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Review Article

Electrocardiologic and related methods of non-invasive detection and risk stratification in myocardial ischemia: state of the art and perspectives

Elektrokardiologische und angrenzende Methoden zur nichtinvasiven Erkennung von Myokardischämien und Risikostratifizierung: Stand der Technik und Perspektiven

Abstract

Background: Electrocardiographic methods still provide the bulk of cardiovascular diagnostics. Cardiac ischemia is associated with typical alterations in cardiac biosignals that have to be measured, analyzed by mathematical algorithms and allegorized for further clinical diagnostics. The fast growing fields of biomedical engineering and applied sciences are intensely focused on generating new approaches to cardiac biosignal analysis for diagnosis and risk stratification in myocardial ischemia.

Objectives: To present and review the state of the art in and new approaches to electrocardiologic methods for non-invasive detection and risk stratification in coronary artery disease (CAD) and myocardial ischemia; secondarily, to explore the future perspectives of these methods.

Methods: In follow-up to the Expert Discussion at the 2008 Workshop on "Biosignal Analysis" of the German Society of Biomedical Engineering in Potsdam, Germany, we comprehensively searched the pertinent literature and databases and compiled the results into this review. Then, we categorized the state-of-the-art methods and selected new approaches based on their applications in detection and risk stratification of myocardial ischemia. Finally, we compared the pros and cons of the methods and explored their future potentials for cardiology.

Results: Resting ECG, particularly suited for detecting ST-elevation myocardial infarctions, and exercise ECG, for the diagnosis of stable CAD, are state-of-the-art methods. New exercise-free methods for detecting stable CAD include cardiogoniometry (CGM); methods for detecting acute coronary syndrome without ST elevation are Body Surface Potential Mapping, functional imaging and CGM. Heart rate variability and blood pressure variability analyses, microvolt T-wave alternans and signal-averaged ECG mainly serve in detecting and stratifying the risk for lethal arrythmias in patients with myocardial ischemia or previous myocardial infarctions. Telemedicine and ambient-assisted living support the electrocardiological monitoring of at-risk patients.

Conclusions: There are many promising methods for the exercise-free, non-invasive detection of CAD and myocardial ischemia in the stable and acute phases. In the coming years, these new methods will help enhance state-of-the-art procedures in routine diagnostics. The future can expect that equally novel methods for risk stratification and telemedicine will transition into clinical routine.

Keywords: resting electrocardiography, exercise electrocardiography, cardiogoniometry, body surface potential mapping, heart rate variability, functional imaging

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Zusammenfassung

Hintergrund: Elektrokardiografische Verfahren stellen nach wie vor die primär wichtigsten Methoden zur kardiologischen Diagnostik dar. Eine Herzischämie geht mit typischen Veränderungen kardialer Biosignale einher, die anhand mathematischer Algorithmen analysiert und für den weiteren klinischen Pfad aufbereitet werden müssen. Die rasant wachsende Biomedizintechnik sowie angewandte Wissenschaften beschäftigen sich intensiv mit neuen Ansätzen zur Auswertung kardialer Biosignale zur Ischämiediagnostik und Risikostratifizierung.

Ziele: Hauptziel dieser Übersichtsarbeit ist es, den gegenwärtigen Stand der Technik sowie neue Ansätze im Bereich elektrokardiologischer Verfahren zur nicht-invasiven Erkennung und Risikostratifizierung von koronarer Herzkrankheit (KHK) und Myokardischämie vorzustellen und zu bewerten. Als Sekundärziel werden die Zukunftsperspektiven dieser Verfahren aufgezeigt.

Methoden: Beginnend mit Expertendiskussionen während des Workshops „Biosignalverarbeitung“ der Deutschen Gesellschaft für Biomedizinische Technik (2008 in Potsdam) sowie anschließenden intensiven Recherchen der Literatur und Datenbanken wurde dieser Review erstellt. Es erfolgte eine Kategorisierung von Verfahren des Standes der Technik sowie ausgewählter neuer Ansätze entsprechend ihrer Einsatzgebiete zur Ischämiediagnostik und Risikostratifizierung. Die Vor- und Nachteile wurden aufgezeigt und die künftigen Möglichkeiten dieser Verfahren in der Kardiologie untersucht.

Ergebnisse: Als Stand der Technik anzusehen ist das Ruhe-EKG (insbesondere geeignet für Erkennung von ST-Hebungsinfarkten) und das Belastungs-EKG (Diagnostik von stabiler KHK). Neue belastungsfreie Verfahren zur Erkennung von stabiler KHK sind die Kardiogoniometrie (KGM) sowie zur Erkennung des Akuten Koronarsyndroms ohne ST-Hebung das Body Surface Potential Mapping, Funktionelle Bildgebung sowie die KGM. Analyse von Herzfrequenz- und Blutdruckvariabilität, T-Wellen-Alternans und Spätpotentialen dienen vorrangig der Erkennung und Stratifizierung des Risikos für letale Arrythmien bei Patienten mit Myokardischämie oder nach durchlebtem Myokardinfarkt. Telemedizin und technologieunterstütztes Wohnen (Ambient Assisted Living) unterstützen das elektrokardiologische Monitoring von Risikopatienten.

Schlussfolgerungen: Es gibt vielversprechende Ansätzen insbesondere zur belastungsfreien nichtinvasiven Erkennung von KHK und Myokardischämie in stabiler Phase und Akutsituation, welche in den nächsten Jahren die Standardverfahren in der Routinediagnostik ergänzen werden. Ebenso neue Verfahren der Risikostratifizierung sowie telemedizinische Techniken werden den Übergang in die Routineanwendung finden.

Schlüsselwörter: Ruhe-EKG, Ergometrie, Kardiogoniometrie, KGM, Mapping-EKG, Herzfrequenzvariabilität, Blutdruckvariabilität, NSTE-ACS, Koronare Herzkrankheit

Introduction

The history of clinical electrocardiography started in 1887 when August Waller recorded the first electrocardiogram on a galvanometer [1]. In 1902, the "Father of Electrocardiography", Willem Einthoven, reproduced the waveforms of the electrocardiogram (ECG) [2] which he named P, Q, R, S and T, and later added the U wave. Einthoven illustrated the cardiac electromagnetic current based on a single vector (dipole) in the middle of an isosceles triangle. His principle definitions are still in use today.

The first commercial electrocardiograph was manufactured by the Cambridge Instrument Company in 1908. In the 1930s, the integrated recording device, the string galvanometer, was replaced by vacuum tube amplifiers, which in turn gave way to modern transistors and electronics [3]. Since then, the ECG has become indispensible in cardiology and enjoys widespread use in general medicine.

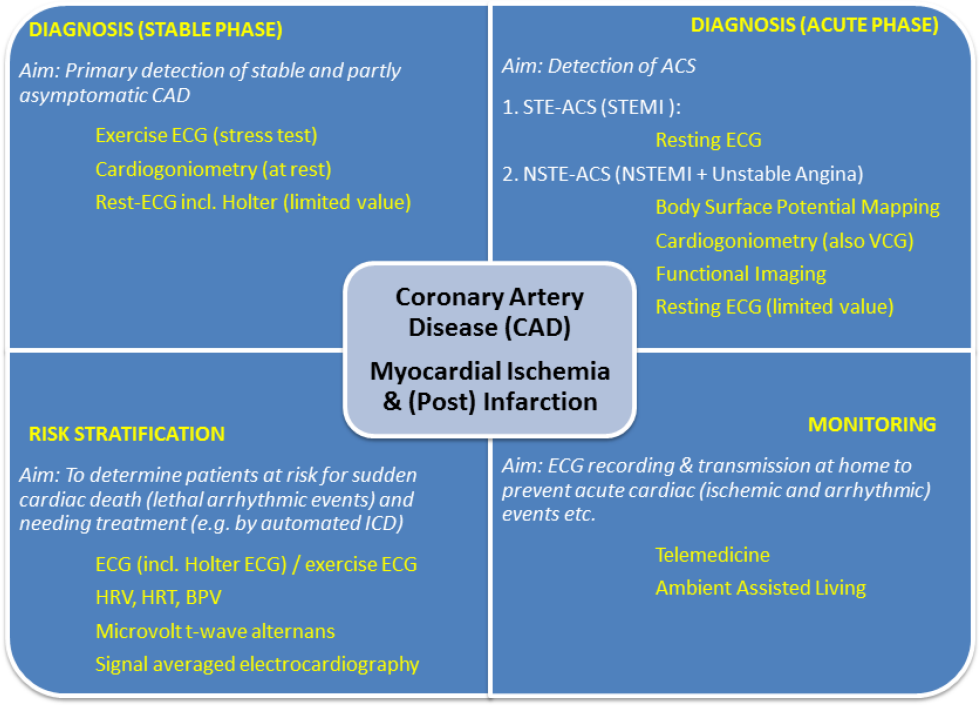

Figure 1: Overview of electrocardiologic and related methods including their intended applications

