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Correlation between P Wave Dispersion, QRS Duration & QT Dispersion in Hospital Events in Cases of Acute Coronary Syndrome

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Introduction

Acute coronary syndrome (ACS) refers to a spectrum of clinical presentations ranging from those for ST-segment elevation myocardial infarction (STEMI) to presentations found in non–ST-segment elevation myocardial infarction (NSTEMI) or in unstable angina. In terms of pathology, ACS is almost always associated with rupture of an atherosclerotic plaque and partial or complete thrombosis of the infarct-related artery.

In some instances, however, stable coronary artery disease (CAD) may result in ACS in the absence of plaque rupture and thrombosis, when physiologic stress (e.g, trauma, blood loss, anemia, infection, and tachyarrhythmia) increases demands on the heart. The diagnosis of acute myocardial infarction in this setting requires a finding of the typical rise and fall of biochemical markers of myocardial necrosis in addition to at least one of the following [1]:

- Ischemic symptoms
- Development of pathologic Q waves
- Ischemic ST-segment changes on electrocardiogram (ECG) or in the setting of a coronary intervention

The terms transmural and non-transmural (sub-endocardial) myocardial infarction are no longer used because ECG findings in patients with this condition are not closely correlated with pathologic changes in the myocardium. Therefore, a transmural infarct may occur in the absence of Q waves on ECGs, and many Q-wave myocardial infarctions may be sub endocardial, as noted on pathologic examination. Because elevation of the ST segment during ACS is correlated with coronary occlusion and because it affects the choice of therapy (urgent reperfusion therapy), ACS-related myocardial infarction should be designated STEMI or NSTEMI.

In 2010, the American Heart Association (AHA) published new guideline recommendations for the diagnosis and treatment of ACS.

Acute coronary syndrome (ACS) is caused primarily by atherosclerosis. Most cases of ACS occur from disruption of a previously non severe lesion (an atherosclerotic lesion that was previously hemodynamically insignificant yet vulnerable to rupture). The vulnerable plaque is typified by a large lipid pool, numerous inflammatory cells and a thin fibrous cap.

Elevated demand can produce ACS in the presence of a high-grade fixed coronary obstruction, due to increased myocardial oxygen and nutrition requirements, such as those resulting from exertion, emotional stress, or physiologic stress (e.g., from dehydration, blood loss, hypotension, infection, thyrotoxicosis, or surgery).

ACS without elevation in demand requires a new impairment in supply, typically due to thrombosis and/or plaque hemorrhage.

A syndrome consisting of chest pain, ischemic ST-segment and T-wave changes, elevated levels of biomarkers of myocyte injury, and transient left ventricular apical ballooning (takotsubo syndrome) has been shown to occur in the absence of clinical CAD, after emotional or physical stress. The

etiology of this syndrome is not well understood but is thought to relate to a surge of catechol stress hormones and/or high sensitivity to those hormones.

The severity and duration of coronary artery obstruction, the volume of myocardium affected, the level of demand, and the ability of the rest of the heart to compensate are major determinants of a patient's clinical presentation and outcome. A patient may present to the ED because of a change in pattern or severity of symptoms.

Typically, angina is a symptom of myocardial ischemia that appears in circumstances of increased oxygen demand. It is usually described as a sensation of chest pressure or heaviness that is reproduced by activities or conditions that increase myocardial oxygen demand. A new case of angina is more difficult to diagnose because symptoms are often vague and similar to those caused by other conditions (eg, indigestion, anxiety) [1].

Clinical Presentation

A summary of patient complaints is as follows:

• Palpitations.

• Pain, which is usually described as pressure, squeezing, or a burning sensation across the precordium and may radiate to the neck, shoulder, jaw, back, upper abdomen, or either arm.

• Exertional dyspnea that resolves with pain or rest.

• Diaphoresis from sympathetic discharge.

• Nausea from vagal stimulation.

• Decreased exercise tolerance.

Stable angina involves episodic pain lasting 5-15 minutes, is provoked by exertion, and is relieved by rest or nitroglycerin. In unstable angina, patients have increased risk for adverse cardiac events, such as myocardial infarction or death. New-onset exertional angina can occur at rest and is of increasing frequency or duration or is refractory to nitroglycerin. Variant angina (Prinzmetal angina) occurs primarily at rest, is triggered by smoking, and is thought to be due to coronary vasospasm.

Increasing public awareness of the typical and atypical presentations of ACS is of the utmost importance for optimal and timely treatment. Many patients do not recognize that their symptoms are cardiac in origin and therefore may delay seeking medical help. Guidelines from the European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA) recommend that patients with established CAD call emergency medical services if they have chest pain that does not resolve after they take a sublingual nitroglycerin tablet.

Diagnosis

As previously mentioned, stable coronary artery disease (CAD) may result in ACS in the absence of plaque rupture and thrombosis, when physiologic stress (eg, trauma, blood loss, anemia, infection, tachyarrhythmias) increases demands on the heart. In such cases, the diagnosis of acute myocardial infarction can be made if workup reveals the typical rise and fall of biochemical markers of myocardial necrosis along with either the development of pathologic Q waves or the presence (on ECG or in the setting of a coronary intervention) of ischemic ST-segment changes. (However, the presence of ischemic symptoms can be substituted for the Q-wave or ST-segment evidence) [1].

Non–ST-segment elevation myocardial infarction (NSTEMI) is distinguished from unstable angina by elevated levels of cardiac enzymes and biomarkers of myocyte necrosis. Differentiation is generally based on three sets of biomarkers measured at 6- to 8-hour intervals after the patient's presentation to the ED. The current definition of NSTEMI requires a typical clinical syndrome plus elevated troponin (or creatine kinase isoenzyme MB [CK-MB]) levels to over 99% of the normal reference (with a coefficient of variation of < 10% for the assay). Given this definition, nearly 25% of patients who were previously classified as having unstable angina now fulfill the criteria for NSTEMI.

Measure cardiac enzyme levels at regular intervals, starting at admission and continuing until the peak is reached or until 3 sets of results are negative. Biochemical biomarkers are useful for diagnosis and prognostication.

Of note, cardiac-specific troponins are not detectable in the blood of healthy individuals; therefore, they provide high specificity for detecting injury to cardiac myocytes. These molecules are also more sensitive than CK-MB for myocardial necrosis and therefore improve early detection of small myocardial infarctions. Although blood troponin levels increase simultaneously with CK-MB levels (about 6 h after the onset of infarction), they remain elevated for as long as 2 weeks. As a result, troponin values cannot be used to diagnose reinfarction. New methods of detecting troponins in the blood can measure levels as low as 0.1-0.2 ng/mL.

Minor elevations in these molecules can be detected in the blood of patients without ACS in the setting of myocarditis (pericarditis), sepsis, renal failure, acute congestive heart failure (CHF), acute pulmonary embolism, or prolonged tachyarrhythmias.

Guidelines released by the European Society of Cardiology (ESC) in August 2011 for the management of non-ST-segment elevation ACSs recommend a scoring system to score the risk of an ischemic event in the short-to-mid term. The guidelines state that bleeding risk can be stratified using the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines) risk score [2].

Electrocardiography

ECGs should be reviewed promptly. Involve a cardiologist when in doubt. Recording an ECG during an episode of the presenting symptoms is valuable. Transient ST-segment changes (>0.05 mV) that develop during a symptomatic period and that resolve when the symptoms do are strongly predictive of underlying CAD and have prognostic value. Comparison with previous ECGs is often helpful.

