-wave. On the surface ECG, ventricular repolarization components include the J-wave, ST-segment, and T- and U-waves. Recent progress in the basic and clinical research of electrical heterogeneity across the ventricular wall has provided exciting insights into the ionic and cellular basis for ventricular repolarization components. This review attempts to summarize our state of knowledge of ventricular repolarization components and their clinical significance.

**J (Osborn) wave.** The J-wave is a deflection following the QRS complex (2). Also referred to as the Osborn wave because of Osborn’s landmark description in the early 1950s (3), a prominent J-wave is often associated with hypothermia and hypercalcemia (2,4). However, a distinct J-wave on the ECG is also commonly observed in people with the early repolarization syndrome and those with idiopathic ventricular tachycardia or fibrillation. (J Am Coll Cardiol 2003;42:401–9) © 2003 by the American College of Cardiology Foundation

From the Main Line Health Heart Center, Wynnewood, Pennsylvania. This study was supported by the American Heart Association, the W. W. Smith Charitable Trust, the Fourjay Foundation, the Adolph and Rose Levis Foundation, and the Sharpe Foundation.

Manuscript received December 18, 2002; accepted April 30, 2003.
larization that could manifest as a J-wave or J-point elevation on the ECG. Direct evidence in support of this hypothesis was recently obtained in an arterially perfused canine ventricular wedge preparation (4). As shown in Figure 1, the size of the J-wave is closely correlated to the I_{to}-mediated AP notch in the epicardium. Therefore, factors that influence I_{to} or its counter (inward) currents in phases 1 and 2 (e.g., hypothermia and heart rate [4,6]) could modify the size and morphology of the J-wave.

Although a higher incidence of ventricular tachycardia (VT) and ventricular fibrillation (VF) has long been observed in hypothermic patients with prominent J-waves (2), the importance of a prominent J-wave in arrhythmogenesis was not recognized until recently, when Brugada syndrome, a clinically malignant entity, was identified (7,8,10,11). As Brugada syndrome is also associated with ST-segment elevation, it will be discussed in detail in the following section.

The ST-segment. The ST-segment is the portion of the ECG that lies between the end of the QRS complex and the beginning of the T-wave. Normally, the ST-segment stays at the same level as the T-P segment. Two changes in the ST-segment are considered clinically important: ST-segment displacement and a change in ST-segment morphology. ST-segment displacement, either upward (elevation) or downward (depression) of more than 1 mm from baseline, is abnormal.

**A. J Wave in a Healthy Young Asian Male**

![Figure 1](image)

**B. Canine Ventricular Action Potentials and ECG**

![Figure 1](image)

**Figure 1.** Cellular basis for the J-wave. (A) A prominent J-wave in lead II was recorded from a healthy, young Asian male. (B) Simultaneous recording of transmembrane action potentials (APs) from epicardial (Epi) and endocardial (Endo) regions and a transmural electrocardiogram (ECG) in an arterially perfused canine ventricular wedge preparation. An I_{to}-mediated AP notch in the epicardium, but not endocardium, was associated with a J-wave. A premature stimulus (S₁ - S₂ = 300 ms) caused a parallel decrease in the amplitude of the epicardial AP notch and J-wave. Modified from Yan and Antzelevitch (4), with permission.
POSSIBLE MECHANISMS RESPONSIBLE FOR ST-SEGMENT ELEVATION. The classic concept for ST-segment elevation is the so-called “injury current” theory, explained as current flow from the injured myocardium, where the cells are partially depolarized, to the uninjured myocardium (12). In animal experiments, however, the injury current measured by using a direct-current coupled amplifier, causes TP-(or TQ) segment depression rather than ST-segment elevation (13,14). In clinical practice, however, the ECG signals are input to an ECG recorder with a high-pass (low-cutoff) filter in order to avoid direct current drift. Under this condition, the TP depression is transformed to apparent “ST-segment elevation” (Fig. 2A). The low-frequency cut-off in the clinical ECG machines may reduce the amplitude of ST-segment elevation resulting from the injury current. More importantly, the ST-segment elevation caused by the injury current alone would theoretically not be associated with any change in the ST-segment morphology (Fig. 2A). All of these indicate that the injury current is not a sole contributor to clinically observed ST-segment elevation.

