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Review

Evolution of our understanding of the aVR sign

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ABSTRACT

In patients presenting with signs and symptoms of an acute coronary syndrome (ACS) the combination of multilead ST depression and ST elevation in lead aVR, the electrocardiographic "aVR sign," has been associated with severe left main coronary artery stenosis or diffuse coronary artery disease and a high risk of death. Recent guidelines even suggest that the aVR sign may represent an ST-elevation myocardial infarction (STEMI) equivalent and therefore, an indication for emergent cardiac catheterization and reperfusion. The specificity of the aVR sign for left main disease, however, has been questioned as multiple additional high-risk clinical conditions have also been shown to be associated with the aVR sign. The purpose of this review is to provide a historic background of the aVR sign and to summarize the evolution of our understanding of this important electrocardiographic (ECG) phenomenon. Using two illustrative cases, we wish to highlight the significant risks associated both with under-appreciation of the aVR sign as well as hastily overreacting to the aVR sign.

Definition of the aVR sign

The aVR sign requires a clinical presentation suggestive of ACS and the ECG finding of diffuse ST-segment depression with ST elevation in aVR. Using an aVR ST elevation of ≥1.0 mm rather than ≥0.5 mm increases the specificity of the aVR sign as a marker of left main or severe 3-vessel coronary artery disease. Many experts also require ST elevation in aVR to be higher than ST elevation in V1 [1], but the significance of such a requisite is questionable.

Brief history of the aVR sign

Not surprisingly, one of the first descriptions of the aVR sign was by the Wellens group in the Netherlands, the same group who also "gave us" the Wellens syndrome and the de Winter sign [2]. Later it was found that the combination of the aVR sign with elevated cardiac troponin levels provided an even more robust prediction of left main or 3-vessel disease than the aVR sign alone [3]. It has also been reported that in ACS, ST elevation in aVR and ST depression in specific combination of other leads could help identify the likely culprit vessel [4,5].

Significance of the aVR sign in acute coronary syndrome

In non-ST elevation ACS, the combination of diffuse ST depression with ST elevation in aVR carries the highest electrocardiographic risk [6]. In one study, the finding of lead aVR ST-segment elevation ≥V1 distinguished a group of patients with left main disease from patients with left anterior descending coronary artery disease with 81% sensitivity, 80% specificity, and 81% accuracy [1]. Death occurred more frequently in patients with higher ST elevations in aVR than in those with less severe elevations [1]. These findings were later confirmed in a larger study in which ST-segment elevation ≥1.0 mm in lead aVR identified severe left main or 3-vessel disease with 80% sensitivity, 93% specificity, 56% positive and 98% negative predictive value [7]. Based on these and similar data, some cardiology society guidelines have designated the aVR sign as a possible STEMI equivalent where consideration should be given to emergent cardiac catheterization and reperfusion [8]. Recently it has also become clear, however, that in addition to ACS, several other critical conditions can result in the aVR sign and missing those conditions may have devastating consequences [9,10]. It is always important, therefore, to evaluate the aVR sign within its clinical context.

Explanation of the aVR sign in global ischemia

It is not entirely clear why ischemia associated with severe stenosis of the left main coronary artery causes ST-segment elevation in aVR. According to one hypothesis, ischemia in the basal part of the intraventricular septum is the cause of ST elevation in aVR. A more simplistic

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explanation is that lead aVR, and to some extent lead V1, have unique positions by "looking" into the left ventricular cavity from the right shoulder, thereby reflecting ischemia of the inner layers of the entire left ventricular wall. According to this concept, ST elevation in aVR is merely a mirror image of severe diffuse ST-segment depression in other leads, a finding that has also been associated with left main or diffuse coronary artery disease [2,7].

Controversies and misconceptions

An important semantic issue is the variable use in the literature of the terms coronary occlusion, coronary obstruction and coronary stenosis [10]. The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) 2013 STEMI guidelines stated that "multilead ST depression with coexistent ST elevation in lead aVR has been described in patients with left main or proximal left anterior descending artery occlusion" [8]. In addition to being vague on how this finding should be acted upon, the term "coronary occlusion" could be interpreted as an indication of thrombotic obstruction warranting emergent intervention. Acute left main obstruction, however, is usually associated with sudden death or cardiogenic shock [11]. A recent study found that aVR ST-segment elevation almost never signified total occlusion of the left main or left anterior descending coronary arteries [12]. We recommend therefore that in the absence of frank STEMI, the term "coronary stenosis" rather than the more confusing "coronary occlusion" or "obstruction" be used.