In the emergency setting, ECG is the most important ED diagnostic test for angina. It may show changes during symptoms and in response to treatment, confirm a cardiac basis for symptoms. It also may demonstrate preexisting structural or ischemic heart disease (left ventricular hypertrophy, Q waves). A normal ECG or one that remains unchanged from the baseline does not exclude the possibility that chest pain is ischemic in origin. Changes that may be seen during anginal episodes include the following:

• Transient ST-segment elevations

• Dynamic T-wave changes - Inversions, normalizations, or hyperacute changes

• ST depressions - May be junctional, downsloping, or horizontal

In patients with transient ST-segment elevations, consider LV aneurysm, pericarditis, Prinzmetal angina, early repolarization, and Wolff-Parkinson-White syndrome as possible diagnoses. Fixed changes suggest acute myocardial infarction.

Diagnostic sensitivity may be increased by performing right-sided leads (V4 R), posterior leads (V8, V9), and serial recordings.

Measurement of CK-MB Levels

CK-MB, the isoenzyme specific to the heart muscle, was the principal biomarker of cardiac injury until troponin supplemented it. In the setting of myocardial infarction, plasma CK-MB concentrations typically rise about 4-6 hours after the onset of chest pain. They peak within 12-24 hours and return to baseline levels within 24-48 hours. Serial measurements obtained every 6-8 hours (at least 3 times) are warranted until peak values are determined.

Measurement of Troponin Levels

The cardiac troponins are sensitive, cardiospecific, and provide prognostic information for patients with ACS. They have become the cardiac markers of choice for patients with ACS. Initial studies on the cardiac troponins revealed a subset of patients with rest unstable angina in whom CK-MB levels were normal but who had elevated troponin levels. These patients had higher adverse cardiac event rates (acute myocardial infarction, death) within the 30 days after the index admission and a natural history that closely resembled patients with NSTEMI.As previously mentioned an elevated troponin level also enables risk stratification of patients with ACS and identifies patients at high risk for adverse cardiac events (i.e, myocardial infarction, death) up to 6 months after the index event [3,4].

In a study by Antman et al. [3], the initial TnI level on admission in patients with ACS correlated with mortality at 6 weeks. CK-MB levels, although sensitive and specific for the diagnosis of acute myocardial infarction, were not predictive of adverse cardiac events and had no prognostic value.

The 2007 American College of Cardiology (ACC) guidelines for NSTEMI recommend that serial troponins be obtained for a definitive rule out at baseline and 6-9 hours later. To establish the diagnosis of acute myocardial infarction, only 1 elevated level above the established cutoff is required. The demonstration of a rising or falling level is needed to distinguish persistently elevated troponin levels (eg, in some patients with renal failure) from those patients with acute myocardial infarction [5].

If myocardial injury is suspected despite negative cardiac-specific troponin findings, additional, sensitive laboratory assays are indicated [6].

Measurement of Myoglobin Level

Myoglobin is not cardiac specific, but it may be detected as early as 2 hours after myocardial necrosis starts. However, myoglobin results should be supplemented with other, more specific cardiac biomarkers, such as CK-MB or troponin.

Myoglobin values have a high negative predictive value when blood is sampled in the first 4-8 hours after onset.

Complete Blood Count Determination

The CBC count helps in ruling out anemia as a secondary cause of ACS. Leukocytosis has prognostic value in the setting of acute myocardial infarction.

Basic Metabolic Panel

Obtain a basic metabolic profile, including a check of blood glucose level, renal function, and electrolytes levels for patients with new-onset angina. Close monitoring of potassium and magnesium levels is important in patients with ACS because low levels may predispose them to ventricular arrhythmias. Routine measurement of serum potassium levels and prompt correction are recommended. Creatinine levels must be considered before using an angiotensin-converting enzyme (ACE) inhibitor and particularly if cardiac catheterization is considered. Use of N -acetylcysteine and adequate hydration can help prevent contrast material–induced nephropathy [7].

A study by Charpentier et al. [8] suggests that a serum glucose level of more than 140 mg/dL is associated with non-ST elevation ACS in patients admitted to an ED for chest pain. However, when this level of blood glucose is added to the conventional diagnostic tools, the result is only a small increase in the ability to classify ACS.

New Biomarkers

Levels of brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-pro-BNP) are elevated in acute MI and provide predictive information for risk stratification across the spectrum of ACS [9,10].

Cavusoqlu et al. [11] suggests that elevated baseline levels of plasma interleukin-10 are associated with long-term adverse outcomes in patients with ACS.

Chest Radiography

Chest radiography helps in assessing cardiomegaly or it may reveal complications of ischemia, such as pulmonary edema. It may also provide clues to alternative causes of symptoms, such as thoracic aneurysm or pneumonia (which can be a precipitating cause of ACS).

Echocardiography

Echocardiograms may play an important role in the setting of ACS. Regional wall-motion abnormalities can be identified with this modality, and echocardiograms are especially helpful if the diagnosis is questionable.

An echocardiogram can also help in defining the extent of an infarction and in assessing overall function of the left and right ventricles. In addition, an echocardiogram can help to identify complications, such as acute mitral regurgitation, LV rupture, and pericardial effusion.

Absence of segmental wall-motion abnormality on echocardiography during active chest discomfort is a highly reliable indicator of a nonischemic origin of symptoms, although echocardiography is of limited value in patients whose symptoms have resolved or who have pre-existing wall-motion abnormalities.

Myocardial Perfusion Imaging

A normal resting perfusion imaging study has been shown to have a negative predictive value of more than 99% in excluding myocardial infarction. Observational and randomized trials of rest and stress imaging in the ED evaluation of patients with chest pain have demonstrated reductions in unnecessary hospitalizations and cost savings compared with routine care.

Perfusion imaging has also been used in risk stratification after myocardial infarction and for measurement of infarct size to evaluate reperfusion therapies. Novel "hot spot" imaging radiopharmaceuticals that visualize infarction or ischemia are currently undergoing evaluation and hold promise for future imaging of ACS.

Cardiac Angiography

For high-risk patients with ACS without persistent ST elevation, angiography with glycoprotein IIb/IIIa inhibition has been recommended. The earlier that coronary angiography is performed, the lower the risk of recurrent ischaemia [12]. This also shortens the hospital stay for those patients.

Computed Tomography Coronary Angiography and CT Coronary Artery Calcium Scoring

CT coronary artery scoring is emerging as an attractive risk stratification tool in patients who are low risk for ACS. This imaging modality exposes the patient to very little radiation (1-2 msV). No contrast is needed, and the study does not have a requirement for heart rate [13].

Other Techniques

Optical coherence tomography (OCT), palpography, and virtual histology are being studied for use in identifying vulnerable plaques. Noninvasive whole-blood test prior to coronary angioplasty may be useful for assessing obstructive CAD in patients without diabetes [14].

Stress cardiac magnetic resonance imaging (MRI) in an observation unit setting has shown to reduce the medical costs, compared with inpatient care, for patients who present with emergent, non-low-risk chest pain, without missing acute coronary syndrome [15].

Diagnostic Consiaeration (D.D)

In patients presenting to the ED with chest pain, a structured diagnostic approach that includes time-focused ED decision points, brief observation, and selective application of early outpatient provocative testing appeared both safe and diagnostically efficient in a study by Scheuermeyer et al. [2] However, some patients with ACS may be discharged for outpatient stress testing on the index ED visit.

Differentials

- Anxiety
- Aortic Stenosis
- Asthma
- Esophagitis
- Gastroenteritis
- Hypertensive Emergencies in Emergency Medicine
- Myocardial Infarction
- Myocarditis
- Pericarditis and Cardiac Tamponade.
- Cardiomyopathy, Dilated

Treatment

Attention to the underlying mechanisms of ischemia is important when managing ACS. A simple predictor of demand is rate-pressure product, which can be lowered by beta blockers (eg, metoprolol or atenolol) and pain/

stress relievers (eg, morphine), while supply may be improved by oxygen, adequate hematocrit, blood thinners (eg, heparin, IIb/IIIa agents such as abciximab, eptifibatide, tirofiban, or thrombolytics), and/or vasodilators (eg, nitrates, amlodipine).

