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Electrocardiographic classification of acute coronary syndromes: a review by a committee of the International Society for Holter and Non-Invasive Electrocardiology ☆

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Abstract

The electrocardiogram (ECG) remains the most immediately accessible and widely used diagnostic tool for guiding emergency treatment strategies. The ECG recorded during acute myocardial ischemia is of diagnostic, therapeutic, and prognostic significance. In patients with myocardial ischemia as a result of decreased blood supply, the initial 12-lead ECG typically shows (1) predominant ST-segment elevation (STE) as part of STE acute coronary syndrome (STE-ACS), or (2) no predominant STE, that is, non–STE ACS (NSTE-ACS). Patients with predominant STE are classified as having either aborted myocardial infarction (MI) or ST-elevation MI (STEMI) based on the absence or presence of biomarkers of myocardial necrosis. The MI may be aborted either by spontaneous or therapeutic reperfusion of the ischemic myocardium before development of myocardial cell necrosis. NSTE-ACS patients are classified as having either unstable angina or NSTE-MI, based also on the absence or presence of biomarkers of mycardial necrosis.

The information obtained from the 12-lead ECG at presentation should be complemented by repeated ECGs especially during symptoms indicative of ischemia and, if applicable, by comparing the findings with reference ECGs. Also, continuous ECG recording in a coronary care setting, including the comparison of ECGs with and without pain, adds to the information gained at patient presentation.

In this article, mechanisms of ischemic ECG changes and the ECG patterns recorded in both STE-ACS and NSTE-ACS are described. ECG patterns of NSTE-ACS, which include ST depression, negative T wave, and even normal ECG, need to be better defined in future studies to correlate them with the severity and extent of ischemia and to explore to what extent they are explained by acute active ischemia or represent consequences of ischemia. One of the aims of this article is to propose a

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classification of the ECG patterns encountered in different clinical scenarios of ACS. How these patterns will aid in guiding the diagnostic and therapeutic process is discussed.

Keywords: Electrocardiogram; Acute coronary syndromes

Myocardial ischemia can occur during 2 pathophysiologic processes: decreased blood supply, in which a coronary artery has been acutely occluded by a thrombus or vasospasm, or increased myocardial demand, in which there has been acutely increased cardiac work by exercise or other stress in the presence of coronary artery disease (CAD). In the electrocardiogram (ECG), myocardial ischemia typically induces a shift of the ST segment. The ST-segment changes are produced by the flow of currents, referred to as "injury currents," that are generated by the voltage gradients across the boundary between the ischemic and nonischemic myocardium during the resting and plateau phases of the ventricular action potential, which correspond to the TQ and ST segments of the ECG. Current guidelines suggest that when these ST-segment shifts reach predetermined threshold values in 2 or more anatomically contiguous body surface ECG leads, a diagnosis of acute ischemia/infarction is indicated.[1] In patients with myocardial ischemia as a result of decreased blood supply, the initial 12-lead ECG typically shows the following:

1) Predominant ST-segment elevation (STE) as part of ST-elevation acute coronary syndrome (STE-ACS); these patients are classified as having either aborted myocardial infarction (MI) or ST-elevation MI (STEMI) based on the absence or presence of biomarkers of myocardial necrosis. The MI may be aborted either by spontaneous or therapeutic reperfusion of the ischemic myocardium before development of myocardial cell necrosis[2]

or

2) No predominant STE, that is, non–STE-ACS (NSTE-ACS); these patients are classified as having either unstable angina (UA) or non–ST-elevation MI (NSTEMI), based also on the absence or presence of biomarkers of myocardial necrosis.[3]

STE-ACS has the homogeneous etiology of transmural ischemia typically caused by fibrin-rich (red) thrombus occluding the infarct-related artery, except in cases of cardiac spasm.[4] NSTE-ACS has heterogeneous etiologies of predominantly subendocardial ischemia frequently caused by a platelet-rich (white) thrombus.[5,6] However, some ECG patterns of NSTE-ACS actually represent "STEMI equivalence" because of the anatomic relationship of the ischemic region to the standard ECG leads. These differences in ECG-based classification have important clinical implications.

During the last few decades, the incidence of STE-ACS has declined, and the incidence of NSTE-ACS has increased.[7] As a result of new diagnostic criteria based on sensitive markers of myocardial injury (troponins T and I), approximately 30% of patients were previously diagnosed with UA, which is now categorized as acute MI.[2,8,9] With the new criteria, striking similarity between the in-hospital and long-term prognoses of STEMI and NSTEMI patients has recently been shown.[10] These changes in patient outcome also reflect improvements in therapeutic strategies.[11]

Most patients presenting with a clinical syndrome compatible with STE-ACS progress into the evolving stages of STEMI, and a minority have aborted MI.[12] However, it should be pointed out that in some cases, STE is secondary to myocardial ischemia that is not thrombosis induced, such as that which occurs with vasospasm. There are also several possible nonischemic causes of STE (such as left ventricular hypertrophy [LVH], early repolarization, pericarditis, etc).

The ECG remains the most immediately accessible and widely used diagnostic tool for guiding treatment strategies. The ECG recorded during acute myocardial ischemia is of diagnostic, therapeutic, and prognostic significance.[13-15] Especially, in STEMI patients, the ECG from the acute phase contains important information about the site and size of the area at risk aiding in selection of appropriate therapy for the individual patient. Prehospital emergency care today can be regarded as an extension of the hospital into society. Therapeutic decisions about reperfusion strategy and treatment logistics, such as where to transport a patient with a suspicion of ACS, are increasingly important.[16] Because the ECG represents only a few seconds of recording, a better appreciation of the often dynamic ischemic process is possible from a series of ECG recordings or from continuous monitoring. The ECG from the acute phase should be compared with previous recordings, if available.[17] If possible, the ECG reading should be performed with the possibility of "zoom" amplification or magnifying glass to better detect small changes in the STE. Regional logistic systems with immediate access to digitally stored ECGs have been developed. From a technical perspective, reference ECGs could be made available anywhere and anytime at the very onset of an acute coronary event through internet-based telemedicine.[18]

In this document, we will first describe the mechanisms of ischemic ECG changes and then the ECG patterns recorded in both STE- and NSTE-ACS. In patients with STE-ACS, the ECG may show patterns other than STE. We want to point out that ECG patterns of NSTE-ACS, which include ST depression (STD), negative T wave, and even normal ECG, need to be better defined in future studies to correlate them with the severity and extent of ischemia and to explore to what extent they are explained by acute active ischemia or represent consequences of ischemia. Because one of the aims of this article is to propose a classification of the ECG patterns encountered in different clinical scenarios of ACS, we will comment on how these patterns will aid in guiding the diagnostic and therapeutic process. Correlation with the clinical picture and findings from echocardiography, scintigraphic studies, cardiac magnetic resonance imaging, and other available technology may be helpful to better understand some mechanisms of these ECG patterns.

