The Clinical Value of the ECG in Noncardiac Conditions

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The critical care physician is confronted daily with patients who present with a great variety of complaints. In patients either suspected of having or being at high risk of cardiac disease, an ECG is a simple, useful, and readily available part of the diagnostic workup. A history of prolonged retrosternal and oppressing pain in combination with ST-segment elevation on the ECG will suggest the diagnosis of a myocardial infarction (MI). However, ST-segment elevation and tall T waves do not invariably mean myocardial ischemia. They can also occur in hyperkalemia, hypothermia, and intracranial hemorrhage. Particularly in the latter case, a wrong diagnosis of ischemic cardiac disease could be dev-astating for the patient if thrombolytic therapy should be started inappropriately. It therefore may be a challenging and sometimes difficult task to interpret an ECG correctly.

In this review, we will discuss the ECG manifestations of electrolyte disorders and acute pulmonary embolism (PE) only briefly, as these are well known. More attention will be given to ECG changes in the following disorders: CNS pathology, esophageal disorders, hypothermia, ECG changes caused by drugs or poisoning, and finally some unusual conditions.

Electrolyte Disorders

Potassium

The potassium ion plays a key role in the normal function of the cells of the human body. In the heart, specific levels of intracellular and extracellular potassium are essential for normal electrical pulse generation and conduction. Disturbances in cardiac conduction, which can lead to ventricular fibrillation or asystole, pose the greatest danger to the patient with hyperkalemia. Hyperkalemia is associated with a distinctive sequence of ECG changes. The relationship between the degree of hyperkalemia and...
the ECG changes, however, is variable, and in rare cases of severe hyperkalemia the ECG may even be normal or near normal. The earliest changes are the appearance of peaked, narrow T waves and a shortened QT interval, which reflect abnormally rapid repolarization (Fig 1). Occasionally, this may be confused with the tall T waves of myocardial ischemia (Fig 2). However, the QT interval is usually normal or prolonged during ischemic episodes.

Further changes of the ECG occur at a plasma K+ concentration > 7 to 8 mEq/L, and these changes are primarily due to delayed depolarization: widening of the QRS complex (the ECG manifestation of slowed ventricular depolarization) and decreased amplitude with widening and eventual loss of the P wave. PR prolongation can also occur, followed sometimes by second-degree or third-degree AV block. ST-segment elevation in leads V1 and V2, mimicking acute MI, has occasionally been reported in severe hyperkalemia. The ST-segment deviation probably is caused by nonhomogenous depolarization in different portions of the myocardium. According to this hypothesis, a voltage gradient is created between normal myocardial cells and those depolarized by potassium, resulting in current flow between these regions. Since dialysis rapidly normalizes the ST-segment elevation, it is also known as the dialyzable current of injury. The final changes are a sine-wave pattern, in which the widened QRS complex merges with the T wave. This is followed by ventricular fibrillation or asystole.

Hypokalemia produces characteristic changes in the ECG that are primarily due to delayed ventricular repolarization. The result is ST-segment depression with decreased amplitude or inversion of the T wave and increased U wave prominence. In severe hypokalemia, an increase in amplitude of the P wave, prolongation of the PR interval, and widening of the QRS complex may all occur.

Hypokalemia is an important cause of acquired long QT syndrome (LQTS), a condition that predisposes to torsades de pointes (TdP), since it delays ventricular repolarization and sets the stage for re-entrant arrhythmias. Hypokalemia also causes arrhythmias due to enhanced automaticity. The risk of hypokalemia-induced arrhythmia is increased in patients with either myocardial ischemia or who are receiving digitalis.

Calcium

Hypercalcemia and hypocalcemia predominantly alter the action potential duration (phase 2 of the action potential), which results in either shortening...
(hypercalcemia) or prolongation (hypocalcemia) of the QT interval. The influence on the QT interval is entirely due to a modification of the ST-segment duration. Both conditions can affect T-wave morphology.2

In severe hypercalcemia, QRS complex and PR intervals frequently are prolonged, and second-degree or third-degree AV block has been reported.2

The J wave, also referred as the Osborn wave, which is considered pathognomonic of hypothermia, has occasionally been reported in hypercalcemia.6 The combination of hypocalcemia and hyperkalemia, as seen in patients with renal insufficiency, produces a characteristic ECG pattern of ST-segment prolongation (from hypocalcemia) with a "tented" T wave (from hyperkalemia).2

**Magnesium**

Magnesium concentrations within the range encountered in clinical practice do not produce specific ECG patterns, at least at normal K and Ca concentration.2 Hypomagnesemia usually is associated with potassium depletion, and the ECG abnormalities are those of hypokalemia.7 Magnesium is essential for the control of intracellular potassium concentration and thus contributes to the electrical stability of the cardiac cell. Its antiarrhythmic potential is well established in the treatment of TdP. Hypermagnesemia is an uncommon clinical condition and is usually encountered in patients with renal failure who have other electrolyte disturbances, particularly hyperkalemia and hypocalcemia, which in themselves produce characteristic ECG changes.7