Approach Consideration

Initial therapy for acute coronary syndrome should focus on stabilizing the patient's condition, relieving ischemic pain, and providing antithrombotic therapy to reduce myocardial damage and prevent further ischemia. Morphine (or fentanyl) for pain control, oxygen, sublingual and/or IV nitroglycerin, soluble aspirin 162-325 mg, and clopidogrel with a 300- to 600-mg loading dose are given as initial treatment.

In complete vessel occlusion without collateralization of the infarct-related vessel, there is little utility in "pushing nitrates".

High-risk patients with non-ST-segment elevation myocardial infarction (NSTEMI ACS) should receive aggressive care, including aspirin, clopidogrel, unfractionated heparin or low–molecular weight heparin (LMWH), intravenous platelet glycoprotein IIb/IIIa complex blockers (eg, tirofiban, eptifibatide), and a beta blocker. The goal is early revascularization.

Intermediate-risk patients with NSTEMI ACS should rapidly undergo diagnostic evaluation and further assessment to determine their appropriate risk category.

Low-risk patients with NSTEMI ACS should undergo further follow-up with biomarkers and clinical assessment. Optimal medical therapies include use of standard medical therapies, including beta blockers, aspirin, and unfractionated heparin or LMWH. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study showed that clopidogrel would be beneficial even in low-risk patients [16].

Patients presenting with cardiogenic shock should undergo percutaneous coronary intervention (PCI) as soon as possible. Cardiogenic shock is associated with a high mortality rate. Pressor agents, such as dopamine, and inotropic agents, such as dobutamine, may be needed.

Pharmacologic Anti Ischemic Therapy

Nitrates

Nitrates do not improve mortality [17]. However, they provide symptomatic relief by means of several mechanisms, including coronary vasodilation, improved collateral blood flow, decrease in preload (venodilation and reduced venous return), and decrease in afterload (arterial vasodilation). Care should be taken to avoid hypotension, because this can potentially reduce coronary perfusion pressure (diastolic BP - LV diastolic pressure).

Beta-Blockers

Beta-blockers are indicated in all patients unless they have the following contraindications:

- Systolic blood pressure less than 90 mm Hg
- Cardiogenic shock
- Severe bradycardia
- Second- or third-degree heart block
- Asthma or emphysema that is sensitive to beta agonists
- Peripheral vascular disease
- Uncompensated CHF

Pharmacologic Antithrombotic Therapy

Aspirin

Aspirin permanently impairs the cyclooxygenase pathway of thromboxane A2 production in platelets, in this way inhibiting platelet function. Aspirin reduces morbidity and mortality and is continued indefinitely [18].

Clopidogrel

Clopidogrel (thienopyridine) inhibits adenosine 5'-diphosphate (ADP)–dependent activation of the glycoprotein IIb/IIIa complex, a necessary step for platelet aggregation. This process results in intense inhibition of platelet function, particularly in combination with aspirin. In the CURE trial, thienopyridine reduced the rate of myocardial infarction by 20% [16].

Clopidogrel is a class I recommendation for patients when an early non-interventional approach is planned in therapy for at least 1 month and ideally up to 1 year. When percutaneous coronary intervention (PCI) is planned, clopidogrel 300-600 mg should be given as early as possible before or at the time of PCI. Clopidogrel, 75 mg daily, is continued for at least 12 months after PCI, if the patient is not at high risk for bleeding, according to 2011 ACCF/AHA guidelines (class I recommendation) [19].

Clopidogrel can be considered an alternative to aspirin in patients with aspirin intolerance or who are allergic to aspirin.

The Group's Findings and Recommendations are Listed below

- Clopidogrel reduces major CV events compared with placebo or aspirin.
- Dual antiplatelet therapy with clopidogrel and aspirin, compared with aspirin alone, reduces major CV events in patients with established ischemic heart disease, and it reduces coronary stent thrombosis but is not routinely recommended for patients with prior ischemic stroke because of the risk of bleeding [20].
- Clopidogrel alone, aspirin alone, and their combination are all associated with increased risk of GI bleeding.
- Clopidogrel requires metabolic activation by cytochrome P450 2C19 (CYP2C19). PPIs that inhibit CYP2C19 are commonly co administered with clopidogrel to reduce the risk of GI bleeding. A study by Simon et al showed that PPI use is not associated with an increased risk of cardiovascular events or mortality in patients who have been treated with clopidogrel for a recent MI, regardless of CYP2C19 genotype [21].

Prasugrel

Like clopidogrel, prasugrel is a thienopyridine ADP receptor inhibitor that inhibits platelet aggregation. It has been approved in the United States and has been shown to reduce new and recurrent myocardial infarctions [22].

Ticagrelor

Ticagrelor (Brilinta) was approved by the US Food and Drug Administration in July 2011 and is the first reversible oral P2Y receptor antagonist. Results from the platelet inhibition and patient outcomes (PLATO) trial showed ticagrelor provides faster, greater, and more consistent ADP-receptor inhibition than clopidogrel [23].

Abciximab, Eptifibatide, and Tirofiban

Glycoprotein IIb/IIIa receptor antagonists include abciximab [24,25], eptifibatide [26], and tirofiban [27]. These drugs inhibit the glycoprotein IIb/IIIa receptor, which is involved in the final common pathway for platelet adhesion and aggregation.

Pharmacologic Anticoagulation Therapy

Un-fractionated heparin

A study by Oler et al. [28] found that unfractionated heparin was associated with a 33% reduction in the risk of myocardial infarction or death in patients with unstable angina who were treated with aspirin plus heparin, compared with patients who were treated with aspirin alone. The FUTURA/OASIS-8 randomized trial found that low-dose unfractionated heparin, 50 U/kg (regardless of use of glycoprotein IIb/IIIa inhibitors), compared with standard-dose unfractionated heparin, 85 U/kg (60 U/kg with Gp IIb/IIIa inhibitors), did not reduce major peri-PCI bleeding and vascular access-site complications [29].

Low–Molecular-Weight Heparin

LMWHs might be superior to un-fractionated heparin in reducing cardiovascular outcomes, with a safety profile similar to that of heparin in patients receiving medical care.

Aside from the possible medical benefits of using LMWH in place of un-fractionated heparin, advantages of LMWH include ease of administration, absence of need for anticoagulation monitoring, and potential for overall cost savings. Although 3 LMWHs are approved for use in the United States, only enoxaparin is currently approved for use in unstable angina. Lev et al. [30] found that the combination of eptifibatide with enoxaparin appears to have a more potent antithrombotic effect than that of eptifibatide and unfractionated heparin.

Factor Xa inhibitors

Use of the oral Xa inhibitor, rivaroxaban (Xarelto), in addition to dual antiplatelet therapy in patients with ACS was recently investigated in the ATLAS ACS2-TIMI 51 trial. Low-dose rivaroxaban (2.5 mg twice daily) resulted in a significant reduction in overall and cardiac mortality whereas use of the higher dose (5 mg twice daily) did not result in a significant mortality reduction. However, both doses were associated with an increased risk of bleeding compared with placebo. Rivaroxaban is not currently approved by the US Food and Drug Administration (FDA) for use in ACS. Another factor Xda inhibitor, fondaparinux (Arixtra), has been studied for use in patients with STEMI who do not undergo PCI [31].

In the Fifth Organization to Assess Strategies in Ischemic Syndromes (OASIS-5) trial, fondaparinux reduced major bleeding and improved net clinical outcome compared with enoxaparin in patients receiving GP IIb/IIIa inhibitors or thienopyridines for ACS [32]. Fondaparinux is not currently FDA approved for use in ACS.

