New approaches to electrocardiographic evaluation of acute myocardial ischemia

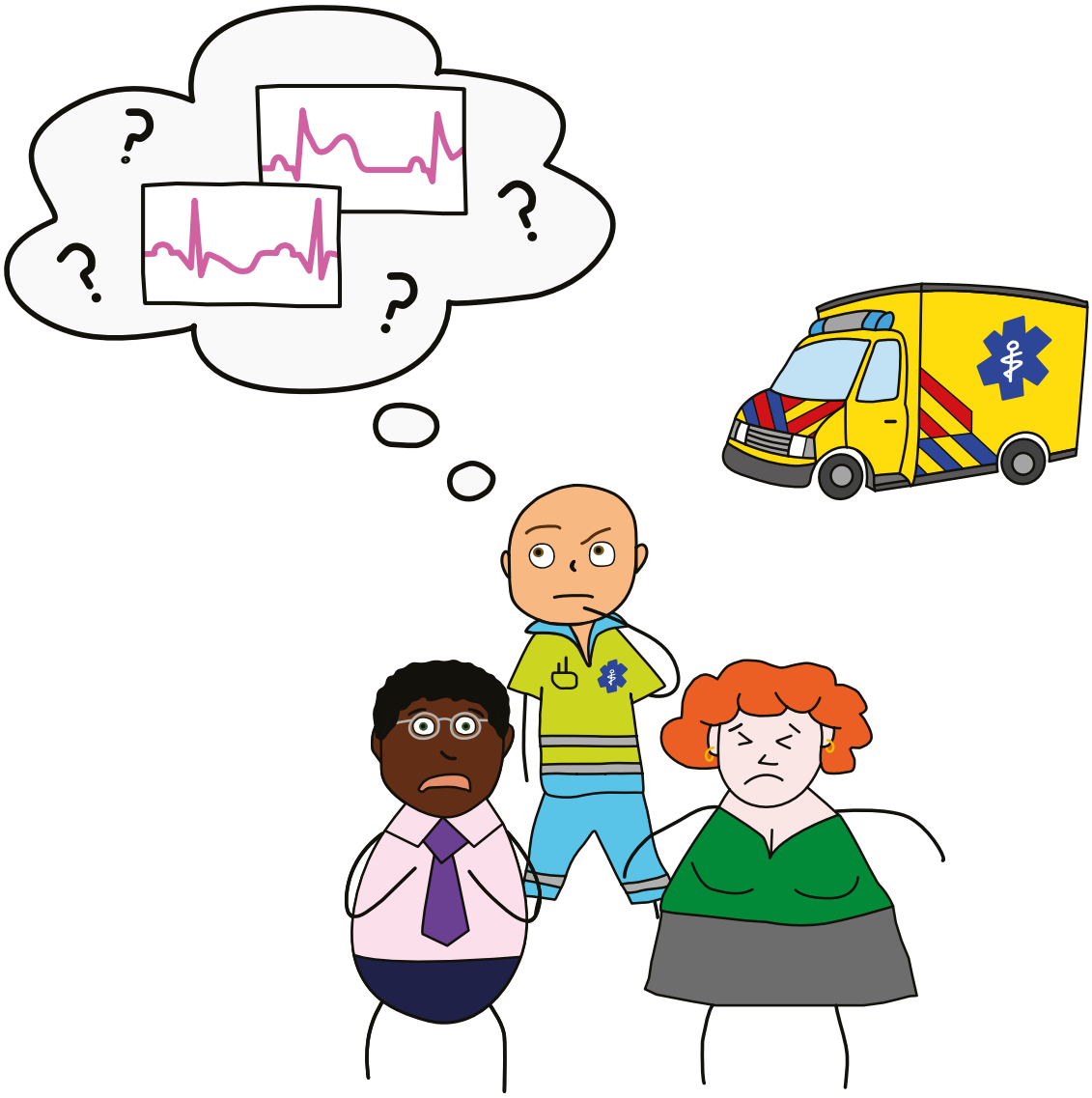
ter Haar, C.C.