**Sodium**

Isolated hypernatremia or hyponatremia has no consistent effect on the ECG, but in patients with intraventricular conduction disturbances caused by hyperkalemia, hypernatremia shortens and hyponatremia prolongs the QRS duration.2

**PE**

PE continues to be considered both an underdiagnosed and overdiagnosed, potentially fatal disorder. In recent years, the diagnostic contribution of relatively new techniques such as echocardiography and spiral CT has been studied intensively. The "classical" S1Q3T3 ECG pattern was described as early as 1935, yet the diagnostic role of ECG in acute PE continues to arouse clinical interest. A number of excellent reviews on this subject have been published in recent years.8,9 In the acute phase of PE, numerous ECG changes may be seen. These include arrhythmias, alteration in conduction, a shift in axis of the QRS complex, and changes in morphology of the P wave, the QRS complex, the ST segment, and the T wave. As shown in Table 1, the ECG findings can be extremely variable, with poor sensitivity and specificity (Fig 3,4). Indeed the ECG may be normal

![Figure 2. Similar changes are found in the initial stage of an acute coronary occlusion (hyperacute, tall T-wave changes in the precordial leads). The QTc interval (399 ms) in this patient, who presented with an occlusion of the left anterior descending coronary artery, is normal.](image)
in up to 27% of the patients. Pre-existing cardiopulmonary disease can mimic several of the abnormalities associated with PE and this decreases the specificity of the ECG. In a recent study, the S1Q3T3 pattern, considered pathognomonic for acute PE by many clinicians, was equally prevalent in patients with and without PE.

The identification of right ventricular dysfunction in patients with PE is an important finding as it correlates with outcome. Only a few reports exist on the relation between the ECG and right ventricular overload. We particularly mention the study of Sreeram et al., as this report includes most of the ECG signs suggested by other investigators as indicative of right ventricular strain. In 49 consecutive patients with proven PE, right ventricular overload, as defined by echocardiography, was identified on 76% of ECGs obtained at hospital admission if three or more of the following ECG findings were found: (1) incomplete or complete right bundle-branch block; (2) S waves in leads I and aVL > 1.5 mm; (3) transition zone shift to V5; (4) Q waves in leads III and aVF but not in lead II; (5) QRS axis > 90° or indeterminate axis; (6) low limb lead voltage < 5 mm; and (7) T wave inversion in leads III and aVF or in leads V1 to V4. The major shortcomings of these studies are their retrospective nature, the lack of a control group, and the exclusion of most patients with preexisting cardiac or pulmonary disease. In addition, the study of Sreeram et al. underscores the poor diagnostic performance of the ECG as a single study, since 26% of patients with severe PE do not demonstrate any ECG abnormality at all. Their message is nevertheless relevant, as this combination of ECG findings assists the clinician in rapidly identifying some patients with severe PE, who may have ECG manifestations of right heart strain.

In conclusion, the role of the ECG as an independent marker for the diagnosis, severity and prognosis of PE is limited. There are no ECG findings that are unequivocally diagnostic of PE. However, the combination of certain ECG findings, in particular those described by Sreeram et al., within the clinical context of a probable PE should raise a high degree of suspicion, and the diagnosis can be confirmed or rejected by a more specific diagnostic test.

CNS Disease

The association of specific ECG changes with intracranial disease has been recognized for > 5 decades. ECG abnormalities occur most often in patients with subarachnoid hemorrhage, but also have been described in cases of ischemic stroke, intracranial hemorrhage, head trauma, neurosurgical procedures, acute meningitis, intracranial space-occupying tumors, and epilepsy.

Cerebrovascular disorders mainly cause abnormalities of ventricular repolarization. The most common

Figure 3. 12-lead ECG from a patient with a massive PE. Echocardiography confirmed the ECG signs of right ventricular strain (symmetrical T-wave inversion in the precordial leads V1 through V4).

Figure 4. This patient also demonstrated signs of major PE: a large thrombus in both main pulmonary arteries (chest CT) and right ventricular dysfunction (echocardiography) were documented. The ECG only revealed sinus tachycardia.
findings are depressed ST segments, flat or inverted T waves, and prolongation of the QTc.\textsuperscript{16} Prolonged QT intervals are associated with the risk of TdP. The most striking ECG changes are usually associated with subarachnoid hemorrhage (SAH). The prevalence of ECG abnormalities in this group of patients varies from 50 to 90%.\textsuperscript{18} As shown in Figure 5, these changes sometimes cannot be differentiated from the changes noted in an acute coronary syndrome and are sometimes interpreted as such. Pathologic Q waves also can develop.\textsuperscript{16} Both the ST-T wave abnormalities and Q waves are often transient but may persist as long as 8 weeks.\textsuperscript{19} Besides changes in ECG morphology, rhythm disorders also occur in CNS disorders. The incidence has been estimated to be > 75%.\textsuperscript{16} Both tachyarrhythmias and bradyarrhythmias can occur. Most of these rhythm problems are benign and include sinus tachycardia and premature atrial and ventricular contractions. Clinically significant arrhythmias, however, are not unusual. New-onset atrial fibrillation has been reported in as many as one third of patients with acute stroke, although it is not always clear whether the atrial fibrillation associated with a stroke is a cause or an effect.\textsuperscript{17} TdP has been detected in 4% of patients with SAH.\textsuperscript{18,20} Cerebrovascular accidents may also be associated with all degrees of AV block.\textsuperscript{21} Complete AV dissociation, however, is rare, and if present is usually of short duration.