Anatomic and physiologic bases of ischemic ECG changes

Several factors will affect the ECG pattern observed in an individual patient with ACS. The most important are

1) the cellular consequences induced by myocardial ischemia from total coronary artery occlusion versus subtotal occlusion with or without distal embolization;
2) the duration of the ischemic process;
3) its myocardial extent: transmural versus subendocardial;
4) its severity: presence of residual flow either by collaterals or by antegrade flow and ischemic or pharmacologic preconditioning;
5) its localization in relation to exploring ECG leads;
6) the presence of underlying abnormalities, such as intraventricular conduction disturbances, LVH, primary or secondary repolarization abnormalities, pacemaker implant, and others; and
7) individual variation in coronary anatomy.

Also, lead system used and properties of the volume conductor will affect the ECG changes. It is important to realize that the ECG pattern changes over time and may be different if it is recorded when the patient is symptomatic or after symptoms have resolved. An early normal ECG recorded when the patient is asymptomatic usually becomes abnormal during pain, and on the contrary, a very abnormal ECG, recorded during an asymptomatic period, may "pseudonormalize" during pain.

Temporal changes are most striking in cases of STEMI. The ECG pattern will be different if the ECG is recorded within minutes to hours from the onset of the ischemic process in comparison to several hours to days later. Because of this, patients with identical pathophysiologic processes may be classified into different operational clinical ACS categories. For example, if a patient has sudden thrombotic occlusion of the left anterior descending coronary artery (LAD), and the ECG is recorded during the occlusive phase, the ECG will show STE in the precordial leads and the patient is classified as having STE-ACS. However, if the coronary flow is spontaneously or therapeutically reestablished before the first ECG is recorded, a deep inverted T wave may be present in leads V1-V3/V4 and the patient may have an initial diagnosis of NSTE-ACS, although the ECG pattern represents an evolutionary phase of STE-ACS.

Eppinger and Rothberger[19] nearly a century ago provoked the appearance of acute injury potential (elevated ST segments) 15 seconds after the injection of silver nitrate deep into the ventricular wall. Since then, the exact mechanisms of ischemic ST-T changes are still under debate. For that reason and taking into consideration the many different factors that interplay in ACS, only some general aspects of mechanisms behind the repolarization ECG changes (ST-T wave) will be discussed. Detailed coverage of cellular physiology in myocardial ischemia is not within the scope of this article. Neither will changes in the P wave, the QRS complex, ECG changes related to ischemia of the conduction system, or special circumstances, such as the apical ballooning syndrome or acute ischemic consequences of congenital malformations, be discussed.[14,20-24]

In vectorcardiography, cardiac electrical activity is recorded as loops: the atrial depolarization (P), ventricular depolarization (QRS), and ventricular repolarization (T) loops. Although vectorcardiography is an excellent tool for training in electrocardiography, and the method has the potential to help in distinguishing acute myocardial ischemia from nonischemic states, its role in the modern era of invasive cardiology could be questioned. For deeper insight into this method, the reader is referred to textbooks and articles on vectorcardiography.[15,25]

ST-segment elevation (STE)

After acute epicardial coronary artery occlusion and after the appearance in the ECG of tall and peaked T waves, STE, representing transmural ischemia, appears if the artery remains occluded.[26] Depending on several factors, such as success of epicardial and myocardial reperfusion and duration of occlusion of the artery, the evolution of these ECG changes may take different pathways. In most cases, the STE resolves and the T waves become inverted, usually with the development of pathological Q waves depending on the resulting amount of necrosis. Even normalization of the ECG is possible after a short episode of vessel occlusion as is the case in aborted thrombotic MI or vasospastic (Prinzmetal) angina.[15,27]

ST-segment depression (STD)

When ischemia is confined primarily to the subendocardium, the overall ST vector typically faces the inner ventricular layer and the ventricular cavity such that the surface ECG leads show STD. This subendocardial ischemic pattern is a frequent finding during spontaneous episodes of angina at rest and represents the typical ECG finding during exercise tests, as energy demands are highest and blood supply most precarious in the inner layers of the myocardium. Typically, maximal STD in demand ischemia is recorded in the precordial leads V4-V6, often associated with STD in the extremity leads II, III and aVF, independently of disease severity or of the localization of stenoses within the coronary arteries. In cases of severe extensive subendocardial ischemia, as in acute subtotal or even total occlusion of the left main coronary artery, the injury vector may be seen as STD in the majority of the ECG leads but as STE in lead aVR. In these cases, extensive ischemia impairs relaxation of the left ventricle, resulting in increase of the left ventricular end-diastolic pressure.[28,29] Inducing global left ventricular ischemia in dogs by hydraulic constriction of the left main trunk resulted in a significant decrease in the endocardial-to-epicardial flow ratio and a significant increase of left ventricular end-diastolic pressure.[30] Also, inducing elevation of the left ventricular pressure by pacing in patients with significant CAD is associated with STD in the ECG.[31]

T wave changes

The genesis of the T wave on a cellular level has been a matter of debate through the entire 20th century.[32] Longer action potential duration in the endocardium than in the epicardium is required to generate the normal positive T wave predominant in most of the 12 standard ECG leads. The

clinical consideration of "T wave changes" has been complicated by use of inconsistent terminology. Recent American Heart Association standards have been established, which include "peaked" for increased positivity and "inverted" for negativity.[33] Transiently peaked T waves with lengthening of the QT interval are the first manifestations of acute myocardial ischemia in case of sudden complete occlusion of an epicardial coronary artery, including coronary spasm.[34-37] Inverted T waves in the early phases of STEMI have been associated with improved patient outcome related to an open infarct-related artery, restored myocardial blood flow, reappearance of the R wave, and better left ventricular function.[38-40] We define inverted T waves when the terminal portion of the T wave is below the isoelectric line.

T wave evolution in ischemic heart disease is not a marker of cell death but is instead caused by changes in the ion channels in regions of the heart that remain viable after an episode of severe ischemia.[28] In patients who develop inverted T waves, episodes of reischemia often manifest as a change in the T wave vector with positive T waves, with or without STE ("pseudonormalization"), in the ischemic region.[41-43]

Patients presenting with T wave changes represent a heterogeneous group, and the underlying mechanism may not be easily appreciated from the ECG at presentation in an individual patient. However, the evidence points to the fact that—just as in demand ischemia during an exercise test in stable CAD—new, isolated, inverted T waves never appear in acute ischemia in ACS.[44,45]

A number of clinical states, besides ischemic heart disease, ranging from entirely benign presentations such as hyperventilation to life-threatening conditions (such as increased intracranial pressure), may be associated with inverted T waves.[45]

ECG patterns in ACS at presentation and during the evolving stages: prognostic and clinical implications

The various ECG patterns in patients with a clinical diagnosis of ACS are described. They represent a wide spectrum of clinical situations with a variable prognosis. The controversy between the clinical classification and the pathophysiologic concept is discussed.

