The Role of ECG in the Diagnosis and Risk Stratification of Acute Coronary Syndromes: An Old but Indispensable Tool

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Abstract

Since its inception in 1902 by Willem Einthoven, the electrocardiogram (ECG) has fundamentally undergone minimal technological advances. Nevertheless, its clinical utility is critical, and it remains an essential tool to diagnose, risk stratify and guide reperfusion and invasive strategies in patients with suspected acute coronary syndromes.

ECG reading can be demanding, with many healthcare professionals lacking the necessary expertise to accurately interpret them. This is exacerbated by the need to constantly revisit old dogmas pertinent to the interpretation of ECGs. Notably, ECG leads record the global electrical activity of the heart towards and away from each electrode rather than local events. The long-held central paradigm that the various ECG leads record local events underneath specific electrodes should therefore be reassessed. For example, ST segment elevation in leads V1 and V2 usually denote antero-apical rather than septal infarction, often a misnomer utilized by the majority of clinicians.

The ECG diagnosis of ST-elevation myocardial infarction (STEMI) is sometimes challenging, and discerning it from non-ST-elevation myocardial infarction (NSTEMI) is of paramount importance to implement timely acute reperfusion therapy. In fact, when qualifications for emergency reperfusion therapy are based on STEMI ECG criteria, nearly one third of cases with acute coronary occlusion are missed. Diagnostic ST elevation in the absence of left ventricular (LV) hypertrophy or left bundle-branch block (LBBB) is defined by a specific set of sex-specific criteria for new ST elevation at the J point in contiguous precordial or limb leads. However, other ECG criteria need to be kept in mind. These include, but are not limited to: new or presumably new left bundle branch block (LBBB), which is often considered as an STEMI-equivalent; ST depression in two or more precordial leads (V1–V4), denoting a true inferolateral transmural myocardial infarction; and the infrequent presentation with hyperacute T-wave changes.

Introduction

The electrocardiogram (ECG), first described by Einthoven more than 100 years ago, has fundamentally undergone *no* major technological changes since its inception in 1902 [1]. This fact itself is striking; there are few, if any, technologies utilized today – in medicine or other fields - that can point to such a history of no improvement. One can put it the other way around and state that the initial technical specification of the ECG were so good that it did not require further development and certainly deserved its Nobel prize in 1924. This inevitably leads us to the question: Is there still a place for such an old technology? More specifically: how is the role of this longstanding modality in modern diagnosis of myocardial infarction?

It is commonly believed that patients with acute thrombotic occlusion of an epicardial coronary artery should undergo emergent reperfusion therapy by either primary percutaneous coronary intervention (pPCI) or thrombolytic therapy. It is accepted that in patients presenting with symptoms compatible with acute coronary syndromes (ACS), ST elevation (STE) above certain thresholds (as defined by the Fourth Universal Definition of Myocardial Infarction document [2]) indicates acute thrombotic occlusion of an epicardial artery and is a class I indication for emergent reperfusion therapy by the current guidelines [3, 4]. Therefore, the ECG retained its central role in the initial evaluation and triage of patients with symptoms compatible with ACS [3, 4]. However, it was reported that up to one third of patients with acute thrombotic occlusion of an epicardial coronary artery do not have STE meeting the thresholds set by the Fourth Universal Definition of Myocardial Infarction, and some do not have STE at all [5, 6]. While we have evidence for the efficacy of reperfusion therapy to reduce mortality in patients presenting with STE in general [7], we have no evidence from randomized controlled trials to support emergent reperfusion therapy for patients with an occluded epicardial coronary artery without STE. Moreover, subgroup analyses from large thrombolytic trials found that thrombolytic therapy reduced mortality in patients with anterior and lateral STE; however, the effect has not reached statistical significance in patients with inferior STE [7, 8]. As subsequent trials comparing pPCI with thrombolytic therapy did not report on inferior STE separately and reperfusion therapy is considered a standard of care for all patients with compatible symptoms and STE [3, 4], this issue could not be solved any more. On the other hand, in a large percentage of patients presenting with STEMI, emergent angiography revealed residual coronary flow (TIMI flow grade 2-3) before pPCI. For example, 47% of the 1,667 patients included in the ASSENT-4 PCI trial had TIMI flow 2-3 before pPCI [9]. Among 1,791 patients with STEMI referred for pPCI, only 1,321 (74%) had preprocedural TIMI flow grade of 0-1 [10]. Thus, not all STEMI patients have complete occlusion of a coronary artery. It is unclear whether STE can occur with incomplete coronary artery occlusion, if a patient had spontaneous partial reperfusion with distal embolization before angiography that causes continuous ischemia, or if recanalization was achieved by the first injection of the dye.

