Acute coronary ischemic events are frequently accompanied by dynamic T wave changes in the electrocardiogram (ECG). A variety of noncoronary events are also known to result in giant negative T waves, global T wave inversion and marked prolongation of the QT interval (1). To our knowledge, acute cardiogenic but nonischemic pulmonary edema has not been previously implicated in this electrocardiographic entity. The purpose of this study is to describe the clinical characteristics and electrocardiographic changes observed in nine patients without known or suspected coronary artery disease who presented with acute pulmonary edema and subsequently developed large T wave inversions with QT prolongation.

METHODS

Over a two-year period from May 1996 through April 1998, nine cases were identified at our Department with the following clinical characteristics: 1) patients without known or suspected coronary artery disease presented with acute cardiogenic pulmonary edema; 2) the ECG on presentation was not suggestive of myocardial ischemia or injury; 3) within 24 h after the initial presentation, several hours after symptom resolution, the ECGs demonstrated large symmetrical negative T waves in multiple leads and markedly prolonged QT intervals; 4) patients ruled out for myocardial infarction; and 5) the presence of significant coronary artery disease was excluded with a high degree of certainty. All patients underwent two-dimensional Doppler echocardiography, and either a stress imaging study or left heart catheterization with coronary angiography. Noninvasive versus invasive testing was chosen based upon age, cardiac risk factors, the presence of chest pain, the presence of Q waves in the ECG and whether or not there were segmental wall motion abnormalities in the echocardiogram. Left ventricular ejection fractions were visually estimated from the echocardiograms. The admission and day 1 ECGs were analyzed using standard criteria for measurements of T wave axis, T wave amplitude and QT interval. Rate correction for the QT intervals was performed using Bazett’s formula (2).
Serum markers of myocardial injury were creatine kinase (CK)-MB until February 1997, and both CK-MB and cardiac troponin-I thereafter. Absence of myocardial injury was established based on a minimum of two negative serum markers drawn at least 8 h apart.

RESULTS

Pertinent clinical and electrocardiographic characteristics of the nine study patients are summarized in Table 1. Ages ranged from 32 to 79 years. Seven of the nine patients were women. The etiology of the pulmonary edema was valvular heart disease in three cases, nonischemic dilated cardiomyopathy in two patients, hypertension, chronic renal insufficiency, acute volume overload and eclampsia in the rest. Acute myocardial injury was ruled out by the initial ECG and by negative serum markers in all. Significant coronary artery disease was ruled out by negative coronary angiograms in three patients, and by the combination of young age, negative cardiac risk factors, absence of chest pain, absence of segmental wall motion abnormalities and a negative stress imaging study in the other six. Left ventricular ejection fractions ranged from 0.30 to 0.60. In those patients with normal ejection fractions, the etiology of congestive heart failure (CHF) was valvular heart disease or left ventricular hypertrophy. In each patient, there was a well-documented cause for heart failure exacerbation, including medical or dietary noncompliance, acute iatrogenic volume overload and eclampsia. No patient presented with headache or other clinical suggestion of subarachnoid hemorrhage or pheochromocytoma. In addition, pheochromocytoma was ruled out by appropriate laboratory studies in two patients who were admitted with markedly elevated blood pressures (cases 5 and 6). Patients were not receiving antiarrhythmic medications on presentation, and no patient had significant hypokalemia or hypocalcemia. Seven of the nine patients had elevated blood pressure, and the heart rate exceeded 100/min in all.