The pathophysiology of these ECG abnormalities is not entirely clear, and several mechanisms have been proposed. Substantial evidence endorses the hypothesis that the ECG changes are the result of myocardial injury. Definite proof of myocardial damage was first demonstrated by autopsy studies and subsequently in reports showing the presence of regional wall abnormalities on two-dimensional echocardiography or at left ventriculography.\textsuperscript{22-24} In a recent study, laboratory confirmation of cardiac injury has been provided by the finding of elevated cardiac troponin I levels in a considerable proportion of patients with acute neurologic disease.\textsuperscript{25}

The next question is how CNS pathology gives rise to ischemic cardiac injury? It is hypothesized that CNS injury may result in excessive sympathetic tone and catecholamine production. The most important control sites of the sympathetic nervous system are found to be the insular cortex, amygdala, and lateral hypothalamus.\textsuperscript{26} In stroke patients, in whom the likelihood of concomitant coronary artery disease (CAD) is high, it is plausible that an increase in sympathetic tone results in increased oxygen demand and hence myocardial damage. However, traffic accident victims and young patients with SAH also demonstrate myocardial damage in the presence of normal coronary arteries. This has been shown in autopsy series.\textsuperscript{26,27} Experimental models and clinical data lend further support to the hypothesis of sympathetic overactivity. Myocardial damage can be produced experimentally by the parenteral administration of catecholamines or by electrical stimulation of specific regions of the brain as the hypothalamus and insula.\textsuperscript{16} The lesions are similar to those found in patients who have either a pheochromocytoma or are cocaine abusers.\textsuperscript{28} Catecholamines probably either have a direct toxic effect on myocardial cells or mediate the vasoconstriction of coronary arteries with subsequent myocardial damage.\textsuperscript{28}

In a substantial number of patients with ECG changes, no evidence of myocardial damage is present. It is likely that reflex mechanisms that give rise to transient electrophysiologic changes in the heart are responsible for the ECG changes observed in these cases.\textsuperscript{29}

**Esophageal Disorders**

The ECG is a standard test in the investigation of the patient with chest pain. The main aim of the evaluation is to exclude cardiac disease. Esophageal disorders are well recognized among the noncardiac causes of chest pain.

Chest pain of esophageal origin is frequently clinically indistinguishable from that of cardiac origin and responds equally well to nitroglycerine. This similarity can be explained by the convergence of

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**Figure 5.** ECG from a patient with an acute subarachnoid hemorrhage. Note the inverted T waves in the precordial and lateral leads, which can mimic the changes seen with myocardial ischemia. In this patient, the QT interval was markedly prolonged (QTc = 613 ms).
afferent signals from heart and esophagus to the same dorsal neurons of the spinal cord.30

Between 10% and 50% of patients with anginal pain who are referred for arteriography are found to have normal coronary arteries.31 An esophageal source of noncardiac chest pain is found in up to 60% of cases, and ECG abnormalities may be found in these patients.32 Changes in T wave morphology and ST segments, characteristic manifestations of myocardial ischemia, may be misleading. Three studies based on either methacholine or ergonovine provocation tests in patients with noncardiac chest pain have reported the occurrence of chest pain associated with esophageal motility abnormalities and ischemic changes on the ECG.33–35 Because of negative cardiac investigation findings (often including coronary angiography), the esophagus was presumed to be the origin of chest pain and ECG abnormalities. This hypothesis however can be questioned since acetylcholine can also induce spasm of the large coronary arteries.36 Even in the absence of large vessel spasm, acetylcholine can provoke angina-like chest pain with ischemic ECG changes, as has been shown in a study of patients with chest pain and normal or near-normal (< 50% reduction in lumen diameter) coronary arteriograms.37 The investigators hypothesized that these findings were the result of myocardial ischemia due to coronary microvascular spasm.