It is more problematic to use the concept of injury current to explain ST-segment displacement in nonischemic or
structurally normal hearts, as in the early repolarization syndrome and Brugada syndrome, conditions in which no “injured zone” is identified. Because the ST-segment corresponds temporally to the AP plateau phase, the difference in plateau potentials within the ventricles could produce true ST-segment elevation. As illustrated in Figure 2B, the depression or loss of the AP dome in the epicardium, but not endocardium, would result in a transmural voltage gradient during repolarization that could manifest as ST-segment elevation. This mechanism likely underlies ST-segment elevation in Brugada syndrome and early repolarization syndrome and perhaps also contributes importantly to that observed in acute myocardial ischemia (11,15,16).

THE EARLY REPOLARIZATION SYNDROME. The early repolarization syndrome is characterized by a distinct J-wave and ST-segment elevation predominantly in the left precordial leads. The early repolarization syndrome is a benign ECG phenomenon (6). ST-segment elevation in this syndrome is thought to be due to depression (partial loss) of the \(I_{\text{ca}}\)-mediated AP dome in the left ventricular epicardium (15). This is supported by clinical observations that heart rate and autonomic tone, which influence \(I_{\text{to}}\), L-type calcium current (\(I_{\text{ca}}\)), and perhaps inward sodium current (\(I_{\text{na}}\)), modify ST-segment elevation in the early repolarization syndrome (6). However, the exact ionic basis for this clinical entity remains unknown.

BRUGADA SYNDROME. Brugada syndrome is associated with polymorphic VT and VF, which result in recurrent syncope and sudden cardiac death (10,17). Despite its malignant features, Brugada syndrome shares many ECG manifestations with the early repolarization syndrome. The ECG of the patient with Brugada syndrome is characterized by a normal QT interval and ST-segment elevation in the right precordial leads (V1 through V3) or inferior leads (II, III, and aVF) in the absence of myocardial ischemia or bradycardia or in the presence of APD-prolonging drugs. Hence, these cells are thought to play an important role in delayed ventricular repolarization, as in long QT syndrome (LQTS).

The ionic basis for the features of M cells that distinguish them from the epicardium and endocardium includes the presence of a smaller slowly activating delayed rectifier potassium current (\(I_{\text{kdr}}\)) but a larger late \(I_{\text{na}}\) (28,29). On the other hand, rapidly activating delayed rectifier potassium current (\(I_{\text{kr}}\), the ionic target by most APD-prolonging agents, is similar in density across the ventricular wall. Therefore, the difference in the \(I_{\text{kdr}}:I_{\text{kr}}\) ratio among three transmural cell types plays an important role in TDR (28,30). Any factors that alter the \(I_{\text{kdr}}:I_{\text{kr}}\) ratio could result in abnormal ventricular repolarization. It has been demonstrated that the mutations of genes that encode \(I_{\text{kdr}}\) and \(I_{\text{kr}}\) account for most forms of congenital LQTS (31).
CELLULAR BASIS FOR THE GENESIS OF AN UPRIGHT T-WAVE. The temporal relationship between transmembrane APs simultaneously recorded from the canine epicardium, M region, and endocardium and the ECG T-wave was first demonstrated in an arterially perfused ventricular wedge preparation (Fig. 4). Separation of the epicardial AP from that of M cells during the plateau phase marks the beginning of the upright T-wave. Under normal conditions, the separation is so gradual that the beginning of the T-wave is difficult to determine. As shown in Figure 4, repolarization of the M cells is temporally aligned with the end of the T-wave (Tendo), whereas repolarization of the epicardium is coincident with the peak of the T-wave (Tpeak). Repolarization of Purkinje fibers usually outlasts that of M cells but fails to generate a wave on the ECG in the canine heart, probably due to their small mass (32). The temporal relationship between cellular electrical activities and the T-wave remains constant under wide ranges of conditions, including hypokalemia and hyperkalemia (Fig. 4). Hyperkalemia produces a steeper slope of AP phase 3, leading to an increase in the transmural voltage gradient. This gives rise to a tall and upright T-wave. The mechanism underlying a change in the T-wave under hypokalemia is more complicated. A pathologic U-wave is often observed. In contrast to hyperkalemia, the AP phase 3 slope during hypokalemia is attenuated, giving rise to small, opposing voltage gradients that cross over, producing a low-amplitude T-wave and the so-called "U" wave (Fig. 4B).