The aVR sign can be present in conditions other than ACS

There are emerging data documenting that the aVR sign is not specific for ACS. ECGs demonstrating the aVR sign have been recorded in patients with a number of important clinical conditions including: severe left ventricular hypertrophy, acute hemorrhagic shock, massive pulmonary embolism, proximal aortic dissection (possibly reflecting involvement of the orifice of the left main coronary artery), myocarditis, following cardiac arrest and in paroxysmal supraventricular tachycardia, especially when the heart rate was excessive [9,10]. At our institution we have seen examples of all of these conditions causing the aVR sign. Interestingly, even under these non-ACS situations the aVR sign frequently signified critical illnesses associated with prolonged hospitalization, shock and high risk of in-hospital death [13,14].

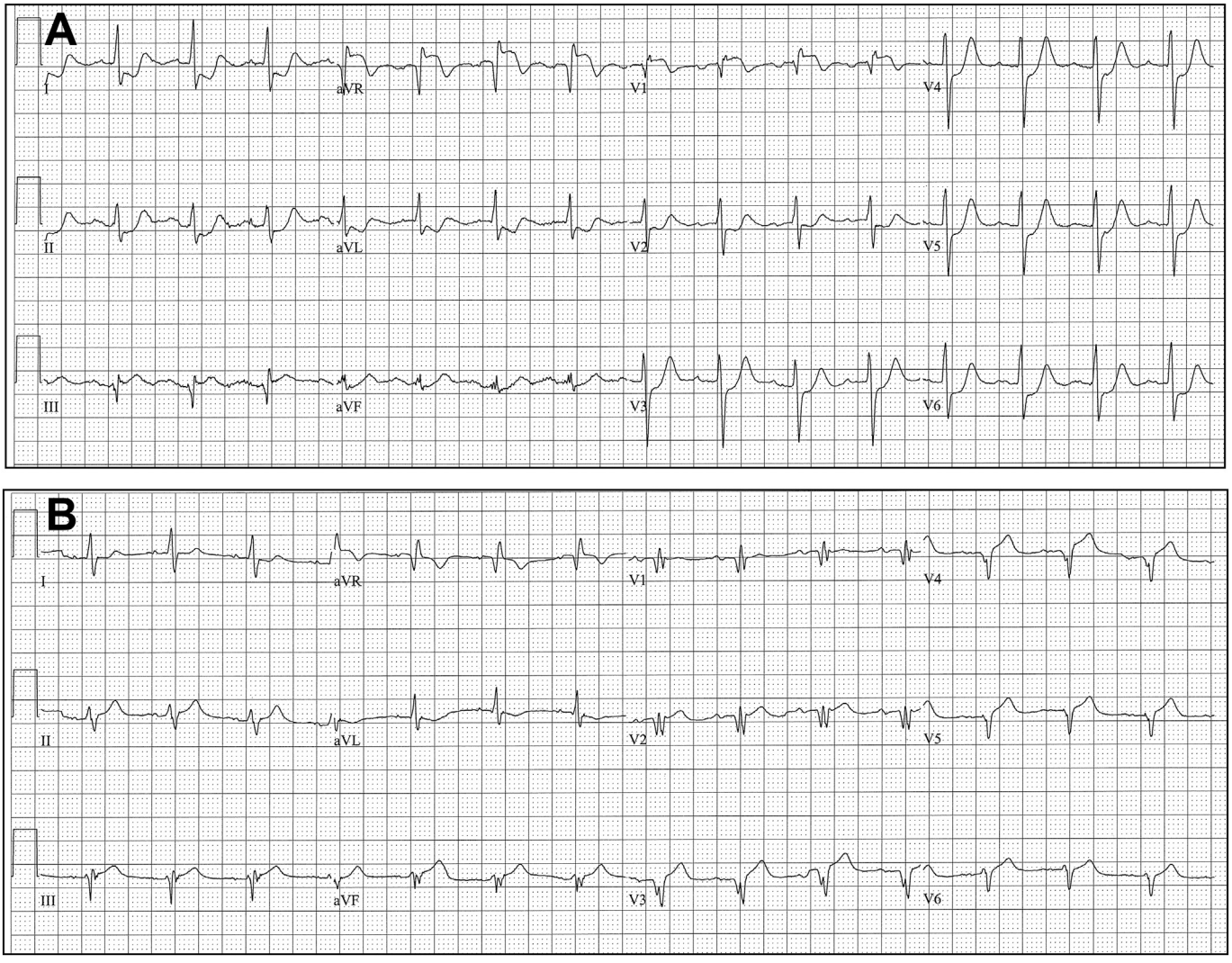

Fig. 1. Panel A. Electrocardiogram demonstrating sinus rhythm with horizontal and downsloping ST-segment depression in the anterolateral leads along with 3 mm ST-segment elevation in lead aVR and 2 mm ST elevation in V1, consistent with the aVR sign. Panel B. Electrocardiogram recorded 5 days after the first ECG demonstrates abnormal Q waves and ST-segment elevation in leads V1-V5. These findings are consistent with recent and extensive anterior infarct. See text.
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Representative case of under-appreciation of the aVR sign

A 64-year-old man was hospitalized for multilobar pneumonia and respiratory failure, intubated and sedated. When ST-segment changes were noted on telemetry, a 12-lead ECG was ordered. At the time the patient was hemodynamically stable, not on any vasopressors or inotropes. Cardiac troponin over the next 24 h peaked at 1.66 ng/mL (normal high, 0.07 ng/mL) and bedside echocardiogram revealed normal left ventricular systolic function, all strong suggestions against STEMI. The ECG (Fig. 1, panel A) showed marked horizontal and down-sloping ST depression in the anterolateral leads with 3 mm ST elevation in aVR and 2 mm ST elevation in V1, a typical aVR sign. The significance of these findings was not immediately recognized. Five days later the patient developed pulmonary edema and cardiogenic shock. The ECG at that time showed signs of extensive anterior myocardial infarction characterized by abnormal Q waves and ST-segment elevation in leads V1-V5 (Fig. 1, panel B). Repeat echocardiogram demonstrated a large area of anteroapical akinesis. Peak troponin was 102.5 ng/mL. Two days later, the patient expired from refractory cardiogenic shock.