Publication date
2020

Document Version
Final published version

License
Other

New approaches to electrocardiographic evaluation of acute myocardial ischemia



C. Cato ter Haar

New approaches to electrocardiographic evaluation of acute myocardial ischemia

C. Cato ter Haar

COLOFON

Layout & cover design: C.C. ter Haar
Printing: Ipskamp Printing Amsterdam www.ipskampprinting.nl
ISBN: 978-94-028-1803-1

Financial support for printing this thesis was provided by: AMC-UvA, uitgeverij Refugium

New approaches to electrocardiographic evaluation of acute myocardial ischemia

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor

aan de Universiteit van Amsterdam

op gezag van de Rector Magnificus

prof. dr. ir. K.I.J. Maex

ten overstaan van een door het College voor Promoties ingestelde commissie,

in het openbaar te verdedigen in de Agnietenkapel

op vrijdag 21 februari 2020, te 10.00 uur

door **Cornelia Catharina ter Haar**

geboren te Leiden

PROMOTIECOMMISSIE

Promotores:	prof. dr. R.J.G. Peters	AMC-UvA
	prof. dr. M.J. Schalij	Universiteit Leiden
Copromotores:	dr. P.G. Postema	AMC-UvA
	dr. ir. C.A. Swenne	Universiteit Leiden
Overige leden:	prof. dr. J.R. de Groot	AMC-UvA
	prof. dr. R.J. de Winter	AMC-UvA
	dr. A.S. Amin	AMC-UvA
	prof. dr. J.W. Jukema	Universiteit Leiden
	dr. J.M.J. Boogers	Universiteit Leiden
	prof. dr. A.P.M. Gorgels	Maastricht University

Faculteit der Geneeskunde

TABLE OF CONTENTS

Chapter

1

Introduction
&
Thesis outline

INTRODUCTION

The dynamics of acute myocardial ischemia

Ischemic heart disease is a leading cause of death with yearly over nine million fatalities worldwide.[1] Myocardial ischemia occurs if the blood flow to the myocardium is insufficient to meet its demand, eventually resulting in irreversible tissue damage.[2] Myocardial ischemia can either be due to decreased blood supply, caused by sudden narrowing or occlusion of a coronary artery, as is the case in acute coronary syndrome (ACS), or due to a sudden increase in demand, *e.g.*, in tachycardia. In ACS, typically, an atherosclerotic plaque ruptures and subsequently thrombus formation occurs. In contrast, myocardial ischemia as a consequence of an increased metabolic demand (secondary ischemia) is caused by an acute extra-coronary change, usually in combination with a pre-existing coronary artery stenosis. Treatment options of the different forms of myocardial ischemia depend on the cause and on the availability of therapeutic options, and include primary percutaneous coronary intervention (PCI), thrombolysis, administration of antithrombotic agents, and/or treatment of the underlying disease causing secondary ischemia.[3-5] Irrespective of the underlying mechanism, acute myocardial ischemia is a serious condition requiring swift detection and therapeutic intervention, because a delayed diagnosis causes a delay in treatment that may lead to irreversible myocardial damage and mortality.[4-6] This challenge is reflected in the sayings "time is muscle" and "muscle is life".[7]

Patient triage

The majority of patients who experience symptoms suggestive of acute myocardial ischemia, typically chest pain, contacts the emergency medical services (EMS).[5] Yearly, this results in about 400,000 EMS evaluations for possible myocardial ischemia in the Netherlands.[8a] Efficient routing of these patients is essential, both for adequate treatment in "true positive" cases and for avoiding unnecessary treatment or inappropriate transportation in "false positive" cases. Therefore, adequate triage in the prehospital phase is pivotal.[9] In this initial triage, patients are quickly assessed for acute myocardial ischemia to determine whether or not they need to be taken to a hospital for treatment. In case of suspected myocardial ischemia, the additional decision is to be made whether or not the patient should be presented to a hospital with facilities for percutaneous coronary intervention (PCI), and whether or not the patient should receive immediate prehospital thrombolysis when such facilities are unavailable or cannot be reached within an acceptable time window (for example on islands, in remote or rural areas or in developing countries).[4,5]

For correct treatment, however, there should be a correct diagnosis. False negative detection of myocardial ischemia results in detrimental delay of necessary treatment, causing more myocardial necrosis and (unnecessary) loss of myocardial function.[6] False positive myocardial ischemia detection on the other hand, can not only lead to unnecessary workloads of emergency departments, but also to invasive diagnostic procedures and/or unnecessary hazardous treatments.