However, the standard 12-lead ECG at rest is often insensitive for diagnosing coronary artery disease (CAD), one of the most frequent causes of death in industrialized countries. The resting 12-lead ECG, still the most common method, is available in every hospital and has been used on nearly every patient. Bicycle and treadmill electrocardiography was developed for cardiologists to detect myocardial ischemia under stress conditions. The standard stress ECG attains a moderate accuracy for CAD and myocardial ischemia, but is of feasibility in screening tests, especially in asymptomatic patients. The 24-hour Holter ECG is used for the primary diagnosis of cardiac arrhythmias. In patients with acute coronary syndrome (ACS), only ST-elevation myocardial infarctions (STEMI) are unequivocally visible on the standard ECG. Non-ST-elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UAP) are identifiable with a low sensitivity only. Enhanced ECG analysis tools are relevant for ischemia diagnosis and risk stratification, but have not become routine diagnostics yet either.

About 15% of people die of sudden cardiac death caused by underlying arrhythmic events [4]. Approximately 50% of all CAD deaths are sudden and unexpected, occurring within 1 hour after a change in cardiac status [5]. Since the introduction of intracardiac electrocardiography by Scherlag in 1969 [6] new therapeutic methods for certain arrhythmia, such as radiofrequency ablation of reentry tachycardia or of atrial fibrillation, have been developed [7], [8]. Here, a challenge for future electrocardiography is to define screening parameters to predict the individual risk of arrhythmic events.

Objectives and methods

The aim of this review is to present the state of the art in electrocardiologic methods for non-invasive detection and risk stratification in coronary artery disease (CAD) with emphasis on myocardial ischemia and its sequelae, secondarily, to explore the future perspectives of these methods. In follow-up to the Expert Discussion as part of the 2008 Workshop on Biosignal Analysis held by the German Society of Biomedical Engineering in Potsdam, Germany [9], we initiated our search of the pertinent literature and databases and compiled the results into this review. Based on the compiled data, we established and then categorized a selection of state-of-the-art methods in and new approaches to the detection and risk stratification of myocardial ischemia. Finally, we determined the pros and cons of each method and explored their future potentials for cardiology. The focus was on trends in non-invasive electrocardiography for cardiac ischemia from the perspective of biosignal analysis and applied science.

Results

An overview of our categorization of the methods into main categories is presented in Figure 1, Table 1 and Table 2. The following describes our analysis of each method by category.

Table 1: Selected electrocardiography-based methods for the detection of myocardial ischemia and CAD in stable and acute phases

Method	Main indications	Advantages	Disadvantages	Future aspects	Ref.
Resting ECG	Detection of STEMI and differential diagnosis for ACS.	Most established standard. Fully automated analyses possible.	Poor detection of stable CAD, unstable angina pectoris and NSTEMI.	Mature method, technical and electronic refinements expected, i.e. Home Care Telemedicine.	[15]
Exercise ECG	Primary detection of stable CAD.	Meta-analyses on >24,000 patients available. Semi-automated analyses possible. Yields feasible prognosis.	Cannot screen ~30% of patients. Mean sensitivity: ~67%. Mean specificity: ~72% in pat. w/out previous myocardial infarction.	Mature method, technical, electronic refinements expected. New configurations with imaging techniques.	[11] [19] [21]
BSPM	Differential diagnosis for NSTE-ACS (NSTEMI + unstable angina) undetectable by ECG.	High spatial resolution.	Complexity of recording, low availability.	New configurations and new generations of electrodes.	[27] [31] [32] [34]
VCG/CGM	Resting detection of stable CAD. Detection of NSTE-ACS (NSTEMI + unstable angina).	CGM easy and stress-free Fully automated analyses. ⇑ Sensitivity ~73%. ⇑ Specificity: ~84%.	VCG is difficult to perform and analyze. Few CGM studies on ~1,000 patients.	Prospective CGM validation on large cohorts ongoing.	[37] [46] [48] [50] [51] [52]

Table 2: Selected electrocardiography-based methods for arrhythmic risk detection and stratification for ACD

Method	Advantages	Disadvantages	Future aspects	Ref.
Signal Averaged ECG	⇑ Temporal resolution, detection of late potentials and fragmentation.	Needs preprocessing. Little standardization. ⇓ specificity.	Underlying procedure for advanced ECG, i.e. detection of arrhythmic risk.	[105] [106] [107] [108] [109]
HRV	Available in Holter and short term recordings. Yields feasible prognosis.	Needs preprocessing. ⇓ Specificity.	⇑ Accuracy by advantaged and nonlinear analyses.	[53] [57] [59]
MTWA	Non-invasive method for sudden cardiac death risk assessment. ⇑ NPV ~95%	⇓ PPV (<20%).	Prospective multicenter studies ongoing.	[85] [86] [87]

State-of-the-art electrocardiography

Resting electrocardiography

While resting ECG may reveal signs of previous infarctions and diagnostically relevant information in ACS, it is inferior for diagnosing CAD in the non-acute (chronic) stage. Typical signs provided by the 12-lead ECG for chronic ischemic injury after myocardial infarction, such as Q-wave, T-wave polarity and R-reduction, are empirically analyzed by sight. Such indicators could be absent especially after tiny, non Q-wave myocardial infarction [10], [11]. A resting ECG might miss the typical sign of ischemia, i.e. ST-segment depression, only demonstrable under exercise conditions. Myocardial ischemia is potentially a reversible functional alteration and mainly alters the repolarization in the affected areas. Primarily, the subendocardial myocardium is affected with the ST-vector pointing from epicardial to endocardial, resulting in an ST-depression in the surface ECG. In transmural injury, the direction of the ST-vectors reverses from endocardial to epicardial and an ST-elevation occurs. ECG changes in acute ischemia are best visualized in limb leads I, II and precordial leads V4–6, which represent the most myocardial mass of the anterior and apical area of the left ventricle. The course of the ST depression is horizontal or descending and can be accompanied by a T-wave flattening or a preterminal negative T-wave. Less common manifestations of acute coronary insufficiency are temporary banking of the T wave or U wave inversion [12].

The 12-lead ECG recorded at rest is central part to the diagnosis of ACS. Figure 2 illustrates different infarction/electrocardiographic phases recorded in STEMI [13]. A STEMI is easily diagnosed when the ECG shows ST-elevations of ≥0.1 mV in at least two sequential limb leads or ≥0.2 mV in at least two sequential precordial leads. In acute STEMI, the 12-lead resting ECG is the leading diagnostic tool for emergencies [14] and life-threatening situations where the indication for invasive angiography needs to be rendered rapidly. Patients with acute chest pain lasting longer that 20 min and a normal resting ECG without ST-elevation can be presumed to have an NSTE acute coronary syndrome (NSTE-ASC, UAP). ECG's sensitivity for detecting true NST-ASC is very low (~20%) [15]. Additional laboratory workups, like the serum troponin T test can help detect myocardial necrosis with suspected underlying coronary occlusion. The troponin T level increases about 4 to 6 hours after the first myocardial damage. UAP should be distinguished from early myocardial infarction as quickly as possible – a diagnosis impacting emergency treatment and prognosis. In all patients at high risk for life-threatening arrhythmias, continuous ECG monitoring and regular analyses of the ST-segment, especially any elevations are imperative [16].