**Figure 3.** The mechanism responsible for J-wave-related arrhythmogenesis. (A) Polymorphic ventricular tachycardia (VT) in a patient with prominent J-waves. Reprinted from Aizawa et al. (5), with permission. (B) Polymorphic VT initiated by phase 2 re-entry in a canine right ventricular wedge in the presence of 2.5 μmol/l pinacidil. The action potentials (APs) were simultaneously recorded from two epicardial sites (Epi 1 and Epi 2) and one endocardial (Endo) site. A loss of the AP dome in Epi 1, but not in Epi 2, led to phase 2 re-entry capable of initiating polymorphic VT.
Under this condition, full repolarization of the epicardium marks the peak of this pathologic U-wave, whereas repolarization of both the endocardial and M cells contributes importantly to the descending limb. The apparent T-U complex is, in fact, a T-wave whose ascending limb is interrupted. The forces that give rise to the pathologic U-wave in hypokalemia are similar to those underlying the T-wave. Therefore, a pathologic U-wave is likely a second component of a bifid or notched T-wave. This clarification is important in two respects. First, the "QT" interval that most clinicians try to measure under hypokalemia encompasses the time from the beginning of the QRS to the end of the first component of the T-wave. This interval may be equal to or shorter than the QT interval under normal conditions (33). The true QT interval should therefore include the pathologic U-wave under hypokalemia. Second, the mechanisms responsible for the pathologic U-waves are likely different from those underlying a physiologic U-wave.

The T_peak-end interval that encompasses the terminal portion of the T-wave closely represents TDR (Fig. 4). This is probably the reason why the terminal portion of the T-wave is "vulnerable," so that an electrical impulse interrupting it (i.e., the R-on-T phenomenon, as shown in Figs. 3 and 5) could potentially produce functional transmural re-entry, leading to the development of polymorphic VT and VF (34-37). The T_peak-end interval, as an index of TDR, has been proved to be clinically useful in assessing arrhythmic risk (36,38-40).

LONG QT SYNDROME. Both the congenital and acquired forms of LQTS represent pathophysiologic states characterized by the appearance of a long QT interval on the ECG, notched T-waves, U-waves, and an atypical polymorphic VT known as torsade de pointes (31,39,41).

Genetic analysis has identified at least five forms of congenital LQTS caused by gene mutations located on chromosomes 3, 7, 11, and 21, which are responsible for defects in $I_{Na}$ (SCN5A/LQT3), $I_{Kr}$ (HERG/LQT2 and MiRP1/LQT6), and $I_{Ks}$ (KVLQT1/LQT1 and MinK/LQT5) (31). The long QT syndrome can be acquired due to the use of drugs, serum electrolyte disturbances, ventricular hypertrophy, and myocardial ischemia (42,43). The mechanisms underlying drug-induced LQTS involve either the

(A) ECG T Wave Shapes Clinically Recorded in Different Serum $K^+$ Concentrations

(B) Canine Ventricular Action Potentials and ECG

Figure 4. Cellular basis for the T-wave. (A) The electrocardiogram (ECG) tracings were recorded in patients with various serum potassium concentrations. A pathologic U-wave was seen under hypokalemia, whereas a tall and upright T-wave was associated with hyperkalemia. (B) Simultaneous recording of action potentials (APs) from epicardial (Epi) and M cells or endocardial cells (Endo), together with a transmural ECG under various extracellular potassium concentrations. Extracellular potassium primarily influenced the AP phase 3 slope (repolarization rate); hyperkalemia accelerated phase 3 repolarization, whereas hypokalemia reduced it. The alteration of AP phase 3 slopes and their interplay among different myocardial layers determined the T-wave morphologies under various extracellular potassium concentrations. A pathologic U-wave was present with hypokalemia. Reprinted from Yan et al. (32), with permission.
Figure 5. The mechanism responsible for the initiation of torsade de pointes (TdP). (A) An R-on-T extrasystole initiated an episode of torsade de pointes in a patient with a prolonged QT interval who was receiving sotalol. (B) Transmembrane action potentials (APs) from the epicardium (Epi) and endocardium (Endo) were simultaneously recorded together with a transmural electrocardiogram (ECG) in an arterially perfused rabbit left ventricle. dl-sotalol, an IKr blocker, markedly prolonged the QT interval and induced phase 2 early afterdepolarization (EAD) in the endocardium. The phase 2 EADs, in turn, produced R-on-T extrasystoles capable of initiating torsade de pointes. Reprinted from Yan et al. (35), with permission.
inhibition of outward currents (I_{Ks}) or the enhancement of the inward current (late I_{Na}) However, most agents that cause clinical torsade de pointes target I_{Ks}. Preferential APD prolongation of M cells is thought to underlie QT prolongation, the phenotypic appearance of abnormal T-waves, the pathologic U-wave, and the development of torsade de pointes (32).