Thrombolysis

Prehospital thrombolysis allows eligible patients to receive thrombolysis 30-60 minutes sooner than if treatment were given in the ED; however, prehospital thrombolysis is still under investigation and has not become a trend, as a result of unproven benefit and an increase in the availability of PCI in many medical centers as an alternative to thrombolysis for STEMI.

Although PCI is the preferred treatment for STEMI, the distance to primary PCI centers and the inherent time delay in delivering primary PCI limits widespread use of this treatment. Prehospital electrocardiographic (ECG) diagnosis and direct referral for primary PCI enables patients with STEMI living far from a PCI center to achieve a system delay comparable to patients who are closer to a PCI center [33].

Coronary Intervention

An early invasive strategy is also indicated in initially stabilized unstable angina/NSTEMI patients who do not have serious comorbidities or contraindications to such procedures and who have an elevated risk for clinical events.

According to the 2011 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines, an early invasive strategy (ie, within 12-24 hours of admission) is a reasonable choice for initially stabilized high-risk patients with unstable angina/NSTEMI; for patients not at high risk, a delayed invasive approach is also reasonable (class IIa recommendation) [19].

Concomitant Therapy

Current guidelines for patients with moderate- or high-risk ACS recommend an early invasive approach with concomitant antithrombotic therapy, including aspirin, clopidogrel, and unfractionated or LMWH. The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial evaluated the role of thrombin-specific anticoagulation with bivalirudin in this patient population. In patients with moderate- or high-risk ACS who were undergoing invasive treatment with glycoprotein IIb/IIIa inhibitors, bivalirudin was associated with rates of ischemia and bleeding that were similar to those with heparin. Bivalirudin alone was associated with similar rates of ischemia and significantly lower rates of bleeding [34].

ECG & Arrhythmia Pathogenesis

Cardiac Activation: Impulse Formation, and Conduction

The heart can be considered as a dipole with a positive and a negative charge. At any given time, cardiac cells are in various stages of activation (i.e., depolarization and repolarization).

The formation (i.e., pacemaking) and timely conduction of an electrical impulse depend on cardiac cells that are strategically placed and arranged in nodes, bundles, and an intraventricular network that end in Purkinje cells. All these specialized cells lack contractile capability, but they can act as pacemakers (i.e., spontaneously generate electrical impulses) and alter conduction speed. The intrinsic pacemaking rate is fastest in the sinus node, located in the right atrium, and is slowest in the Purkinje cells.

The intraventricular conduction network includes the common bundle of His and its right and left bundle branches, which extend along the septum toward their respective ventricles. The left bundle branch is a diffuse structure that fans broadly over the septum toward the two mitral valve papillary muscles. In the left bundle branch, two divisions can usually be distinguished; they are called anterior and posterior but are indeed superior and inferior, respectively. Because the right bundle branch remains compact until it reaches the distal interventricular septal surface (where it branches into the septum and toward the lateral right ventricular wall), many authors consider the intraventricular conduction system to be trifascicular [35].

These intraventricular conduction pathways are composed of Purkinje cells with both pacemaking and rapid impulse conduction capabilities. Purkinje fibers branch into networks that extend just beneath the endocardial surface.

The normal activation sequence begins at the midseptum, continues in the epicardial right ventricular wall near the apex, then at the lateral and basal LV, and ends at the basal septum.

The wavefront departs from the sinus node and travels through the right and left atria in a centrifugal manner. On arrival at the atrioventricular (AV) node, the impulse is delayed, allowing for a sequential, rather than simultaneous, contraction of the ventricles after the atria. Because the Purkinje system provides a specialized path for rapid activation, the entire ventricular mass can be depolarized in a short time (similar to the depolarization timing of the much smaller atria). The impulses then proceed slowly from endocardium to epicardium throughout both ventricles [36].

Electrical Bases for Electrocardiography and Vectorcardiography

Differences in cardiac potentials of a single cardiac cell or a small group of cells do not produce enough current to be detected on the body surface. Electrical representation on the ECG depends on the activation of most of the atrial and ventricular masses. The depolarization process produces a relatively high-frequency ECG waveform. The earliest QRS complex is recorded in right precordial leads. While depolarization persists, the ECG recording returns to baseline. Repolarization is then represented by the ST segment and the T and U waves. Once the cells are in their resting state, the ECG records a flat baseline.

Normal Electrocardiographic Waveforms

Overview:

The waves on the ECG represent a coincident voltage gradient generated by cellular electrical activity within the heart. The origin of the cardiac impulse in the sinus node is electrocardiographically mute; the initial recordable wave for each cardiac cycle is the P wave, which represents the spread of activation through the atria. Ventricular activation results in the QRS complex, which may appear as one (monophasic), two (diphasic), or three (triphasic) individual waveforms. Low-amplitude or narrow waves are denoted by lowercase letters (e.g., q wave) and taller, wider waves are denoted by capital letters (e.g., Q wave).

The T wave represents ventricular recovery and is sometimes followed by a small upright deflection, the U wave. The ST segment is the interval between the end of ventricular activation (the plateau phase of the action potential) and the beginning of ventricular recovery. The QT interval measures the time from ventricular activation onset to end of ventricular recovery. At low heart rates the PR, ST, and TP segments are at the same horizontal level (i.e., the isoelectric line), considered the baseline for measuring various waveform amplitudes [37].

P Wave

The first part of the P wave represents the activation in the right atrium, and the middle and final sections of the P wave are recorded during left atrial activation. The normal P wave is rounded and upright in leads I and II and from V2 to V6. Its maximum amplitude is 0.25 mV in lead II (or 25% of the R wave), and its duration is 0.08 second. The P-wave axis is approximately 60 degrees. The intrathoracic position of the right and left atria determines that the activation front be directed first anteriorly, then posteriorly. The right atrium faces lead V1, in which the initial portion of the P wave appears positive while its terminal part appears negative.

Ta Segment

The Ta segment (or Ta wave) represents atrial repolarization and may be seen in physiologically normal individuals, but it is more often obscured by the QRS complex and the early part of the ST segment. The Ta wave

direction is opposite that of the P wave. It represents the atrial repolarization .Normally not seen as it is buried in the large QRS. Prominent Ta wave may produce PR segment depression and mimic a pathologic Q wave.

PR Interval

The time from onset of the P wave to onset of the QRS complex (whether its first wave is a Q or an R wave) is the PR interval. It encompasses the time between the onset of atrial depolarization in the myocardium adjacent to the sinus node and the onset of ventricular depolarization in the myocardium adjacent to the Purkinje network. A major portion of it is inscribed during the slow conduction through the AV node. The normal PR interval measures 0.12 to 0.22 second. The PR interval increases with age. It shortens as heart rates increases; this effect depends on higher sympathetic and lower vagal tones. Incremental atrial pacing at rest, however, prolongs the PR interval. The time from the end of the P wave to the onset of the QRS complex is called PR segment and repesents the conduction delay in the AV node.

QRS Complex

The QRS complex represents ventricular activation. The contour of the QRS complex is peaked because it is composed of high-frequency signals. The normal ventricular activation can be summarized in four vectors : (a) initial septal activation from left to right and anteriorly (inferiorly or superiorly), producing a positive deflection (R wave) at right recording sites; (b) an overlapping wave of excitation involving both ventricles, with the vector directed inferiorly and slightly to the left, which inscribes the midportion of the QRS complex; (c) unopposed activation of the apical and central portions of the LV and of the right ventricle with a resultant vector oriented posteriorly, inferiorly, and to the left; the posteriorly positioned LV is much thicker, and its activation predominates over that of the more anterior right ventricle, with a resulting negative deflection (i.e., S wave) in aVR and in right precordial leads and in an R wave in leads I, II, III, aVL, and left precordial leads; and (d) activation of the posterior basal portion of the LV and septum with a vector directed superiorly and posteriorly, which completes the S wave in V5 and V6.