Moreover, chest discomfort, STE and elevated cardiac biomarkers of necrosis should not be automatically classified as STE myocardial infarction (STEMI), as many patients have non-ischemic etiology of STE (Table 1) [11, 12]. In some of these patients, anti-platelet therapy, anticoagulation or reperfusion therapy are not beneficial and could even be harmful. However, it is also important to note that patients with baseline nonischemic STE could have STEMI (for example, patients with baseline STE secondary to left ventricular hypertrophy or early repolarization).

The entity of (spontaneously) reperfused STEMI with residual STE has not been fully addressed by the guidelines. Patients with spontaneous reperfusion at presentation (improvement in symptoms and partial resolution of STE compared to a previous ECG) have a relatively good prognosis without pPCI [13, 14]. As these patients do not have ongoing active ischemia, coronary revascularization is usually indicated to prevent re-ischemia/ re-infarction, rather than for myocardial salvage [15]. This can be achieved urgently, as in high-risk non STEMI (NSTEMI), rather than by using the time frame of pPCI protocols for STEMI. The most recent European Society of Cardiology (ESC) STEMI guidelines from 2017 state: "Early angiography (within 24 h) is recommended if symptoms are completely relieved and STE is completely normalized spontaneously or after nitroglycerin administration (provided there is no recurrence of symptoms or ST-segment elevation)" [3]. Yet, those with resolution of symptoms but with residual STE (despite having clear decrease in the magnitude of STE compared to the original ECG) should be treated according to this indication: "Reperfusion therapy is indicated in all patients with symptoms of ischemia of <12 h duration and persistent STE" [3, 4]. This statement does not emphasize "ongoing" symptoms and therefore includes patients in whom symptoms resolved but who continued to have STE. At least, thrombolytic therapy should not be administered to patients with spontaneous reperfusion despite having residual STE, as the current recommendation states: "If timely pPCI cannot be performed after STEMI diagnosis, fibrinolytic therapy is recommended within 12 h of symptom onset in patients without contraindications" [3, 4].

In the majority of patients with typical presentation, typical ECG changes of STE before reperfusion therapy and typical ECG evolution along with typical rise and fall in cardiac troponins, the diagnosis is straightforward. However, in a considerable percentage of patients, especially those with atypical presentation, the diagnosis of STEMI cannot be absolutely confirmed, even after adjudication at discharge, if the initial angiography does not show acute thrombotic occlusion of an epicardial artery. For example, we are not always certain that segmental regional wall motion abnormalities or scar detected by cardiac magnetic resonance imaging (cMRI) are new. A patient with pre-existing coronary narrowing can have Takotsubo cardiomyopathy with ECG evolution and regional wall motion abnormalities. The only clue can be a relatively low increase in cardiac troponin compared to the ECG changes and regional wall motion abnormalities.

The subtypes of STEMI — correlations with imaging and coronary angiography

The traditional subclassification of the types of STEMI were developed before coronary angiography and imaging modalities such as echocardiogram, nuclear studies and cMRI became available. The original assumption was that the various ECG leads record local events underneath the specific electrodes. For example, as leads V1-V2 are placed up on the thorax, they should record events occurring in the basal part of the interventricular septum. Therefore, Q waves (and subsequently STE) limited to V1-V2 are called "septal" infarct and in some textbooks and web sites depicts to correlate with infarction of the basal interventricular septum. However, it seems that the original paradigm was inaccurate, and these leads mainly record the global electrical activity of the heart towards and away from each electrode, rather than local events. What was called "septal" should now be called anteroapical infarct (see below).

a. STEMI due to Left anterior descending (LAD) coronary artery occlusion

The LAD travels along the anterior interventricular groove and supplies the interventricular septum (septal branches) and the anterior and anterolateral segments of the free wall of the left ventricle. In some patients, the LAD is short and does not supply the apex (in up to 22% of patients), while in others

the LAD wraps around the apex and continue into the posterior interventricular groove supplying variable parts of the inferior and inferolateral segments. Infarction secondary to LAD occlusion almost always involves the distal septal, anterior and anterolateral segments, unless the apical segments are supplied by collaterals (pre-existing tight LAD stenosis) or bypass grafts.