The electrocardiographic findings are summarized in Table 1 and are illustrated in Figures 1 and 2. Two patients with chronic atrial fibrillation presented with rapid ventricular response; the other patients had sinus tachycardia. Five patients had left ventricular hypertrophy by voltage, and two patients had chronic incomplete or complete right bundle branch block. In each patient, the admission ECG demonstrated nonspecific ST and T wave changes and normal or near-normal corrected QT intervals (Table 1). Within 24 h after normalization of the clinical symptoms, new deep T wave inversions developed in multiple leads. Inverted T waves were recorded in the anterior chest leads in all patients (Fig. 1), and in five cases, global T wave inversion was present (Fig. 2). The QT intervals were markedly prolonged. The corrected QT intervals exceeded 500 ms in eight of the nine cases, and exceeded 600 ms in two. The mean (± SD) QT intervals on presentation and in the day 1 ECGs measured 431 ± 34 and 559 ± 52 ms, respectively. The amplitudes of the inverted T waves in the day 1 ECGs varied significantly with the maximum negative T wave amplitudes ranging from 0.3 to 2.4 mV. In four patients, the longest rate-corrected QT interval in subsequent electrocardiograms (ms); RHD = rheumatic heart disease; R/O CAD = clinical data and imaging studies used to rule out a probable coronary etiology of acute pulmonary edema; each patient also had at least two negative serum markers of myocardial injury; T ampl = maximum amplitude of inverted T waves in mm (10 mm/mV); VOLUME = acute volume overload.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Etiology</th>
<th>R/O CAD</th>
<th>ECHO; EF</th>
<th>BP adm</th>
<th>QTc adm</th>
<th>QTc max</th>
<th>T ampl</th>
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<td>1</td>
<td>44</td>
<td>F</td>
<td>RHD-MR, MVR</td>
<td>CATH</td>
<td>4+MR; 0.55</td>
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<td>F</td>
<td>DCM-MR, AF</td>
<td>CATH</td>
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<td>369</td>
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<td>3</td>
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<td>F</td>
<td>ECLAMP SIA</td>
<td>AGE, CRFs, CP ECHO</td>
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<td>4</td>
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<td>F</td>
<td>HTN, AF</td>
<td>CP, ECHO ADO-SPECT</td>
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<td>M</td>
<td>HTN, DCM</td>
<td>AGE, CRFs, CP ADO-SPECT</td>
<td>LVH; 0.35</td>
<td>203/132</td>
<td>480</td>
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<td>MR</td>
<td>CATH</td>
<td>2+MR; 0.60</td>
<td>158/103</td>
<td>422</td>
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</table>

ADO-SPECT = adenosine myocardial perfusion SPECT scan; AF = atrial fibrillation; AR = aortic regurgitation; BP adm = blood pressure on admission (mm Hg); CATH = cardiac catheterization with coronary angiography; CP = no history of chest pain and absence of chest pain with index event; CRFs = chronic renal insufficiency; ECG = electrocardiogram (ms); QTc max = the longest rate-corrected QT interval in subsequent electrocardiograms (ms); RHD = rheumatic heart disease; R/O CAD = clinical data and imaging studies used to rule out a probable coronary etiology of acute pulmonary edema; each patient also had at least two negative serum markers of myocardial injury; T ampl = maximum amplitude of inverted T waves in mm (10 mm/mV); VOLUME = acute volume overload.
daily ECGs were recorded for up to seven days. In each case, there was a gradual complete resolution of the T wave inversion and QT prolongation.

Patients responded promptly to conventional management of acute pulmonary edema and remained clinically stable and asymptomatic thereafter. In each case, however, hospital stays were prolonged by the perceived need to proceed with further diagnostic workup based on the dramatic electrocardiographic changes. There was no in-hospital mortality.

DISCUSSION

Dynamic ST and T wave changes during acute cardiac events are generally believed to signify myocardial ischemia (3). It has long been recognized, however, that coronary disease is less likely responsible when gross T wave deformities and marked prolongation of the QT interval develop many hours after an acute event (4). Acute central nervous system disorders, primarily subarachnoid hemorrhage and hemorrhagic stroke, seem to be the leading causes (5). In addition, status epilepticus (6), massive pulmonary embolism (7), pheochromocytoma (8) and a variety of other metabolic abnormalities and drug effects including cocaine (9) may result in T wave inversions with QT prolongation. Furthermore, a phenomenon termed “cardiac memory” has been demonstrated in humans and in experimental animals (10,11). Cardiac memory is a characteristic shift in the T wave axis after periods of intermittent left bundle branch block, intermittent preexcitation, ventricular pacing and ventricular tachycardia where the T vector during narrow complex rhythm is predicted by the vector of the QRS of the preceding wide complex arrhythmia.

Clinical characteristics. To our knowledge, cardiogenic pulmonary edema that is not due to an acute coronary event has not been previously recognized to cause delayed development of massive T wave inversion and QT prolongation. In this report, we present nine cases accumulated over a two-year period from a community-based general internal medicine practice where diffuse and occasionally global T wave inversion and significant QT prolongation occurred after resolution of an episode of acute pulmonary edema. In each case, there was no evidence of acute myocardial injury, and significant coronary artery disease was subsequently ruled out. Other causes of diffuse T wave inversion with QT prolongation were absent. None of the patients had intermittent left bundle branch block, ventricular tachycardia or an implanted pacemaker. The etiology of CHF and the cause of the acute exacerbation were diverse but well defined. Several patients had known valvular heart disease,
hypertensive heart disease, nonischemic dilated cardiomyopathy and chronic renal insufficiency. Acute pulmonary edema was triggered by medical or dietary noncompliance, severe hypertension, acute volume overload and, in one case, eclampsia.