A. Transmural ischemia

1. ECG pattern: STE

1.1. Typical STE-ACS pattern

Acute total occlusion of an epicardial coronary artery or a major side branch is typically represented as STE in the frontal and/or transverse planes, associated with STD, which is often recognizable in some leads and usually of less magnitude than the STE (Fig. 1). However, in some cases of left circumflex (LCx) or right coronary artery (RCA) occlusion, the initial ECG may show STD due to the fact that the injury vector is directed to the posterior thorax (see Section STEMI equivalent: mirror-image pattern). In anterior MI, when the maximal STE is in leads V2 to V4, the culprit artery is almost exclusively the LAD. In case of STE-ACS with STE in the extremity leads II, III, and aVF, frequently associated with STD in V1 to V3, the culprit artery is the RCA or the LCx. The infarct-related artery and the location of occlusion may be determined by using specific algorithms.[13,47-49] Studies related to this topic differ considerably with respect to the number of patients, exclusion criteria, and also in temporal relationship between ECG recording and coronary angiography. There is also wide variation in reported sensitivity (12%-100%) and specificity (40%-100%) of the algorithms used by the different authors. Recording additional leads for more accurate diagnosis of right ventricular infarction (lead V4R) in patients with inferior STEMI and of posterior chest leads (V7-V9) in patients with STD in the right precordial leads V1-V3 has been recommended.[2,3,50,51]

Clinical implications: In patients with STE-ACS, the characteristics of the ST segments contain important information about the culprit artery and the site of occlusion with respect to side branches.

1.2. STEMI equivalent: mirror-image pattern

Perloff[52] in 1964 described the typical pattern of a "strictly posterior" MI involving STD in leads V1-V2 and prominent R wave in V1. Recently, it has been demonstrated by comparison with cardiac magnetic resonance images in the subacute MI phase that this area is actually lateral.[53] Precordial STD, typically in V1-V3/V4, is found in ~50% of patients with inferior acute MI fulfilling criteria for reperfusion therapy.[54] If the culprit lesion is distal to the first marginal branch in a nondominant LCx, or distal to the right ventricular branches of an RCA with predominant posterolateral distal branches, the area of transmural ischemia is confined to the midbasal inferolateral left ventricular segments. The resultant injury vector is directed toward leads placed on the posterior thorax (leads V7-V9), resulting in STE in these leads.[55] In most cases, there is STE, sometimes not fulfilling criteria for reperfusion therapy, in leads II, III, aVF, and/or V6 (Fig. 2). There are even cases without STE in any of the traditional 12 ECG leads.[56] Some NSTE-ACS patients with LAD disease may also have STD in leads V1-V3/V4 (see Section STD of regional subendocardial ischemia). The posterior chest leads V7 to V9 may help in differentiating these 2 clinical entities. Whether the ratio of amplitudes of the STD and of the T wave in the different ECG leads further aids in differentiating the 2 ECG patterns needs to be further explored.

Clinical implications: In patients with suspicion of ACS, STD in the right precordial leads V1-V3/V4 represents with high probability a "mirror pattern" of transmural injury in the midbasal inferolateral region of the left ventricle and is usually associated with a culprit lesion in the LCx or the RCA. According to the American College of Cardiology/American Heart Association guidelines for STEMI, patients with STD in the right precordial leads, especially when accompanied by STE in the posterior chest leads (V7-V9) or even small STE in the inferior leads or in lead V6, should receive acute reperfusion therapy even in the absence of significant STE in any of the traditional 12 ECG leads.[2]

2. ECG pattern: other than STE

2.1. Hyperacute phase: tall T waves

In acute coronary artery occlusion, hyperacute T waves usually persist for only a brief period and are typically

followed by STE. Sometimes, the tall T wave may be a more persistent ECG pattern expressing grade 1 of ischemia,[57-59] especially in patients with preexisting significant stenosis of the culprit artery and rich collateral circulation to the ischemic zone. In an individual patient, the exact cutoff point for a pathologically high T wave is difficult to define because the range of normal for T waves in different leads is wide. However, T waves in acute ischemia are characteristically symmetric. Follow-up ECGs or continuous recording is recommended to identify dynamic changes (transient patterns) (Fig. 3).

There are many clinical situations, other than ischemic heart disease, such as hyperkalaemia, early repolarization, and ventricular hypertrophy, which may present tall and peaked positive T waves. Also, persistent tall T waves may be the expression of a mirror pattern of chronic lateral myocardial ischemia.[15]

Clinical implications. In patients with transient peaking of the T waves in the precordial leads recorded during chest pain, the probability of CAD is very high. Because this state may progress to STEMI, the patients should have close surveillance with follow-up ECGs or continuous recording. Guideline-based antiplatelet and anticoagulant therapy and invasive evaluation are recommended. However, currently, this ECG pattern is not an indication for reperfusion therapy, unless STE appears.

2.2. Postacute phase: deeply inverted T waves in the precordial leads

In 1955, Pruitt et al[60] found an association between a distinct ECG pattern—inverted T waves of 5 mm or more in lead V3 (no or less T wave inversion in lead V5) without changes in the QRS complex or LVH—and clinical evidence of CAD. In the 1980s, it was shown that almost 20% of consecutive patients admitted because of an impending acute MI developed a similar ECG pattern, minimally elevated or isoelectric ST segments and inverted T waves in the precordial leads, without changes in the QRS complex, within 24 hours (the Wellens sign).[61] Of patients who did not have bypass surgery, 3 of 4 developed a usually extensive anterior MI within a few weeks of admission. In a later study, in which most patients underwent invasive treatment, the ECG finding was strongly associated with significant stenosis in the proximal portion of the LAD.[62] More than half of the patients had a critical narrowing of the artery, 1 in 5 with total occlusion and collateral flow to the LAD territory. During an attack of chest pain, the ST-T changes normalized (pseudo-normalization), and STE