[a] Extrapolated from 1.3 million ambulance rides, and, according to our study (Chapter 9), the fact that in about 1/3 of rides an ambulance ECG was recorded for the detection of myocardial ischemia.

In countries like the Netherlands where call-to-balloon times are short,[10] urgent catheterization is performed; this procedure is accompanied by significant risks[11] and high costs.[12] Alternatively, in many regions in the world prehospital thrombolytics are the standard of treatment because PCI facilities are not available at close range.[13] This treatment may lead to severe complications, in particular intracranial hemorrhage.[13,14]

Prehospital diagnostic tools

Unfortunately, diagnosing patients with myocardial ischemia can be challenging since patients often present with non-specific complaints.[15] Therefore, there is a need for objective diagnostic tools for myocardial ischemia detection. In the prehospital setting, these tools need to be rapid and practical, and, ideally, interpretation should be largely independent of the expertise of ambulance professionals. These diagnostic tools will aid in correct decision making and hence reduce morbidity and mortality.[4,5] Although experiments are performed with prehospital measurements of myocardial ischemia, biomarkers such as high-sensitive troponin, plasma troponin levels will rise only after a certain duration of myocardial ischemia, when necrosis has occurred. Moreover, this measurement is time consuming. Therefore, this approach cannot be used in the very early pre-necrosis stage of ischemia.[16,17] In contrast, ischemia-induced wall motion abnormalities can be observed by echocardiography even before clinical symptoms appear.[18] However, a reliable echocardiogram for the purpose of myocardial ischemia detection should be performed by specifically trained professionals with dedicated echocardiographs, and this is very rarely available at the EMS services.[19] Additionally, in patients with a history of coronary artery disease, previously recorded echocardiograms would have to be available for comparison.

Fortunately, the prehospital electrocardiogram (ECG), represents a quick, easy, non-invasive, low-burden, low-cost and universally available tool for myocardial ischemia detection.[4,5,9] However, while electrocardiographic criteria for myocardial ischemia have been updated repeatedly,[20] considerable room for improvement remains.[20,21]

Myocardial ischemia-induced ECG changes

Since the electrocardiogram reflects heterogeneity in myocardial action potential morphology and timing of electrical activation throughout the heart, any change in action potential morphology and/or timing induced by ischemia alters the ECG.[22,23] Despite the fact that all phases of the action potential are subject to ischemia (Figure 1),[22] current diagnostic criteria for myocardial ischemia mainly focus on ST-segment elevation or depression (usually measured at the J point)[3,4] originating from ischemia-induced phase 2 and phase 4 action potential changes.[3]

Ischemia can also reduce conduction velocity, altering QRS morphology and QRS duration.[24] In addition, T-wave morphology changes can occur due to large repolarization gradients in the heart, due to shortening of the action potential in the ischemic zone.[25,26] In addition, overall changes can occur, *e.g.*, ischemia-related heart rate increase or decrease, changing relationships between the spatial orientations of depolarization and repolarization, amongst others expressing as changes in the QRS-T spatial angle.[27] A clear example of ischemic ECG changes manifesting throughout the entire QRST wave shape is provided in Figure 2, in which both a non-ischemic and an ischemic ECG of the same patient are provided.

This figure is only available in the printed thesis.

Figure 1.