Gastroesophageal reflux is a more important cause of angina-like pain than esophageal motility disorders.38 Acid installation in the esophagus may trigger myocardial ischemia and ECG changes in patients with concomitant CAD.39–41 An elevated sympathetic discharge with a resultant increase in myocardial oxygen demand and reduction in coronary blood flow (as measured by intracoronary Doppler catheter) have been proposed as the underlying mechanism.40,41 These experimental findings, however, have not been supported by clinical studies. The role of gastroesophageal reflux and motility disorders in inducing chest pain in patients with CAD has been studied by correlating episodes of chest pain with findings of esophageal manometry, measurement of pH and ECG recording.42 Most pain episodes were not associated with acid reflux or ECG signs of myocardial ischemia, and pain was rarely preceded by a reflux episode. Hence, acid reflux does not seem to induce myocardial ischemia. Furthermore, in a group of patients with no underlying cardiac disease, reflux did not produce any ECG changes.43 In conclusion, both cardiac and esophageal disease may produce similar chest pain, and these two entities frequently coexist, thereby confusing the clinician. The documentation of ECG abnormalities is an important finding, as it makes the diagnosis of an esophageal disorder unlikely.

HYPOTERMIA

Accidental hypothermia is not uncommon during the winter months. Elderly people are particularly at risk, as they often live alone in inadequately heated rooms. One study in Scotland suggested that hypothermia probably accounts for > 4,000 hospital admissions and > 1,000 deaths per year.44 Characteristic ECG changes occur in patients with hypothermia (Fig 6). Knowledge of these changes may facilitate a rapid diagnosis. The Osborn wave, also known as the J wave, is the most striking ECG feature in hypothermia. It is a “hump-like” deflection between the QRS complex and the early part of the ST segment.45 The amplitude and the duration of the wave increase with decreasing body temperature. The J wave is most prominent in leads facing the left ventricle and in the inferior limb leads.46 With rewarming, the amplitude decreases but the J wave can persist 12 to 24 h after restoration of body temperature.46 The electrophysiologic origin of the J wave was recently clarified.47 It is caused by a transmural voltage gradient created by the presence of a prominent action potential notch in the epicardium but not endocardium. The notch configuration of the action potential is explained by more prominent transient outward potassium current in epicardial compared to endocardial layers. As such, a distinct J wave or elevated J point has been described in subjects with the “early repolarization syndrome,” a normal variant. Under hypothermic conditions, the channel remains open longer. This causes an increase in the amplitude and width of the action potential notch in the epicardium but not endocardium, giving rise to the Osborn wave on the ECG. The Osborn wave is not specific for hypothermia, as it may be seen in hypercalcemia, certain CNS lesions, particularly of the hypothalamus and, as already mentioned, can appear as a normal variant.48

Other ECG features of hypothermia include shivering artifacts due to muscular tremor (which may not be evident clinically), sinus bradycardia, QRS prolongation, and prolongation of the PR interval and QTc.48 With decreasing body temperature, rhythm abnormalities are a cause for concern. Atrial fibrillation is common below 32°C, and the risk of ventricular fibrillation is high when body temperature is lower than 28°C.49

DRUGS ASSOCIATED WITH ACQUIRED LQTS

Both cardiac drugs and other medications can cause ECG changes. Many antiarrhythmic drugs display a proarrhythmic effect. In recent years, reports of TdP and syncope or cardiac arrest during therapy with antihistamines, antibiotics, GI proki-
netic drugs, and others have drawn attention to the potential proarrhythmic effects of noncardiovascular drugs. TdP is a specific type of proarrhythmia and is classically described as a pause-dependent polymorphic ventricular tachycardia occurring in the setting of the congenital or acquired LQTS. We will mainly discuss the acquired form. LQTS is a disorder of cardiac repolarization that is characterized by prolongation of the QTc. The QT interval is the ECG measure of the total duration of the depolarization and repolarization phases of the ventricular action potential. Lengthening of the repolarization phase results in the LQTS. The acquired LQTS is almost always associated with drugs that prolong the QT interval, although other causes have been reported (Table 2). An extensive list of these drugs can be found at http://www.torsades.org.

Different ion currents contribute to the repolarization phase of the ventricular action potential. Current knowledge underscores the importance of the potassium ion channels. Congenital LQTS is a heritable ion channel disease caused by one of several mutations in the genes coding for the sodium or potassium ion channel proteins. Mutations of the

Figure 6. Top, A: ECG from a patient with severe hypothermia (23.8°C at presentation). Osborn waves (as depicted by the arrows) are present in all leads. Bottom, B: After patient rewarming (35.9°C), the Osborn waves disappeared. The QT interval was still prolonged (QTc = 591 ms).
genotypes. This has been demonstrated in studies by mutations that underlie the LQT2 and LQT6 syndrome-delayed rectifier, which is the channel affected monly the Ikr-subtype, the rapidly activating potassium channel, most com-

impairment of cardiac repolarization. Prevention and T wave and U wave abnormalities. T wave

Table 2—Main Causes of Acquired LQTS*

<table>
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<th>Drugs</th>
<th>Cardiac</th>
<th>Noncardiac</th>
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<tr>
<td></td>
<td>Quinidine, disopyramide, procainamide, sotalol, ibutilide, azimilide, amidarone, phenylamine, bepridil</td>
<td>Erythromycin, grepafloxacin, moxifloxacin, pentamidine, amantadine, chloroquine, trimethoprim-sulamethoxazole, phenothiazines, haloperidol, tricyclic antidepressants, terfenadine, astemizole, ketoconazole, itraconazole, probucol, ketanserin, cisapride, papaverine, tacrolimus, arsenic trioxide</td>
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Electrolyte disturbances

