Advanced ECG in 2016: is there more than just a tracing?

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Summary

The 12-lead electrocardiogram (ECG) is the most frequently used technology in clinical cardiology. It is critical for evidence-based management of patients with most cardiovascular conditions, including patients with acute myocardial infarction, suspected chronic cardiac ischaemia, cardiac arrhythmias, heart failure and implantable cardiac devices. In contrast to many other techniques in cardiology, the ECG is simple, small, mobile, universally available and cheap, and therefore particularly attractive. Standard ECG interpretation mainly relies on direct visual assessment.

The progress in biomedical computing and signal processing, and the available computational power offer fascinating new options for ECG analysis relevant to all fields of cardiology. Several digital ECG markers and advanced ECG technologies have shown promise in preliminary studies. This article reviews promising novel surface ECG technologies in three different fields. (1) For the detection of myocardial ischaemia and infarction, QRS morphology feature analysis, the analysis of high frequency QRS components (HF-QRS) and methods using vectorcardiography as well as ECG imaging are discussed. (2) For the identification and management of patients with cardiac arrhythmias, methods of advanced P-wave analysis are discussed and the concept of ECG imaging for noninvasive localisation of cardiac arrhythmias is presented. (3) For risk stratification of sudden cardiac death and the selection of patients for medical device therapy, several novel markers including an automated QRS-score for scar quantification, the QRS-T angle or the T-wave peak-to-end-interval are discussed.

Despite the existing preliminary data, none of the advanced ECG markers and technologies has yet accomplished the transition into clinical practice. Further refinement of these technologies and broader validation in large unselected patient cohorts are the critical next step needed to facilitate translation of advanced ECG technologies into clinical cardiology.

Key words: advanced ECG; digital ECG marker; ECG imaging

Introduction

It is more than a century ago that Willem Einthoven introduced the string galvanometer [1] and it was in 1924 that he was awarded the Nobel Prize for medicine or physiology for his invention [2]. The 12-lead electrocardiogram (ECG) has since become the most frequently performed cardiovascular test and approximately 200 million ECGs are recorded worldwide each year. It is an essential diagnostic tool in clinical cardiology and critical for evidence-based management of patients with most cardiovascular conditions including patients with acute myocardial infarction, suspected chronic cardiac ischaemia, cardiac arrhythmias, heart failure and implantable cardiac devices. In contrast to many other techniques in cardiology, the ECG is simple, small, mobile, universally available and cheap, all of which make the ECG a particularly attractive diagnostic method.

The progress in biomedical computing and signal processing, and the available computational power of microcontrollers and processors offer fascinating new options for ECG analysis, including improved filtering effects, morphology feature analysis [3], frequency content analysis [4], vectorcardiography analysis [5] and ECG imaging [6].

Regardless, the look of the standard 12-lead ECG has remained the same and the interpretation still relies mainly on direct visual assessment. The criteria for ECG interpretation have hardly changed over the past 25 years [7–11]. Using these conventional criteria, relevant limitations of the ECG leave, however, significant unmet clinical needs in various field of cardiology.

Even though no digital 12-lead ECG marker has made the transition into clinical cardiology yet, some advanced ECG markers and technologies have shown promise in small preliminary studies. Further refinement of these technologies and broader validation in large unselected patient cohorts are the critical next step needed to facilitate translation of these and other advanced ECG technologies into clinical cardiology. This article reviews promising novel surface ECG technologies for (1) detection of acute myocardial infarction (AMI) and ischaemia; (2) identification and management of patients with cardiac arrhythmias;...
and (3) risk stratification for sudden cardiac death and selection of patients for medical device therapy.

Detection of acute myocardial infarction and ischaemia

Current role of the ECG in the detection of acute myocardial infarction

AMI is a major cause of death and disability worldwide. As highly effective treatments are available, early and accurate detection of AMI is crucial [12–14]. Clinical assessment, the 12-lead ECG and measurement of cardiac troponin form the three cornerstones of the early diagnosis of AMI in the emergency department [14]. The particular importance of the ECG is its pivotal role in identifying patients with complete occlusions of large epicardial vessels. A complete vascular occlusion results in transmural ischaemia, the maximal grade of ischaemia, which is reflected by ST-elevation. This subgroup of patients with so-called ST-elevation myocardial infarction (STEMI) is at highest risk for adverse events and needs immediate reperfusion therapy [15]. However, only a minority of AMI patients presents with transmural ischaemia and ST-elevation, whereas the majority of AMI patients has only nontransmural ischaemia, which result in either ST-depression, T-wave inversion or no ECG change at all. This group of AMI patients with nontransmural ischaemia and without ST-elevation are summarised as having non-ST-elevation myocardial infarction (NSTEMI).