The QRS complex measures 0.07 to 0.10 second and increases with the subject's height [38]. The QRS complex is measured from the beginning of the first appearing Q or R wave to the end of the last appearing R, S, or R' wave. It tends to be slightly longer in male patients. The onset of the QRS complex is not recorded simultaneously in all ECG leads; this has implications when measuring QRS duration. The earliest QRS onset is recorded in right precordial leads [39]. Computerized QRS measurements have the advantage of integrating information from the 12 leads.

Q Waves

A Q wave is a negative deflection at the onset of the QRS complex. It indicates that the net direction of early ventricular depolarization forces is oriented away from the positive axis of the recording lead at least by 90 degrees. Normal septal activation results in a rapid q wave in leads I, II, III, aVL, V5, and V6. The presence of Q waves in V1, V2, and V3 or the absence of small q waves in V5 and V6 is abnormal. Positional factors may also result in the inscription of prominent but narrow Q waves. If the septal vector is horizontal, Q waves may appear in lead aVF; if the electrical axis is vertical, Q waves may appear in aVL. Precordial lead electrodes misplaced in a high position may determine the inscription of Q waves and a pseudoinfarction pattern. In right precordial leads, qr and qS complexes may be normal.

R Waves

The first positive wave of the QRS complex is the R wave, regardless of whether it is preceded by a Q wave. The second activation vector results in an R wave in leads II and III, and the third vector produces an R wave in leads I, II, III, aVL, aVF, V_5, and V_6. The precordial leads provide a panoramic view of the cardiac electrical activity progressing from the right ventricle to the thicker LV; consequently, the R wave increases its amplitude and duration from V1 to V_4 or V_5. An rS pattern in leads V_3R and V_4R is normal. The R wave amplitude in V_5 and V_6 varies directly with LV dimension during exercise and with positional changes. Reversal of the normal sequence with larger R waves in V_1 and V_2 can be produced by right ventricular enlargement. When a second positive deflection occurs in any lead, it is called R.

S Waves

A negative deflection following an R wave is an S wave. The third vector produces an S wave in leads aVr, V_1, V_2, V_3, and occasionally, V_4. The S wave in the precordial leads is large in V_1, larger in V_2, and then progressively smaller from V_3 through V_6. This sequence could be altered by ventricular enlargement. The last vector directed superiorly and posteriorly, may result in a terminal S wave in leads I, V_5, and V_6. Leads V_{4R} and V_{3R} show an rS morphology in 80% of normal subjects [40].

ST Segment

The ST segment represents the time period in which the ventricular myocardium remains depolarized. The term ST segment is used whether the QRS complex ends in an R wave or in an S wave. At its junction with the QRS (i.e., J point), the ST segment forms a nearly 90-degree angle and then proceeds horizontally until it curves gently into the T wave. Slight up sloping (particularly in leads V_1 to V_3, and in V_{4R} V_{3R}), downsloping, or horizontal depression of the ST segment may occur as a normal variant. The ST-segment length and appearance are influenced by factors that alter the duration of ventricular activation, such as exercise and BBB.

T Wave

The T wave represents exclusively uncanceled potential differences of ventricular repolarization (i.e., both spatial and temporal dispersion of repolarization) among the epicardium, M cells, and endocardium. The

T wave accounts for 8% or less of the total time-voltage product of the heart. The T wave has a rounded but asymmetric shape, with the initial deflection longer than the terminal deflection. The peak of the T wave marks repolarization completion of the epicardial cells. The end of the T wave is temporally aligned with repolarization of the M cells. The M-cell repolarization is outlasted by that of the Purkinje cells, itself unlikely to generate an ECG wave.

The T-wave amplitude does not normally exceed 0.5 mV in limb leads or 0.10 mV in precordial leads. The T-wave vector and polarity are concordant with the R-wave vector. The T wave is always positive in lead I, nearly always positive or isoelectric in lead II, and may have any polarity in leads III and aVF. In precordial leads, the T wave is usually upright.

U Wave

When present, the U wave is a small, rounded wave following the T wave. It is most prominent in leads V_2 to V_3 and it usually shows the same direction as its preceding T wave, but in some patients it may be discordant [41].

The U wave results from the last repolarization components. It may be generated by repolarization of the Purkinje network or by repolarization of the M cells [42,43].

QT Interval

The QT interval measures the time from the beginning of the QRS complex until the end of the T wave. It estimates the duration of both ventricular depolarization and repolarization, but it is used mainly as an estimate of ventricular recovery time. The term QT is used whether the QRS complex begins with a Q or an R wave.

Accurate QT measurements are elusive. One reason is that on a given ECG, the end of the T wave is not always obvious; its terminal portion may be isoelectric or merge with a U wave. This partially explains why the precise duration of the QT interval is notoriously difficult to determine, even by cardiologists, and to standardize [44]. The problem has not been satisfactorily solved by automated programs, because of technical factors regarding acquisition of digital ECG signals.

The duration of the QT interval is affected by numerous physiologic variables. These include autonomic influences, circadian rhythms, electrolytes, and hormones. For example, the JT interval (i.e., the interval between the J point and the end of the T wave) is significantly shorter in men than in women, probably because repolarization is modulated by testosterone [45]. Repolarization and the QT interval are also affected by drugs, an important reason to monitor QT-interval duration.

Another main factor influencing the QT interval is heart rate between the QT and the RR intervals is an inverse relationship that is nonlinear: as the heart rate increases, the QT interval initially shortens markedly and then shortens more gradually. Thus, QT-interval values require adjustment. The normal QT-interval values for a given heart rate are determined with mathematic formulas that estimate the corrected QT interval (QTc). Of the several QT correction formulas, that of Bazett (QTc = QT/RR) is the most widely used. The normal value of QTc is up to 0.39 second in men and 0.44 second in women. Yet with the Bazett formula, the QTc remains undercorrected (i.e., artificially shortened) during bradycardia, whereas it paradoxically lengthens at faster rates [46].

Abnormal Electrocardiogram (WAVES)

P-Wave Abnormalities

Abnormalities of the P wave reflect disorders of atrial pressure or volume, or an anomalous origin of the cardiac impulse.

Right Atrial Abnormality: Right atrial enlargement has classically been diagnosed in the presence of the following: (a) tall, peaked P waves in leads II, III, and aVF (0.25 mV in lead II) (P pulmonale); (b) a P-wave axis 75 degrees; and (c) a positive deflection of the P wave in V_1 or V_2 0.15 mV [47]. These ECG signs, however, correlate poorly with anatomic findings. The P-wave amplitude may paradoxically decrease as right ventricular hypertrophy progresses. Also, P-wave signs have relatively low sensitivity to detect pure right atrial enlargement. The most sensitive ECG manifestations of right atrial abnormality in patients with low prevalence of coronary disease, no chronic pulmonary disease, and no left-sided heart disease seem to be QRS changes in lead V_1 (R/S ; presence of Q) (in the absence of RBBB). In addition, ST-segment depression 0.05 mV in II or aVF (probably representing a prominent atrial repolarization (Ta) wave) is highly specific.

Left Atrial Abnormality: Left atrial enlargement is characterized by the following: (a) a notched P wave with a duration 0.12 second (mitral), best observed in leads II and V1; and (b) a wide terminal negative deflection in lead V1 (0.1 mV amplitude per 0.4 second duration). The terminal force of the P wave correlates better with left atrial volume and weight than with atrial pressure. No characteristic of the P wave correlates with atrial size [48]. The left atrial enlargement pattern signals an intraatrial conduction disturbance; thus, the term left atrial abnormality is preferred.