- Hypokalemia, hypomagnesemia, hypocalcemia
- Severe bradycardia
- Sick sinus syndrome, high-grade AV block
- Poisons and recreational drugs
- Cocaine, organophosphorus compounds
- Cerebrovascular diseases
- Intracranial and subarachnoid hemorrhage, stroke, encephalitis
- Other causes
- Hypothyroidism, hypothermia, myocardial ischemia, protein-sparing fasting, autonomic neuropathy, HIV disease

*Adapted from Kahn and Hohnloser.

potassium genes KvLQT1 and HERG, which under-

lie the LQT1 and LQT2 genotypes, together cause some 90% of cases. TdP may occur with all anti-

rhythmic drugs that block sodium or potassium channels and thus result in myocardial repolarization abnormalities. However, it is mainly described for class Ia and III antiarrhythmic drugs, which block the delayed rectifier potassium current. Noncardiac drugs, capable of prolonging the QTc interval, act by blocking a cardiac potassium channel, most commonly the Ikr-subtype, the rapidly activating potassium-delayed rectifier, which is the channel affected by mutations that underlie the LQT2 and LQT6 genotypes. This has been demonstrated in studies with terfenadine, an antihistaminergic agent, and erythromycin, a macrolide antibiotic.

In the majority of cases of drug-induced LQTS, predisposing factors can be identified. In an analysis of 250 patients treated with cisapride who acquired QT prolongation, risk factors were identified in 74% of cases: inhibition of cytochrome P-450 3A4 by other drugs was the most frequent (47%), followed by electrolyte abnormalities (32%), and co-administra-

Drugs that inhibit the hepatic cytochrome P-450 enzyme (ketocazole, itraconazole, erythromycin) can decrease the metabolism of drugs such as terf-

enadine, astemizole, or cisapride, and may result in additive effects. Similarly, hepatic or renal failure may enhance the QT interval-prolonging effect of various drugs. This explains the increased incidence of sotalol-associated TdP reported in patients with impaired renal function. Other drugs that prolong action potential duration, such as phenothiazines and haloperidol, may play a role. Older age, female sex, structural heart disease (including left ventricular hypertrophy, low left ventricular ejection fraction, myocardial ischemia), and slow heart rate also facilitate drug-induced prolongation of the QTc. Finally, in some patients with drug-induced LQTS, an underlying genetic predisposition has been demonstrated. LQTS has several ECG manifestations. The main feature is QTc prolongation. The QT interval is measured from the beginning of the QRS complex to the end of the T wave, preferably at a paper speed of ≥ 50 mm/s. A discrete and separate U wave should not be included in the measurement of the QT interval. Methods for QT measurement have several limitations and vary among investigators. It is recom-

The QT interval shows considerable intraindividual and interindividual variability and varies with heart rate, gender, age, autonomic tone, and time of the day. QT measurements should be corrected for heart rate. QTc may be calculated from the observed QT interval (QT0) using the formula of Bazett, where the QTc is equal to the QT0 divided by the square root of the RR interval in seconds (QTc = QT0/√RR). QTc is prolonged when it is > 450 ms in men or > 470 ms in women. In children aged 1 to 15 years, < 460 ms represents the upper limit of normal. Two caveats should be noted. First, the suggested QTc values are an arbitrary cut-off, as QTc values > 500 ms have been observed in healthy individuals. Second, QTc prolongation does not occur in 6 to 12% of patients who carry a genetic mutation. Nevertheless, a prolonged QTc interval, especially values > 500 ms, should be a reason for concern and should be considered as a contraindication for the use of drugs capable of prolonging the cardiac repolarization. Other ECG features include increased QT dispersion and T wave and U wave abnormalities. T wave and U wave changes are more frequent in the congenital form of the LQTS. The patient with LQTS is at risk for TdP. The clinical picture of TdP can range from a brief, asymptomatic, self-terminating arrhythmia episode to one of single or recurrent syncope or sudden cardiac death. The arrhythmia is characterized by a continuous alteration in morphology, amplitude, and polarity of the QRS complexes, whose peaks twist
around the isoelectric baseline (hence the term **torsades de pointes** or twisting of the points) as originally described by Dessertenne. TdP typically occurs after a prolonged QTc in the preceding sinus beats. Especially in acquired LQTS, TdP is triggered by a typical short-long-short QRS complex interval initiation sequence (Fig 7). To explain this feature, we quote the brilliant description of Khan:

> The initiation of TdP is dependent on a pause in the electrical activity created by a longer cycle length, which may be secondary to an extrasystole or bradycardia. The longer cycle length usually precedes the last supraventricular beat before the initiation of TdP. In a typical short-long-short sequence, a supraventricular beat is followed by an extrasystole (short cycle). This extrasystole is followed by a supraventricular beat after a long postextrasystolic pause (long cycle); this supraventricular beat, which has a longer QT interval than the preceding supraventricular beats, is followed by a ventricular beat that is the first beat of the TdP.