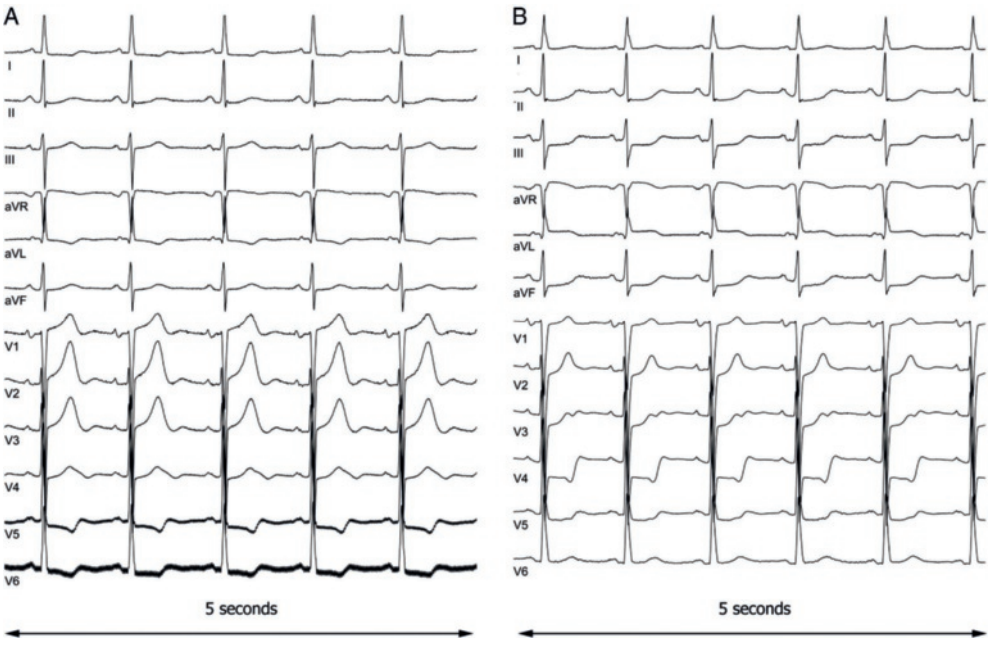


Figure 2. QRST changes with ischemia.
Part of a continuous 12-lead ECG recorded during elective percutaneous transluminal angioplasty (PTCA) in a patient with left-ventricular hypertrophy. Panel A: baseline. Panel B: ischemia, after 3 minutes of PTCA-related balloon occlusion. Visible ECG changes with ischemia include changes in QRS morphology, in QRS duration, in J amplitude, in the ST segment and in T-wave morphology. Figure taken from Ter Haar *et al.*[28] with permission.

Overlap between ischemic and non-ischemic ECGs

Although myocardial ischemia causes multiple electrocardiographic changes, myocardial ischemia detection on a single ECG is not straightforward because of a large overlap between ischemic and non-ischemic ECG patterns in the population. First, pre-existing (cardiac) pathology, *e.g.*, left ventricular hypertrophy or left ventricular aneurysm, can hinder interpretation of the ECG suspected of myocardial ischemia.[29,30] Additionally, healthy individuals can have an ECG pattern mimicking that of myocardial ischemia.[31,32] Moreover, in both health and disease, considerable variability of ECGs between individuals exists, for instance due to difference in age, sex and/or ethnicity.[20,33] Therefore, uniform myocardial ischemia thresholds in the ECG, as proposed in the international guidelines,[3-5] are necessarily associated with diagnostic error.[30,34] Approaches to correct for interindividual variability may include further refinement of the guidelines (*e.g.*, ethnicity-based), and intra-individual ECG comparison, in which the electrocardiogram of the patient during acute complaints is compared to a electively previously-recorded (*i.e.*, non-ischemic) electrocardiogram.

