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Emerging ECG methods for acute coronary syndrome detection: Recommendations & future opportunities

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ABSTRACT

Despite being the mainstay for the initial noninvasive assessment of patients with symptomatic coronary artery disease, the 12-lead ECG remains a suboptimal diagnostic tool for myocardial ischemia detection with only acceptable sensitivity and specificity scores. Although myocardial ischemia affects the configuration of the QRS complex and the STT waveform, current guidelines primarily focus on ST segment amplitude, which constitutes a missed opportunity and may explain the suboptimal diagnostic performance of the ECG. This possible opportunity and the low cost and ease of use of the ECG provide compelling motivation to enhance the diagnostic accuracy of the ECG to ischemia detection. This paper describes numerous computational ECG methods and approaches that have been shown to dramatically increase ECG sensitivity to ischemia detection. Briefly, these emerging approaches can be conceptually grouped into one of the following four approaches: (1) leveraging novel ECG waveform features and signatures indicative of ischemic injury other than the classical ST-T amplitude measures; (2) applying body surface potentials mapping (BSPM)-based approaches to enhance the spatial coverage of the surface ECG to detecting ischemia; (3) developing an inverse ECG solution to reconstruct anatomical models of activation and recovery pathways to detect and localize injury currents; and (4) exploring artificial intelligence (AI)-based techniques to harvest ECG waveform signatures of ischemia. We present recent advances, shortcomings, and future opportunities for each of these emerging ECG methods. Future research should focus on the prospective clinical testing of these approaches to establish clinical utility and to expedite potential translation into clinical practice.

Introduction

Every year, around 3.9–5.8 million Adults in the U.S. are evaluated at an emergency department for a chief complaint of chest pain [1,2]. Nearly two thirds (63%, IQR 38%–81%) of these patients are admitted to the hospital for further evaluation. Among all of those evaluated for chest pain, a small subset of patients (i.e., 5.1%–8.4%) are diagnosed with acute myocardial infarction [3,4]. Although the initial evaluation includes the standard 10-s 12-lead ECG [5–7], this test has historically lacked adequate sensitivity in detecting acute ischemia. A large meta-analysis with pooled sample size of >24,000 patients found the overall sensitivity and specificity of dynamic ST changes on the 12-lead ECG to be 68% and 77%, respectively [8]. In fact, this sensitivity can vary anywhere from 23% to 100% depending on the spectrum of disease severity under investigation [9]. Fig. 1 illustrates the spectrum of coronary artery disease and potential classification systems.

Current guidelines primarily rely on ST segment amplitude of the standard ECG for defining diagnostic criteria of acute myocardial infarction [6]. These criteria are driven by the need to identify patients with acute ongoing ischemia that might benefit from reperfusion therapy, not necessarily for screening patients for any ACS. Accordingly, nearly 43%–60% of patients with ACS present with neither ST deviation nor T wave inversion [10,11]. Given that prior studies have indicated that significant ST elevation (STE) is precipitated by transmural ischemia associated with total coronary occlusion, current practice guidelines broadly define ongoing myocardial ischemia into STE-ACS

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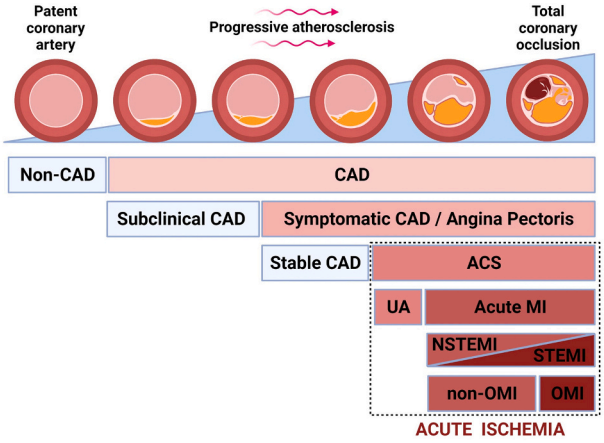

Fig. 1. Classification systems across the spectrum of coronary artery disease. This figure shows the spectrum of coronary artery disease (CAD) as a function of severity and extent of atherosclerosis plaque progression, ranging from patent coronary artery (far left) to total coronary occlusion (far right). Among patients who develop symptomatic CAD, including those evaluated for chest pain or angina-like symptoms, a subset is diagnosed with acute coronary syndrome (ACS). This group is subclassified, based on biomarker-evidence of myocardial necrosis, as either acute myocardial infarction (MI) or unstable angina (UA). Those with acute MI can be further subclassified, based on the presence of ST elevation on the ECG, as either ST elevation myocardial infarction (STEMI) or without ST elevation (NSTEMI). The STEMI and NSTEMI patients overlap in terms of presence or absence of total occlusion (depicted as triangles across the continuum in the figure). Alternatively, the same group with acute MI can be subclassified, based on angiographic TIMI flow criteria, as either occlusion (OMI) or non-occlusion (non-OMI) myocardial infarction. Unlike STEMI, OMI classification better aligns with focal angiographic findings since this group exclusive contains patients with total coronary occlusion. Color gradient indicates the severity of disease. This Figure was created with http://BioRender.com.