Representative case of over-reaction to the aVR sign

A 69-year-old woman experienced sudden-onset midsternal chest and neck pain with associated nausea and diaphoresis. The initial heart rate was 70 bpm and systolic blood pressure 90 mmHg. The prehospital ECG, which was transmitted to our Emergency Department, demonstrated diffuse ST depression with ST elevation in aVR, all appropriately recognized by the interpretation software (Fig. 2, panel A, blue bracket). The physician agreed but also added the diagnosis of STEMI (red bracket), and activated the STEMI team. Upon arrival to the ED, the patient continued to have tearing chest pain concerning for possible aortic dissection. Chest X-ray demonstrated markedly widened mediastinum and CT angiogram confirmed a large proximal (type A) thoracic aortic dissection (Fig. 2, panels B and C). "Code STEMI" was cancelled and an esmolol infusion was immediately initiated. The patient underwent complex surgery which included ascending aortic replacement, hemiarch repair, graft to the right axillary artery, thoracic endovascular aortic repair and reconstruction of the left main coronary artery orifice. After a complicated hospital course, the patient was transferred to a rehabilitation facility. After debriefing, the general consensus by several providers was that emergent cardiac catheterization for presumed STEMI could have been disastrous.

How do acute care providers view the aVR sign?

There are no published data on how providers view and act upon a finding of the aVR sign. We recently gave a series of ECG quizzes to our emergency medicine residents. One of the cases was a patient with a 2-week history of recurrent chest pain where the ECG showed the aVR sign. The five treatment choices offered included both urgent and immediate cardiac catheterization. Twenty-eight of the 30 responders (93%) chose immediate cardiac catheterization. We viewed these responses, as well as the events surrounding our case 2, as demonstrating an astute recognition of the aVR sign by our residents and faculty, but also a widespread misinterpretation on how to act upon it. Of note, according to Doximity the reputation of our emergency medicine residency program ranks #5 of 220 programs in the United States and #1 in the South.