LAD occlusion causes STE in the precordial leads, mainly V2-V4 (with STE in V2 more than in V1) (Figure 1)[16]. Proximal right coronary artery (RCA) occlusion can also cause STE in the precordial leads due to right ventricular involvement. However, in such cases STE in V1 can be equal or greater than in V3. However, this was found only in 35% of the patients with RCA infarction [17] (Figure 2).

Involvement of large proximal diagonal branches in patients with proximal LAD occlusion induces ischemia of the basal anterior segment and STE can be seen in leads I and especially aVL (Figure 1)[18, 19] with reciprocal ST depression (STD) in the inferior leads [20]. On the other hand, STD in aVL in anterior STEMI predicts LAD occlusion distal to the first diagonal branch [21]. cMRI showed that in patients with anterior STEMI, STE in aVL is associated with ischemia of the basal anterior segment [22].

Occlusion of the first diagonal branch itself typically causes STE in leads I, aVL and V2 and reciprocal STD in the inferior leads, but usually without STE in V3-V4. These leads occasionally show upsloping STD with tall T waves [23, 24].

Occlusion of the LAD proximal to the first septal branch can cause STE in lead aVR, new right bundle branch block (RBBB), STD in V5, and STE in V1 $\geq$ 2.5 mm [21, 25]. Yet, Birnbaum Y et al. reported no association between STE in V1 and LAD occlusion proximal to the first septal branch [16]. Moreover, cMRI confirmed that the basal segments are rarely involved in patients with STE limited to V1-V4. Those infarcts affect the mid and distal anterior and anteroseptal segments [26].

Isolated STE in V4-V6 without STE in V1-V3 are usually caused by left circumflex (LCX) coronary artery occlusion or occlusion of distal diagonal branches [16]. It is commonly believed that STE in V1-V6 is associated with more distal anterolateral and apical involvement and a larger area at risk than STE limited to V1-V4. However, using echocardiographic evaluation, no differences in the distribution or extent of regional wall motion abnormalities were found in patients with anterior STEMI with or without concomitant STE in V5-V6 [27]. Compared with patients with STE in V1-V6, those with anterior STEMI with STE limited to V1-V3 more often have uninvolved significant coronary branches supplying the apex or a proximal occlusion of a short LAD [28]. However, they can also have proximal occlusion of a long LAD, suggesting that the ischemic vector of the basal segment cancels out the ischemic vector of the apex [28]. cMRI on the other hand, suggested a larger ischemic area at risk among patients with STE in V1-V6 compared to V1-V4, with more distal lateral segment involvement; however, there were no differences in the involvement of the other segments [26].

Concomitant STE in the inferior leads in patients with anterior STEMI usually signifies distal occlusion of a wrapping LAD with ischemia of the apical inferior segments or occlusion of an LAD that supplies collaterals to the inferior segments in patients with pre-existing right coronary artery occlusion [16, 29]. Despite having STE in multiple leads, these infarctions are relatively small and are confined to the apical segments. However, in patients with an occlusion of a wrapping LAD before the first diagonal branch, the vector causing STE in I and aVL and the vector causing STE in the inferior leads can cancel each other and no ST deviation can be seen in the limb leads [30]. Thus anterior STEMI without ST deviation in the

limb leads can be caused by distal occlusion of a short LAD (relatively small infarction) or by proximal occlusion of a wrapping LAD (a relatively large infarction) [30, 29].

b. STEMI due to total left main (LM) occlusion.

Most patients with acute myocardial infarctions secondary to LM thrombus present with sub-occlusion of the LM trunk. However, rarely patients present with total occlusion of the LM. The ECG changes resemble the STEMI pattern of proximal LAD occlusion: STE in the precordial leads + I and aVL and STD in the inferior leads [31]. RBBB with left anterior hemiblock is frequently seen. As the LCX is involved (inducing STD in aVR and V1-V4), the ischemic vector of the anterior segments tends to be attenuated, and in contrast to STEMI due to proximal LAD occlusion, there can be no or lesser degree of STE in V1 [32, 31].

c. Inferior STEMI

Inferior STEMI can be caused by either right coronary artery (RCA) or LCX occlusion. STE is seen in leads III, aVF and II and reciprocal STD in lead aVL and occasionally in I [33]. If no reciprocal STD is seen in aVL, there is high likelihood that the STE in the inferior leads is not due to STEMI (except in cases of proximal LCX occlusion, see below).