Whereas major advances in the early identification of NSTEMI patients have recently been achieved by the development of more sensitive cardiac troponin assays [16–25], progress in the analysis and interpretation of the 12-lead ECG has been very limited over years and the criteria applied have remained virtually unchanged for more than a decade, focusing on ST-depression and T-wave inversion [14]. On the basis of these current ECG criteria, at least 25% of patients with AMI present with no diagnostic ECG abnormalities [18].

Current role of the ECG in the detection of myocardial ischaemia in the assessment of stable coronary artery disease

The incidence of coronary artery disease (CAD) eventually leading to AMI and severe heart failure is still increasing, mainly in emerging nations [26, 27]. The early detection of CAD and of exercise-induced myocardial ischaemia (as its pathophysiological hallmark) before the occurrence of a first AMI is one of the most important challenges in current cardiology [28–30]. For many years, exercise ECG testing has remained the most widely accessible and relatively inexpensive method for initial evaluation of suspected obstructive CAD and for assessment of its severity [31]. The ST-segment depression criteria recommended for detection of exercise-induced ischaemia have also been unchanged for years [32]. Clinical usefulness has, however, been limited by poor sensitivity of these standard criteria; almost 50% of patients with exercise-induced ischaemia have a false negative stress ECG, and this number is even higher in females [33, 34]. Hence, a large number of patients with suspected CAD require further investigation by imaging modalities including stress echocardiography, cardiac MRI or myocardial perfusion single photon emission tomography (MP-SPECT). In spite of being standard procedures in noninvasive detection of stress-induced myocardial ischaemia nowadays, all of them have several limitations, since they are mainly available in larger hospitals only, operator dependent, expensive, time consuming, and bound to radiotracer exposure in case of SPECT. Therefore, there is an unmet clinical and economical need for an easily applicable and cost-effective method to rule-in or rule-out stress-induced myocardial ischaemia [35].

Novel ECG markers assessing ventricular depolarisation for ischaemia detection

While the traditional criteria of ST-segment changes and T-wave changes focus on ventricular repolarisation, myocardial ischaemia also affects ventricular depolarisation, which occurs during the QRS complex (fig. 1). However, quantification of QRS changes is more challenging than that of ST-segment changes because these changes are only subtle in many electrophysiological and anatomical situations. Several computationally generated ECG markers not recognisable as an observer’s eye have been reported to occur during ischaemia, including amplitude changes of the R- and S-waves [3, 36] and changes in QRS slopes, angles and vectors [37, 38]. A more sophisticated approach focuses on high-frequency components within the QRS complex (HF-QRS) [4, 39]. Those HF-QRS components are very low in amplitude and are normally filtered out by conventional ECG devices. They originate from the fragmentation of the electrical activation wavefront caused by branching of the conduction system. In ischaemic regions, local slowing of conduction velocity reduces the wavefront fragmentation, causing changes in the intensity and morphology of HF-QRS signals [40]. Therefore, HF-QRS signals decrease in the presence of ischaemia. Recently, a high resolution exercise-ECG system that provides automated HF-QRS analysis has become commercially available. A recent pilot study reported that, with this system, HF-QRS analysis was more sensitive and more specific than ST-segment analysis to detect inducible ischaemia in patients undergoing MP-SPECT stress test [4]. Given that no standard values are established for HF-QRS or for the other novel ECG markers of depolarisation...
tion, their application for now seems most feasible in patients undergoing exercise stress testing. The baseline ECG before the stress test in each patient may serve as its own “healthy” control for comparison with the ECG at maximal workload. Nevertheless, the algorithm detecting CAD was adapted to the case of ACS without any available baseline in the frame of a Swiss-Israeli collaboration funded by the European Union (Eurostars E15495 HRQRS), the first results of which will be available soon.