versus NSTE-ACS. However, a scoping review of literature amassing over 79,456 patients shows that 40% of patients with diagnostic ST elevation have no total coronary occlusion and ~ 25% of patients with no diagnostic ST elevation have, in fact, total coronary occlusion (Table 1). The outcome in these studies was primarily defined as acute coronary lesion with 100% total occlusions requiring revascularization during primary percutaneous coronary intervention, excluding patients with prior coronary stents or bypass surgeries. Data in this table highlights the discrepancy between observed ST elevation on the standard ECG and focal angiographic findings, questioning the use of STE as the sole basis for diagnostic criteria in clinical practice. Determining who would benefit from reperfusion therapy, thus, remains an adjudicated diagnosis.

Table 1
Relationship between total coronary occlusion and ST-elevation pattern on the 12-lead ECG.

Author	Diagnostic STE on 12-lead ECG		No diagnostic STE on 12-lead ECG	
	Total occlusion	No total occlusion	Total occlusion	No total occlusion
Dixon (2008) [12]	–	–	7199	23,187
Wang (2016) [13]	10,211	17,514	4856	23,344
Karwowski (2017) [14]	2949	1630	723	1995
Figueras (2018) [15]	–	–	110	450
Meyers (2021) [16]	67	0	41	126
Tanka (2021) [17]	84	50	14	83
WEIGHTED TOTAL (n = 79,456)	13,311 (60%)	19,194 (40%)	12,943 (23%)	44,219 (77%)

To address the shortcomings of the current classification system, a new conceptual paradigm has been recently proposed, namely occlusion versus non-occlusion myocardial infarction (OMI vs. non-OMI) [18]. The latter paradigm has two distinct advantages. First, it prompts the use of numerous ECG features indicative of ischemia to identify patients who might benefit from reperfusion therapy, rather than using surrogate outcomes defined by the ECG itself like STEMI (i.e., "self-fulfilling prophecy" paradox). This definition conceptually shifts the diagnostic mindset away from assessing whether ST elevation exists or not (i.e., treat the patient not the ECG). Second, this paradigm emphasizes that not all patients need to be diagnosed by the ECG. Patients presenting to the emergency department with angina-like symptoms need to be triaged into one of three categories, each with its own implications: (1) those who do not have acute ongoing ischemia and can be rapidly identified by rule-out protocols (e.g., troponin, HEART score) [19–21] and can be safely discharged home; (2) those with acute ischemia who can be risk stratified by ECG findings, troponin, or stress tests and require admission for anti-ischemic therapy and potential early coronary angiography; and (3) those with acute ischemia and ongoing loss of viable myocardium requiring emergent reperfusion. Such a triage system prompts the use of the ECG in conjunction with other diagnostics, which aligns well with current clinical workflow and practice recommendations [7]. This paper will broadly focus on the role of the ECG in detecting acute myocardial ischemia (i.e., box with dashed red line in Fig. 1). Exploring the role of the ECG across this triage continuum has implications for both ruling in and ruling out ACS, including the subset with severe coronary occlusion (i.e., STEMI or OMI).

The ECG basis of acute ongoing ischemia

The detection of ischemia using surface ECG is not a simple task; it comes with both conceptual and technical challenges. ACS occurs as a results of atherosclerotic plaque rupture that stimulates the formation of platelet-fibrin aggregates. Platelet activation may result in a thrombus that completely occludes the epicardial coronary artery, a partially occlusive thrombus, or small aggregates that shower downstream, occluding small arterioles. This process therefore results in a wide spectrum of ischemia: transient, persistent, or vacillating; complete or partial, and encompassing a spectrum from microscopic to extremely large myocardial territory. From these considerations alone, it is easy to understand why a single 12-lead ECG, representing only 10 s of a dynamic and complicated process, can have such wide variability in diagnostic accuracy.

While ACS is fundamentally a problem of coronary flow, for the interpretation of the ECG, it is necessary to focus on the electrophysiological consequences. During an ischemic episode, diminished flow due to coronary occlusion induces regional metabolic derangements, which in turn disproportionately distort the morphology of the action potential and the propagation of excitation in various myocardial segments. Given that the surface ECG measures potential differences, detectable ECG changes arise only if the positive pole of an ECG lead is facing a myocardial region with such action potential distortions and the resulting tissue-scale currents, often called `injury currents' (Fig. 2A). However, these distortions are summative in nature, so injury currents flowing in opposite directions might cancel or attenuate changes observed in a given ECG lead (Fig. 2B). Thus, a more comprehensive approach for myocardial ischemia detection should be based on two aspects [22]: (1) evaluating waveform morphology over the entire depolarization and repolarization phases (temporal characteristics), rather than voltage at a given time point like J + 80; and (2) evaluating relative inter-lead distortions in waveform morphology across all myocardial segments in the 12 leads (spatial characteristics), rather than absolute changes in isolated ECG leads. Using these broad conceptual principles, the following section discusses four emerging approaches to enhance the ECG detection of ischemia: (1) techniques based on novel temporal-spatial measures of global ventricular repolarization dispersion; (2)