The RCA travels along the right atrioventricular groove, supplying branches to the right ventricular free wall and the right atrium. If dominant, the RCA supplies the posterior descending artery (PDA) and usually also left ventricular branches. Right ventricular involvement (in patients with proximal RCA occlusion) causes STE in the right precordial leads (V3R and V4R) that can extend to the precordial leads V1-V4. As the LCX does not supply the right ventricle, LCX infarctions do not induce STE in the right precordial leads. STD is often seen in leads V1-V4 in STEMIs caused by either LCX or mid- or distal- RCA occlusion [34]. While traditionally thought to be a sign of involvement of a vertically oriented basal inferior or basal inferolateral segments (so called “posterior” infarction), a recent ECG-cMRI correlation study has demonstrated that STD in V1-V3 in patients with inferior STEMI is caused by an extension of the ischemic area at risk into the inferoseptal segments, irrespective of being proximal or distal. STD in V1-V3 was correlated with greater projection of the ischemic area at risk on the frontal plane, leading to pure reciprocal changes (Figure 3)[35].

The LCX traverses along the left atrioventricular groove, supplying a variable number of obtuse marginal and distal branches to the inferior and inferolateral segments of the left ventricle. If dominant, the LCX continues as the PDA in the posterior interventricular groove. Some authors suggested that STE in V4-V6 is more common in patients with LCX STEMI than in RCA STEMI [16]; however, others have not confirmed this observation.

Acute occlusion of a proximal obtuse marginal branch manifests as STE in I and aVL with reciprocal STD in the inferior leads and with STD in V2 [23]. In cases with LCX occlusion distal to the first obtuse marginal branch, the magnitude of the reciprocal STD in aVL is attenuated [36]. However, STEMIs secondary to distal LCX occlusion that involve mainly the PDA should cause an ECG pattern that is similar to that of distal RCA occlusion, without an ability to distinguish between the two [36, 16].

Theoretically, occlusion of a dominant LCX proximal to the first obtuse marginal branch can result in cancellation of the ischemic vectors in the limb leads, as the ischemia induced by the obtuse marginal branch involvement (STE in I and aVL) and the inferior leads (STE in the inferior leads) are directed in

opposite directions. Thus, a relatively large ischemic area at risk can result in only minimal ST deviation in the limb leads with only STD in V1-V4 and/or STE in V5-V6.

An ECG-cMRI correlation study suggested that in patients with inferior STEMI, STE in V4-V6 indicates a larger ischemic area at risk with more apical, distal lateral and mid-inferolateral involvement, but less basal inferior involvement that in those with isoelectric ST in these leads [37]. This can be seen in patients with LCX infarction, but also in patients with RCA infarction who have a large posterolateral branch supplying the distal lateral segments [38]. On the other hand, STD in V4-V6 is associated with concomitant LAD disease or three vessel disease [16, 34].

NSTE Acute Coronary Syndrome (NSTE-ACS)

The STEMI/NSTEMI paradigm is based on the assumption that STE in the ECG in the majority of patients with acute MI is associated with acute total occlusion of the infarct-related artery, while subtotal occlusion manifests as STD with or without T-wave inversion (TWI). However, when qualification for emergency reperfusion therapy is based on STEMI ECG criteria, nearly one third of cases with acute coronary occlusion are missed [5]. The most frequent scenario is “mirror-image” STD in leads V1-V3 with no STE or only minor STE in the inferior leads or leads V5-V6. If the initial ECG is recorded after acute ischemia resolves, the ECG may show TWI without ST deviations. Another reason for missed acute coronary occlusion is STE not fulfilling the STEMI criteria (minor STE, one lead STE or STE in non-contiguous leads). Looking for reciprocal ST/T changes may aid in the diagnostic workup in these cases. To emphasize the importance of recognizing NSTE-ACS patterns that may indicate acute coronary occlusion, the concept of occlusive MI was recently introduced [5].