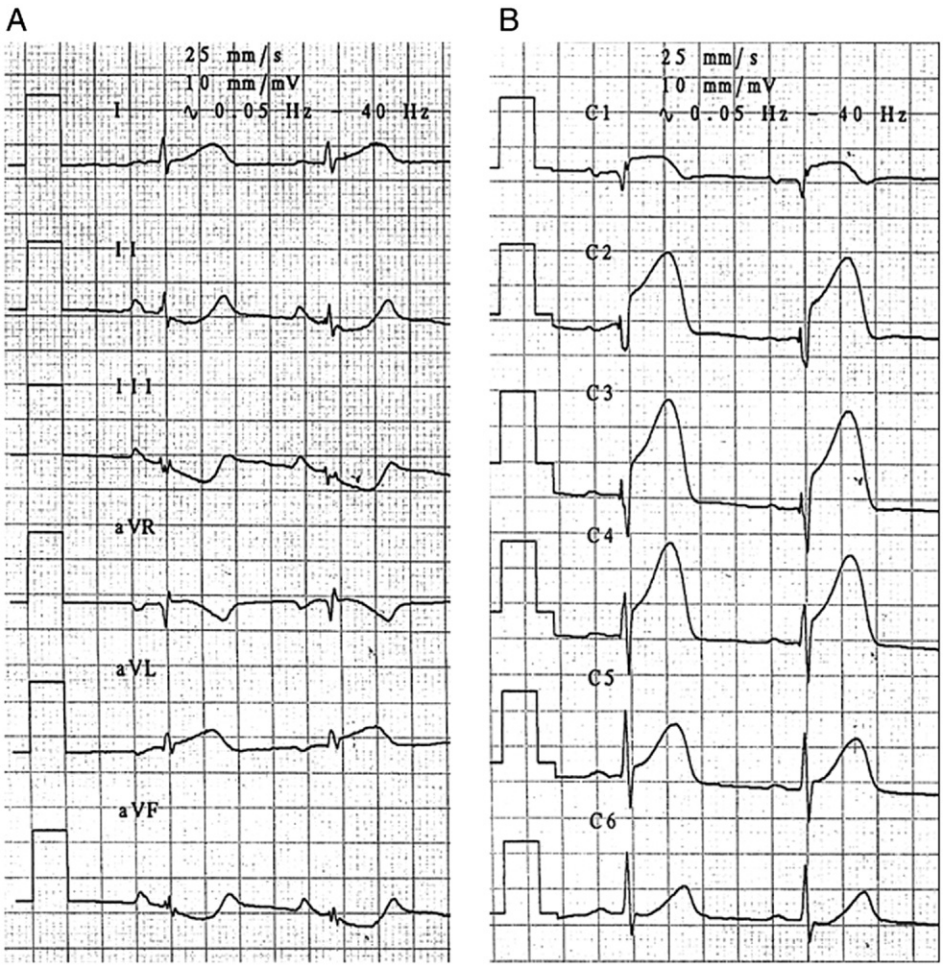

Fig. 1. Typical STE is present in all precordial (B) leads except C6 and also in the extremity (A) leads I and aVL. STD is present in the extremity leads II, III, and aVF. This ECG pattern has been associated with an occlusion of the proximal part of the LAD. STE without Q waves or inverted T waves represents the "window-of-opportunity" for reperfusion therapy before irreversible myocardial necrosis develops.[46]

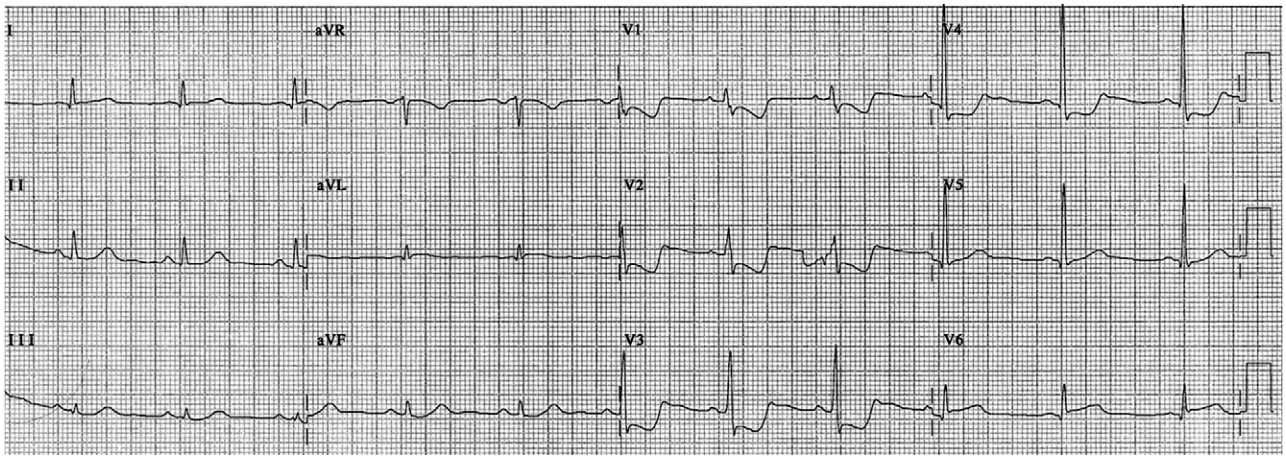

Fig. 2. 12-Lead ECG recorded during chest pain in a patient with acute occlusion of the LCx coronary artery. No significant lesions were present in the other coronary arteries. The ECG shows STD in leads V1 to V4 and only minor STE, not fulfilling (STEMI) criteria, in leads I, aVL, and V6.

even appeared. Long-term follow-up showed excellent prognosis after invasive treatment, and normalization of the ECG changes in most of the patients. Also, the ECG pattern has been linked to transient anterior wall motion abnormalities in patients with UA and significant LAD disease (Fig. 4).[63]

This ECG pattern, that is, inverted T waves in the precordial leads V1/V2-V3/V4 (leads with predominantly rS-configuration), is classified as NSTE-ACS. However, in most cases, it is not recorded during the symptomatic ischemic phase, but during the "postischemic" reperfusion phase—spontaneous or induced by reperfusion therapy—of