Different kinds of arrhythmias, particularly ischemia-associated ventricular arrhythmias could indicate myocardial ischemia and be critical and live threatening. New conduction disorders such as left bundle branch blocks are suspicious for acute myocardial ischemia. Such arrhythmias and conduction disorders are often initially diagnosed by resting ECG and then weighed into the differential diagnosis along with clinical signs andlaboratory results for acute myocardial infarction. Current procedure can be enhanced by advanced diagnostic methods and intensive caremonitoring [17].

Exercise electrocardiography

The 2002 AHA/ACC Guidelines on exercise testing [11] define two main groups for whom exercise testing is indicated 1) patients with suspected obstructive CAD and 2) patients with a documented myocardial infarction or prior coronary angiography demonstrating significant disease or verified CAD. Figure 3 shows typical pathological and physiological changes.

Knowledge of a patient's pre-test probability is recommended and required [18]. According to Bayes' theorem, the probability of a patient having the disease after a test has been carried out is the product of the disease probability before the test and the probability that the test was accurate. A meta-analysis of 147 consecutively published reports involving 24,074 patients undergoing both coronary angiography and exercise testing revealed a wide variability in sensitivity and specificity for exercise ECG [19] These studies demonstrated a mean sensitivity of 67% and a mean specificity of 72% in patients without previous MIs.

A special type of ECG uses three to six additional leads. Small studies have shown that a 15-lead stress ECG can improve sensitivity compared to the 12 standard channel recordings (from 52% to 89% in one-vessel diseases, from 71% to 94% in two-vessel diseases, and from 83% to 95% in three-vessel diseases). The additional leads of the 15-to-18-channel ECG also allow improved identification and risk stratification particularly of right ventricular ischemia and infarction [20].

The fact that many patients are not able to perform adequate bicycle exercise testing or do not reach the target heart rate is the main disadvantage of exercise ECG. In one study investigating the prognostic significance of exercise testing on 6,296 patients treated with thrombolytic agents secondary to myocardial infarction, Villella et al. showed that the exercise ECG examination was contraindicated in 62.5% [21]. Patients unable to exercise because of physical limitations that affect exercise capacity (e.g. arthritis, amputations, severe peripheral vascular disease, severe chronic obstructive pulmonary disease, or general debility) should undergo pharmacological stress testing in combination with imaging. In this context, Figure 4 provides an overview of the compiled guidelines.

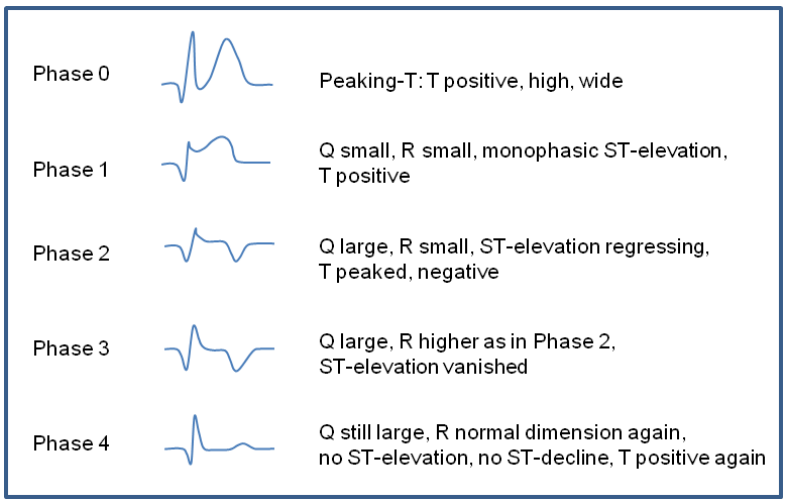

Figure 2: Electrocardiographic phases of STEMI adapted from the Pschyrembel database [13]

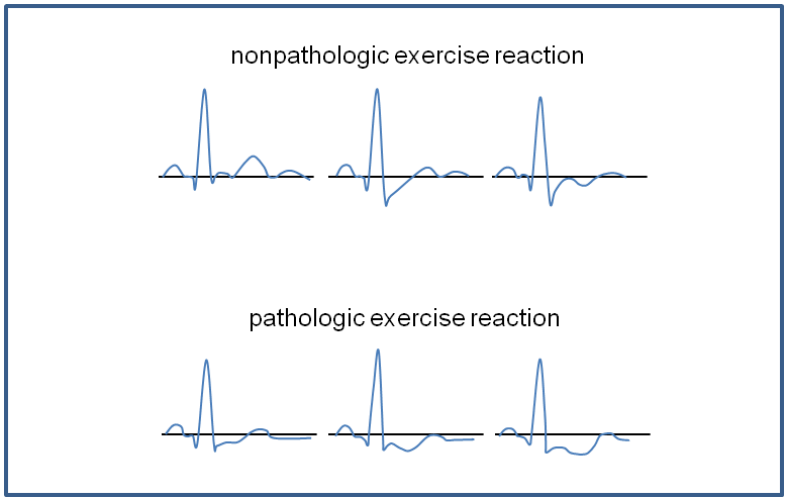

Figure 3: Nonpathologic (top) and pathologic (bottom) exercise ECG reactions adapted from Pschyrembel database [13]

Enhanced electrocardiographic approaches

Signal averaged electrocardiography

Signal-averaged ECG was introduced in the 1970s and primarily focuses on His bundle recordings and detection of patients at high risk of sudden cardiac death after myocardial infarction and is shown in Figure 5 [22]. Microvolt level ventricular late potentials (VLP) are frequently detected in patients with ventricular tachycardia (VT), especially after myocardial infarction. The late potentials correlate with delayed and disorganized activation in small areas of the myocardium. The prognostic significance was reviewed in 1987 [23] in 778 patients; VT or sudden cardiac death (SCD) increases in abnormal signal averaged ECG from 0.8–3.5% to 16.7–28.9%. VLP assessment offers a practical and low-cost tool for the clinical cardiologist to recognize the possible electrophysiological substrate underlying life-threatening ventricular arrhythmias [24]. However, one of the most important problems in VLP analysis is the high number of false positive results. In combination with heart rate variability (HRV) analysis VLP could enhance the risk stratification [25].

The main task in recording low-level bioelectrical signals from the heart is to reduce extraneous noise. By signal averaging the level of noise that contaminates the ECG can be decreased. The sources of noise are skeletal muscle activity, electrodes and electrical noise from amplifiers. Muscle noise cannot be eliminated by filtering, because its frequency content is similar to high-frequency (over 25 Hz) cardiac potentials. Averaging 100 cycles will reduce noise 10fold [26]. However, some problems of the applied sequential averaging techniques remain as e.g. the missing but presupposed stationarity of biosignals and the dependency on time stable events leading to an at least smoothing effect in potentials with beat-to-beat varying distance to the trigger point (R peak). Indices from time domain and frequency domain were developed to characterize VLPs. Later on VLPs could be extracted from magnetocardiogram and from 24-hour Holter recordings.