Novel ECG markers assessing ventricular repolarisation for ischaemia detection

In addition to the traditional markers of ventricular repolarisation, i.e. ST-segment deviation and T-wave inversion, parameters from vectorcardiography quantifying ventricular repolarisation such as T-wave axis and T-loop morphology have been studied as potential markers of myocardial ischaemia. Myocardial ischaemia induced by coronary occlusion during cardiac revascularisation resulted in a significant change of T-wave axis as well as T-loop morphology [41]. Similarly, among unselected patients presenting with chest pain, an abnormal T-wave axis was more frequently found in patients with AMI than with other causes of chest pain [42].

ECG imaging for ischaemia detection

A limitation of current criteria is their focus on the presence of a threshold amount of ST-segment change. This necessarily leads to false positive and false negative diagnoses. Several groups have suggested methods for improving the accuracy of the 12-lead ECG and facilitating interpretation by using graphic tools to display the ECG-information on polar or Mercator maps [43–45]. However, all these methods rely on ST-segment deviation with all its inherent limitations.

One approach to overcoming some of the limitations of ST-deviations in the normal 12-lead ECG is to use high-density electrode mapping to allow for better “ECG imaging”. The clinical performance of such an 80-lead ECG system with 64 anterior and 16 posterior leads was assessed in a large study with 1830 unselected patients presenting with chest pain: using the additional leads, the rate of STEMI patients increased from 5.0% to 6.3% [46]. The system, however, is both difficult to apply and to interpret because of the large number of electrodes, and up to 10% of all ECGs had to be excluded from analysis owing to poor quality recordings [46]. More recently, a Canadian group has used high-density ECG data obtained from J-point measurements in 120 leads to calculate the unipolar epicardial surface potential map by use of the mathematical inverse solution method. Using the input of continuously reduced lead sets, it finally was possible to estimate the unipolar epicardial potential map using the information from the standard 12-lead ECG alone [47]. These epicardial potentials were then used to create a 17-segment polar map, which showed a good correspondence with simultaneously acquired MP-SPECT images in patients with acute ischaemia [48]. Furthermore, this method seemed to allow distinction between cardiac conditions with acute ischaemia and those with nonischaemic problems such as pericarditis or left ventricular hypertrophy (fig. 2) [49]. Even though this latter method in particular has shown potential in these small pilot studies, nothing is known about its value for identification of NSTEMI patients and validation in larger cohorts of unselected chest pain patients is needed.

Novel ECG technologies for identification and management of patients with arrhythmias

Current role of the ECG in the identification and management of patients with arrhythmias

The 12-lead ECG is the most important technology for diagnosis and management of patients with cardiac arrhythmias [50–52]. It allows the diagnosis of the ongoing arrhythmia and in, most cases, also a crude localisation of the arrhythmia origin. It assists in the selection of the appropriate treatment strategy for the individual patient, including the selection of patients suitable for catheter ablation therapy. Unmet clinical needs include the identification of patients with paroxysmal atrial fibrillation (AF) while in sinus rhythm, the prediction of success after catheter ablation in AF patients and a more accurate noninvasive localisation of arrhythmias, which could also be used to guide catheter ablation.

Is identification of patients with paroxysmal atrial fibrillation possible in sinus rhythm?

AF is the most commonly encountered paroxysmal atrial fibrillation. It is of particular medical and economic importance because of its association with embolic stroke. The identification of patients with paroxysmal AF is important to en-
able stroke prevention by initiation of oral anticoagulation therapy [51]. Traditionally, patients are screened for subclinical paroxysmal AF by use of 24-hour Holter monitoring. This, however, has a limited diagnostic yield as a result of false negative results. Prolonged monitoring (using wearable or implantable loop recorders) is therefore more frequently used recently in clinical practice and has significantly increased the rate of AF detection [53, 54]. A reliable method to identify patients with or at increased risk for paroxysmal AF during sinus rhythm could remarkably improve management of patients with subclinical paroxysmal AF and has the potential to reduce embolic strokes.

Markers obtained from advanced P-wave analysis in the 12-lead ECG are of particular interest for this. The goal of these markers is to detect subclinical atrial remodelling, the morphological substrate for AF, and they therefore can be found in patients with or at risk for AF [55]. Markers that have been associated with AF in large longitudinal cohort studies are a prolonged P-wave duration >120 ms, P-wave dispersion >58 ms (difference between the widest and the narrowest P-wave in a 10 sec ECG), abnormal P-wave axis and increased P-wave area [56–59]. With currently available digital P-wave indices, however, the odds ratio rarely exceeds a value of 2 [56–58]. Additional markers with better discrimination are needed before they can be clinically applied.

