Global T-wave Inversion on Electrocardiogram: What Is the Differential?

Olayinka Afolabi-Brown, MD,1 D. Lynn Morris, MD,1,2 Vincent M. Figueredo, MD1,2
1Einstein Heart and Vascular Institute, Einstein Medical Center, Philadelphia, PA; 2Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA

Global T-wave inversion as seen on electrocardiogram is associated with a variety of pathophysiologic states, including cardiac, pulmonary, and cerebrovascular disease, and acute electrolyte disorders. Although some of these are chronic conditions, others are acute emergencies, necessitating early diagnosis and treatment. This article reviews and provides examples of possible etiologies of global T-wave inversion on electrocardiogram.

© 2014 MedReviews®, LLC

The T wave on electrocardiogram (ECG) represents ventricular repolarization. On a normal ECG, the T wave has the same polarity as the QRS complex. The T wave is asymmetric and broad, with a slow upstroke that rapidly returns to the isoelectric line following its peak.

The T wave represents the electrical forces resulting from recovery of activated ventricular muscle fibers to their resting states. Thus, a major factor influencing T-wave configuration is the temporal and spatial pattern of myocardial excitation. Altered patterns of excitation secondarily alter the patterns of recovery and, thus, the form of the T wave. The other major factor influencing T-wave configuration is independent of the pattern of excitation and is due to the nonhomogeneous nature of...
the recovery process; that is, variations in the shape and the duration of individual action potentials of the myocardial cell population. Differences in repolarization of various ventricular areas (eg, endocardial and epicardial) result in measurable electrical forces, the temporal and spatial patterns of which determine the magnitude and form of the T wave.1

Global T-wave inversion refers to T-wave inversions in all standard leads except the aVR lead. A study reviewing 30,000 consecutively interpreted ECGs described 100 ECGs with this pattern.2 After a follow-up period of 11 years,3 the presence of global T-wave inversions did not imply a poor prognosis with long-term prognosis dependent on the underlying or associated disease. We review conditions that can manifest as global T-wave inversion on ECG (Table 1).

**Figure 1.** (A) Electrocardiogram (ECG) of an 89-year-old man presenting with chest pain. (B) Coronary angiogram demonstrating a severe distal left main stenosis (arrow). The patient also had an occluded right coronary filling via left collaterals. (C) ECG 1 week later. Patient refused revascularization options and removal of intra-aortic balloon pump for medical therapy and was lost to follow-up.

**TABLE 1**

<table>
<thead>
<tr>
<th>Conditions That Can Manifest as Global T-wave Inversion on Electrocardiogram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left main coronary artery or equivalent acute myocardial infarction</td>
</tr>
<tr>
<td>Takotsubo cardiomyopathy</td>
</tr>
<tr>
<td>Kounis syndrome</td>
</tr>
<tr>
<td>Apical hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Acute pericarditis</td>
</tr>
<tr>
<td>Acute cerebrovascular event</td>
</tr>
<tr>
<td>Electrolyte abnormalities</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Pulmonary edema</td>
</tr>
</tbody>
</table>

132 • Vol. 15 No. 2 • 2014 • Reviews in Cardiovascular Medicine
Left Main Coronary Artery or Equivalent Acute Myocardial Infarction

The T-wave inversion and QT interval prolongation in acute myocardial infarction (MI) are thought to be predominantly caused by prolongation of the action potential.4 Deep inverted T waves in the acute phase of MI have been shown to indicate an abundantly stunned myocardium.5 The corresponding coronary involvement with such ECG changes suggests left main or “left main equivalent” disease. Representative ECGs of patients with acute MI secondary to left main and left main equivalent disease acute MI are shown in Figures 1 and 2.

Takotsubo Cardiomyopathy

Takotsubo cardiomyopathy, or left ventricular apical ballooning syndrome, is generally characterized by transient systolic dysfunction of the apical and/or mid segments of the left ventricle that mimics MI, but in the absence of obstructive epicardial coronary artery disease. The ECG can show diffuse ST-segment elevation, deep T-wave inversions, and QT-interval prolongation during the early phase.6 ECG examples are shown in Figures 3 and 4. The pathophysiology of Takotsubo cardiomyopathy is not well understood. Several mechanisms for the reversible cardiomyopathy have been proposed, including catecholamine-induced myocardial stunning, ischemia-mediated stunning due to multivessel epicardial or microvascular spasm, and myocarditis. In a study comparing patients with Takotsubo cardiomyopathy and patients with acute anterior MI with minimal enzymatic release, the time course of the ECG
changes, as well as the left ventricular dysfunction, was similar between both cardiac disorders, although the T-wave inversion was deeper and the QT interval longer in Takotsubo cardiomyopathy.6