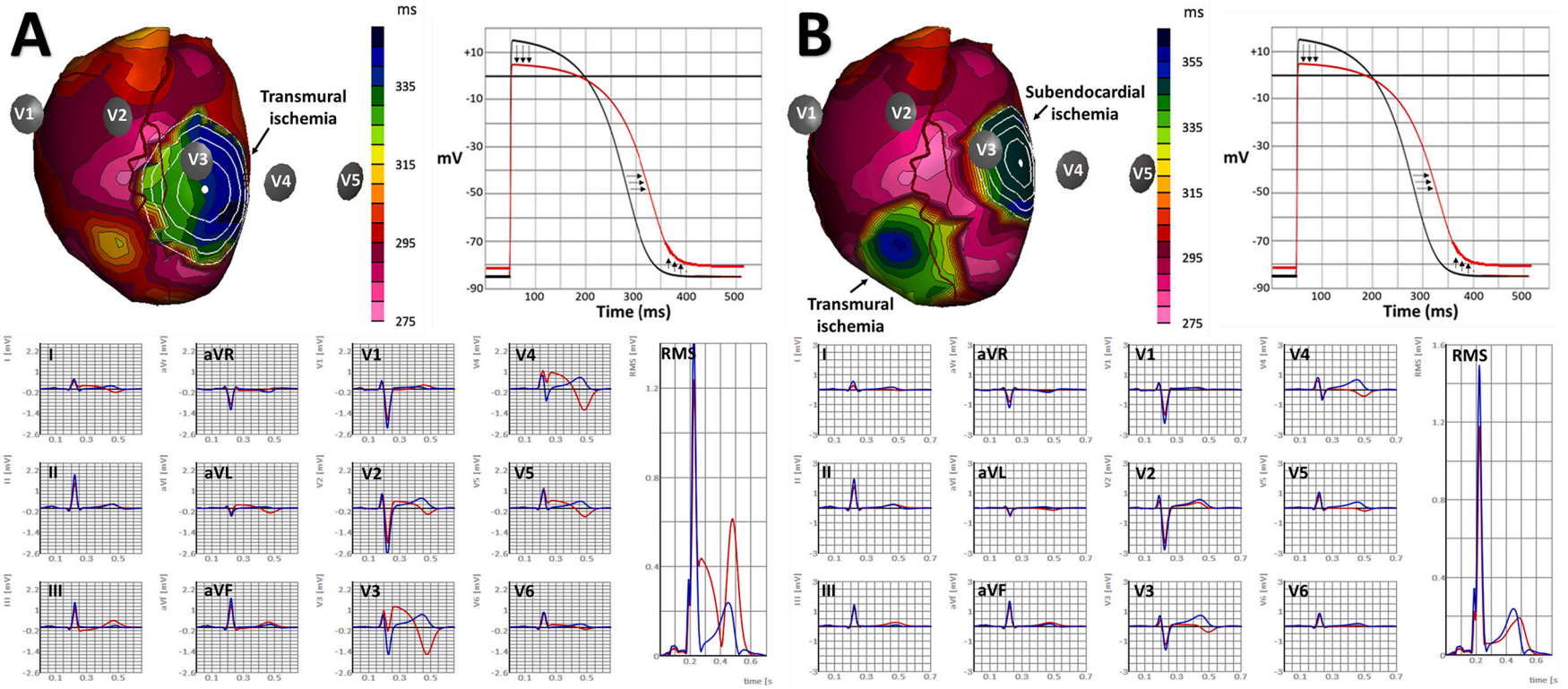

Fig. 2. Limitations of ST amplitude on surface ECG as a sole marker of myocardial ischemia.
(A) cardiac model of anterior wall epicardial ischemia with corresponding ST elevation on V3 to V5 of the 12-lead ECG. (B) cardiac model of anterolateral and inferior-apical epicardial ischemia with corresponding attenuation of ST changes on the 12-lead ECG. This figure was generated using ECGSIM (http://www.ecgsim.org) [23].

techniques that aim to increase the spatial coverage of the ECG using body surface potentials mapping (BSPM) principles; (3) techniques based on modeling cardiac potentials from surface ECG (ECG imaging); and (4) techniques based on artificial intelligence (AI) and machine learning. Although these four techniques are not mutually exclusive, they can serve as a general guiding framework to conceptually categorize the rapidly emerging literature on ECG detection of ischemia.