Recent evidence suggests that left atrial abnormalities may be responsible for cardioembolic stroke even in the absence of detectable AF [60] or without a temporal relationship to AF episodes [61]. Accordingly, it is conceivable that anticoagulation therapy might be beneficial for patients with significant left atrial abnormalities in the absence (or before the occurrence) of AF. If so, the above P-wave markers indicating left atrial abnormalities would be perfectly suited for patient screening.

**Prediction of success after catheter ablation in atrial fibrillation patients**

Over the past 15 years, catheter ablation of AF has become a well-established and widely performed minimally invasive interventional therapy for many symptomatic AF patients [51, 62]. However, long-term AF recurrence rates are still up to 50% after single procedures. In addition to procedural limitations, a large extent of atrial remodelling is a key factor responsible for higher recurrence rates [63].

Hence, procedural assessment of the extent of atrial remodelling is critical for appropriate patient selection in order to maximise success after catheter ablation. While left atrial diameter and volume obtained by echocardiography are most commonly used to do so, advanced markers of P-wave analysis are an even more easily accessible way to quantify atrial remodelling. Indeed, P-wave duration, P-wave dispersion and P-wave terminal force in lead V1 have been found to be predictors of recurrence after catheter ablation in patients with paroxysmal AF [64, 65]. However, in most studies, the predictive value of the P-wave markers was not independent from those obtained with echocardiography. For now, imaging modalities remain the standard to assess atrial remodelling, but ongoing research might identify better, independent ECG markers to be used in patient selection for catheter ablation.

**EGC mapping for noninvasive localisation of arrhythmias and to guide ablation procedures**

Besides the diagnosis of an arrhythmia type and mechanism, the 12-lead ECG is also the standard technology for noninvasive localisation of arrhythmias, including localisation of accessory pathways in Wolff-Parkinson-White syndrome, of focal origins in atrial tachycardias or premature ventricular contractions (PVC) and of exit sites in ventricular tachycardias. However, the 12-lead ECG records the reflection of electrical activity on the surface of the body, not the heart itself. Accordingly, it has limited spatial resolution, the localisation information provided is often inaccurate and the mechanism of the arrhythmia reflected by its activation sequence cannot be assessed. A more accurate localisation of the arrhythmia origin therefore requires percutaneous transvascular point-by-point mapping, most often with the support of three-dimensional mapping systems. This technology however is invasive and time-consuming.

EGC mapping is a noninvasive method combining an ECG vest with >250 electrodes for high resolution recording of body surface electrical potentials with the detailed heart-torso anatomical geometry obtained from chest computed tomography. Using the electrical as well as the anatomical information, the local electrical signals over the entire epicardial surface of the entire heart can be calculated using the inverse solution method (fig. 3) [6].

The reliability of arrhythmia localisation by this novel method was compared head-to-head with the current standard invasive endocardial arrhythmia mapping technology using three-dimensional mapping systems. ECG mapping was able to localise the origin of a variety of arrhythmias including accessory pathways and PVCs as well as atrial fibrillation origin.

**Figure 3**

**Overview of the components of the ECG mapping system.**

The key component of the mapping system is the 252 electrodes that are embedded in a vest that can easily be placed on a patient torso. With the vest on, a computed tomographic (CT) scan of the chest obtains the precise anatomical relation between the 252 electrodes on the vest and the epicardial surface of the heart. Once this anatomic relation is defined, 1500 unipolar electrograms can be calculated from the 252 electrodes using the inverse solution method. Next, isopotential, isochronal, and voltage maps can be reconstructed out of the 1500 unipolar electrograms. (Reproduced from Cakulev et al. [60] with permission. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Wolters Kluwer Health. Please contact healthpermissions(at)wolterskluwer.com for further information.)
and ventricular tachycardias noninvasively with similar accuracy to the invasive mapping methods (fig. 4) [6, 66, 67]. In addition, ECG imaging has the advantage of identifying the tachycardia mechanism within just a few heart beats, because it provides simultaneous global activation mapping of the entire heart. The conventional invasive technology using sequential point-by-point mapping is much more time consuming and can be unsuccessful in a relevant proportion of patients because of the infrequent occurrence of the arrhythmia. Preliminary work has recently taken advantage of the global mapping property of ECG imaging in patients with persistent atrial fibrillation [68]. Using ECG imaging, the authors were able to identify driver domains in distinct areas of the right and left atrium the day before the ablation procedure. Targeting those predefined areas for ablation during the procedure, they were able to achieve AF termination with significantly less ablation compared with a control group (ablation time 28 vs 65 min) [68].