It is generally accepted that a focal activity initiates the onset of torsade de pointes, whereas functional re-entry is responsible for its maintenance (32,35,44). Disproportional AP prolongation of M cells in response to APD-prolonging agents, low extracellular potassium, and bradycardia can result in a marked increase in TDR that serves as a reentrant substrate. The focal activity is derived from phase 2 early afterdepolarization (EAD) and its transmural propagation, as shown in Figure 5 (35,42).

T-WAVE ALTERNANS. T-wave alternans, defined as a beat-to-beat change in T-wave morphology, amplitude, and/or polarity, usually heralds the onset of ventricular arrhythmias or sudden cardiac death in patients who have various pathophysiologic conditions (45,46). T-wave alternans is invariably associated with an alternate change in the QT and T_{peak-end} intervals (42,46).

Recent studies have demonstrated that T-wave alternans is the ECG manifestation of a beat-to-beat change in TDR (42,47). In T-wave alternans associated with ventricular hypertrophy and failure, the endocardium or subendocardium displays a significantly alternate change in APD (42), a phenomenon that may be secondary to intracellular calcium alteration in the presence of a robust sarcoplasmic reticulum function (48). Phase 2 EAD may be generated from the endocardium or subendocardium during a beat with a longer APD, leading to polymorphic VT (42).

U-wave. A physiologic U-wave in the presence of a normal serum potassium concentration is defined as a small deflection following the T-wave. Its height is generally less than one-fourth of the T-wave height. The T-U junction is usually situated at or close to the isoelectric line, but it may be deviated positively or negatively (49). On the other hand, a pathologic U-wave under hypokalemia is usually similar to or larger than the T-wave, and the T-U junction is often above or below the isoelectric line.

Several hypotheses have been proposed to explain the genesis of the U-wave, which represents the last repolarization component of the ventricles (49). The likely sources responsible for the physiologic U-wave include EAD of the ventricular myocardium or delayed repolarization of the Purkinje network. However, experimental data have shown that EAD generated from the endocardium or subendocardium fails to inscribe a U-wave on the ECG (35). M cells, due to their delayed repolarization properties and voluminous mass within the ventricle, were initially thought to be the cellular basis of the physiologic U-wave (9). As discussed in the previous section, M cells electrically coupled with the endocardium and epicardium play a determining role in the genesis of the T-wave and pathologic U-wave. The hypothesis that the Purkinje network is responsible for the physiologic U-wave seems most plausible, as repolarization of subendocardial Purkinje fibers is temporally aligned with the expected appearance of the U-wave on the ECG (50). However, direct experimental evidence supporting this hypothesis is still lacking.

Summary. Inscription of the J (Osborn) wave, ST-segment displacement, and the T-wave on the ECG is the consequence of electrical heterogeneities among the ventricular epicardium, M cells, and endocardium during ventricular repolarization. The transmural voltage gradient secondary to the difference in the I_{Ks}-mediated AP notch between the epicardium and endocardium underlies the genesis of the J-wave. Moreover, exaggeration of this gradient has been linked to the development of polymorphic VT and VF in Brugada syndrome and acute myocardial ischemia. The ST-segment can deviate upward (elevation) or downward (depression) by either of the following two cellular mechanisms, or both: 1) an injury current due to a difference in resting membrane potentials between injured and uninjured myocardium; and 2) a voltage gradient generated by a difference in AP plateau amplitudes. Intrinsically different repolarization properties among the epicardium, M cells, and endocardium, as well as their interplay, are responsible for various morphologies of the T-wave and pathologic U-wave. The T-wave is a symbol of TDR. The T_{peak-end} interval as an index of TDR is clinically useful in assessing arrhythmic risk in LQTS.

Reprint requests and correspondence: Dr. Gan-Xin Yan, Main Line Health Heart Center, 100 Lancaster Avenue, Wynnewood, Pennsylvania 19096. E-mail: yanganxin@cs.com.

REFERENCES

10. Brugada P, Brugada J. Right bundle branch block, persistent ST-segment elevation and sudden cardiac death: a distinct clinical and