Novel ECG signatures of ischemia

Given that current clinical practice relies on the visual inspection of ECG waveforms, a consensus report by renowned experts in the field has identified 7 visual patterns indicative of coronary occlusion (or STE-ACS equivalent) [24] beyond the criteria recommended by current practice standards: ST depression in V1 to V3; prominent positive T waves; upsloping ST depression with tall T waves; small inverted T waves in V1 to V3; deep negative T waves in precordial leads; and widespread ST depression with elevation in aVR and V1. Similar ECG patterns have also been proposed as indicative of coronary occlusion [18]: ST depression in V1 to V4; hyperacute T waves; subtle ST elevation; reciprocal ST depression; acute pathologic Q waves; and loss of terminal S wave. However, defining these ECG patterns relies heavily on the visual assessment of waveform morphology and, thus, introduces a high degree of subjectivity and inter-rater variability among ECG interpreters.

A more objective assessment is possible based on computing indices that can quantify the temporal-spatial magnitude of ischemia-induced global repolarization dispersion. One such index is T-wave complexity, defined as the ratio of the 2nd to 1st eigenvalues of principal component analysis (PCA) of the ST-T waveform in the perpendicular ECG leads (I, II, V1-V6) [25]. A larger ratio would indicate more dispersed repolarization signal likely due to regional variations in signal propagation due to ischemia. Al-Zaiti et al. found that T-wave complexity moderately correlates with infarct size ($r = 0.41$) and has sensitivity/specificity for detecting NSTE-ACS of 0.57 / 0.76 [26]. Using dynamic changes in T wave complexity during exercise-induced myocardial ischemia has been shown to boost sensitivity and specificity for detecting focal myocardial ischemia on SPECT to 0.80 and 0.83, respectively [27]. These findings indicate that this metric is likely sensitive to both mild and more advanced stages of ischemia and infarction. A similar metric is the V-index which quantifies the repolarization times of myocytes across myocardial segments. Abacherli et al. have shown that a larger v-index has sensitivity/specificity for detecting acute myocardial infarction of 0.78 / 0.50 [28]. Another intuitive index is the spatial QRS-T angle, which quantifies the deviation between mean QRS vector and mean T vector. Although non-specific for ischemia, Strebel et al. have shown that a larger QRS-T angle has sensitivity/specificity for detecting NSTE-ACS of 0.78 / 0.91 [29]. Patients with STEMI and pacing were excluded from this analysis, but not those with LVH (i.e., <10% prevalent). Further indices previously described include the beat-to-beat lability in repolarization signal, defined as sum root mean square over the ST-T waveform of averaged consecutive beats (non-alternans component) or odd/even paired beats (alternans component) [30]. The incremental value of these novel features over standard ECG criteria has yet to be established in prospective clinical trials.

BSPM-based approaches for ischemia detection

Conceptually, acute cardiac ischemia can manifest on the surface ECG if—and only if—the positive pole of an ECG lead is facing that ischemic region. ECG changes are attenuated if the infarct is in a location only weakly sensed by the lead fields of the standard 12-lead ECG. Thus, ECG methods with wider spatial coverage as derived from BSPM can improve the sensitivity of ischemia detection relative to only 12 leads. Numerous studies have nicely demonstrated this incremental gain in performance. In the OCCULT-MI trial, an 80-lead BSPM provided an incremental 27.5% increase in STEMI detection versus the 12-lead [31]. Such 80-lead BSPM has been shown to yield sensitivity and specificity for occlusion myocardial infarction detection of 0.91 and 0.72, respectively [32]. The wider spatial coverage of BSPM has been shown to be specifically useful in increasing the diagnostic yield in patients with left circumflex occlusion in patients with nondiagnostic baseline 12-lead ECG [33]. Although BSPM was shown many years ago to have higher sensitivity, it has not been employed clinically because it requires new equipment and much more laborious lead placement.

One innovative approach to overcome this limitation, and perhaps one of the most potentially impactful techniques, is the derived vessel-specific ECG leads (VSEL) method [34,35]. The VSEL technique reconstructs, based on data from the 12-lead ECG, three new ECG leads optimized for the detection of the occlusion of each of the three main coronary arteries (Fig. 3). The derivation is based on weighted coefficients estimated from the unique BSPM distributions observed during balloon angioplasty experiments. These three easy-to-read leads not only can be reconstructed from the standard 12-lead ECG without the need to apply additional electrodes, but also can provide superior spatial evaluation of the presence and anatomic location of acute cardiac ischemia. In a recent analysis, Ahmad et al. showed that the use of VSEL leads boosts the sensitivity and specificity of ECG interpreters for detecting ischemia from 0.68 and 0.62 to 0.91 and 0.73, respectively [36].