Subtypes of NSTE-ACS

a. Global ischemia

STD in many (≥ 7-8) leads, often with the maximal changes and associated TWI in leads V4-V5, has been associated with left main or severe 3-vessel disease and poor outcome [39, 40]. It may be difficult to identify the angiographic culprit lesion in these cases. However, if the left main coronary artery is involved, the artery is almost never totally occluded [41, 40]. According to the Supplementary Data of the recent European Guidelines for ACS without persistent STE, the presence of STD >1 mm in ≥6 leads in conjunction with STE in aVR and/or V1, particularly if the patient presents with hemodynamic compromise, suggests multivessel ischemia or severe left main coronary artery stenosis [42]. The guidelines do not specifically address possible therapeutic implications of STD in many leads (global ischemia do not specifically address possible therapeutic implications of STD in many leads (global ischemia). On the other hand, the ESC STEMI Guidelines propose a pPCI strategy if this ECG manifestation is associated with symptoms indicative of ongoing ischemia [3].

STD in many leads is not specific for left main or 3-vessel disease. A similar ECG pattern may exist as a more or less persistent ECG manifestation of left ventricular remodeling (“LVH”) for example in

hypertensive or valvular heart disease and cardiomyopathies [43]. Normalization of the STD when the ischemic symptoms subside is an indicator of ACS [44].

b. STEMI equivalent “mirror-image” pattern

In ACS patients with STD maximally seen in leads V1-V3 without significant STE, it is important to consider the possibility of a totally occluded culprit artery and need for immediate reperfusion therapy — the “mirror-image” STEMI pattern. In acute coronary artery occlusion, the reciprocal changes of STE with positive T waves is STD with negative T waves. Therefore, in the acute stage of ACS with STD in leads V1-V3, the T waves are usually negative [15]. Associated minor STE (not fulfilling the criteria for reperfusion therapy) in the inferior leads and/or leads V5-V6 strongly indicate acute total occlusion.

c. Hyper-acute T waves

The “hyper-acute” T wave can be the first ECG manifestation of acute coronary artery occlusion. In a small proportion of patients, this tall, symmetrical, positive T wave persists even for many hours without the development of STE despite a totally occluded epicardial coronary artery [45]. The ECG pattern was associated with low in-hospital mortality but with subsequent development of Q-wave infarction and a decline of left ventricular function in patients with poor collateral circulation [45, 46]. There are no established criteria to aid in the differential diagnosis from non-ischemic conditions. New minor STE, reciprocal STD and TWI may aid in the diagnosis. The Guidelines recommend follow-up ECGs or ST monitoring in cases with possible hyper-acute T waves, and if associated with clinical suspicion of ongoing myocardial ischemia (despite adequate anti-ischemic treatment), an immediate invasive strategy is recommended [42]. The statement seems to be supported by cMRI, where the findings in patients with persistent hyper-acute T waves resemble those of typical anterior myocardial infarction with nearly transmural necrosis in the large myocardial area supplied by the LAD [47].

d. STD with hyperacute T waves - the “de Winter sign”

The characteristic pattern of upsloping STD with tall and broad T wave — the “de Winter sign” — was found in 2% of patients who underwent pPCI for a proximal left anterior descending coronary artery occlusion [48]. The ECG pattern signifies culprit artery occlusion, and in one small series, one-week mortality was 27% [49]. The ST-segment may occasionally manifest as non-upsloping instead of upsloping while the majority present with poor R-wave progression in affected leads [50]. Based on the scientific evidence available, we consider this ECG pattern as a “STEMI equivalent”, and despite the lack of prospective trials, an emergent reperfusion strategy should be considered in these patients.

e. Terminal T-wave inversion - the “Wellens’ syndrome”

In patients with symptoms indicating acute coronary syndrome and deep TWIs in the precordial leads, especially in the leads V2-V4 — the “Wellens sign” — there is high probability for an acute coronary syndrome with left anterior descending coronary artery disease [51, 52]. According to the most recent European NSTE-ACS guidelines, the evidence regarding the prognostic impact of isolated TWI is conflicting [42]. In the diagnostic algorithm and recommendation for triage of NSTE-ACS patients, TWI is not even included. However, the “Wellens’ sign” should be considered as a post-ischemic “fingerprint” of acute myocardial ischemia with a risk for total occlusion of the culprit artery [53]. Pseudonormalization of the T waves implies re-occlusion, and may be followed by STE. Anti-thrombotic therapy is indicated, while the timing of invasive evaluation is dependent on the overall risk of the patient.