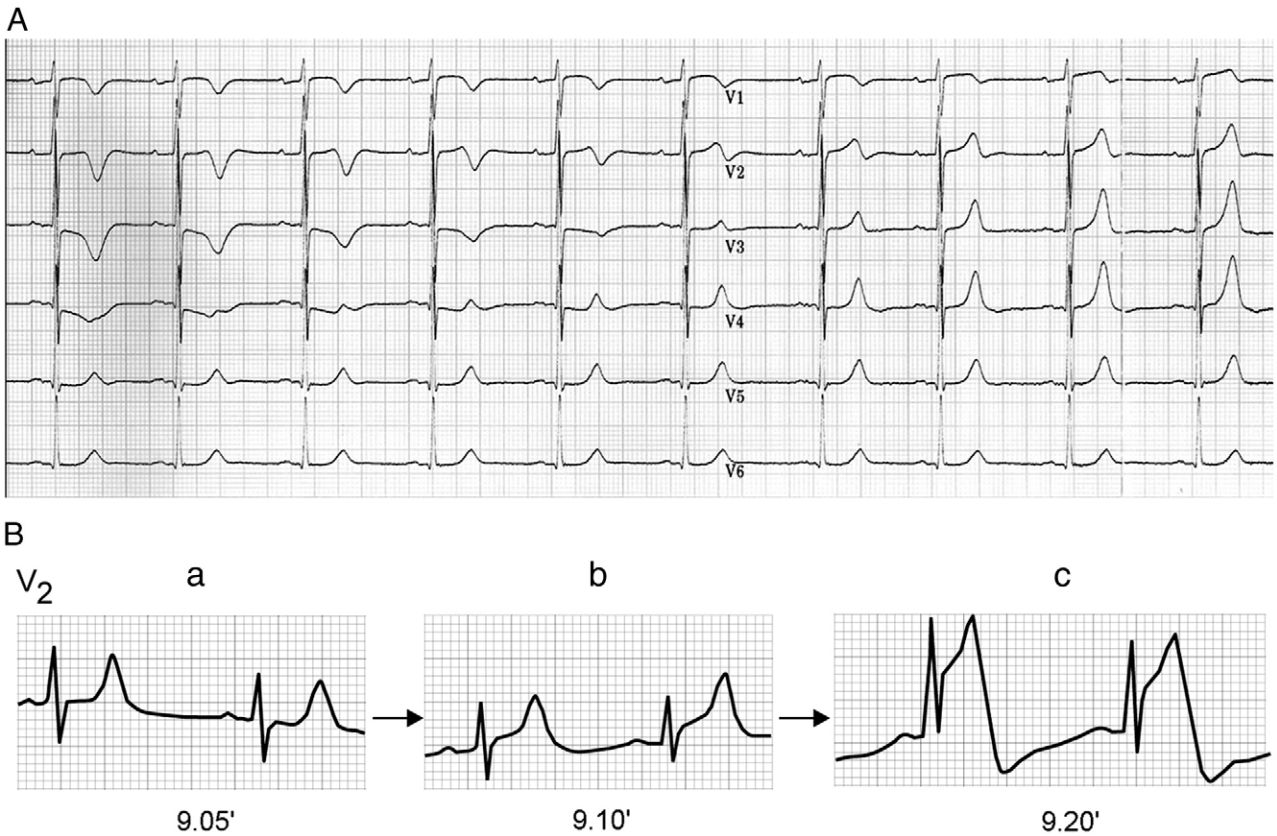

Fig. 3. A, During balloon occlusion, one can appreciate the dynamic nature of ischemic ECG changes (precordial leads V1-V6). At the start of balloon occlusion (first complex), in lead V3, a deep inverted T wave is present. In the last complex, during balloon occlusion, the T wave is peaked positive without STE (pseudo-normalization). This represents grade I of ischemia. After 1 minute of balloon occlusion, concomitant STE (transmural ischemia) was present (not shown). B, In another patient, during acute chest pain, a tall, peaked T wave with an iso-electric ST segment in lead V_2 represents the only ECG sign of ischemia (a). Five minutes later, STE appears (b), followed within ten minutes by R wave increase and S wave decrease (c), indicating severe ischemia.

an anterior STE-ACS. In case of spontaneous reperfusion, there is a potential for impending reocclusion, especially if not recognized and treated aggressively.

Clinical implications: Inverted T waves with isoelectric or minimally elevated ST segments in leads V1/V2-V3/V4 in combination with a clinical suspicion of ACS are indicative of a "post-ischemic state" of the anterior wall, most likely caused by a significant stenosis in the proximal portion of the LAD with an open infarct-related artery or a totally occluded artery with good collateral circulation. Prompt initiation of antithrombotic and anti-ischemic medication should be considered. After thrombolysis or percutaneous coronary intervention, this ECG pattern indicates successful reperfusion. Guidelines recommend urgent invasive evaluation in case of recurrent angina despite intense antianginal treatment. In case of dynamic, symptomatic, or silent T wave changes on follow-up, routine invasive evaluation within 72 hours is mandatory.[3]

B. Subendocardial ischemia

1. NSTE-ACS ECG patterns

The STD that is typical of NSTE-ACS can be caused by either circumferential or regional subendocardial ischemia.

1.1. STD of circumferential subendocardial ischemia

The 12-lead ECG is valuable in appreciating the extent of myocardial ischemia in NSTE-ACS. Widespread STD during anginal pain present in 6 or more leads, often with inverted T waves, has been associated with autopsy-proven subendocardial MI caused by left main-, left main equivalent-, or severe 3-vessel disease.[13,64,65] However, if the ECG is recorded when symptoms resolve, it may even be normal.[66] Sudden occlusion of the left main coronary artery may present as widespread STD and inverted T waves with STE only in lead aVR, or alternatively, as STE-ACS with severe hemodynamic compromise and high probability of cardiogenic shock and/or ventricular fibrillation (Fig. 5).[66-69]

The first reports in the literature of the ECG changes associated with severe subendocardial ischemia/infarction appeared in the 1940s, with confirmation in larger series in the 1950s.[64,70-73] Sclarovsky et al[65] confirmed the importance of the direction of the T wave from both anatomic and prognostic perspectives. Inverted T waves associated with STD in the precordial leads during chest pain were associated with high in-hospital mortality and severe CAD in coronary angiography. Peaked T waves correlated with a favorable outcome and less severe disease. The findings were confirmed in patients with elevated troponin levels and nontachycardia-induced, transient, ischemic STD during anginal pain.[44]

Prominent STD has been associated with an increased likelihood of 3-vessel and left main CAD.[74,75] High probability of death or MI when not receiving early coronary angiography in patients with 6 or more leads with inverted T waves and concomitant STD was shown. Also, in patients with NSTE-ACS, STD and inverted T waves in leads V4 to V6 proved to be an independent predictor of 1-year mortality, whereas STD with positive T waves in the same leads and STD and/or T wave inversion in other lead groups (I and aVL; II, III, aVF; V1-V3) were not independently associated with 1-year mortality.[76]

In consecutive patients with angiographically proven left main CAD, the most frequent ECG pattern observed during pain was STD, especially evident in V3 to V5 (maximal in lead V4) and STE in leads V1 and aVR.[66] Almost identical ECG changes were present in an exercise test performed in most patients, indicating similar pathophysiologic processes. The same investigators showed an association between an ECG pattern during active chest pain showing STD in leads I, II, and V4-V6 and STE in lead aVR, and severe CAD in angiography.[77] In multivariate analysis, STE 0.5 mm or more in lead aVR has been a stronger predictor than troponin for left main coronary artery or 3-vessel disease.[78] In patients presenting with a first NSTEMI, increasing STE in lead aVR predicted in-hospital morbidity, mortality, and risk of 3-vessel or left main disease.[79] STE in

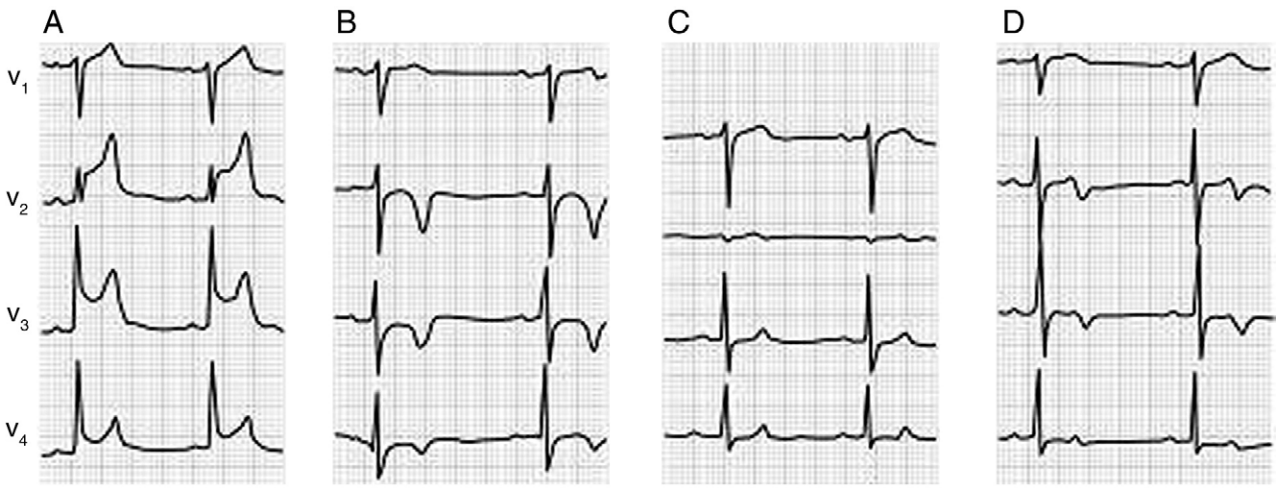

Fig. 4. Four consecutive ECGs (precordial leads) from a patient with acute occlusion of the LAD. Typical STE is seen in leads V1 to V4 during the occlusive phase (A). ST-resolution with inverted T waves represents myocardial reperfusion (B). Reocclusion manifests as pseudo-normalization of the T waves (C). Reappearance of negative T waves is evident when ischemia has subsided (D). (Please note technical error in C, lead V_2.)