Body surface potential mapping

Multichannel ECG provides comprehensive 3-dimensional data of the electrical currents from the heart on the body

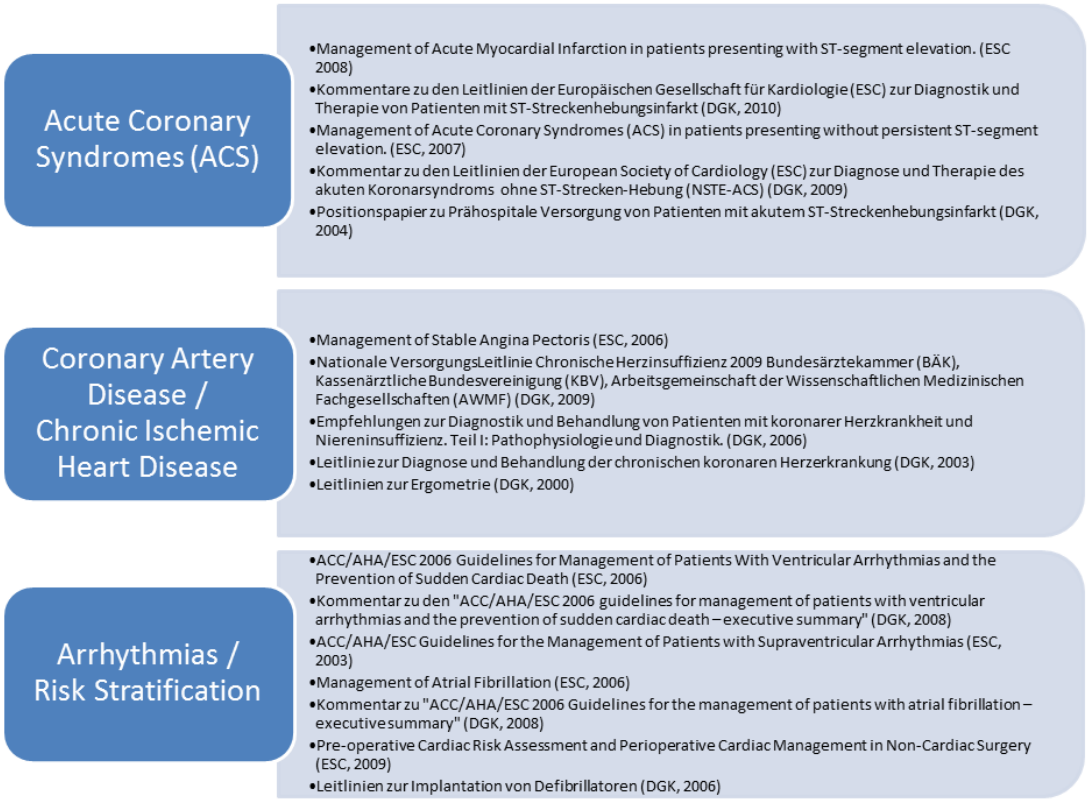

Figure 4: Overview of the guidelines issued by the European Society of Cardiology (ESC) and German Society of Cardiology (DGK) considering electrocardiologic and related methods concerning acute and stable ischemic situations and risk stratification

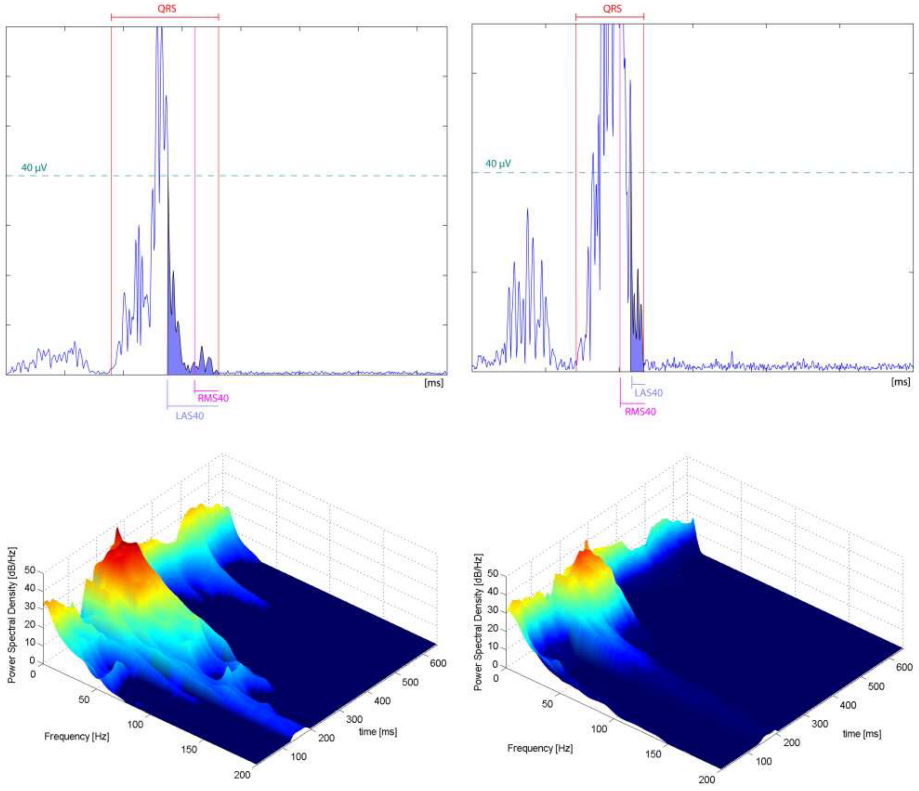

Figure 5: Example for high-resolution ECG

Top: Sum vector, Bottom: 3 dimensional frequency spectrum; Left: Patient with late potentials at high risk for sudden cardiac death with prolonged QRS in sum vector (low-amplitude electrical signal which occurs in the terminal QRS complex or within the ST segment) and enhanced high frequency components in the spectrum. Right: Patient with low risk profile and no late potentials, see also [22].

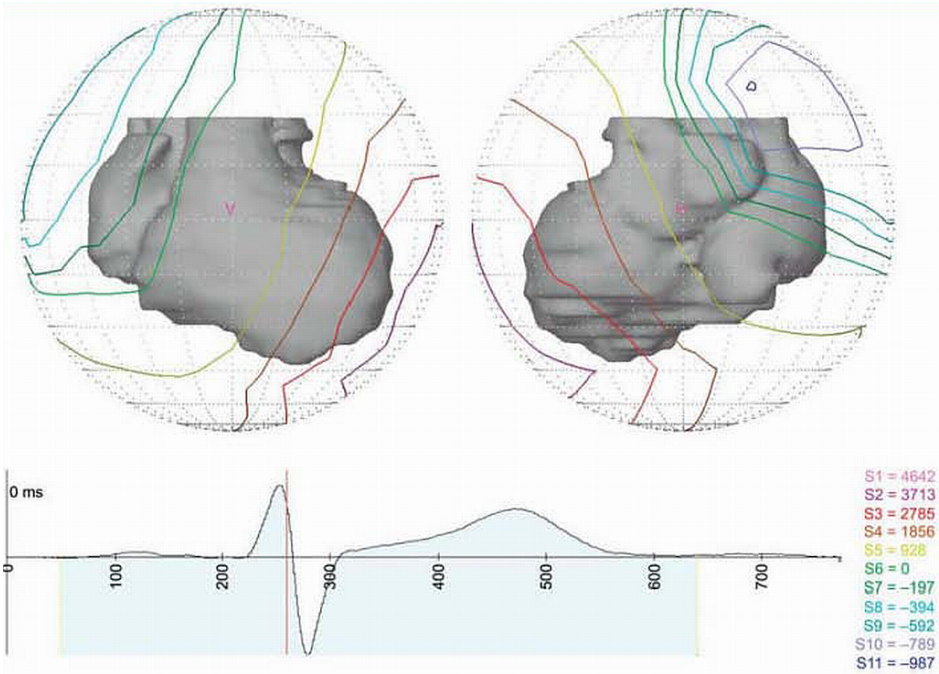

Figure 6: Corrected body surface potential map at the time point 260 ms (cursor position)
Eleven amplitude levels from S11 to S1 in mV are shown (V - front view; H - back of the sphere and the heart). With the kind permission of [28].

surface and can give access to high-resolution spatiotemporal analyses in patients with suspected CAD. Body surface potential mapping (BSPM) (Figure 6) uses 64 or more electrodes (as many as 120) to record and measure electrocardiac activity over a much larger portion of the torso than the traditional 12 lead-ECG [27], [28].
BSPM features different approaches for registering different cardiac conditions and has been used for diagnosing old inferior myocardial infarctions, localizing the bypass pathway in Wolff-Parkinson-White syndrome and recognizing ventricular hypertrophy. BSPM may show potential in ascertaining the location, size, and severity of infarcted areas in acute myocardial infarction and identify the effects of interventions to reduce infarct size [29], [30], [31]. More research into the value of BSPM in diagnosing ACS is needed [32], [33].
Alternative lead systems must be compared to standard 12-lead ECG in well-designed clinical studies to achieve clinical acceptance. While, Lefebvre and Hoekstra (2007) demonstrated the usefulness of BSPM in the emergency department in their large-scale OCCULT-MI trial [34], this new technology is limited by the complexity of records and analyses requiring up to 120 leads, overly sophisticated instrumentation and dedicated personnel. The use of a larger number of leads in BSPM may provide clinically relevant information for specific patients groups. Ongoing research continues on BSPM, but its clinical effectiveness has not been established in larger studies.