EP modeling & inverse ecg solution

Electrocardiographic modeling refers to correlating extracellular potentials (electrograms) at the epicardium to observed ECG signals at the body surface. These models can simulate ECGs for various activation and excitation-propagation sequences. Alternatively, ECG Imaging refers to the mathematical reconstruction of the cardiac electrical activity, e.g., epicardial electrograms, using measurements obtained by surface ECG electrodes. These data ensemble techniques require mapping the ECG-derived time-voltage data to a 3-D model of the heart and the thorax [37]. By estimating the electrograms, various characteristics of the activation and repolarization phases can be used to detect and localize the extent and location of ischemic zones. Using 3-D geometric model of the human ventricles and torso, Lines et al. showed that ST elevation is a suboptimal metric for the identification of early ischemia of modest spatial extent as compared to several T-wave metrics [38]. T-wave peak and T-wave duration were more sensitive to regional ischemia of medium size, whereas T-wave area was more sensitive to even smaller ischemic regions. This is an unsurprising finding given that the hyperacute T-wave, which is basically the area under the T-wave, is a known markers of evolving ischemia and coronary occlusion [39]. Furthermore, using ECG Imaging, Marrus et al. showed that patients with ischemic myocardial injury have prolonged activation index and diminished recovery index as compared to their healthy counterparts [40]. In a different study model, Good et al. have shown that using Laplacian eigenmaps to compute an abstract space index from 600 electrogram time signals is superior in detecting transient ischemia compared to other approaches [41].

One limitation of many ECG imaging techniques is lack of clinical utility in an emergency department setting. One promising technique to overcome this limitation is known as *Cine*-ECG [42]. Cine-ECG is a novel method to image the anatomical location of the average activation and recovery sequence in the heart from the time-voltage signals of the 12-lead ECG. To enable the rapid use of this approach, van Dam et al. computed the normal limits of the average activation sequence from ~6500 normal ECGs [43], allowing quick and simple visualization of abnormal deviations in the electrical pathway in various 3D anatomical directions (Fig. 4). A recent report by Faramand et al. demonstrated that abnormal recovery pathway on Cine-ECG could detect acute coronary syndrome with sensitivity and negative predictive value of 0.83 and 0.94, respectively [44]. An important finding, captured as an example in Fig. 4, is that there was diagnostic information not only during the ST