aVR greater than in V1 was a predictor of left main disease in a series also including STE-ACS.[80] Also, in some patients with proximal LAD occlusion, the initial ECG may show this pattern.[81]

STE in aVR is occasionally accompanied by STE in lead III and widespread STD maximal in leads V4 to V6.[82] The potentially fatal scenario caused by acute occlusion of the RCA, supplying the anterior left ventricular wall through collateral circulation to a chronically occluded LAD, was first described in the 1940s.[83]

The ECG pattern of diffuse STD with inverted T waves in the lateral precordial leads and concomitant STE in lead aVR can be seen in various other clinical situations associated with an increased left ventricular end-diastolic pressure, such as rest angina with sinus tachycardia, chronic MI with restrictive remodeling, and in exercise tests, supporting the pathophysiologic basis for the ECG changes proposed in the present document (Section ST segment depression).[84,85]

Clinical implications: ACS patients with STD in 6 or more leads, maximal in leads V4 to V6, especially when associated with inverted T waves and STE in lead aVR, should have high priority for urgent invasive evaluation because of high probability of severe angiographic CAD. No randomized clinical studies have evaluated the possible role for thrombolytic therapy in these patients. However, considering the anatomic and physiologic bases for the ECG pattern and the well-documented ineffectiveness of thrombolytic therapy in NSTEMI, we strongly recommend not to subject patients to the bleeding hazards related to these compounds.

1.2. STD of regional subendocardial ischemia

Some ACS patients with 1-vessel disease but without total coronary artery occlusion present with angina at rest, typically caused by plaque rupture or erosion with flow restriction. In these patients, myocardial ischemia is restricted to the myocardial segment supplied by 1 coronary artery or its side branch (Fig. 6). In general, the ECG manifestations of regional subendocardial ischemia are less well defined than those of circumferential subendocardial ischemia or of transmural ischemia. Characteristically, the number of leads with STD is usually less than 6. In the 1970s, it was shown that angiographically documented subtotal occlusion of the LAD produced STD in leads V2 to V4, whereas during temporary total vessel occlusion, STE in the same leads was present.[86,87] Later, it was shown that STD with positive T waves in the precordial leads was associated with single-vessel disease.[65] The authors noted increase in the amplitude of the T wave and more downward displacement of the ST segment as long as the ischemic event endured. A likely cause of the increased T wave

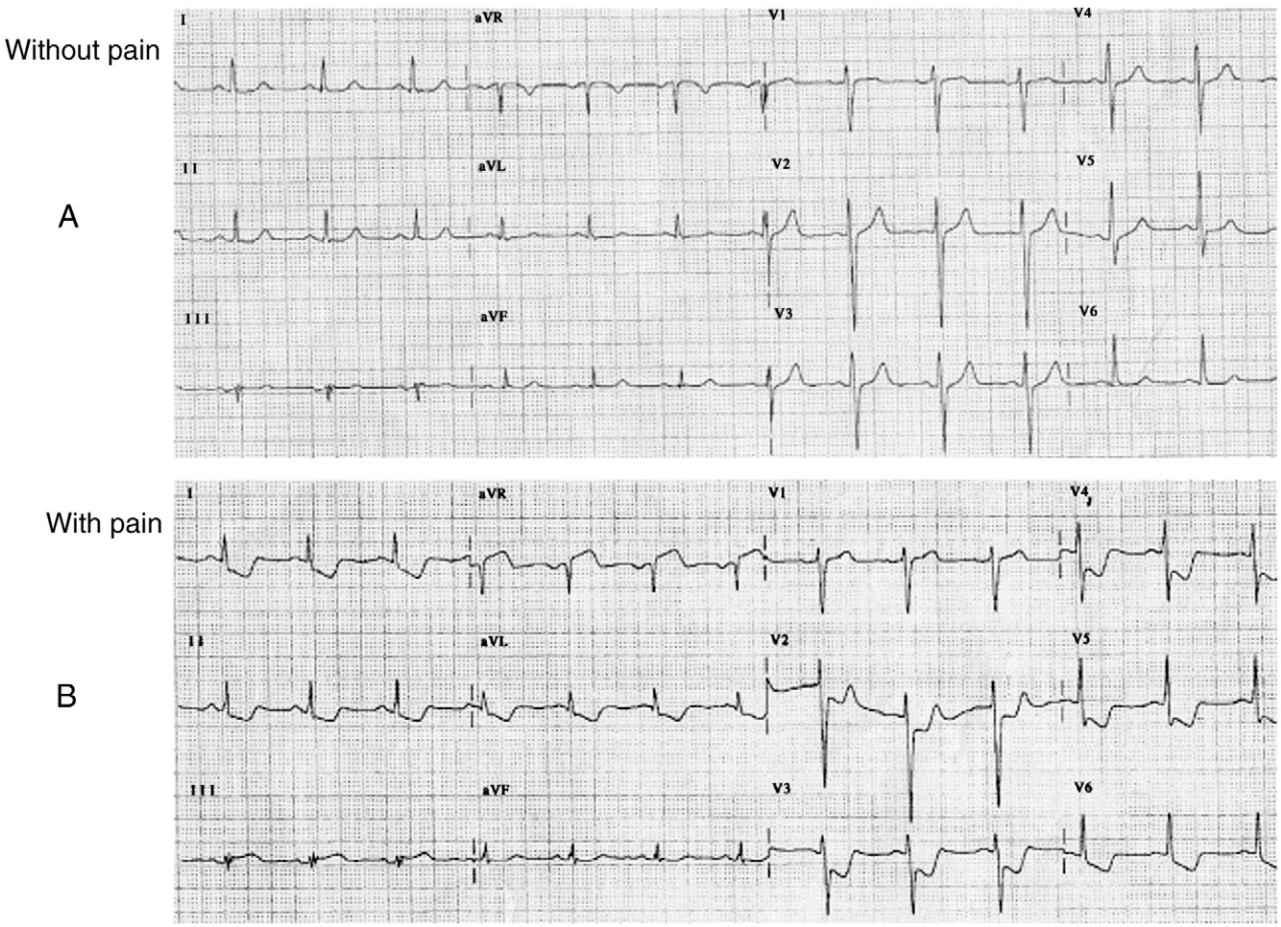

Fig. 5. In a patient with left main CAD, the ECG is normal when the patient is asymptomatic (A). During chest pain, the ECG pattern of circumferential subendocardial ischemia—widespread STD with inverted T waves and concomitant STE in lead aVR—is present (B).