The novel technology of ECG imaging, however, still has relevant limitations. First, further clinical validation is needed, given that robust correlations of intracardiac mapping data with surface ECG mapping data during arrhythmias is rare. Among other problems, distinction of re-entrant mechanisms from focal mechanisms in the presence of delayed conduction is as yet unresolved. Second, the resolution for mapping of arrhythmias even from the high-voltage generating ventricles is in the range of 1–1.5 cm. The smaller atrial signals, particularly in diseased or ablated atria, further compromise resolution. Third, current systems are unstable in the sense that very small modifications of the original data result in multiple possible and highly erroneous solutions. Nevertheless, this novel and innovative approach certainly has the potential to improve remarkably the noninvasive localisation and characterisation of arrhythmias, to optimise the planning before catheter ablation, to shorten procedure duration and to improve procedural outcome.

**Novel ECG technologies for risk stratification for sudden cardiac death in patients with heart failure, channelopathies or cardiomyopathies, and selection of patients for medical device therapy**

**Current role of the ECG in risk stratification for sudden cardiac death and selection of patients for medical device therapy**

Sudden cardiac death (SCD) is the most feared consequence of almost all forms of heart disease. In Western countries, 50–100 sudden unexpected cardiac deaths occur per 100000 population every year [69]. Ventricular tachycardia and ventricular fibrillation account for about half of the events. Risk stratification for SCD in patients with heart failure, channelopathies (such as Brugada syndrome or long QT syndrome) and cardiomyopathies (such as hypertrophic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy) is important to optimise treatment and to allocate medical resources. One particular challenge is the selection of candidates for implantable cardioverter defibrillator (ICD) therapy for primary prevention of SCD.

From studies performed over the past two decades, it was learned that ICDs can prevent SCD in many forms of heart diseases [70, 71]. Current guidelines recommend ICD implantation for primary prevention of SCD in patients with heart failure and a left ventricular ejection fraction ≤35% [72]. With regards to channelopathies and cardiomyopathies, the role of ICD implantation for primary prevention of SCD is much less clear. Taken together, current risk stratification is suboptimal: only a minority of patients receiving ICDs will receive appropriate shocks. Conversely, the majority of SCD events occur in patients with an LVEF >35%, most of whom, according to current guidelines, are not candidates for an ICD [73].

The 12-lead ECG is a simple and cheap test providing information associated with anatomical (presence and extent of myocardial scar) and electrophysiological (repolarisation heterogeneity) cardiac pathological features. While markers obtained from the Holter ECG, including heart rate turbulence or T-wave alternans, may play a role in patient selection for ICD therapies, the 12-lead ECG currently is hardly used clinically for risk stratification in heart failure patients.

In the subgroup of patients with heart failure and complete left bundle-branch block (LBBB), cardiac resynchronisation therapy (CRT) offers a benefit in terms of heart failure symptoms and mortality [74]. The 12-lead-ECG is recommended for selection of patients for CRT implantation [74]. However, with the criteria recommended by current guidelines [74], approximately one third of patients undergoing CRT implantation do not obtain a relevant clinical benefit (“nonresponse”). A better knowledge of the pathophysiological conditions of the underlying heart muscle...
Novel ECG markers assessing ventricular depolarisation for risk stratification of SCD