Apical Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathies (HCMs) are genetic diseases of the cardiac sarcomere with autosomal dominant patterns of inheritance. HCMs are caused by mutations in a number of genes, most of which encode components of the contractile apparatus. Apical HCM is an uncommon morphologic variant of HCM in which the hypertrophy of the myocardium predominantly involves the apex of the left ventricle. These patients do not have left ventricular outflow tract obstruction, but may have midventricular obstruction. A pattern of giant negative T waves and high QRS voltage on the ECG can be seen.7 Initially described in Japan, rare cases have also been reported in Asian Indians (Figure 5).8 The most conspicuous findings are high QRS voltages with absence of septal Q waves. There are also extremely deep T waves in the precordial leads, especially in leads V4 and V5, where the apical segment potentials are most clearly reflected. Mean QRS axis in the frontal plane is within normal limits (between 0° and +90°) in all cases.

Acute Pericarditis

The ECG pattern of acute pericarditis in some ways resembles the pattern seen with acute ST-elevation MI (STEMI); however, acute pericarditis can be distinguished from transmural ischemia by more extensive lead involvement in pericarditis without the presence of reciprocal ST-segment

134 • Vol. 15 No. 2 • 2014 • Reviews in Cardiovascular Medicine
depressions seen in acute MI. The typical pattern of ECG changes in acute pericarditis range from diffuse ST elevations acutely (stage 1), through pseudonormalization with descent of the J points to baseline and T wave flattening (stage 2), followed by diffuse T-wave inversion (stage 3), and, finally, restitution to the baseline ECG (stage 4). Stage 1 alone is frequently the only ECG finding if the patient is promptly treated with nonsteroidal anti-inflammatory drugs. Patients may appear to skip or pass through stages rapidly (Figure 6). In a study by Spodick, stage 3 T-wave inversions in both limb and precordial leads were recorded in 32 of 50 consecutive patients who had unequivocal clinical evidence of acute pericarditis. In most cases, ST-segment deviation results from direct injury to the epicardial region by the agent responsible for the pericarditis. Because inverted T waves commonly develop with pericarditis in those leads in which elevated ST segments had previously occurred, it has been postulated that the duration of the repolarization in the previously injured epicardial muscle layer is sufficiently lengthened to bring about a net reversal of the direction of this process.

Acute Cerebrovascular Event

Several neurologic causes of ECG changes have been described in the literature, including acute cerebrovascular accident (embolic or hemorrhagic), transient ischemic attack, subarachnoid hemorrhage, subdural hematoma, and seizure (Figures 7 and 8). The electrocardiographic changes commonly seen in cerebrovascular accidents include large and inverted T waves, prolonged QT intervals, and large U waves. Sinus tachycardia, sinus bradycardia, and rhythm abnormalities in the form of atrial fibrillation, junctional tachycardia, and ventricular premature contractions can be seen. These ECG changes have been ascribed to neurohumoral factors, including alterations in sympathetic and parasympathetic tone.

Electrical stimulation of a variety of sites in the central nervous system in animal models has been shown to produce electrocardiographic changes. Right stellate stimulation or left stellate ablation has been shown to cause low or inverted T waves in dogs. Unilateral section of sympathetic fibers to the ventricles results in localized areas of refractory period prolongation which can account for T wave changes.
Electrolyte Abnormalities

Potassium plays an important role in maintaining the electrical potential across the cellular membrane, as well as in depolarization and repolarization of the myocytes. Alterations in serum potassium levels can have dramatic effects on myocardial cell conduction, which can lead to ECG changes. The earliest ECG change associated with hypokalemia is a decrease in the T-wave amplitude. As potassium levels decline further, ST-segment depression and actual T-wave inversions can be seen. The PR interval can be prolonged and there can be an increase in the amplitude of the P wave. With even lower serum potassium levels, the classic ECG change associated with hypokalemia is the development of U waves. Hypokalemia can present with global T-wave inversions (Figure 9).

Electrocardiographic changes attributable to alterations of serum sodium are rare. ECG changes seen with hypernatremia include low voltage, QT prolongation, and T-wave flattening. Cases of T-wave inversion, mimicking ischemia, have been described. We present a case of diffuse T-wave inversion associated with hypernatremia in Figure 10.