amplitude is K+ ATP–dependent hyperpolarization of the myocytes.[28] The presence of STD with positive T wave in the same precordial leads has been described as regional subendocardial ischemia due to LAD occlusion.[13] Apart from the association with LAD disease, the ECG pattern has been connected to a total occlusion of the first diagonal, the first obtuse marginal, or the intermediate side branch. A similar ECG pattern, STD with positive T waves may be present in regional transmural ischemia caused by total occlusion of the LCx or the RCA (mirror-image of STE and a negative T wave of reperfusion; Fig. 2; see Section STEMI equivalent: mirror image pattern).[88]

Clinical implications: Patients with STD and positive T waves in the precordial leads represent a subgroup with high probability of 1-vessel disease, usually significant LAD stenosis or side branch occlusion, treatable with percutaneous coronary intervention (PCI).

Patients with NSTE-ACS may present with flattened or mildly inverted T waves and/or negative U waves as the only abnormality (Fig. 7). During anginal pain, the appearance of inverted T waves is almost exclusively associated with the presence of STD. However, the STD may be rather mild, and the inverted T wave may be more evident, and hence, these patients may be classified as having only T wave changes. However, isolated inverted T waves often represent postischemic reperfusion changes. The determination of the culprit vessel in case of NSTE-ACS presenting with slightly inverted T waves is not as straightforward as in case of total vessel occlusion with transmural ischemia. If the T wave inversion is present in leads V1/V2-V3/V4, significant stenosis of the proximal LAD is probable (the Wellens sign; see Section Postacute phase: deeply inverted T waves in the precordial leads and Fig. 4). The relationship between inverted T waves and coronary angiography or multislice computed tomography findings in other than LAD disease needs to be further explored.

The prognosis of patients presenting with inverted T waves without STD is similar to or only slightly worse than the prognosis of patients with a normal ECG.[89,90] Transient U wave inversion or increase in U wave amplitude may be due to myocardial ischemia, and in case of location to the precordial leads, there is high probability for LAD disease.[91,92] Transient U wave inversion is, however, seldom seen as an isolated abnormality in spontaneous ischemia.

Inverted T waves are not specific for ACS. Differential diagnostic alternatives, such as hyperventilation, pulmonary embolism, stroke, electrolyte disturbances, and others should be considered.

Clinical implications: Isolated T wave inversion influences patient prognosis only when it appears in the precordial leads as the Wellens sign.

C. Normal ECG

In large randomized trials of NSTE-ACS, the proportion of patients with normal ECG has been in the range of 15% to 20%.[93,94] However, it should be pointed out that it is exceptional to have a normal ECG recorded during pain of cardiac ischemic origin, except in case of so-called pseudonormalization.[66,95] One reason for the absence of ECG changes in case of ACS is the cancellation of vectors from anatomically opposite ischemic areas, resulting in masking of extensive ischemia. Even if ACS is confirmed, the prognosis is better in cases with normal ECG compared with patients with ST changes.[89]

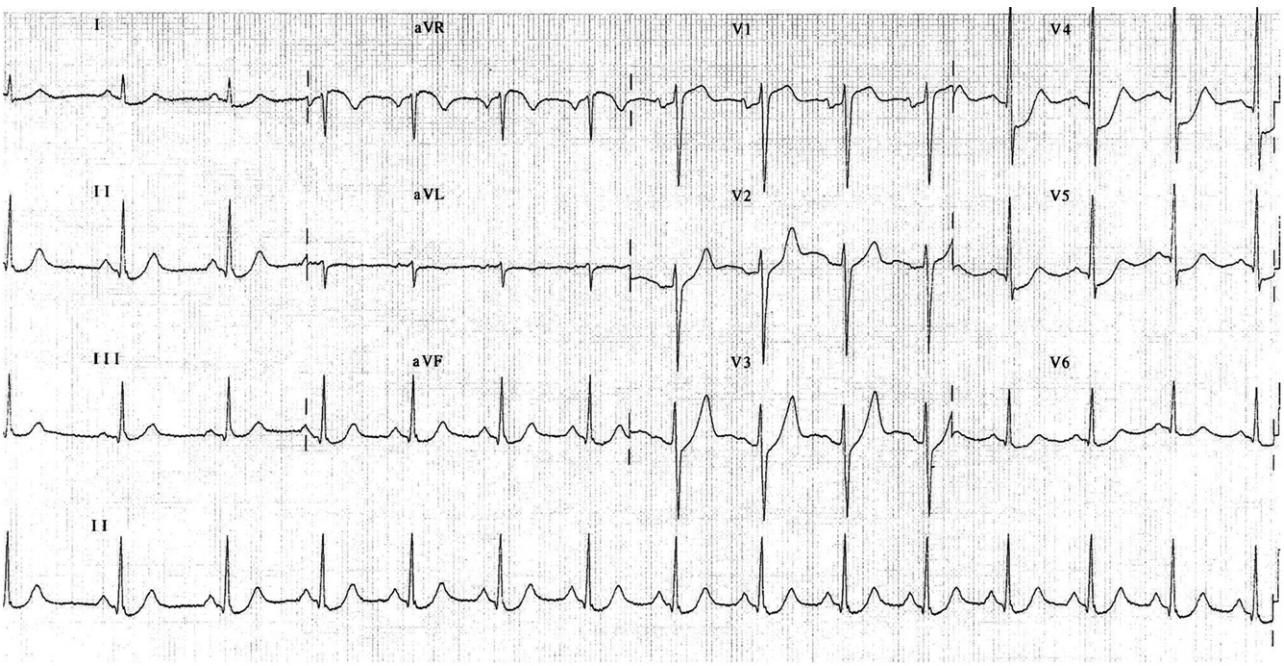

Fig. 6. The ECG was recorded during an episode of chest pain in a patient with single-vessel CAD. On angiography, there was a 95% stenosis of the midpart of the LCx coronary artery. The ST segment is depressed in leads I, II, aVF, and V3-V6. These leads with STD show positive T waves. The ST segment is elevated in leads aVR and V1. A second ECG recorded when the patient was pain free showed no significant ST changes.

D. ECG patterns in the presence of confounding factors

Up to 25% of patients presenting with NSTE-ACS will have changes confounding ECG interpretation, such as bundle branch block, LVH, the Wolff-Parkinson-White pattern, or paced rhythm. Confounding factors affect the ECG interpretation to a variable degree. More detailed description of this topic is not part of this document.