Integrated 12-lead electrocardiographic and 3D vectorcardiographic approach

Although a multitude of information can be derived from the routinely used scalar 12-lead electrocardiogram, interpretation of the spatial orientation of an ECG abnormality is complicated due to different sensitivities[35] and non-straightforward directions of lead vectors (*i.e.*, spatially quite differently orientated than schematically set out in most textbooks).[36] Computation of the 3D vectorcardiogram (VCG)[36,37] from the 12-lead ECG[38,39] results in three additional leads, the X, Y and Z lead. The VCG is orthonormal, *i.e.*, the X, Y and Z leadvectors have equal sensitivities and are orthogonally oriented (aligned with the main anatomical axes of the body). The vectorcardiographic representation of the electrical activity of the heart facilitates the dynamic construction of the heart vector (amplitude and spatial orientation of the momentaneous electrical activity of the heart throughout the cardiac cycle). The addition of the derived VCG to the 12-lead ECG facilitates the use of vectorcardiographic variables such as the ST difference vector, which has proven useful for myocardial ischemia detection because it increases by ischemia and points in the direction of the ischemic area.[21,40,41] Moreover, the ventricular gradient (VG),[42] *i.e.*, the spatial integral of the heart vector over the QRST complex,[43] requires a VCG (rather than the scalar ECG) for its calculation. The ventricular gradient represents the heterogeneity of action potential morphology throughout the heart. Since myocardial ischemia alters the entire action potential morphology[22] and, hence, the entire QRST complex, the change in the ventricular gradient reflects all ischemia-induced electrocardiographic changes.

Aim of this thesis

This thesis is aimed at exploring the possibility of enhanced electrocardiographic myocardial ischemia evaluation by correction for interindividual variability in the ECG. Using a previously recorded ECG of the same patient for comparison, the detection of acute myocardial ischemia may be tailored to the individual patient. The results of these investigations may potentially improve the electrocardiographic detection of myocardial ischemia in patients and aid in better decision making and selection of treatment, thus eventually resulting in a better prognosis for the patient.

THESIS OUTLINE

PART I. ECG changes during hyperacute myocardial ischemia

Part I of this thesis is based on a classical database (the STAFF III database) of continuously recorded ECGs while hyperacute myocardial ischemia is induced by elective balloon occlusion in 84 patients with stable angina.[44] In **Chapter 2** investigations are performed on the ST and the ventricular gradient difference vectors, ΔST and ΔVG, computed by subtraction of the preprocedural ECG from the ischemic ECG after three minutes of balloon inflation. The specific relation between these difference vectors and their behavior during ischemia with respect to magnitude and spatial orientation, is further investigated in **Chapter 3**. In **Chapter 4** investigations are made on the diagnostic value of the ΔST and ΔVG vectors using variable thresholds to detect myocardial ischemia. Also, a comparison is made with current ST-elevation criteria for myocardial infarction. In **Chapter 5** investigations are performed on whether ischemic changes measured at a fixed time point after the onset of the QRS-complex can be valuable, as opposed to usual measurement of myocardial ischemia at the J point (which is often difficult to define).

PART II. Non-ischemic ECG changes and variants

Part II concerns ischemia-like ECG changes and variations under non-ischemic conditions. Electrocardiographic ECG changes, not due to ischemia, but essentially purely due to the passing of time in combination with possible progression of disease, are assessed in **Chapter 6**, thus investigating the diminishing validity with time (the "expiration date") of a reference ECG. **Chapter 7** further explores non-ischemic ECG variants, by assessing the prevalence of electrocardiograms exceeding the ST-elevation myocardial infarction (STEMI) thresholds in apparently healthy individuals, with the focus on ethnic diversity.

PART III. Subtraction electrocardiography to detect myocardial ischemia

In Part III the method of subtraction electrocardiography for the purpose of myocardial ischemia detection is put to the test. First, in **Chapter 8**, ΔST and ΔVG vectors are used to discriminate cases of myocardial ischemia (originating from the same STAFF III dataset as studied in Part I of this thesis) from controls (two outpatient clinic ECGs of the same patient, recorded 1-2 years apart), and compared to the diagnostic performance of the current STEMI criteria. Finally, in **Chapter 9**, by studying 1,425 patients presenting to the EMS with acute complaints suggestive of myocardial ischemia, subtraction electrocardiography is explored in the real prehospital situation. The diagnostic performance of difference descriptors for the detection of myocardial ischemia is evaluated by subtracting a non-ischemic previously made ECG from the ambulance ECG and compared with a gold standard: the retrospectively assessed presence or absence of myocardial ischemia, using all available clinical information in every individual case.