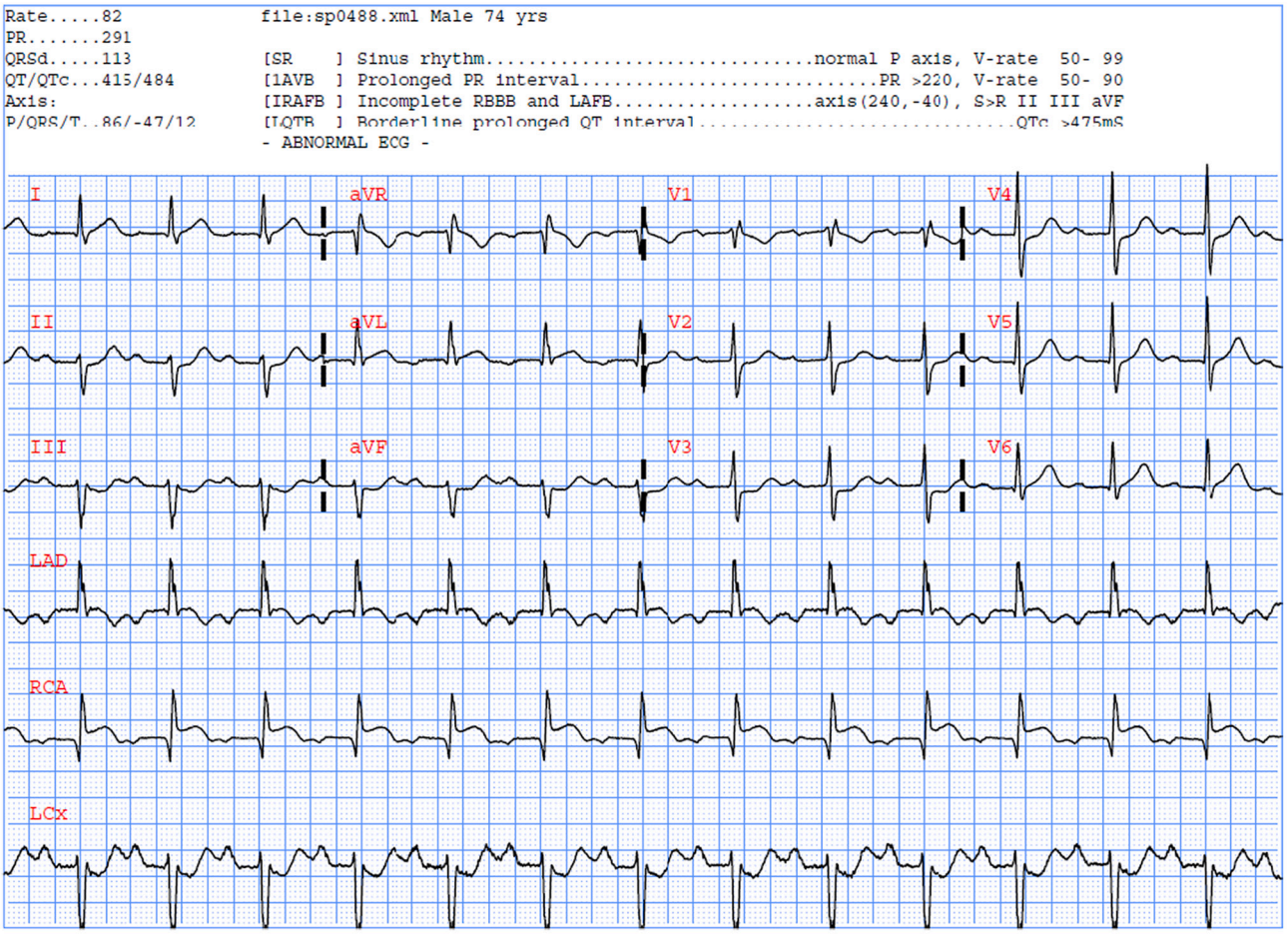

Fig. 3. Selected example of a 12-lead ECG with VSEL display.
This 12-lead ECG was obtained on a 74-year-old male evaluated at the emergency department for chest pain of 2 h duration. There is subtle STE in lateral leads and reciprocal changes in inferior leads with borderline ST depression and T wave inversion in anterior leads, collectively indicating a pattern associated with severe infarct. However, the automated computer interpretation failed in capturing these patterns and indicated no ischemia or infarct. The derived VSEL shows clear STEMI of RCA with abnormal ischemic patterns in LAD and LCX. The patient experienced cardiac arrest at the emergency department, and after successful resuscitation he was referred for urgent angiography that revealed 90% RCA occlusion, 60% LCX occlusion, and 50% LAD occlusion. RCA: right coronary artery; LAD: left anterior descending; LCX: left circumflex.

segment of the Cine-ECG, but throughout the whole STT segment.

AI-based approaches for ischemia detection

Acute myocardial ischemia affects the configuration of the QRS complex and ST-T waveform morphology disproportionately across the 12 ECG leads. This means that different waveform measurements (e.g., duration, amplitude, and area of Q-wave, R, R`, QRS, ST, T-wave, T_{peak}, $T_{peak\text{-}end}$) need to be interpreted collectively while considering intra-lead dynamics. These lead-specific measurements also need to be interpreted within the context of global inter-lead ECG characteristics (e.g., axis, angles, loops, vectors), which also depend on body build, age, and may other factors. The morphology and configuration of these waveforms (e.g., upsloping, downsloping, concavity, symmetry, notching, etc.) also contain important prognostic information that must be considered. Thus, the process of 12-lead ECG interpretation involves many complex aspects and parameters, making it a highly multi-dimensional space problem. Humans are good in pattern recognition, which makes ECG interpretation an art. However, current diagnostic ECG criteria follow a rule-based logic (e.g., if "amplitude at J+80 > 0.1 mV": then "…"). These over-simplified decision rules are based on linear mathematical representations (e.g., logistic regression models) that are not adequately suitable for highly dimensional space. Accordingly, numerous AI techniques have been shown to provide powerful tools to solve such highly dimensional, non-linear mathematical representations.

The simplest and most intuitive use of AI for ECG interpretation is through supervised machine learning using human-curated ECG features. In this approach, the raw ECG signal is preprocessed and known waveform features are extracted and then fed into a classifier (e.g., support vector machine, random forest, gradient boosting, neural network). The classifier is first trained on a subset of the sample to fine-tune hyperparameters of the classifier and then tested on the remaining subset of the sample to derive performance metrics [45]. Using this approach, Al-Zaiti et al. explored the utility of 554 hand-crafted ECG features for predicting NSTE-ACS in patients with chest pain [11,46,47]. Using a hybrid approach of data-driven algorithms combined with knowledge from experts, a reduced subset of features (k = 73) outperformed both expert clinicians and automated computer software with a gain of 37% and 52% in sensitivity, respectively, without any loss in negative predictive value (>94%).