Vectorcardiography and cardiogoniometry

Einthoven's Nobel prize-winning illustration of the cardiac electromagnetic current was based on a single vector (dipole) in the middle of an isosceles triangle. The electrical and geometrical requirements for his hypothesis were a spherical body surface with a homogeneous volume conductor and only one source for the dipole in the middle.
Because a single human heart cycle does not quantitatively fulfill these conditions, a method for analyzing 3D electrocardiography data, known as vectorcardiography (VCG) was developed the late 1930s and many different VCG lead methods advanced since then [35], [36], [37]. The most common is the 7-lead method developed by Frank [38]. VCG was especially popular from the 1950s to 1980s. A widely published method, it was mainly used for ischemia diagnosis and has proved its potential in principle [39], [40], [41], [42], [43], [44], [45]. For example, Mengden et al. retrospectively showed that VCG using 5 parameters for discriminant analysis has a sensitivity of 77.8% and a specificity of 78.4% in diagnosing a coronary condition compared to coronary angiography [39]. Difficult to interpret, VCG never became established as a routine method and, despite new approaches for use in ischemia [46], has lost importance.
Rubulis has summarized the results of VCG studies and publications from the Karolinska Institute, Stockholm on the analysis of T-vectors and T-loop morphology in myocardial ischemia. He showed significant differences in ventricular repolarization in patients with CAD [47] compared to the healthy control group, even in the ab-

sence of major co-morbidities. At rest, the areas under the T-loop and its shape and roundness significantly differed between CAD patients and healthy controls. Mostly, acute ischemia consistently reduced T-loop planarity and increased its roundness and area under T-loop [47]. Rubulis further investigated the relationship between the size and location of myocardium at risk and the ventricular repolarization response during ischemia (during elective PCI and Tc-99m-sestamibi administration). Ventricular repolarization measures during maximum ischemia were compared with baseline measurements and the changes were related to the myocardium at risk and the occluded artery. He found significant correlations between the size of myocardium at risk and ST-segment alterations and changes of T-loop planarity, shape and roundness. In a longitudinal cohort study, Rubulis followed 187 CAD patients for 8±1 years. Cardiovascular death was independently predicted by a prolonged QRS duration and a widened QRS-T angle (spatial angle between maximum vectors of R-loop and T-loop). Myocardial infarction was most consistently predicted by increased T-loop planarity [46].

Cardiogoniometry

Cardiogoniometry (CGM, Figure 7) is a spatiotemporal vectorcardiographic advancement of the VCG principle. CGM was introduced by Sanz [48] and further developed and tested in patients with stable CAD by Schuepbach [49]. CGM uses three bipolar electrocardiographic derivatives and automatically analyses a 12-second recording taken at rest using a programmed score. The original scoring system used in the retrospective cohort yielded a sensitivity of 73% and a specificity of 87%. In a prospective cohort, CGM showed a sensitivity of 64% and specificity 82% [50].

For global CAD detection by CGM, Huebner et al. systematically developed a stenosis-specific parameter set [51]. A total of 658 study patients, matched for age, BMI, and gender, were angiographically assigned to 8 stenosis-specific CAD categories or to the controls. One CGM parameter possessing significance ($P<0.05$) and the best diagnostic accuracy was matched to one CAD category. The area under the ROC curve was .80 (global CAD versus controls). A set containing 8 stenosis-specific CGM parameters described variability of R vectors and R-T angles, spatial position and potential distribution of R/T vectors, and ST/T segment alterations.

Further prospective validation of these algorithms is ongoing to evaluate the impact of CGM for early discrimination of non-ST-segment elevation ACSs (NSTE-ACS). The initial results of the prospective multicenter trial CGM@ACS was presented by Toelg et al. (2010). CGM's sensitivity to detect NSTE-ACS patients was 73%. These preliminary results indicate that CGM has a high potential for detecting patients with NSTE-ACS probably earlier than troponin levels [52].

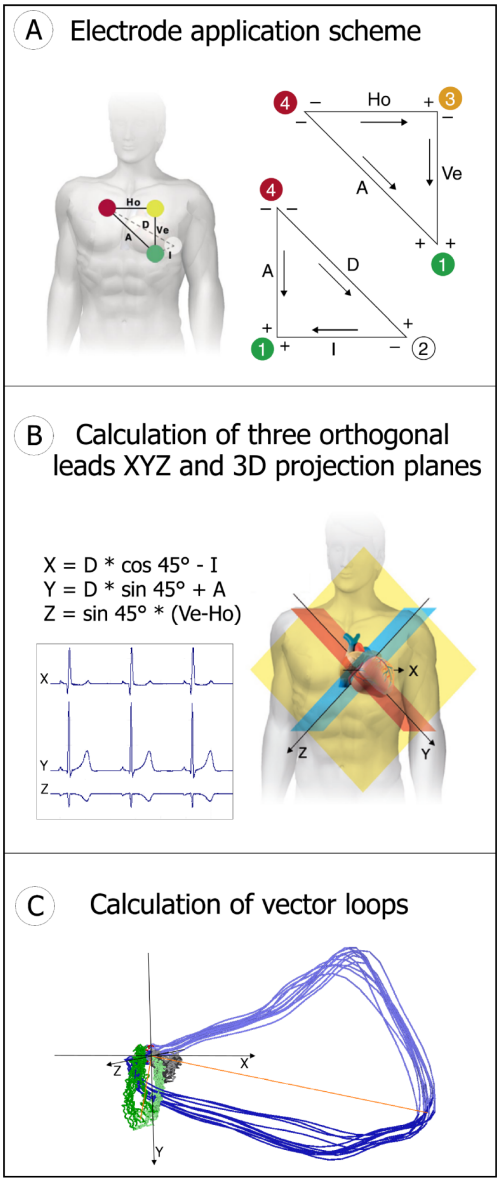

Figure 7: Principles of cardiogoniometry

A) Four electrodes are placed at four points on the patient's thorax as follows: Point 1 (green) at point V4 of Wilson, i.e. in the 5th intercostal space in the mid-clavicular line; point 2 (white) sagittal to electrode 1 on the back (point V8 of Wilson); point 3 (yellow) is located perpendicularly above electrode 1 at 0.7 times the distance between points 1 and 2; point 4 (red) is placed to the right of point 3 at the same distance as between points 1 and 3. The leads are defined as follows: 4-2 D (dorsal), 4-1 A (anterior), 2-1 I (inferior), 4-3 Ho (horizontal), 3-1 Ve (vertical). B) Points 4-2-1 define the oblique sagittal plane OSP (red); points 4-3-1 define the frontal plane (yellow). The third plane (blue) is orthogonal to the two other planes and contains point 3; it is the sagittal plane perpendicular to the OSP. Projection x is oriented in an antero-dorsal direction and lies in the OSP and the sagittal plane perpendicular to the OSP. Projection y is oriented in a baso-apical direction and lies in the OSP (4-2-1) and the frontal plane (4-3-1). Projection z is oriented in a supero-inferior direction relative to the OSP and lies in the frontal plane (4-3-1) and the sagittal plane perpendicular to the OSP. C) Vector loops from projections x, y and z can be calculated within a Cartesian coordinate system. Figure shows R-Loops (blue) and T-loops (green) of 12 heart cycles and maximum vectors of both (red), calculated on median cycle.

Thus far, the advantages of VCG and CGM over standard electrocardiographic methods in ACS, prognostic evaluation and risk stratification have not been proven in larger studies. Recent smaller VCG studies have confirmed in principle the value of these methods in diagnosing CAD and acute ischemia and also in risk stratification for SCD.