The first 12-lead ECG marker of ventricular depolarisation assessed was the QRS duration (QRSd), which was found to correlate with cardiovascular mortality in the general population [75] as well as in patients with structural heart disease [76]. In order to detect and quantify myocardial scar with the 12-lead ECG, a manual QRS score was developed assessing 54 criteria and 10 leads, and assigning up to a maximum of 32 points for indicators of scarring, adjusted for conduction abnormalities (bundle-branch block patterns and LV hypertrophy), with each point corresponding to 3% of LV mass [77]. A good correlation between the estimated amount of LV scar based on the ECG QRS score and the amount of LV scar on cardiac MRI was found [78], which also makes the QRS score a marker of potential interest in assessing residual viability after myocardial infarction. Also, the QRS score correlated well with inducibility of VT during electrophysiological study [78] and with the occurrence of ICD shocks in primary prevention patients (hazard ratio for VT/VF events 0.5 in patients with a QRS score of 0) [79]. However, manual calculation of the QRS score takes up to 10 minutes per ECG, which precluded clinical application. An automated version of the QRS score was recently developed that adjusts for conduction abnormalities and measures all the 54 criteria automatically [80]. When using the automated QRS score to screen entire health system ECG databases, a QRS Score ≥5 was associated with an increase in mortality (odds ratio 2.33) [80]. The agreement between the manually adjudicated and the automated QRS score was high and the average absolute differences between the two scores was only 1.2 ± 1.5 points [81].

Another indicator of myocardial scar is fragmentation of the QRS complex (fQRS). Indeed, the presence of a fQRS was found both in postinfarct patients [82, 83] and in patients with nonischaemic cardiomyopathies [84]. The presence of fQRS was associated with an increase in mortality and arrhythmic events in stable CAD patients as well as in patients with ACS [84]. Limitations of the fQRS include its qualitative visual definition, which is left to the interpreters experience as well on the appropriate ECG filter settings. An automated quantitative measurement of fQRS therefore seems to be the next step needed in order to allow its use in clinical practice.

Novel ECG markers assessing ventricular repolarisation for risk stratification of SCD

Using the standard 12-lead ECG, research assessing repolarisation has primarily focused on markers reflecting repolarisation heterogeneity that are available from a single ECG beat. The simplest of these markers has been the QTc interval. Outside the inherited long-QT syndromes, a prolonged corrected QT interval was also predictive of sudden death in the general population [85], as well as in patients with CAD [86]. Based on data from SCD survivors, the early repolarisation pattern has been recognised as a potential risk marker for SCD [87]. This was confirmed in population-based epidemiological data, but the observed increase in risk was only 1.28, which seemed too small to be used in clinical practice at the moment [88]. The QRS-T-angle measured between the QRS-vector and the T-wave vector reflects depolarisation-repolarisation heterogeneity [89]. It was found to predict cardiac death in the general population [90], cardiac-related admissions and death in patients with chronic heart failure [91], and adverse events after AMI [92], with hazard ratios reaching up to 2 for patients with an abnormal QRS-T-angle. Given that the QRS-T-angle can be calculated easily in an automated fashion, it has been used successfully to screen entire health system ECG databases to identify patients at increased risk of death [80]. The dispersion of the QT-interval, measured as the difference between the shortest and the longest QT interval of all 12 leads, is another method to assess repolarisation heterogeneity. It was assessed as a marker for risk stratification in patients with chronic heart failure as well as in postmyocardial infarction patients [93, 94], but ultimately failed to be predictive in prospective studies [95].

The T-wave peak to T-wave end interval (Tpe) has more recently been shown to correlate with transmural as well as regional dispersion of repolarisation [96]. Clinically, the Tpe predicted SCD in the general population [97] as well as in patients with CAD [98], and appropriate ICD therapies in patients undergoing ICD implantation for primary prevention of SCD [99]. While the clinical value of individual markers has remained limited so far, it is conceivable that a combination of ECG risk markers will help to improve identification of patients at risk of SCD.

Novel ECG technologies to improve patient selection for cardiac resynchronisation therapy