PART IV. Summary and future perspectives

This thesis is concluded by Part IV including English and Dutch summaries in **Chapters 10 and 11**, respectively. Finally, future perspectives and concluding remarks are provided in **Chapter 12**.

REFERENCES

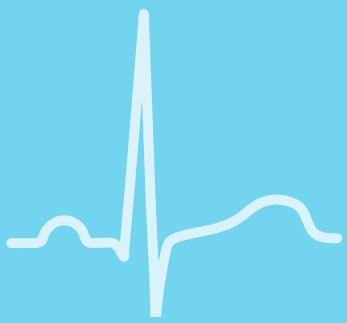
1. World Health Organisation. 2018.
2. Hedstrom E, Engblom H, Frogner F, *et al.* Infarct evolution in man studied in patients with first-time coronary occlusion in comparison to different species - implications for assessment of myocardial salvage. J Cardiovasc Magn Reson. 2009;11:38.
3. Thygesen K, Alpert JS, Jaffe AS, *et al.* Fourth Universal Definition of Myocardial Infarction (2018). Circulation. 2018;138:e618-e651.
4. Ibanez B, James S, Agewall S, *et al.* 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2017;39:119–177.
5. O'Gara PT, Kushner FG, Ascheim DD, *et al.* 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. Circulation. 2013;127:e362-425.
6. Bacharova L, Mateasik A, Carnicky J, *et al.* The Dipolar ElectroCARdioTOpographic (DECARTO)-like method for graphic presentation of location and extent of area at risk estimated from ST-segment deviations in patients with acute myocardial infarction. J Electrocardiol. 2009;42:172-80.
7. Wilson JM. When relativity has no relevance. Tex Heart Inst J. 2010;37:159-60.
8. Ambulancezorg. FACTS & FIGURES 2016.
9. Ting HH, Krumholz HM, Bradley EH, *et al.* Implementation and integration of prehospital ECGs into systems of care for acute coronary syndrome: a scientific statement from the American Heart Association Interdisciplinary Council on Quality of Care and Outcomes Research, Emergency Cardiovascular Care Committee, Council on Cardiovascular Nursing, and Council on Clinical Cardiology. Circulation. 2008;118:1066-79.
10. Hermans MPJ, Velders MA, Smeekes M, *et al.* Call-to-balloon time dashboard in patients with ST-segment elevation myocardial infarction results in significant improvement in the logistic chain. EuroIntervention. 2017;13:e564-e571.
11. Whitehead N, Williams T, Brienesse S, *et al.* Contemporary Trends in Stroke complicating Cardiac Catheterization. Intern Med J. 2019.
12. Cooper CJ, El-Shiekh RA, Cohen DJ, *et al.* Effect of transradial access on quality of life and cost of cardiac catheterization: A randomized comparison. Am Heart J. 1999;138:430-6.
13. Iyengar SS and Godbole GS. Thrombolysis in the era of intervention. J Assoc Physicians India. 2011;59 Suppl:26-30.
14. Eriksen UH, Molgaard H, Ingerslev J, *et al.* Fatal haemostatic complications due to thrombolytic therapy in patients falsely diagnosed as acute myocardial infarction. Eur Heart J. 1992;13:840-3.
15. Brieger D, Eagle KA, Goodman SG, *et al.* Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group: insights from the Global Registry of Acute Coronary Events. Chest. 2004;126:461-9.
16. Alghamdi A and Body R. BET 1: Prehospital cardiac troponin testing to 'rule out' acute coronary syndromes using point of care assays. Emerg Med J. 2018;35:572-574.
17. van der Laarse A, Cobbaert CM, Gorgels AP, *et al.* Will future troponin measurement overrule the ECG as the primary diagnostic tool in patients with acute coronary syndrome? J Electrocardiol. 2013;46:312-7.
18. Nesto RW and Kowalchuk GJ. The ischemic cascade: temporal sequence of hemodynamic, electrocardiographic and symptomatic expressions of ischemia. Am J Cardiol. 1987;59:23C-30C.
19. Charron C, Templier F, Goddet NS, *et al.* Difficulties encountered by physicians in interpreting focused echocardiography using a pocket ultrasound machine in prehospital emergencies. Eur J Emerg Med. 2015;22:17-22.
20. Macfarlane PW, Browne D, Devine B, *et al.* Modification of ACC/ESC criteria for acute myocardial infarction. J Electrocardiol. 2004;37 Suppl:98-103.
21. Man S, Rahmattulla C, Maan AC, *et al.* Acute coronary syndrome with a totally occluded culprit artery: relation of the ST injury vector with ST-elevation and non-ST elevation ECGs. J Electrocardiol. 2014;47:183-90.
22. Downar E, Janse MJ and Durrer D. The effect of acute coronary artery occlusion on subepicardial transmembrane potentials in the intact porcine heart. Circulation. 1977;56:217-24.
23. Kleber AG, Janse MJ, van Capelle FJ, *et al.* Mechanism and time course of S-T and T-Q segment changes during acute regional myocardial ischemia in the pig heart determined by extracellular and intracellular recordings. Circ Res. 1978;42:603-13.
24. Surawicz B. Reversible QRS changes during acute myocardial ischemia. J Electrocardiol. 1998;31:209-20.
25. Surawicz B. ST-segment, T-wave, and U-wave changes during myocardial ischemia and after myocardial infarction. Can J Cardiol. 1986;Suppl A:71A-84A.
26. Meijs LP, Galeotti L, Pueyo EP, *et al.* An electrocardiographic sign of ischemic preconditioning. Am J Physiol Heart Circ Physiol. 2014;307:H80-7.