The term pseudo-P pulmonale denotes a prominent P wave in inferior leads that is caused by left, rather than right, atrial abnormality. The P wave revealed is enlarged only in its terminal portion, which in V1 is markedly negative.

Biatrial Enlargement

Biatrial enlargement is characterized by tall P waves in lead II and notched and broad P waves in leads I and II, with a terminal negative deflection in V1.

Ta Wave

Ta waves may be prominent in atrial hypertrophy or infarction and during pericarditis that has not been promptly detected. In the presence of atrial enlargement, the Ta wave is prolonged and may displace the ST segment, which appears depressed.

PR Interval

A short PR interval in the presence of a normal P-wave axis suggests an abnormally rapid conduction pathway within the AV node or its surroundings (i.e., a bundle of cardiac muscle connecting atria directly with ventricles). An impulse that bypasses the AV node leads to early activation of the ventricular myocardium (ventricular preexcitation). This creates the potential for the electrical impulse to reenter into the atria, producing a tachyarrhythmia (the Wolff-Parkinson-White [WPW] syndrome). When a short PR interval is accompanied by an abnormal P-wave direction, the site of impulse origin has moved from the sinus node to a position closer to the AV node. A prolonged PR interval with a normal P-wave axis indicates a delay in impulse transmission at some point in the pathway between the atrial and ventricular myocardium.

QRS Complex

The absence of R-wave progression from V_1 to V_5 may indicate LV necrosis. In precordial leads, the notching or slurring of the QRS complex is more sensitive than the presence of Q waves to detect anterior infarction, but it is less specific [49]. A cause of apparent loss of left precordial R waves is the rightward mediastinal shift induced by a left pneumothorax [50]. In dextrocardia, normal R-wave progression may be observed by recording leads V_1 to V_{5R}.

Q Waves

Conditions associated with abnormal Q waves include myocardial infarction or injury, LV hypertrophy (LVH) or dilatation, and intraventricular conduction disturbances (left BBB [LBBB], ventricular pacing and WPW syndrome). Less frequent causes of Q waves include infiltrative myocardial disease, chronic obstructive pulmonary disease (in precordial leads), acute pulmonary embolism, pneumothorax, and misplacement of precordial electrodes [51].

ST Segment

Alterations of the ST segment include elevation and depression, which depend on either of the following two cellular mechanisms, or both: (a) an injury current resulting from a difference in resting membrane potentials between injured and uninjured myocardium; and (b) a voltage gradient generated by a difference in AP plateau amplitudes.

The most important cause of ST-segment elevation is myocardial injury. Another cause is ventricular asynergy, which can produce a pseudoinfarction pattern [52]. Depression of the ST segment occurs during myocardial ischemia and when ventricular repolarization is altered.

QT Interval

Long QT Interval

The malfunction of cardiac channels may lead to an intracellular excess of positive ions (sodium or potassium). This excess prolongs ventricular repolarization and, consequently, the QT interval. A prolonged QTc is a predictor of cardiovascular mortality even in the absence of overt heart disease [53]. Causes of long QT interval include myocardial ischemia, cardiomyopathies, hypokalemia, hypocalcemia, autonomic influences, drug effects, hypothermia, and genetics (congenital long QT syndrome).

Ischemia

Acute myocardial ischemia may induce an initial, transient QT shortening followed by extreme QT prolongation. Changes in the QT interval often accompany T-wave or U-wave inversion [54]. The QT interval usually normalizes within 72 hours, while inverted T waves may persist.

Hypertrophic Cardiomyopathy

The QT and QTc are prolonged in patients with hypertrophic cardiomyopathy, as a consequence of the increased LV mass [55].

Hypothermia

Hypothermia (core temperatures 35°C) is associated with sinus bradycardia, which, in turn, is associated with prolongation of the QT interval. In some patients, however, the QTc interval is also abnormal.

Autonomic Dysfunction

Patients with diabetes, alcoholism, and other disorders that cause autonomic dysfunction may show prolonged QT and QTc intervals [56].

Drugs

Antiarrhythmic drugs, the antibiotics erythromycin and ketoconazole, the antihistamine agents astemizole and terfenadine, the phenothiazines, and terodiline all have been associated with prolongation of both the QT and QTc intervals, with torsade de pointes, and with sudden death [57].

When new drugs are under clinical development, it is important to test for a propensity to dangerous arrhythmias such as torsade. Because this is unfeasible, regulatory agencies instead require testing for drug-related changes in the QT interval [58].

Recently, the selective serotonin reuptake inhibitors and the newer antipsychotic agents (e.g. clozapine, risperidone) have been reported to be associated with arrhythmias and prolonged QTc interval [59]. A list of drugs associated with QT-interval prolongation is continuously updated on the Internet [60].

Congenital Long QT Syndrome

Various mutations in ion channel genes cause congenital long QT syndrome (QTc > 0.46 seconds). 5 to 10% of gene carriers for this disorder, however, have QTc durations within normal range [61]. Patients with the syndrome may also have marked sinus bradycardia. The T wave is often notched or biphasic, or it alternates its morphology or polarity (T-wave alternans) [62-64]. Prominent U waves may also be present. The extreme prolongation of the QT interval can result in pseudo 2:1 AV block when every other P wave falls during or before the preceding T wave. The long QT-3 variety seems to be caused by mutations in the SCN5A gene, which may also underlie the Brugada syndrome.

Short QT Interval

In the short QT syndrome, QTc intervals measure less than 320 milliseconds [65]. Patients (including children) have a high incidence of ventricular tachyarrhythmias, syncope, sudden cardiac death, or atrial fibrillation.

T Wave

Abnormalities of the T wave (usually consisting of inverted T waves) are seen in a number of conditions. The T wave is a sensitive detector of repolarization differences over the myocardium, but the magnitude of T-wave changes is not proportional to the extent of myocardium with repolarization abnormalities [66]. Negative T waves have classically been classified in primary when they result from changes in the duration, shape, or amplitude of ventricular action potentials (as in ischemia, myocarditis, pericarditis, drug effects), and as secondary when changes affect not the ventricular action potential but the activation sequence (as in BBB, ventricular pacing, ventricular hypertrophy, cardiomyopathies, and WPW syndrome) [67]. This mechanistic dichotomy, however, may be challenged in light of the phenomenon of T-wave memory and perhaps also by that of T-wave alternans, changes that could result from a combination of mechanisms or from ventricular electrical remodelling [68].

The term T-wave abnormality has been called into question by the finding that negative T waves that develop in infarct-related ECG leads shortly after thrombolysis are associated with improved survival [69]. It appears, however, that such T waves must be dynamic (i.e., revert to positive over time, with exercise, or with dobutamine) to predict myocardial viability and favorable outcome [70,71]. Abnormalities of the T wave on a resting ECG of male patients have been shown, conversely, to predict cardiovascular mortality [72].

Ischemic Heart Disease

Myocardial Ischemia and Injury

Occlusion of a coronary artery or one of their branches leads to interruption of the blood supply and causes myocardial ischemia and injury. During myocardial ischemia, myocytes partially depolarize, and their membrane resting potential is reduced (i.e., becomes less negative). The action potential duration and amplitude then decrease. Local injury currents develop between ischemic and nonischemic cells that manifest in the ECG as ST-segment deviation toward the specifically involved area.