Pheochromocytoma

Pheochromocytomas are catecholamine-secreting tumors that arise from chromaffin cells of the adrenal medulla. ECG changes observed in patients with pheochromocytoma are thought to result from enhanced α- and β-adrenergic receptor stimulation. The most constant and clinically important ECG changes concern the T wave, ST segment, and U wave. As shown in Figure 11, global T-wave...
Global T-wave Inversion on Electrocardiogram

inversion has been described in pheochromocytoma. In the absence of underlying cardiac disease, the ECG changes in patients with pheochromocytoma often revert to normal patterns after tumor removal, suggesting a role for elevated catecholamine.

Pulmonary Embolism

Patterns of ECG changes described in pulmonary embolism include sinus tachycardia, right bundle branch block (RBBB), pulmonary P wave, the S3_Q3_T3 pattern, and anterior ischemic pattern (T-wave inversion in leads V1-V4). Some patients present with no ECG abnormality. Global T-wave inversion has been described in pulmonary embolism (Figure 12). It was postulated that the observed global T-wave inversion and QT prolongation during the acute phase of pulmonary embolism was the result of histamine-induced myocardial ischemia at a cellular level; histamine-induced transient coronary vasospasm is another possible explanation. In experimental pulmonary embolism, histamine, a humoral factor released from the lung tissues in pulmonary embolism, was found to worsen myocardial hypoxia directly by uncoupling mitochondrial oxidative phosphorylation in both ventricles and indirectly via its pulmonary arterial vasoconstrictive effect.

Pulmonary Edema

Global T-wave inversion has been described in a case series of patients without known or suspected coronary artery disease who presented with acute cardiogenic pulmonary edema. Inverted T waves were recorded in the anterior chest.
leads in all 9 patients, and global T-wave inversion was present in 5 cases. In each case, there was no evidence of acute myocardial injury, and significant coronary artery disease was subsequently ruled out. Although in the presented cases a coronary etiology was essentially ruled out, subendocardial ischemia due to elevated wall stress, high end-diastolic pressure, and decreased coronary arterial flow during cardiogenic pulmonary edema could still have been operative.

**Kounis Syndrome**
Hypersensitivity reactions such as angioedema or anaphylactoid reaction secondary to medications is common. Allergic angina or allergic MI, also known as Kounis syndrome, is secondary to mast cell degranulation with a surge in the serum concentration of inflammatory mediators. This may present as unstable angina with normal ECG, non-ST-segment elevation MI with ST-segment depression, or symmetrical deep T-wave inversions (Figure 13) or STEMI.

**Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia**
Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a genetically determined heart muscle disorder...
Global T-wave Inversion on Electrocardiogram

Conclusions

Global T-wave inversion is associated with a variety of pathophysiologic states, including cardiac, pulmonary, and cerebrovascular diseases, as well as acute electrolyte disorders. Although some of these are chronic conditions, many are acute emergencies, necessitating early diagnosis and treatment. Recognition of these possible acute etiologies of global T-wave inversion is therefore of great importance.

References

5. Nakajima T, Kagoshima T, Fujimoto S, et al. The deeper the negativity of the T waves recorded, the greater is the effectiveness of reperfusion of the myocardium. Cardiology. 1996;87:91-97.


**Figure 13.** Electrocardiogram (ECG) of a 51-year-old woman who presented with angioedema secondary to angiotensin-converting enzyme inhibitor. Her peak troponin-I was 0.24 ng/mL and electrocardiogram showed symmetrical deep T-wave inversions. Cardiac catheterization was unremarkable. Echocardiogram showed normal left ventricular systolic function with no regional wall motion abnormalities, excluding Takotsubo cardiomyopathy. (B) Follow-up ECG 1 month later.

**MAIN POINTS**

- The T wave on electrocardiogram (ECG) represents ventricular repolarization that results from recovery of activated ventricular muscle fibers to their resting states.

- T-wave configuration is influenced by the temporal and spatial pattern of myocardial excitation and the shape and the duration of individual action potentials of the myocardial cell population.

- Global T-wave inversion refers to T-wave inversions in all standard leads except the aVR lead and is associated with a variety of pathophysiologic states, including left main coronary artery or equivalent acute myocardial infarction, Takotsubo cardiomyopathy, Kounis syndrome, apical hypertrophic cardiomyopathy, acute pericarditis, acute cerebrovascular event, electrolyte abnormalities, pheochromocytoma, pulmonary embolism, and pulmonary edema.

- Although some of these etiologies of global T wave inversions are chronic conditions, many are acute emergencies, necessitating early diagnosis and treatment. Recognition of these possible acute etiologies of global T-wave inversion is therefore of great importance.