Analysis of cardiovascular variability – risk stratification methods

Heart rate variability and heart rate turbulence

The clinical importance of autonomic control became apparent in the late 1980s, when heart rate variability (HRV) was confirmed to be strong and independent predictor of mortality after acute myocardial infarction. There was a significant relationship between the autonomic nervous system and cardiovascular mortality, including sudden cardiac death. Thanks to the availability of high frequency 24-h electrocardiographic Holter recorders, HRV can potentially provide additional valuable insight into physiological and pathological conditions and risk stratification in different cardiac diseases [53], [54], [55]. There are many commercial available automated HRV measurement devices utilizing variety of methods [56], [57], [58], providing cardiologists with a seemingly simple tool for both research and clinical studies.

In 1996, a Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology defined time and frequency domain parameters for the evaluation of the autonomic regulation [59]. The simplest parameters to perform are the time domain measures. With these methods either the heart rate at any point in time or the intervals between successive normal complexes are determined. Various spectral methods [59] for the analysis of the tachogram have been applied since the late 1960s. Power spectral density (PSD) analysis provides the basic information of how power (i.e. variance) is distributed as a function of frequency.

The Framingham study included HRV data from 2501 patients initially free of coronary artery disease or coronary heart failure, showing that a reduced HRV predicted an increased risk for subsequent cardiac events [60]. In another study, the ARIC (Atherosclerosis Risk in Community) study on 2252 patients, a decrease in the high frequency band (HF power) was a significant predictor for an ischemic event [61].

In a study including 715 patients two weeks after myocardial infarction, Bigger et al. tested whether short-term power spectral measures of RR variability predicts all-cause mortality or arrhythmic death. Here, power spectral measures of RR variability proved excellent predictors of all-cause, cardiac, and arrhythmic mortality and sudden death. Patients with low values were 2 to 4 times as likely to die over an average follow-up of 31 months as were patients with high values [62]. The slope of the power-law relationship predicts death in post-infarction patients [63]. According to the authors' observations, a steep power-law slope was a powerful predictor of all-cause mortality or arrhythmic death and predicted these outcomes better than the traditional HRV parameters of the frequency domain.

A multivariate approach [64] yielded the best prediction for all-cause mortality and sudden arrhythmic death. This study enrolled 572 survivors of acute myocardial infarction. During follow-up, 43 patients died (all-cause mortality), 13 of them died from ventricular tachycardia/ventricular fibrillation, 14 from sudden arrhythmic death, 22 from sudden death and 34 from cardiac death. A combination of four HRV parameters from all domains (time and frequency domain, symbolic dynamics) in this multivariate approach improved the diagnostic precision more than twofold. Other post-infarction studies have shown that a reduced short-term scaling exponent is a more powerful predictor of mortality than the traditional measurements of HRV [65], [66].

More recently, fractal heart rate variability has been shown to retain its prognostic power even for patients taking beta-blockers after an acute myocardial infarction [67]. In the DIAMOND study, a reduction in the short-term fractal exponent was the most powerful predictor of all-cause mortality in 446 survivors of acute myocardial infarction. The exponent predicted both arrhythmic and nonarrhythmic cardiac death [68].

In 1999, the analysis of the heart rate turbulence (HRT), which describes the fluctuations of the RR interval after ventricular premature beats, was introduced. HRT is usually described by two parameters, the turbulence onset and the turbulence slope. The turbulence onset describes the difference between the mean of the two sinus RR intervals before and the first two sinus RR intervals after the ventricular premature depolarization divided by the mean of the last two sinus RR intervals before the ventricular premature depolarization. The turbulence slope is defined as the highest slope of the regression line over any of the five successive sinus beat RR intervals during first 20 sinus beat RR intervals after a ventricular premature depolarization [69].

It is expected that the intensified investigation of interactions and couplings between heart rate and respiration and between heart rate and blood pressure, respectively, with a variety of methods particular from nonlinear dynamics will not only increase our knowledge about the complex autonomic regulation [70], [71], [72], [73], [74], [75] but will lead us to an enhanced diagnostics and therapy.

In addition to the well-accepted application in cardiology, HRV has also drawn attention in other important application fields as e.g. intensive care medicine. Werdan et al. showed that, in patients with multiorgan dysfunction syndrome, a drastic reduction in HRV was observed, both the sympathetic as well as the vagal component, correlating with an unfavorable prognosis [76]. They further found that endotoxin can interfere with the pacemaker current and sympathetic tone, thereby altering heart rate variability and bridging autonomous nervous system and inflammation. Furthermore, a reduction of HRV is seen with increasing age [77], indicating somewhat of cardiac

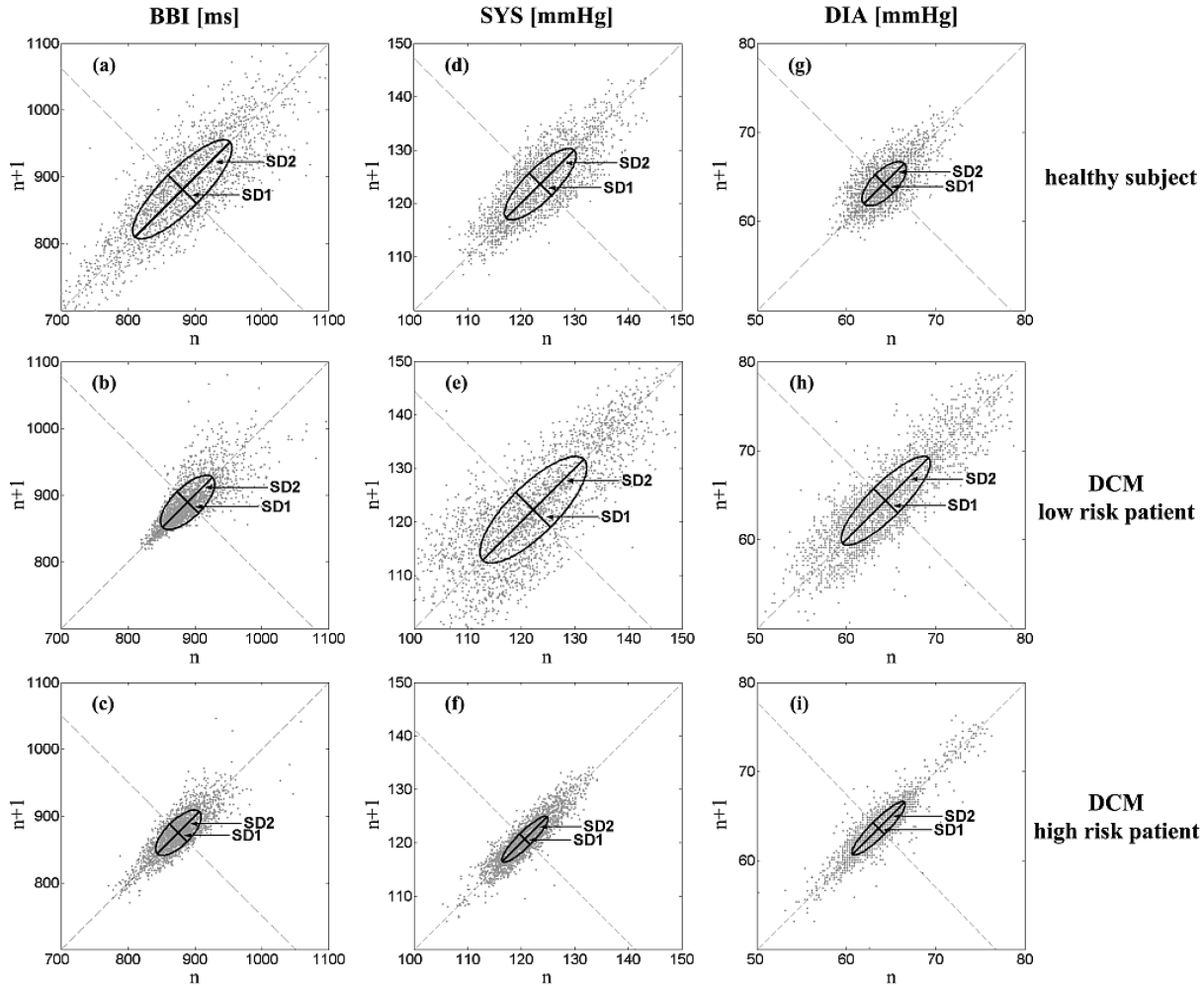

Figure 8: Poincaré plots calculated from HRV (tachogram, a-c), from BPV (systolic d-f SYS; diastolic g-i DIA) blood pressure time series of a healthy subject (top row), a DCM patient with low risk (middle row) and a DCM patient with high risk (bottom row), see also [83]

ageing [78]. Finally HRV exhibits a considerable gender dependency [79].