The first ECG change is the development of peaked, tall T waves, followed by elevation of the ST segment [73]. The ischemic zone is electrically more negative than its surrounding myocardial area during the recovery phase. Thus, while ST-segment elevation is still present or after it has subsided, the T waves become inverted in relation to the QRS complexes. The T-wave inversion may regress within minutes or may persist for several months [74]. These T-wave changes are not specific or sensitive for the diagnosis of myocardial ischemia. Factors other than ischemia (e.g., reperfusion, sympathetic denervation) may conceivably have a role in the genesis of negative T waves.

For the diagnosis of myocardial injury, one of the following criteria is required:

(a) Elevation of the origin of the ST segment at the J point of 0.10 mV in two or more limb or precordial leads V4 to V6 or 0.20 mV in two or more precordial leads V1 to V3 or

(b) Depression of the origin of the ST segment at the J point of 0.10 mV in two or more leads V1 to V3 or ST-segment elevation greater than 0.10 mV in two or more leads V7 to V9. Severe degrees of ischemia are associated with distortion of the later part of the QRS complex, which reverses after the acute phase [75].

A highly specific marker of myocardial injury is alternans of the ST segment. Electrical alternans consists of alternans of the degree of ST-segment elevation, and it is secondary to variations in action potential duration or amplitude. Alternating ST-segment elevation and depression have not been reported. The classic notion that transmural injury is characterized by ST-segment elevation while nontransmural (subendocardial) injury is characterized by ST-segment depression has not been confirmed with imaging studies [76].

When insufficient coronary blood flow persists after the myocardial metabolic reserves have been depleted, the process of necrosis or myocardial infarction begins [77]. Permanent new Q waves develop at some point after ST-segment elevation or depression has occurred. In ECG leads in which rapid q waves are normally present, these waves may become pathologically wide.

Subendocardial Injury

Ischemia secondary to an increased metabolic demand (e.g., exercise) initially affects the subendocardium. Myocytes are less susceptible to ischemia during electrical depolarization than during electrical recovery; this is why the ECG changes involve mainly the ST-T waveforms (and much less the QRS complex).

Initial changes include a depression of the J point of at least 0.10 mV and a horizontal or downward sloping of the ST segment toward the T wave. The T wave may or may not be altered in the same direction as the ST segment. T-wave inversion may be secondary to ST-segment depression or it may change as a direct manifestation of delayed repolarization in the ischemic myocardium. The ST-segment depression of subendocardial injury resolves rapidly after removal of the cardiovascular stress. When the ST-segment depression persists in the absence of increased LV workload, the diagnosis of subendocardial infarction should be considered. Ischemia-related ST-segment depression may also occur as a mirror phenomenon of injury that has induced ST-segment elevation in the myocardial area opposite the surface electrode.

Acute ST-Segment Elevation Myocardial Infarction

The evolutionary changes during acute infarction include (a) ST-segment elevation often preceded by tall T waves, (b) abnormal Q waves, and (c) return of ST-segment elevation to baseline with T wave inversion. The most typical change involves ST-segment elevation, which decreases significantly after the first 12 hours of chest pain [78].

In some patients, multiple episodes of ST-segment elevation and resolution occur after thrombolytic therapy. Moderate ST-segment elevation usually persists for several days; its persistence beyond 2 weeks suggests ventricular aneurysm. If coronary reperfusion is rapidly achieved, Q waves may not develop.

Clinical Value of the Electrocardiogram during Acute Myocardial Infarction

In general, the 12-lead ECG is specific but only moderately sensitive to detect acute myocardial injury [79,80]. Systematically recording leads V_{4R}, V_8, and V_9 (i.e., a 15-lead ECG) increases the probability of detecting ST-segment elevation, with no decrease in specificity [81]. The infarction descriptors anterior, inferior, and lateral have classically been attributed to occlusions of the LAD, right coronary artery (RCA), and left circumflex artery (LCX), respectively. Other terms such as apical, septal, high lateral,and posterior are also in use. However, the 12-lead ECG is only moderately accurate to determine the anatomic location of acute infarction, and the correspondence of some ECG terms with the pertinent site of infarction is rather poor. The ECG is most sensitive to detect acute occlusion of the LAD and is least sensitive for involvement of the circumflex artery. Automated diagnoses (i.e., provided by the electrocardiographer) are specific but not sensitive; their most promising application is in the prehospital setting [82-84]. Among patients presenting to the emergency department with chest pain and ST-segment elevation in the 12-lead ECG, the cause of ST-segment elevation is often uncomplicated LVH [85].

Established Myocardial Infarction

Most infarctions consist of areas of both transmural and nontransmural necrosis that change quantitatively over time and whose correlation with the development of Q waves or their absence, respectively, is poor. The classification of Q-wave versus non Q-wave infarcts discriminates between larger and smaller infarcts [86].

During acute myocardial injury and while the ST segment is still elevated, abnormal Q waves begin to develop as a consequence of both the loss of electrical forces in the necrotic area and the effect of the resultant force directed away from the area. Pathologic Q waves can be recorded from all myocardial regions that depolarize early during the cardiac cycle. The posterobasal area depolarizes late, thereby producing positive QRS waveforms in the precordial leads opposing this zone (i.e., V_1 and V_2).

The Q waves of infarction correlate with percent scar tissue [87]. Although in most patients Q waves persist indefinitely, in 15% to 30% of cases they disappear or regress. Small, rapid r waves may also result from post reperfusion recovery of electrical activity. Other patients presenting with chest pain accompanied by biologic markers of cardiac necrosis develop repolarization changes followed by non pathologic, small q waves or r waves of diminished amplitude. Some of these non Q-wave infarctions result from injury of the left inferoposterior wall. In these cases, in leads V_1 to V_4 of the initial ECG, there is usually horizontal ST-segment depression, as opposed to the downsloping ST-segment depression of anterior infarcts.

For many patients with non Q-wave infarction, the underlying angiographic finding is a recanalized vessel [88]. The prognosis of non Q-wave infarction is markedly predicted by the admission ECG [89].

Electrocardiogram During and after Reperfusion Therapy

Approximately half of patients arriving to a medical center within 1 hour of chest pain present with abnormal Q waves. These Q waves predict a larger infarct size but do not offset the benefits of reperfusion therapy [90]. Thrombolytic therapy and primary percutaneous coronary intervention, when successful, accelerate the ECG evolutionary changes of acute infarction. The early appearance of T-wave inversion and rapid, complete resolution of ST-segment elevation (even in one single ECG lead) have been associated with patency of the infarct-related artery and with improved survival [91-93].

Conversely, incomplete resolution of either the ST-segment elevation or a concomitant ST-segment depression predicts increased mortality [94].

Clinical Value of the Electrocardiogram in Established Myocardial Infarction

Autopsy, echocardiographic, and angiographic studies have shown that the 12-lead ECG has a limited capability to diagnose established myocardial

infarction [95,96]. The accuracy of the ECG depends on both the infarct location and size, and it may be hampered by the presence of intraventricular conduction defects, LAFB, Q-wave regression, multiple infarctions (e.g., an anterior infarct may reduce tall R waves in V1 to V2 from a previous posterior infarct), and LVH.

Infarct Size

Several methods have been developed to estimate the area of damaged myocardium after an acute coronary event. It appears that, in terms of prognosis, the most accurate scoring system is the Cardiac Infarction Injury Score (CIIS) [97].

The Future

The clinical use of the ECG has withstood the passage of time. The ECG is often the initial test demonstrating cardiovascular abnormalities, a role now expanded with the use of ECG in prehospital diagnosis and telemedicine [98].

Current emphasis in ECG research is on the study of dynamic patterns inherent in certain parameters (especially ventricular repolarization) with the aid of ambulatory recordings and newer, potent digital storage and analysis techniques. Attempts at improving the resolution of standard electrocardiography have relied on an increase in the number of recording electrodes (body surface mapping) and on an improvement in the signal-to-noise ratio of the higher-frequency signals by averaging and filtering (signal-averaged ECG). These techniques are promising, but their roles in clinical practice are still unclear.