Conclusions:

The ECG has a major role in the diagnosis, risk stratification and triaging of patients with suspected ACS. However, interpretation of the ECG should be integrated with the clinical evaluation of the patient. In the majority of patients, the diagnosis of STEMI is straightforward; however, in many cases, especially in those with atypical presentation, prior history of MI, cardiomyopathy or conduction disorders, diagnosis can be uncertain even after coronary angiography. The clinician evaluating patients with suspected ACS should be familiar with the differential diagnosis of STE and NSTE-ACS patterns indicating acute total coronary artery occlusion. The ECG records the electrical activation of the heart towards and away from each electrode rather than local events. Thus, the traditional nomenclature is inaccurate. The number of leads with STE and the sum of STE only roughly correlate with the size and distribution of the ischemic area at risk due to the effect of vector cancelation.

Table 1: Common causes of non-ischemic STE

STE secondary to LVH.
STE secondary to conduction abnormalities (left bundle branch block, nonspecific intraventricular conduction abnormalities, accelerated idioventricular rhythm, electronic ventricular pacing).
Brugada pattern
Wolf Parkinson White pattern
Early repolarization pattern (with or without notched J-points) [54].
Old myocardial infarction/ aneurysm
Spontaneously reperfused myocardial infarction
Pericardial inflammation (pericarditis, myocarditis, esophageal rupture [55])
Acute cholecystitis/ pancreatitis [55]
Aortic dissection
Pulmonary emboli [56]
Takotsubo syndrome
Hypercalcemia [57]
Hyperkalemia [58]

Figure 1: Anterior STEMI due to proximal occlusion of a short LAD. There is STE in aVL, V2-V4 with mild reciprocal STD in the inferior leads.

Figure 2: ECG of a patient with STEMI due to proximal RCA occlusion. There are Q waves and ST elevation in II, aVF and III. There is also STE in V1-V6. There is reciprocal STD in I and aVL. The R waves in V1-V2 are taller than in V3, supporting inferolateral (posterior) infarct. STE in III is greater than in II, suggesting RCA infarction.

Figure 3: a. Inferolateral STEMI. There is STE in the inferior leads (STE in III > II, indicating RCA infarct), reciprocal STD in I and aVL. There is ST depression in V1-V3 and STE in V4-V6. **b.** In inferior STEMI, STD in V1-V4 is a reciprocal change and correlates with the vertical projection of the inferior-inferolateral ischemic vector.