### Drug-Induced ECG Changes and Cardiac Toxicity

In this section, we highlight the typical ECG abnormalities associated with the use, or mainly abuse, of the psychotropic agents lithium and tricyclic antidepressants (TCAs), and the stimulants cocaine and amphetamines. A short discussion of the cardiovascular side effects of chemotherapeutic agents is also provided.

TCAs were previously the mainstay of antidepressant pharmacotherapy, but they have been largely replaced by selective serotonin reuptake inhibitors as first-choice agents. The main reasons are the comparable efficacy of both agents and the better safety profile of selective serotonin reuptake inhibitors, including minimal cardiovascular effects. TCAs block the reuptake of several neurotransmitters in the CNS, such as norepinephrine, serotonin, and dopamine. Their anticholinergic activity, and (especially) a quinidine-like effect on the heart, explain the cardiovascular effects. Sinus tachycardia is a frequent finding and is ascribed to the anticholinergic effect. The quinidine-like effect consists of blockade of the fast sodium channel in the cell membrane (class I effect) and interaction with the outward delayed rectifier potassium current (class III activity). This results respectively in conduction defects (PR prolongation, QRS widening, and heart block) and repolarization abnormalities (QTc prolongation). As with quinidine, second-degree or third-degree AV block, ventricular arrhythmias (TdP), and sick sinus syndrome are toxic effects of TCAs. The negative inotropic effect contributes to hypotension in TCA overdose. Rhythm and conduction abnormalities in addition to hypotension are the clinical manifestations of cardiac toxicity. Impeding cardiovascular toxicity in adult patients is usually preceded by specific ECG abnormalities: the majority of patients at significant risk will have a QRS interval duration > 100 ms or a rightward shift (130° to 270°) of the terminal 40 ms of the frontal plane QRS vector (Fig 8). The latter finding is characterized by a negative deflection of the terminal portion of the QRS complex in lead I and a positive deflection of the same portion in lead aVR. The documentation of these ECG abnormalities is important, as it mandates ICU monitoring for at least 24 h. ECG
changes are rare at therapeutic levels and more likely in those with preexisting heart disease.

Lithium exerts minimal cardiac effects at therapeutic doses in most patients. Benign, reversible T-wave changes (including inversion and flattening) are seen in approximately 20 to 30% of patients treated with lithium. ECG abnormalities of clinical significance are mainly documented at toxic levels: they include all kinds of arrhythmias (sinus node dysfunction is well documented) and QTc prolongation.

Cocaine and amphetamines are common drugs of abuse. In a 1999 survey in the United States, an estimated number of 1.5 million people were active users of cocaine. Both drugs act as powerful sympathomimetic agents and may induce the typical ECG changes of myocardial ischemia and MI due to coronary spasm even in the absence of risk factors for atherosclerosis.

The intensive care physician is increasingly being involved in the management of patients with cancer. The adverse effect of chemotherapeutic agents is one of the main reasons for admitting a patient with cancer to the ICU. Although the toxic effects to the bone marrow and GI tract are well recognized, physicians are less familiar with the cardiovascular toxicity from antitumor drugs. A wide variety of ECG changes, including arrhythmias, nonspecific ST and T-wave abnormalities, decreased QRS voltage, and prolongation of the QTc interval, have been described. Instead of being specific for a class of chemotherapeutic agents, ECG changes in general are a reflection of the drug-mediated toxic action on the heart.

Anthracyclines are the chemotherapeutic agents most widely recognized for causing cardiac toxicity. Acute toxicity, occurring during or just after a single dose, is rare, and consists of nonspecific ECG abnormalities and all kinds of arrhythmias. Rare causes of sudden death, acute heart failure, or fatal myocarditis have been reported. Chronic anthracycline-induced cardiotoxicity is more common, usually appears within 1 year of treatment, but also may become apparent only many years after completion of therapy. It manifests clinically as congestive heart failure or life-threatening arrhythmias. The most common risk factor for the development of chronic anthracycline-induced cardiomyopathy is total cumulative dose of the drug.

Several other anticancer drugs have been associated with cardiotoxicity, although less frequently than anthracyclines. 5-Fluorouracil is typically associated with angina-like chest pain, often accompanied by ischemic changes on the ECG. Less frequent manifestations include arrhythmias, MI, contractile dysfunction, and sudden death. Most cardiac effects are acute, occurring during 5-fluorouracil infusion or shortly afterwards, and are usually reversible when the drug is withdrawn. Of the several proposed mechanisms, coronary vasospasm has been suggested to be a main contributing factor. Myocardial ischemia and infarction have also been attributed to cisplatin. Of the many observed cardiac events, paclitaxel has been reported most commonly to cause asymptomatic bradycardia. High doses of cyclophosphamide and ifosfamide may cause acute severe heart failure and malignant arrhythmias with sometimes fatal outcome. The most serious cardiovascular effects of the interferons and interleukin-2 include systemic hypotension, supraventricular and ventricular arrhythmias, MI, and severe, usually reversible, congestive cardiomyopathy.