Pathogenesis of Arrhythmia after Acute Coronary Syndrome

The initiation and maintenance of life-threatening ventricular arrhythmias (ventricular tachycardia and ventricular fibrillation) in the setting of myocardial ischemia and infarction result from the complex interaction of multiple factors. These include damaged myocardium, arrhythmia triggers, reperfusion, and various modulating factors. The pathogenesis may be different, with scar formation being of primary importance, with ventricular arrhythmias occurring one week or more after myocardial infarction (MI). This card will review these mechanisms in detail, with particular attention to arrhythmias occurring in the first 48 hours.

Mechanisms of Arrhythmia Formation

Life-threatening periinfarction ventricular arrhythmias result from interplay among three basic components:

• The damaged myocardium, which produces a substrate capable of developing reentrant circuits. It has been observed that complex ventricular arrhythmias are associated with a larger infarction and with early left ventricular dilatation and remodeling, perhaps due to ventricular stretching and electromechanical feedback [99,100].

• Arrhythmia triggers, including spontaneous ventricular arrhythmias, variations in cycle length, and heart rate.

• Modulating factors, such as electrolyte imbalance, dysfunction of the autonomic nervous system, elevated levels of circulating catecholamines, continued ischemia, and impaired left ventricular function. These factors may act on both substrate and triggers to induce arrhythmias.

The proper milieu for the development and maintenance of ventricular arrhythmias is ultimately based upon the rapid and profound effects acute myocardial ischemia has on the electrophysiologic characteristics of the myocyte. Changes in the resting membrane potential and in the inward and outward ionic fluxes during the action potential lead to alterations in conduction, refractoriness, and automaticity of cardiac muscle cells, all of which contribute to the occurrence of ventricular arrhythmias [101].

An increase in QT dispersion on the electrocardiogram, which reflects differences in ventricular repolarization times between normal myocardium and myocardium within the periinfarction ischemic zone, may predict an increase in risk for ventricular fibrillation early in the course of a myocardial infarction [102]. Early coronary reperfusion after an acute myocardial infarction reduces QT dispersion which may reduce electrical instability [103].

Cardiac Denervation

Sympathetic efferent fibers en route to the left ventricle cross at the atrioventricular groove, travel within the superficial subepicardium in a base-to-apex direction and penetrate the myocardium to innervate the endocardium. A transmural myocardial infarction can damage the sympathetic fibers and result in functional denervation of the myocardium apical to the area of the infarction. Animal and human studies have shown that, after an infarction, regions of the ventricular myocardium below the infarcted zone have no uptake of iodine-123-metaiodobenzylguanidine (MIBG), a radiolabeled guanethidine analog that is actively taken up by sympathetic nerve terminals, even though this tissue remains viable, as indicated by persistent thallium uptake [104-106].

Moreover, this denervated tissue fails to exhibit afferent reflexes in response to bradykinin or nicotine and its refractoriness is not altered by stimulation of the vagus nerve or the stellate ganglion [107].

However, this zone does manifest denervation hypersensitivity and is supersensitive to infused norepinephrine or isoproterenol; it has a greater shortening in refractoriness compared to normal myocardial tissue. The resulting heterogeneity in refractoriness, induced by circulating catecholamines, is a potential mechanism for arrhythmogenicity after infarction. Reinnervation of the periinfarction area, but not the infarcted tissue, and the loss of supersensitivity occur within 12 months after the infarction [108].

Role of Thrombus and Ischemic Preconditioning

The incidence of life-threatening ventricular arrhythmias in the presence of intracoronary thrombus is greater than that associated with coronary artery ligation or balloon occlusion, despite a similar amount of ischemia [109,110].

In one animal study, for example, an increased incidence of ventricular fibrillation due to more conduction slowing during the first few minutes was noted with ischemia induced by intracoronary thrombus compared to coronary artery ligation [110].

The electrophysiologic effect of the thrombus lasted only a few minutes, suggesting an association between thrombin and the rapid release of ischemic metabolites, such as LPGs and lysophosphatidylcholines, and their accumulation in ventricular myocytes [111-113].

The Occurrence of Reperfusion Arrhythmias follows a Bell-Shaped Curve

As the duration of ischemia increases in experimental animals, so do reperfusion arrhythmias. The peak incidence occurs at 5 to 10 minutes after the onset of ischemia, presumably due to depletion of ATP stores become depleted [114,115].

These experimental observations may be applicable to humans. A recent pooled analysis of intracoronary thrombolytic trials suggested that life-threatening arrhythmias during reperfusion were more likely to occur when the interval between the onset of infarction and thrombolytic therapy was short (analogous to animal models) [116].

The rate of lysis may also be important. Serious arrhythmias are more common when thrombolytic agents are given directly into the coronary artery and lysis is rapid; they are less frequent when intravenous thrombolytic agents are used [116].

Thrombolytic therapy is usually given clinically more than two to four hours after the onset of coronary occlusion, when significant myocardial infarction is already present. It therefore seems likely, from the preceding observations, that ischemia rather than reperfusion is responsible for the majority of serious arrhythmias seen in patients with acute MI. This hypothesis is supported by trials of intravenous thrombolytic therapy that did not demonstrate any increase in life-threatening arrhythmias that could be attributed to reperfusion, although frequent ventricular premature beats and accelerated idioventricular rhythm do occur and may be a marker of reperfusion [117,118].

Reperfusion arrhythmias should be managed in an identical fashion to other types of arrhythmias, although data suggest that antiarrhythmic drugs are less effective in this setting. At present, there are no prophylactic therapeutic maneuvers that have been proven to reduce the incidence of these events, but there is interest in the possible efficacy of calcium channel blocking agents and free radical scavengers, such as superoxide dismutase and adenosine. As an example, dipyridamole, an inhibitor of cellular uptake of adenosine that may reduce intracellular calcium, was evaluated in one study of 61 patients undergoing primary angioplasty for an acute anterior wall myocardial infarction [119].

Pretreatment with dipyridamole prevented all episodes of accelerated idioventricular rhythm and ventricular tachycardia, which occurred in 18 and 8 percent, respectively, of patients not receiving pretreatment. In addition, dipyridamole terminated arrhythmia in all nine patients who developed a sustained ventricular tachyarrhythmia after reperfusion.

Correlation between ECG Waves & Events

Atrial fibrillation (AF) is a frequent complication of acute myocardial infarction (AMI), with reported incidence of 7% to 18%. The incidence of congestive heart failure, in-hospital mortality, and long-term mortality is higher in AMI patients with AF than in AMI patients without AF. P wave duration on signal-averaged ECG (PWD) and P wave dispersion on standard ECG (Pd) are noninvasive markers of intra-atrial conduction disturbances, which are believed to be the main electrophysiological cause of AF.

PWD and Pd both measured in a very early period of AMI are useful in predicting AF [120].

QRS prolongation with or without bundle branch block (BBB) has been associated with adverse outcome in myocardial infarction; we examined the relationship between QRS duration and outcome in a broad spectrum of patients with acute coronary syndrome (ACS).

In patients presenting with a broad spectrum of suspected ACS, QRS prolongation—particularly in the setting of LBBB—is an independent predictor of in-hospital and 1-year mortality [121].

For patients with chest pain and non-diagnostic initial ECG, ACS risk is high if QTD and QTcD values are greater than 40 Ms. Therefore, QTD and QTcD can help identify patients with acute coronary syndrome who present with chest pain and a nondiagnostic initial ECG. However, poor operator characteristics of QT dispersion could limit its value as a diagnostic test in the clinical setting [122].