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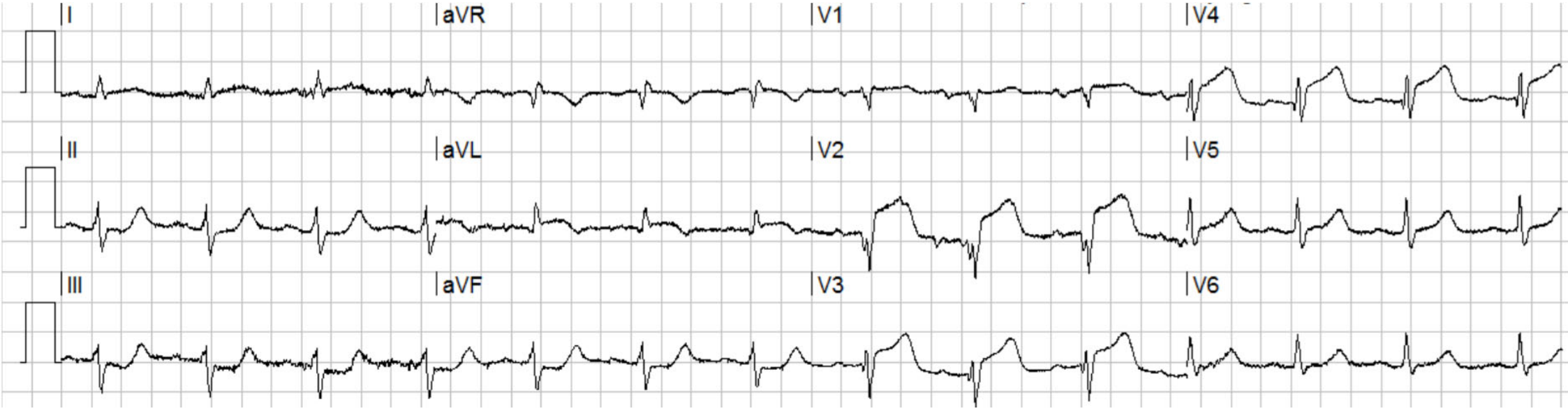
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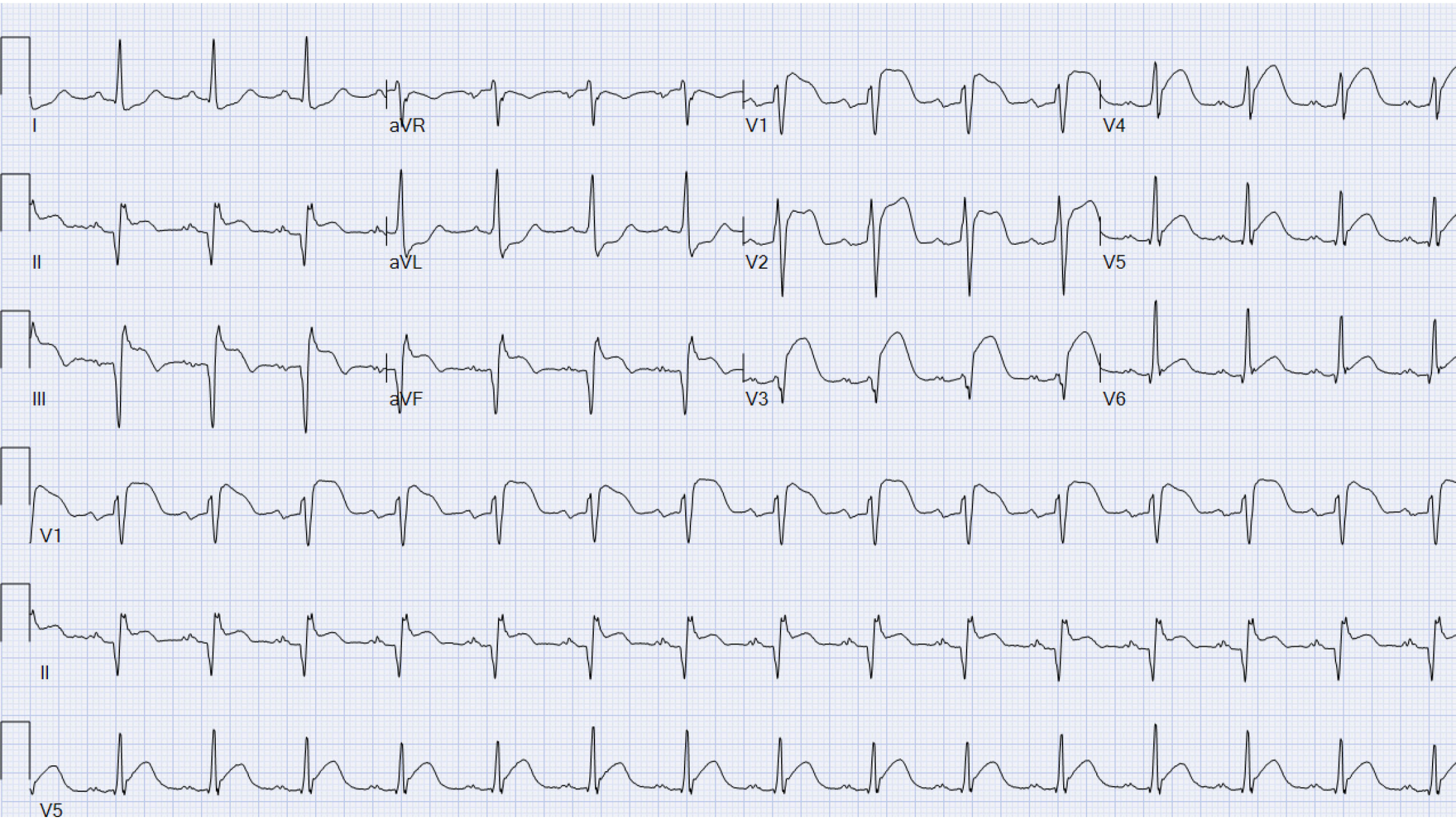
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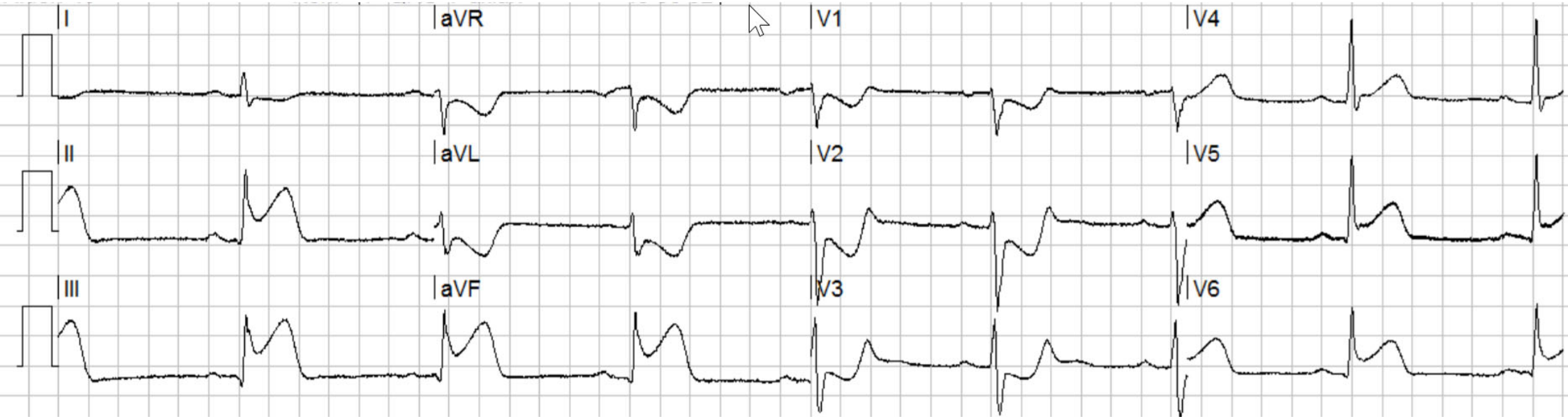