An alternative use of AI for ECG interpretation is through deep learning using raw ECG signal. In this approach, raw ECG signals from each of the 12 leads are fed in a multi-layered neural network with varying architectures (e.g., convolutional, recurrent, long/short-term memory). The neural network is either fed the actual waveform data (e.g., 1-D array of time-voltage data) or an ECG image (e.g., 2-D matrix of signals and time that has the format of image pixels). In either

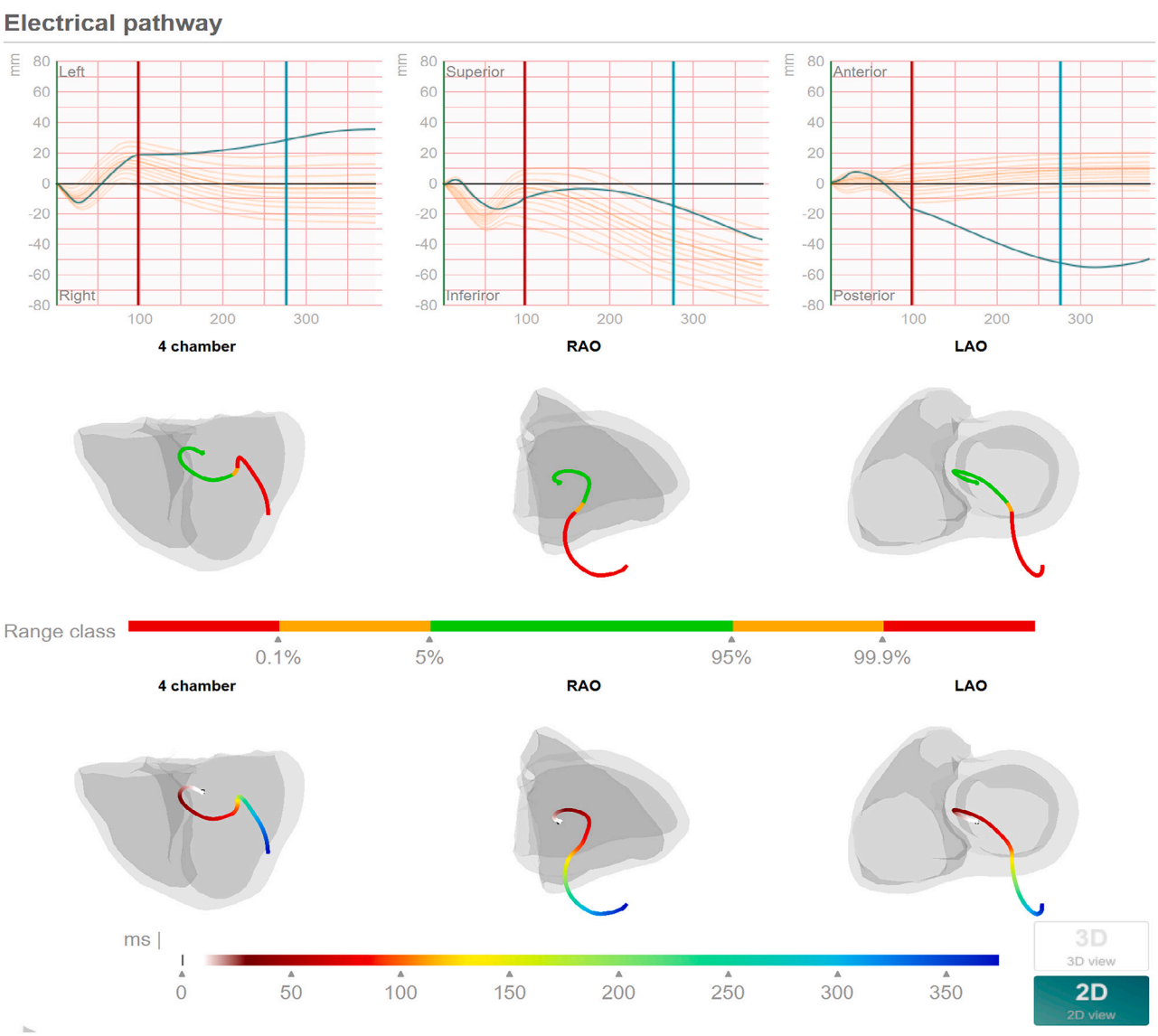

Fig. 4. Selected example of cine-ECG display derived from a standard 12-lead ECG.
This Cine-ECG shows the anatomical location of the average activation sequence from the same 12-lead ECG displayed in Fig. 3. The upper panel compares the average electrical pathway (green line) to normal limits in the general population (orange line). It indicates abnormal deviation toward left lateral and posterior myocardial walls. The middle and lower panels visualize this sequence to the anatomic location (red being outside the normal position boundaries in the middle panels. In the lower panels the colors indicate the time in ms (see bottom color bar). These findings are compatible with the angiographic findings of LCX coronary involvement affecting the posterolateral myocardial wall.