Blood pressure variability

While most studies on autonomic control are performed by HRV analysis, spontaneous blood pressure variability (BPV) is used increasingly as additional and complementary 'window' into cardiovascular control mechanisms. Beat-to-beat registration of systolic and diastolic blood pressure has been evaluated in different cardiac diseases [80], [81]. There is a significant correlation to baroreflex sensitivity in patients with hypertension independently of age and systolic blood pressure and also data about the increase of BPV in early stage of hypertension. Besides ischemic cardiomyopathy, BPV analysis has prognostic value in hypertensive heart disease and dilated cardiomyopathy, reflecting the clinical relevance of BPV for autonomic control physiology and cardiac risk stratification [81], [82]. While HRV did not contribute to risk stratification in patients with dilated cardiomyopathy (DCM), BPV analysis yielded significant parameters. Nonlinear dynamics indices (primary developed for HRV analysis and adapted to BPV analysis) as Short Term Symbolic Dynamics (STSD) and Poincare Plot analysis (PPA, Figure 8) differentiated best between low and high risks (maximum sensitivity: 90%, specificity: 90%) [83].

Microvolt T-wave alternans

Patients who survive a myocardial infarction, particularly those with residual left ventricular dysfunction, are at risk of serious arrhythmic events and SCD. This risk is often assessed as a sustained, microvolt phenomenon with exercise [84]. Microvolt T-wave alternans (MTWA) test is a novel non-invasive method for assessing repolarization alternans and is useful for estimating an individual's risk for SCD. The test is comparable to a stress ECG and carried out on a treadmill. MTWA measures an extremely subtle beat-to-beat fluctuation in the T-wave segment of a patient's heartbeat that is a specific marker of arrhythmic vulnerability and the likelihood of a sudden cardiac death.

Repolarization alternans is a sensitive marker of underlying abnormalities in electrical structure. A negative exercise MTWA identifies patients at low risk of serious events,

but a non-negative result is limited by poor positive predictive accuracy. A meta-analysis incorporating 19 studies (2,608 subjects) found an overall positive predictive value of MTWA for arrhythmic events to be 19.3%, a negative predictive value of 97.2%, and the univariate relative risk for an arrhythmic event of 3.77. The authors concluded that MTWA testing has great value for predicting ventricular tachyarrhythmic events, but is also very limited in its use because the predictive value of MTWA varied significantly depending on the population studied [85].
The REFINE study compared the MTWA test to HRV parameters and the cardiac functional marker of left ventricular ejection fraction after myocardial infarction. So far, only the combination of abnormal MTWA plus impaired autonomic tone has reliably predicted the risk of sudden cardiac death after myocardial infarction as the secondary outcomes of all-cause mortality and fatal or nonfatal cardiac arrest [86].
The ongoing prospective multicentre ABCD study is comparing MTWA to invasive electrophysiology as the "gold standard of risk stratification" for use in guiding prophylactic implantable cardioverter defibrillator (ICD) insertion. Of 566 patients followed for a median of 1.9 years, 39 (7.5%) met the primary endpoint of appropriate ICD discharge or SCD within 1 year. Primary results showed that MTWA achieved 1-year positive (9%) and negative (95%) predictive values that were comparable to an electrophysiological study (11% and 95%, respectively) [87].

Electrocardiography in combination with imaging techniques (functional imaging)

The great potential of functional imaging (electrocardiography combined with imaging techniques), also known as cardiac hybrid imaging, allows a comprehensive evaluation of coronary artery disease by yielding morphological and functional information. The SPECT/CT and PET/CT hybrid are examples of methods that noninvasively provide unique information that improves diagnostic assessment and risk stratification and also impacts decision-making for revascularization in patients with coronary artery disease.
Functional imaging is also of relevance for noninvasively visualizing cardiac electrical activity throughout the three dimensional myocardium. Therefore, the combination of a spatiotemporal reconstruction technique with an imaging method will result in an electrocardiographic functional imaging. The clinical relevance was shown in invasive mapping systems: the inclusion of a thoracic volume san – which was performed before the investigation – can be used for a better guidance for interventions like catheter ablation of arrhythmias.
Non-invasive functional imaging provides insights to electrocardiographic alterations in myocardial ischemic or infracted areas. To solve the inverse problem of electrocardiography, a computer model of the individual heart of a patient based on a 3D-MRI dataset can be used. Source distributions inside the heart are simulated using a cellular automaton. With a finite element method, the corresponding BSPM is calculated. Characteristic parameters like duration and amplitude of transmembrane potential or velocity of propagation are optimized for selected tissue classes or regions in the heart to fit simulated data to the measured data. This way the source distribution and its time course of an individual patient can be reconstructed [88].
He and Wu developed novel electrocardiographic tomography techniques to image cardiac current density distributions within the myocardium [89]. A realistic geometry inhomogeneous heart-torso model based on tomographic imaging was used to localize the site of origin of cardiac activation, show the cardiac activation sequence and image the transmembrane potential distribution within the 3D anisotropic myocardium. The spatio-temporal coherence of ventricular excitation processes has been utilized to derive the activation time from the estimated time course of equivalent current density defined as the spatial gradient of transmembrane potential.

Monitoring

Telemedicine

Telemedicine is a rapidly developing application of modern communications and information technologies to deliver clinical data to users, for example, from general practitioners to hospitals. Care at a distance is an old practice that was often conducted by post or radio. Nowadays, this medical information is transferred by telephone, the Internet or other networks. Two types of homecare telemedicine are in use [90]: 1) monitoring of vital biosignals combined with a feedback and 2) teaching approach (home nurse call). Mobile devices transfer ECG and other vital data to a telemetry platform on demand and on a daily basis. Telemetry platforms are accessible via a medical backup during 24 hours. Data are analyzed online and telephone visits will follow immediately if vital parameters are out of normal range [91].
Mobile device transfer ECG can be useful in early detection of ACS and silent ischemia, especially after work hours and on weekends, and could also pre-categorize patients into STEMI and other coronary syndromes during the pre-hospital phase [92]. Data on telemedicine show feasibility, cost effectiveness and reduction of hospitalization rates and time in cardiac patients with chronic heart failure [93]. Fewer resources for inpatient care of an increasingly older population require new approaches for ambulatory disease management, particularly in the chronically ill. Home care telemedicine may improve the ambulatory care of elderly patients with chronic cardiac diseases and support the health systems.

Ambient Assisted Living

Ambient Assisted Living (AAL) is a technology and innovation funding program of European countries, supported by the European Commission [94] aimed to extend the time the elderly can live at home by increasing their

autonomy and providing assistance for their daily activities. Vital signs monitoring and fall detection in domestic and outdoor environments is important for preserving independence. This requires the monitoring of data from accelerometers in addition to the usual vital signs especially outside the home. The high incidence of CAD and myocardial infarction in the elderly warrant the inclusion of ischemia electrocardiography in the AAL concepts. Early diagnosis and therapy of myocardial infarction could prevent heart failure and disability. In cardiac patients with CAD, a multichannel ambulatory ECG is preferable to a one-channel system for excluding acute STEMI in suspected acute ischemia. Myocardial infarction and cardiac arrhythmias are the main cardiac diseases targeted for AAL monitoring.

A new telemonitoring project called CAALYX (Complete Ambient Assisted Living Experiment) was set up to monitor detailed data about the user's medical status and location [95]. Other projects have investigated the feasibility of passive wireless in-home monitoring systems that transmit data from biological variables and everyday habits (body position, movements) to a central monitoring station for use in the telemedicine activities of the Health Telematic Network for home help only [96]. Continuous mobile ECG systems with percutaneous connectors, leads and cables present obvious disadvantages like restricting mobility and causing skin irritations. Persons with more severe cognitive impairment are less likely to accept mobile monitoring systems. This is a relevant limitation for systems in geriatric medicine [97]. Modern biomedical solutions use implanted systems for the wireless in-vivo monitoring of physiological parameters [98]. Another approach includes alternative electrode systems technologies, e.g. textile integrated solutions inserted in body area networks systems. Improved microsystems technology will substantially increase the range of implantable biomedical devices and body area networks related solutions in the coming years [99].