Poisons That Result in ECG Changes

Cardiac toxicity is a common finding in patients who have been poisoned with a wide variety of chemical agents. Poisons that result in ECG changes include carbon monoxide (CO), cyanide, organophosphates, arsenic, or even specified herbal therapies. Poisoning with cardiovascular drugs is relatively rare and will not be discussed, as the ECG effects and toxicity of these agents can generally be predicted based on their class effect.

CO poisoning is considered one of the most common acute intoxications, with an average of
40,000 cases per year in the United States.\textsuperscript{76,77} The toxic effects of CO are the result of tissue hypoxia. CO has an affinity for hemoglobin, which is 200 times as great as that of O\textsubscript{2} and interferes with the release of O\textsubscript{2} from oxyhemoglobin, thus decreasing the amount of O\textsubscript{2} available to the tissues. By binding to mitochondrial cytochrome oxidase, CO also inhibits cellular respiration. The ECG is a useful tool to evaluate possible myocardial toxicity. Alterations of the ST segment and T wave are the most common abnormalities. They reflect the oxygen deficit at the level of the myocardial cell and are frequently accompanied by biochemical and pathologic evidence of necrosis (Fig 9).\textsuperscript{78} Ischemic ECG changes represent one of the standard indications for hyperbaric O\textsubscript{2} in a patient with CO poisoning, in addition to chest pain, metabolic acidosis, and significant neurologic impairment.\textsuperscript{77}

Cyanide poisoning often occurs in the setting of smoke inhalation, where combined CO and cyanide toxicity occurs. Cyanide binds to cellular cytochrome oxidase and thus interferes with aerobic O\textsubscript{2} utilization. The ECG abnormalities are similar to those of CO poisoning.

Organophosphates complex with the acetylcholinesterase enzymes, leading to phosphorylation and deactivation. The resultant accumulation of acetylcholine causes initial stimulation, then exhaustion of cholinergic synapses. The toxicity mainly results from muscarinic and nicotinic symptoms. The cardiovascular symptoms are bradycardia, following a tachycardia compensating the hypoxia due to respiratory muscle weakness, rare atrial fibrillation, or ventricular tachycardia.\textsuperscript{78}

ECG changes resulting from heavy metal poisoning are mainly described in arsenic exposure. QTc prolongation and T-wave inversion may persist months after clinical recovery. Rarely, TdP and ventricular fibrillation occur during acute toxicity.\textsuperscript{79}

Herbal therapies are increasingly being used: in a recent survey, the use of self-prescribed herbal medicines within the United States general population increased from 2.5% in 1990 to 12.1% in 1997.\textsuperscript{80} Many herbal remedies have proven beneficial effects, but some have the potential to cause serious toxic effects, either directly or through herb/drug interactions. Cardiac adverse effects are typical after the ingestion of oleander, a plant containing cardiac glycosides. The clinical picture resembles digitalis toxicity, which includes life-threatening ventricular tachyarrhythmias, bradycardia, and heart block.\textsuperscript{81} An example of herb/drug interaction includes the decreased bioavailability of digoxin and cyclosporine when these drugs are combined with St John’s wort.\textsuperscript{82} This interaction can have serious consequences, as has been reported.\textsuperscript{83} Another source of toxicity is contamination of herbal preparations with heavy metals, including arsenic.\textsuperscript{84}

**ECG Abnormalities Related to Electrical Injury**

An estimated 1,100 to 1,300 deaths occur annually in the United States from electrical injury (including lightning strike).\textsuperscript{85} One third of patients presenting with an electrical injury manifest a cardiac component, and death from electrical injury most commonly stems from cardiac arrest. Changes in the ECG are frequently observed and may be trivial or life threatening. The most commonly reported ECG abnormalities are sinus tachycardia and nonspecific changes in the ST segment and T wave.\textsuperscript{85} Numerous rhythm and conduction disturbances may occur, the majority of which run a benign course. Direct myocardial injury, anoxia secondary to cardiopulmonary arrest, and autonomic instability explain many of the cardiac manifestations of electrical injury, including the above-mentioned ECG changes.\textsuperscript{86}

Electroconvulsive therapy is mainly used in the treatment of depression that has proved resistant to medications. The electrically induced seizure produces autonomic nervous system activation, which underlies the cardiovascular complications.\textsuperscript{87} Typical ECG abnormalities include ischemia-like changes (T-wave inversion, ST-segment depression, and new pathologic Q waves) and various arrhythmias. Signifi-
Cant and persistent ECG changes are especially prevalent among patients with preexisting cardiac disease.88