Our case series does not allow a characterization of patients who present with acute pulmonary edema and then develop T wave inversion with QT prolongation compared with those patients with pulmonary edema in whom these dynamic electrocardiographic changes are absent. It is of note, however, that there was a striking female preponderance similar to what was observed by Walder and Spodick in their series of patients with global T wave inversion (1). Also, the majority of patients had normal or near normal left ventricular ejection fractions, and had either diastolic heart failure or pulmonary edema due to valvular heart disease. All patients were tachycardic on admission and the majority had elevated blood pressure. All responded promptly to diuretic management and had an uneventful hospitalization thereafter. The T wave inversion and QT prolongation developed many hours after clinical stabilization, and usually lasted for several days. There was a gradual and simultaneous resolution of the T wave inversion and QT prolongation, although the tempo of the resolution of the electrocardiographic changes has not been systematically tested.

Possible mechanisms. In general, the electrophysiologic mechanism responsible for large T wave inversion with QT prolongation is not fully understood (1,4–11). 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. In addition, an acute rise in the cardiac sympathetic tone either via an increased sympathetic outflow from the central nervous system or through other systemic mechanisms including pheochromocytoma seems to be present under a variety of conditions that result in diffuse T wave inversion and QT prolongation. Similar changes were observed after stressful events (12,13). Rapid intravenous administration of epinephrine to dogs results in prolongation of the electrocardiographic QT interval (14). It is tempting to speculate that in our patients with acute cardiogenic pulmonary edema as well, an increased sympathetic tone was a factor in the subsequent electrocardiographic changes. Because, however, the direct influence of the autonomic nervous effect is short lasting, an acute rise in the sympathetic tone would not in itself explain why it took several days for the T wave inversion to resolve.

An alternative explanation for the observed T-QT changes involves the electrical heterogeneity in the ventricular wall. Recently, it has been demonstrated that the human ventricles have at least four electrophysiologically and functionally distinct cell types: epicardial, M, endocardial and Purkinje (15). The epicardial and M cells exhibit different sensitivity to changes in K⁺, rate of stimulation, ischemia and drugs compared with the endocardial cells. Besides, the epicardium exhibits more profound changes in action potential duration than does endocardium during acute ischemia (16,17); these changes are even more pronounced under the influence of adrenaline (16). The differential responsiveness of epicardium and endocardium to ischemia (and probably to the hypoxia and metabolic changes like those occurring in acute pulmonary edema) results in dispersion of repolarization between the ischemic epicardium and endocardium (17), and may explain the diffuse change in the ventricular gradient responsible for the large inverted T waves and prolonged QT intervals. It is interesting to note that in our case series, most patients had significant left ventricular hypertrophy due to valvular heart disease or arterial hypertension. This too may account for a greater heterogeneity within the ventricular mass, thus favoring a change of the ventricular gradient.

Limitations. Only a prospective study evaluating all patients who present with acute pulmonary edema with serial ECGs would give us a clear indication about the prevalence of the described electrocardiographic phenomenon, and whether the observed T-QT changes are more characteristic of a noncoronary rather than a coronary etiology. Also, we did not systematically study the exact time course of the observed ECG changes in all of our patients. Long-term follow-up was incomplete.

Summary. Patients with cardiogenic pulmonary edema may develop deep negative T waves and QT prolongation after resolution of the acute event. The electrocardiographic changes are similar to those associated with acute subarachnoid hemorrhage, other acute central nervous system disorders, pheochromocytoma and after the resolution of sustained ventricular tachycardia or ventricular pacing. As is true for other causes of global T wave inversion, these electrocardiographic changes have no immediate prognostic implication for hospitalized patients, and there seems to be a female preponderance (1). The electrophysiologic mechanism, prevalence, exact time course and long-term prognostic significance of these findings in patients hospitalized for pulmonary edema are presently unknown.

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REFERENCES