approach, the multilayered neural network can extract features, and map them to a known outcome of interest (e.g., myocardial infarction). Despite the diminished explainability, these deep learning techniques are gaining growing popularity in the field of electrocardiology since there is no need for human oversight over feature engineering. A recent systematic review has identified six studies that used deep learning for acute myocardial infarction detection [48]. Five of these studies used a limited subset of the open source MIT-PTB dataset in which the positive class consisted of patients with classical ECG-confirmed STEMI, explaining the over-optimistic performance of sensitivity and specificity ~0.98 in these studies. The remaining study in this meta-analysis [49], however, used real-world data from chest pain patients and demonstrated that deep learning on raw 12-lead ECGs could identify patients with significant coronary occlusion with sensitivity and specificity of 0.79 and 0.87, respectively. A more comprehensive analysis of >365,000 patients published after this meta-analysis showed that deep learning analysis of 12-lead ECG data yields average sensitivity and specificity of 0.93 and 0.95 for the diagnosis of myocardial infarction [50]. However, the ascertainment of this outcome was based on ECG over-reading by a consensus committee (i.e., most likely using standard practice recommendations), which suggests that this study did not fully explore the role of deep learning in detecting acute myocardial ischemia in nondiagnostic 12-lead ECGs where the real unmet clinical need is. Thus, it is imperative that clinicians critically examine which AI-based prediction models can add value to patient care from the AI models that do not [51].

Another related machine-learning approach is based on unsupervised learning and data reduction techniques. This approach includes the use of a training step and a non-linear transform to achieve a reduction in the dimension of the data space and thus identify predictive patterns. Good et al. applied the Laplacian Eigenmap transform to identify three dominant parameters from the resulting abstract space [41]. These three parameters created manifolds that varied in time but they captured enough information to predict the onset of acute

myocardial ischemia more rapidly and with improved sensitivity and specificity than conventional approaches [52].

Conclusions & future recommendations

Patients with chest pain present with varying degrees of manifestations and ECG findings across the continuum of coronary artery disease. Using ECG thresholds to diagnose ongoing ischemia due to acute occlusion of an epicardial coronary artery is a bit problematic. While a proportion of patients with ACS have ongoing ischemia and symptoms (e.g., patients with STEMI or OMI), a large proportion of ACS do not have active ischemia while first seen by the medical team. ECG manifestations in ACS patients would then include a combination of features indicative of ongoing ischemia as well as features indicative of post-ischemic changes. In this commentary, we review numerous emerging ECG methods for optimizing the noninvasive detection of acute myocardial ischemia across the spectrum of ACS in clinical practice.

First, numerous studies focus on describing unique visual waveform patterns (e.g., occlusion MI patterns) and/or computing quantitative ECG features (e.g., T wave complexity) as novel markers of myocardial ischemia. A strength of these studies is that the standard 12-lead ECG is widely available and easy to use, and the sensitivity for OMI when using ECG features that do not rely on ST elevation is even far higher. However, many of these patterns and features have been evaluated in offline retrospective analyses. Exploring the incremental gain of these patterns and features over the Fourth Universal definition of MI criteria in prospective clinical testing is warranted to drive the adoption of these approaches in the clinical workflow.

A second group of studies focused on the role of BSPM in boosting the 12-lead ECG sensitivity to myocardial ischemia. Despite significant gains in accuracy, these techniques remain impractical in emergency settings. The VSEL technique is a promising approach to bridge this gab by enhancing the spatial coverage of the 12-lead ECG without the need to apply additional electrodes (Fig. 3). The clinical utility of these new ECG leads is yet to be determined in prospective clinical testing, including evaluating the impact on experts' accuracy and confidence in interpretation.

A third group of studies focused on EP modeling and inverse ECG solution to model activation and recovery pathways as a mean to detect and localize ischemia. Similar to BSPM studies, many of these approaches remain impractical in clinical practice, especially in an emergency department setting. A novel technique that can overcome these limitations and can be easily deployed in current practice is Cine-ECG (Fig. 4). Mapping the activation sequence over an anatomical model of the ventricles can be intuitive to clinicians and can help easy localization of regional myocardial ischemia and might be potentially powerful in combination with AI algorithms. However, studies on the role of Cine-ECG in myocardial ischemia detection are in an initial research phase.

Finally, a growing body of literature explores the role of AI in the ECG diagnosis of myocardial ischemia. Few studies used a traditional approach by implementing data-driven feature selection on hand-crafted ECG metrics followed by supervised machine learning with very promising results. Other studies directly applied deep learning to raw ECG signal without any domain-driven feature selection. The availability of real-world large clinical datasets and concerns about outcome ascertainment remain major obstacles in this growing are of science. Future AI research in this area should focus on hybrid neural networks that take as input both hand-crafted ECG features (including novel quantitative markers of repolarization dispersion) and raw ECG signal and that are trained against ECG-independent gold reference standards (i.e., biomarker and angiographic findings).

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CRediT authorship contribution statement

Salah Al-Zaiti: Conceptualization, Writing – original draft, Writing – review & editing, Visualization, Funding acquisition. **Robert Macleod:** Writing – review & editing. **Peter Van Dam:** Visualization, Writing – review & editing. **Stephen W. Smith:** Writing – review & editing. **Yochai Birnbaum:** Writing – review & editing.

Declaration of Competing Interest

Peter Van Dam is a co-owner of ECG-Excellence, The Netherlands.

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