Miscellaneous Conditions

Misplacement of ECG electrodes is a common cause for errors in ECG interpretation. Reversal of the right arm with the left leg electrode creates the pattern of an inferior MI89. Placing the precordial electrodes too high on the chest may mimic an anterior MI (poor R-wave progression) or the pattern of right bundle-branch block (rSR’ complex).89 ECG artifact such as produced by body movement or a poor skin-electrode contact can simulate life-threatening arrhythmias and

Figure 10. ECG before (top, A) and after (bottom, B) thoracentesis for tension pneumothorax. Note the presence of sinus tachycardia and signs suggestive of right ventricular strain (right-axis deviation, clockwise rotation of the heart, and concomitant Q waves in leads II, III and aVF, a rSR’ pattern in lead V1, and large S waves in leads I, aVL, and the lateral precordial leads).
as a result expose patients to unnecessary diagnostic and therapeutic procedures, including cardiac catheterization and the implantation of cardiac devices.90

The finding of nonspecific ST-T wave abnormalities, defined as < 1-mm ST-segment depression or ST-segment elevation with or without an abnormal T wave on the ECG, is a frequent cause for concern. Indeed, up to 8% of adult patients with chest pain treated in the emergency department who presented with either a normal ECG or nonspecific ST-T abnormalities had a final hospital diagnosis of acute MI.91 However, transient ST-segment changes have been documented during ambulatory monitoring in up to 8% of patients without obstructive CAD.92 Nonspecific repolarization abnormalities have been described during ambulatory ECG monitoring following a meal, after a change in body position, or after a Valsalva maneuver.93 Up to 15% of apparently healthy subjects with hyperventilation have nonspecific ST-T changes.94

Correct interpretation of ST-T changes requires knowledge of the clinical context and the cardiac risk profile of the patient. Overreliance on a normal ECG finding in a patient with a classical history of anginal chest pain is dangerous. Conversely, nonspecific ST-T wave abnormalities in a patient with atypical chest pain and a low probability of CAD allows early discharge from the emergency department. A considerable number of these patients probably have a panic attack or hyperventilation.

Most of the ECG changes that occur during pregnancy can be explained by the physiologic adaptations in response to pregnancy. As the heart moves toward a horizontal position because of uterine enlargement, there is a (leftward or rightward) shift of the QRS axis.95 The increase in size and left ventricular mass, as documented by echocardiography, may result in increased left ventricular voltage. Sinus tachycardia and premature atrial and ventricular beats are also considered as normal. Minor ST-T wave changes have also been reported in pregnancy and are interpreted as normal in an asymptomatic woman.96

The use of contrast agents during cardiac catheterization is frequently accompanied by ECG changes. These include prolongation of the QRS complex, increase in the QT interval, marked shifts in the ST segment, and T-wave morphology (T-wave inversion or peaking in the inferior leads).97 The inhibitory action on the sinoatrial and atrioventricular node explains the transient bradyarrhythmia in many patients and the occasional effect of complete AV block or sinus arrest. Also ventricular fibrillation, reported in 0.6 to 1.3% of patients, is often attributed to the use of contrast material.98

Contrast agent toxicity is at least partly mediated by hyperosmolarity. In predisposing to ventricular fibrillation, contrast-induced transient hypocalcemia may be another contributing factor.99 The lower incidence of significant arrhythmias and other ECG changes when using low-osmolarity contrast material and the reduction of the calcium-binding potential for newer agents have further reduced the incidence of ventricular fibrillation. This would appear to substantiate the postulated mechanisms.100

Pulmonary emphysema, a condition characterized by lung hyperinflation, produces several anatomic changes that affect the ECG in unique ways.101 The downward displacement of the diaphragm and the heart produces a rightward shift of the QRS axis in the frontal plane and poor progression of the R wave in the precordial leads, simulating anterior MI. This latter finding is explained by the relatively high position of the precordial electrodes in relation to the heart. They are often at the level of the base of the heart and therefore record a negative ventricular potential.102 Compression of the heart into a more vertical position explains the prominent P waves in leads II, III, and aVF, and as a result of exaggerated atrial repolarization PR-segment and ST-segment depression in the same leads.101 Low voltage of the QRS complexes, especially in the left precordial leads, is the effect of the lowered electrical transmission resulting from the hyperinflated lungs.101

Tension pneumothorax is mostly diagnosed early on a purely clinical basis. Unexpected ECG findings, due to positional changes of the heart, may give rise to confusion, particularly suspicion of PE (Fig 10).

CONCLUSION

Although most of the ECG abnormalities detected in patients in the emergency department or ICU are caused by primary cardiac diseases, ECG changes do not invariably imply a cardiac abnormality. A thorough knowledge of the ECG manifestations of noncardiac conditions, commonly seen in critical care settings, may result in rapid diagnosis and correct treatment of potentially life-threatening disorders. Misinterpretation of the ECG may even expose the patient to wrong therapeutic options, with serious risks.

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1574

Critical Care Review


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