Discussion and conclusions

This review has analyzed the state of the art of electrocardiologic methods and categorized them according their intended applications (Figure 1, Table 1 and Table 2). Now, we will discuss their current relevance and future potentials, weighing the advantages and disadvantages.

Resting electrocardiologic methods

Except for diagnosing STEMI, state-of-the art electrocardiography does not provide enough data to detect stable CAD and acute myocardial ischemia in the resting patient. Myocardial ischemia caused by coronary stenosis, potentially reversible at rest [100], is primarily detectable by exercise ECG.

In a vanguard study [50], the use of cardiogoniometry at rest – as an example for a spatiotemporal vectorial ECG approach – compared to standard exercise ECG had shown promising results for the diagnosis of CAD. Further studies with larger populations, especially with reference standards displaying myocardial perfusion are necessary with regard to both a further prospective validation of the method for the diagnosis of stable CAD and the development of methods for diagnoses in the acute phase [25]. The reasons why asymptomatic or stable CAD may be detected by electrophysiological investigations at rest, although the coronary stenoses may not be hemodynamically relevant at the examination due to the heart flow reserve, still need to be explained. In this regard, the pathophysiological mechanisms that theoretically lead to stunning, hibernating myocardium and reversible mechanical dysfunction in patients with coronary artery disease summarized by Mazzadin et al. in their review may provide a hypothetical explanation for the changes in enhanced electrocardiographic parameters [101]. Even in the absence of frank (symptomatic) myocardial ischemia, atherosclerotic coronaries can cause electrophysiological changes.

Promising new electrocardiographic approaches using high-resolution registration technology, signal averaging and the use of multiple channels can detect alterations in current density distribution caused by myocardial ischemia and may also detect discrete myocardial injury at rest. These methods are classified as new diagnostic tools for diagnosing CAD.

Risk stratification methods

The methods most suitable for establishing which patients are at risk for sudden cardiac death (lethal arrhythmic events) who require treatment (Figure 1) are ECG (including Holter ECG/exercise ECG), HRV, HRT, BPV, MTWA and signal averaged electrocardiography.

In general, new parameters for risk stratification need to be introduced to better render indications for implantable cardioverter defibrillators (ICD) [102]. The number needed to treat to save one life with an ICD is above 10 patients over 2-year period, while an ICD was projected to add 1–3 QALY, but costs between $70,000 and $100,000. These recommendations for ICD in primary prevention of sudden cardiac death in ischemic and non-ischemic cardiomyopathy patients are primarily based on ejection fraction.

All nonlinear methods of HRV assess qualitative properties rather than the magnitude of the signal and have been shown to deliver incremental and additional prognostic information under various pathophysiological conditions compared with the conventional measures of heart rate fluctuations. These novel approaches can also complement traditional time- and frequency-domain analyses of cardiovascular variabilities [103]. However, for complex analyses of cardiovascular oscillations, a multivariate approach (combining parameters from different domains) is essential [104].

Nowadays, alternans analysis, subsumed under MTWA, is one of the methods with the highest level of evidence for stratifying risks ranging from ventricular tachyar-

rhythmia to sudden cardiac death where analysis concentrates on the spatial and temporal heterogeneity of the repolarization phase.

Functional imaging

3D electrocardiographic methods seem to be one of the more challenging tasks for detecting patients at the risk of sudden cardiac events. Spatiotemporal registration can identify focal irregularities in current density distribution caused by local myocardial ischemia or myocardial scars. The advantages of low signal-to-noise ratio by signal averaged registration modus of the electric field could be used with high-resolution registration techniques. Advances in computation technology could provide fast analyses of such complex data sets.

The analyses of the spatiotemporal coherence of ventricular excitation processes are highly promising and may lead to the establishment of a three dimensional cardiac electrical imaging technology for functional cardiac imaging for better indication and aiding of invasive cardiac applications.

In the context of ischemia, functional imaging could also be the basis for a future non invasive stress testing providing focal ischemia detection. The combination with pharmacological stress offers the possibility for the use in elderly patients who were not able to do exercise testing.

Innovative imaging methods have been developed to image the functional status of the heart from echocardiography, magnetic resonance, PET, SPECT or CT scan combined with electrical spatiotemporal data, making hybrid technology ready for clinical use. In cardiology, promising new insights are possible by demonstrating local metabolism in acute and chronic ischemia. Electrocardiographic functional imaging should demonstrate similar effects, e.g. caused by local metabolic alteration in ischemia, but without additional contrast media or radionuclides.

Monitoring in daily life

Future electrocardiography will integrate methods like telemedicine and AAL into daily life to record and transmit ECG from the home for the early detection and prevention of acute cardiac events. The European Union's AAL program addresses the needs of the ageing European population by reducing innovation barriers, aimed at lowering future social security costs. Supporting self-supply for the elderly with mobile diagnostic instruments for the homes, daily life or cars is a fascinating medical engineering project for the future. Physiological parameters monitoring should be combined with modern information technologies and supportive ambulatory care. New homecare technologies targeting the elderly and their typical physical and mental limitations will allow them to stay home longer. Electrocardiography will be key to ambient assisted living solutions.

Closing remarks

There are promising approaches for the non-invasive detection and risk stratification of myocardial ischemia by enhanced electrocardiographic methods alone or in combination with imaging technologies in patients with suspected CAD or ACS.

Based on our analysis of the state of the art in electrocardiology, we submit the following prognostic hypotheses for the next 5 years: The standard ECG will continue to play a major role in primary diagnostics, particularly to detect STE infarctions in the presence of ACS symptoms. The detection of NSTE-ACS that was previously hardly, if all, possible by these standard methods, will be enabled by more recent ones, such as cardiogoniometry or BSPM. Because of its suboptimal accuracy in relation to load and examination time, the rank of exercise ECG for the primary detection of stable CAD will drop. In this setting, both imaging procedures and modern exercise-free and shorter examinations (e.g. cardiogoniometry) will assume a greater role. Methods for analyzing cardiovascular variability will become more relevant for identifying patients at-risk for life-threatening arrhythmias and for guiding the implantation of defibrillators. HRV and BPV based on advanced analytical methods of non-linear dynamics will supplement the established methods of T-wave alternans for risk stratification in a variety of clinical pictures. In the near future, functional imaging techniques will remain at the research level, while their introduction into routine diagnostics is not anticipated. Quite the opposite can be expected from telemedical technologies: In light of the fast-paced advances, homecare monitoring will transition rapidly from the current pilot project stage to clinical routine.

List of abbreviations

- ACS: Acute coronary syndrome
- ACD: Acute coronary disease
- BPV: Blood pressure variability
- BSPM: Body surface potential mapping
- CAALYX: Complete Ambient Assisted Living Experiment
- CAD: Coronary artery disease
- CGM: Cardiogoniometry
- DCM: Dilated cardiomyopathy
- ECG: Electrocardiography
- HR: Heart rate
- HRV: Heart rate variability
- MTWA: Microvolt T-wave alternans
- NSTE-ASC: Non-ST-elevation acute coronary syndrome
- NSTEMI: Non-ST-elevation myocardial infarction
- PCI: Percutaneous coronary intervention
- PPA: Poincare plot analysis
- QALY: Quality-adjusted life years
- SCD: Sudden cardiac death
- STE-ASC: ST-elevation acute coronary syndrome = STEMI
- STEMI: ST-elevation myocardial infarction

- STSD: Short-term symbolic dynamics
- UAP: Unstable angina pectoris
- VCG: Vectorcardiography
- VLP: Ventricular late potentials
- VT: Ventricular tachycardia

Notes

Conflicts of interest

Thomas Huebner is CTO and holds minor shares in enverdis GmbH. Michael Schuepbach and Ernst Sanz hold shares in KGMed GmbH. The other authors have nothing to disclose.

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