Unresolved issues

It is evident that in STE-ACS, with some limitations, the 12-lead ECG gives valuable information about the degree and extension of ischemia and also about the location of the occluded artery. The same is not the case for NSTE-ACS. The ECG pattern of circumferential subendocardial ischemia is rather straightforward, although large prospective studies are needed to find ECG characteristics, such as the direction of the T wave, that could differentiate the most urgent cases with left main disease from the somewhat less severe cases with 3-vessel disease.

The ECG pattern of regional subendocardial ischemia should be explored in closer detail in prospective studies. In cases of STD in V1-V3/V4 with positive T waves, subtotal occlusion of the LAD has been reported. However, when the STD is present in the lateral and/or inferior leads, the culprit artery is not easily determined (Fig. 6).

The pattern of symmetrical, inverted T waves in leads V1/V2-V3/V4 (the Wellens sign) is well known from the literature, but the mechanism behind flat or inverted T waves of low amplitude in leads with a prominent R wave is less well defined. The following observations indicate that isolated inverted T waves do not represent active, ongoing myocardial ischemia:

a) Inverted T waves appear in the resolution phase of STEMI.
b) Inverted T waves appear after reperfusion in STEMI
c) Inverted T waves *without* STD almost never appear in a positive exercise test or in NSTE-ACS during anginal symptoms.
d) NSTE-ACS with inverted T waves has better prognosis than NSTE-ACS with STD.

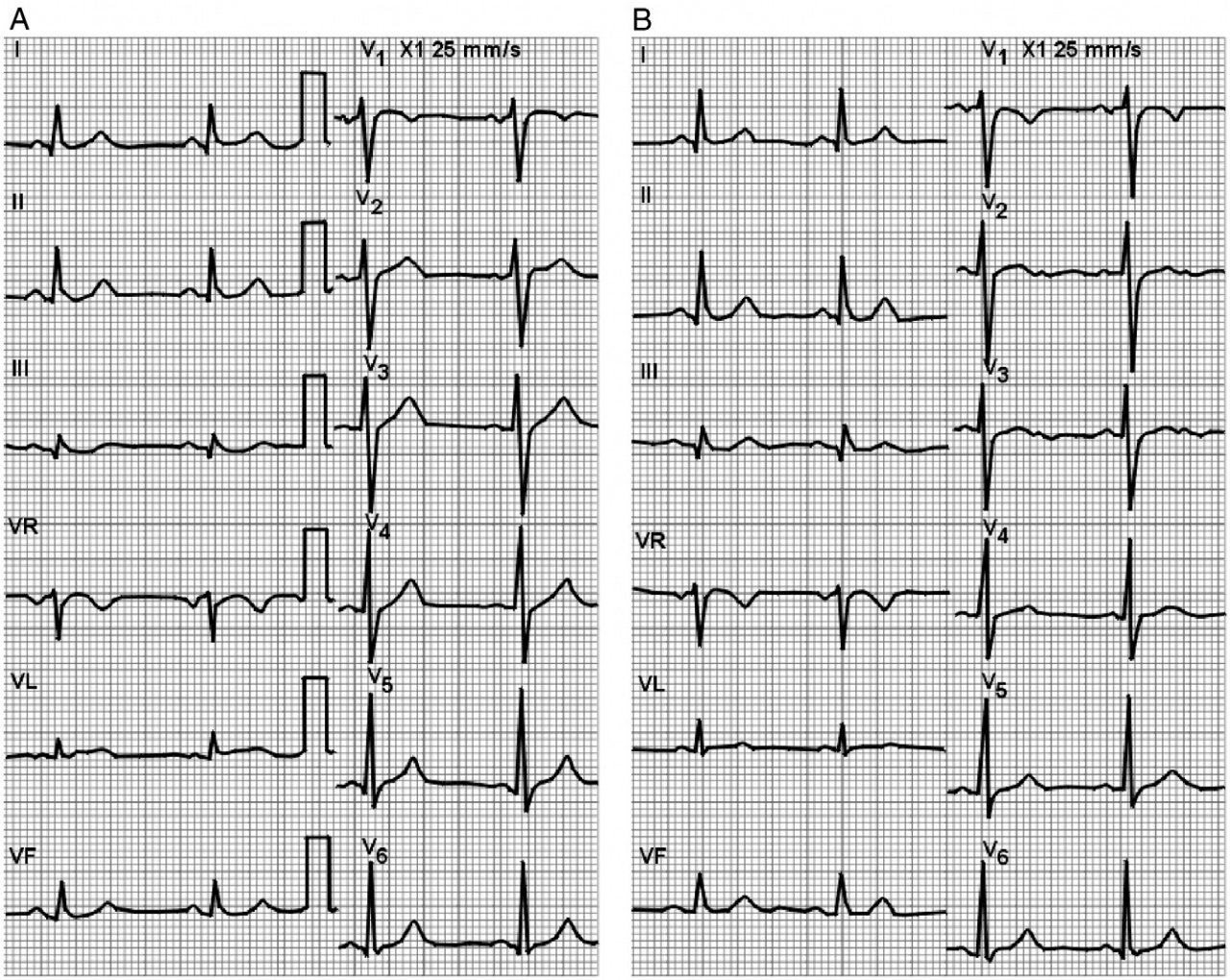

Fig. 7. A patient with atypical chest pain presented very discrete changes in the V2 and V3 leads: slightly negative U waves with slightly positive T waves (B). However, the changes are significant when compared with the previous ECG (A). The exercise stress test showed ischemic STD, and the coronary angiography showed a proximal LAD stenosis treated with PCI.

However, in patients with ACS, prospective trials are needed to determine if all these aspects can be confirmed. Also, the significance of different ECG patterns in subpopulations, such as after bypass surgery and with preexisting ECG changes, such as ventricular hypertrophy, need better confirmation. The clinical significance of different evolving patterns of inverted T waves also needs to be explored. T-wave normalization within a few days post-STEMI may carry different prognostic information compared with T wave inversion persisting for a long time.

Concluding remarks

The 12-lead ECG is a well-documented and clinically important tool for the evaluation of patients presenting with suspected ACS. Despite limitations, like the presence of chronic changes, the ECG adds considerable information for risk stratification and clinical decision support for treatment strategies.

The information obtained from the 12-lead ECG at presentation should be complemented by repeated ECGs especially during symptoms indicative of ischemia, and if possible, by comparing the findings with reference ECGs. Also, continuous ECG recording in a coronary care setting, including the comparison of ECGs with and without pain, adds to the information gained at patient presentation.

Use of tele-ECG consultations from emergency health care professionals to experts in ECG interpretation should be encouraged. ECG-based diagnostic algorithms help in speeding the decision process in the prehospital setting and in busy emergency departments.

The role for techniques enabling extended recording sites, such as body surface mapping, in the acute setting to improve ischemia detection, needs to be proven.

The understanding of pathophysiologic mechanisms of different ECG manifestations of myocardial ischemia will improve during the next few years, thanks to correlation with new technology, such as cardiac magnetic resonance imaging and multislice computed tomography, and also to new information from basic research.

Finally, the authors of this document strongly recommend performing well-designed studies to evaluate the significance of distinct ECG patterns in different patient groups with ACS.

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