Summary and recommendations

- Diffuse ST depression with simultaneous ST elevation in lead aVR is the hallmark of the aVR sign. ST elevation can also be present in V1. The higher the ST elevation, the more severe the prognosis.
- Regardless of its etiology, the electrocardiographic aVR sign usually reflects a high-risk condition that warrants urgent evaluation and management.
- If the clinical presentation is suggestive of acute coronary syndrome, the aVR sign can indicate severe left main or multivessel coronary artery stenosis but not acute thrombotic obstruction. Thus, the aVR sign is not a STEMI equivalent.
- If alternative causes have been ruled out, urgent, but not necessarily immediate, cardiac catheterization and reperfusion is warranted. In the absence of contraindication, consideration should be given to the use of intravenous beta-blocker.
- Anchor bias toward STEMI in the setting of aVR sign can be disastrous

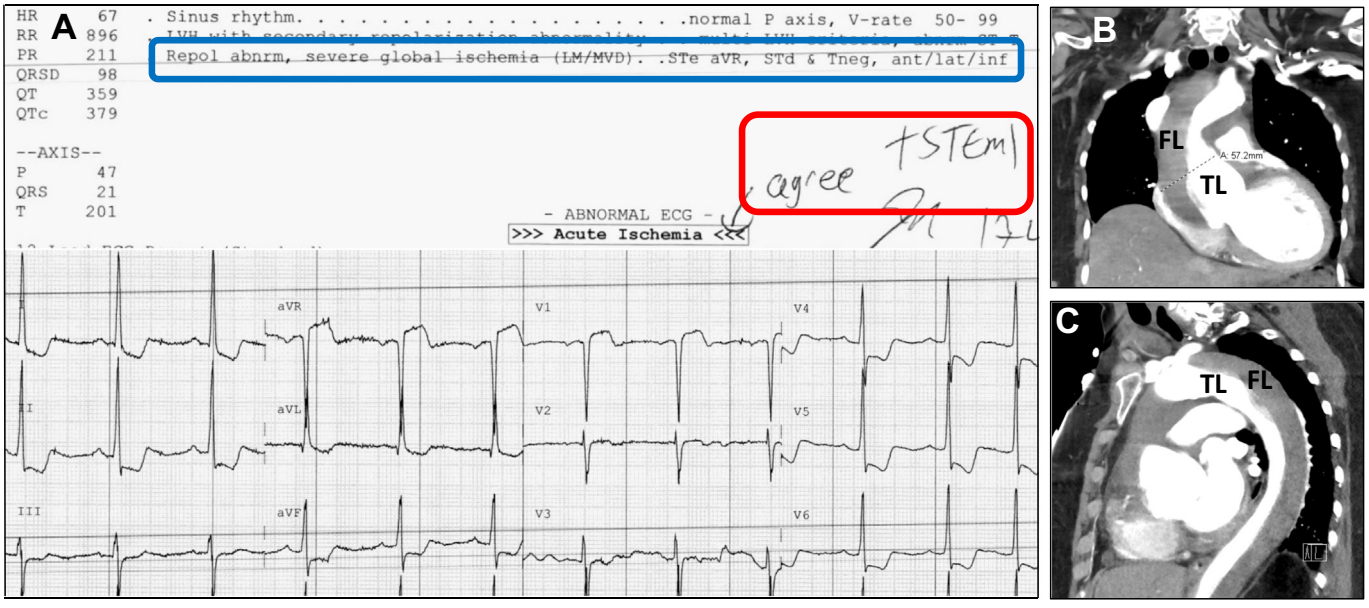

Fig. 2. Panel A. Transmitted prehospital electrocardiogram demonstrating horizontal and downsloping ST-segment depression in the anterolateral leads along with 3 mm ST-segment elevation in lead aVR and 2 mm ST elevation in V1, findings consistent with the aVR sign. Note the appropriate interpretation software diagnosis (blue bracket) as well as the physician over-read indicating STEMI (red bracket). Panels B and C. Chest CT of the ascending and descending thoracic aorta, respectively, demonstrated an extensive proximal (type A) aortic dissection. The transverse diameter of the ascending aorta, true lumen (TL) and false lumen (FL) combined, was 57.2 mm. See text.

given alternative causes including severe LVH, hemorrhagic shock, myocarditis, massive PE, type A acute thoracic aortic dissection, and supraventricular tachycardia.

- Physicians need to be educated about the high risk of missing the aVR sign in patients who present with acute chest pain, but also about the fairly wide differential diagnosis of this ECG phenomenon. Online SUPPLEMENTARY MATERIAL lists strategies to optimize diagnostic accuracy in patients who present with the aVR sign.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jelectrocard.2019.07.014.

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