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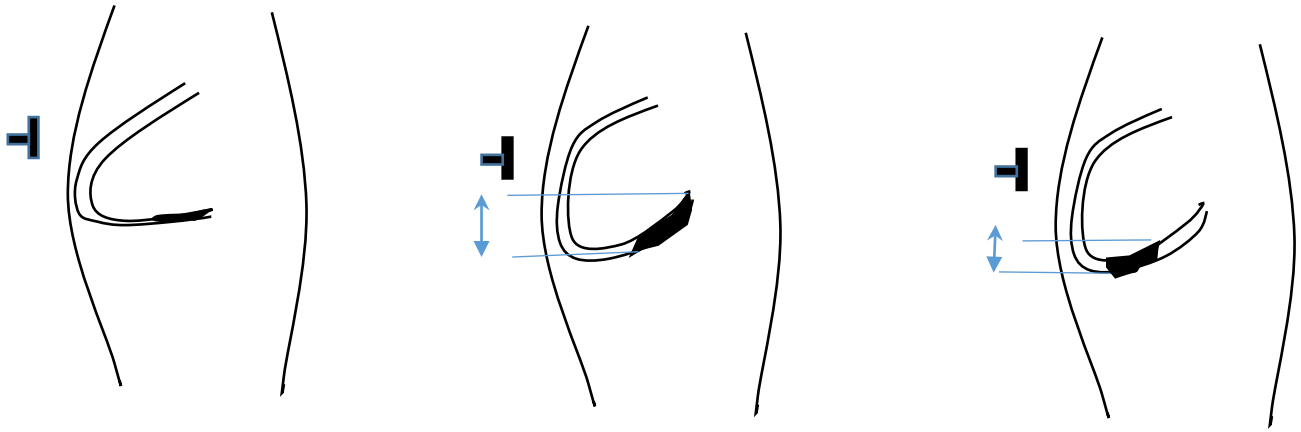

No vertical projection
No STD

Basal vertical projection causing STD in V1-V4

Distal vertical projection causing STD in V1-V4