While initial CRT studies included patients with prolonged QRS duration regardless of the underlying bundle-branch block morphology [100], subsequent subgroup analysis revealed that best results are seen in patients with LBBB and severe QRS prolongation of >150 ms [101, 102]. The QRS score as described above has been used to predict a favourable response to CRT. It was found that patients with a low estimated LV scar burden (QRS score 0–3) had a response rate of 78% compared with a response rate of only 45% in patients with a QRS score >9 [103]. The QRS score can therefore be used to identify a subgroup of severely sick patients with a large amount of LV scar who are unlikely to benefit from CRT despite the presence of LBBB. More recently, parameters from vectorcardiography have been used to predict a favourable response to CRT [5]. The three-dimensional area of the QRS complex, which combines QRS duration and electrical force of ventricular activation, performed best and predicted CRT response in LBBB patients better than QRS duration (area under the curve 0.78 vs 0.62, p = 0.03) [5]. And, finally, ECG imaging as described above has been used to study electrical dyssynchrony in patients undergoing CRT, who had LBBB or nonspecific intraventricular conduction disturbance (NICD) [104]. The noninvasive measurement of ventricular electronic uncoupling, and the difference between LV and RV activation time, predicted CRT response better than QRS duration or the presence of LBBB and, in particular identified all NICD patients who had a favourable response to CRT.
This technology therefore might assist in the identification of potential CRT responders in the absence of LBBB.

**Outlook**

Despite the promising preliminary data presented, none of the advanced ECG markers and technologies has yet accomplished the transition into clinical practice. The reasons for this are twofold: with some of the markers, the added clinical benefit is only modest, while other markers lack sufficient clinical validation. A close and open collaboration between ECG engineers in academic institutions and the industry on the one side and clinical cardiologists on the other side is now critical to improve the novel technologies further. And adequate datasets from large clinical studies with digital ECG data available for analysis are needed for broader validation of the novel technologies in large unselected patient cohorts. Successful completion of the above two tasks has the potential to allow the transition of several advanced ECG markers and technologies into routine clinical practice, which could shift the role of the surface ECG in clinical cardiology as outlined in table 1.

**Conclusions**

The remarkable progress in biomedical computing, signal processing and computational power has generated novel ECG markers and technologies. These offer new opportunities to address current unmet needs in clinical cardiology in (1) the diagnosis of AMI and detection of myocardial ischemia; (2) identification and management of patients with cardiac arrhythmias; and (3) risk stratification of sudden cardiac death and selection of patients for medical device therapy. Further refinement of these technologies and broader validation in large unselected patient cohorts are the next step needed to facilitate translation of advanced ECG technologies into clinical cardiology.

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**References**


**Table 1: Unmet clinical needs.**

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ECG = electrocardiogram; AMI = acute myocardial infarction; AF = atrial fibrillation; SR = sinus rhythm; SCD = sudden cardiac death; CRT = cardiac resynchronisation therapy


McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33:1787–847.


Figure 1

Normal sinus beat from lead II of a 12-lead ECG. Period (A) marks the ventricular depolarisation occurring during the QRS complex. Period (B) marks ventricular repolarisation consisting of the ST-segment and the T-wave.
Figure 2
Polarmap of the unipolar epicardial surface potentials obtained at the J-point with ECG imaging in a patient with an left circumflex artery occlusion.

Epicardial unipolar potential distribution obtained from J-point measurements. Yellow to red areas indicate positive potentials and green areas indicate negative potentials. Following the American Heart Association standard 17 segment model, the central part of the image corresponds to the left-ventricular apex and the outermost segments correspond to the basal part of the left ventricular myocardium.
Figure 3

Overview of the components of the ECG mapping system.

The key component of the mapping system is the 252 electrodes that are embedded in a vest that can easily be placed on a patient torso. With the vest on, a computed tomographic (CT) scan of the chest obtains the precise anatomical relation between the 252 electrodes on the vest and the epicardial surface of the heart. Once this anatomic relation is defined, 1500 unipolar electrograms can be calculated from the 252 electrodes using the inverse solution method. Next, isopotential, isochronal, and voltage maps can be reconstructed out of the 1500 unipolar electrograms (reproduced from Cakulev et al. [66] with permission)
Figure 4
Maps obtained from ECG mapping and standard invasive mapping in a patient with incessant atrial tachycardia.
On the left side of the figure, the map obtained with ECG mapping demonstrated focal activation of the left atrium, with the earliest site of activation on the left atrial roof. On the right side of the figure, the CARTO map with the site of successful ablation that terminated the tachycardia. As can be appreciated, the ECG mapping techniques successfully identified both the tachycardia mechanism as well as the site of earliest activation (reproduced from Cakulev et al. with permission).
LAA = left atrial appendage; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; RAA = right atrial appendage; RSPV = right superior pulmonary vein; RIPV = right inferior pulmonary vein; SVC = superior vena cava