27. Strebel I, Twerenbold R, Wussler D, *et al.* Incremental diagnostic and prognostic value of the QRS-T angle, a 12-lead ECG marker quantifying heterogeneity of depolarization and repolarization, in patients with suspected non-ST-elevation myocardial infarction. Int J Cardiol. 2019;277:8-15.
28. ter Haar CC, Maan AC, Warren SG, *et al.* Difference vectors to describe dynamics of the ST segment and the ventricular gradient in acute ischemia. J Electrocardiol. 2013;46:302-11.
29. Brady WJ, Perron AD, Ullman EA, *et al.* Electrocardiographic ST segment elevation: a comparison of AMI and non-AMI ECG syndromes. Am J Emerg Med. 2002;20:609-12.
30. McCabe JM, Armstrong EJ, Kulkarni A, *et al.* Prevalence and factors associated with false-positive ST-segment elevation myocardial infarction diagnoses at primary percutaneous coronary intervention-capable centers: a report from the Activate-SF registry. Arch Intern Med. 2012;172:864-71.
31. Zarafshar S, Wong M, Singh N, *et al.* Resting ST amplitude: prognosis and normal values in an ambulatory clinical population. Ann Noninvasive Electrocardiol. 2013;18:519-29.
32. Birnbaum Y. The burden of nonischemic ST-segment elevation. J Electrocardiol. 2007;40:6-9.
33. Macfarlane PW, Katibi IA, Hamde ST, *et al.* Racial differences in the ECG--selected aspects. J Electrocardiol. 2014;47:809-14.
34. Shamim S, McCrary J, Wayne L, *et al.* Electrocardiograhic findings resulting in inappropriate cardiac catheterization laboratory activation for ST-segment elevation myocardial infarction. Cardiovasc Diagn Ther. 2014;4:215-23.
35. Horáçek BM. Lead Theory Comprehensive Electrocardiology: Springer-Verlag; 2011.
36. Man S, Maan AC, Schalij MJ, *et al.* Vectorcardiographic diagnostic & prognostic information derived from the 12-lead electrocardiogram: Historical review and clinical perspective. J Electrocardiol. 2015;48:463-75.
37. Frank E. An accurate, clinically practical system for spatial vectorcardiography. Circulation. 1956;13:737-49.
38. Kors JA, van Herpen G, Sittig AC, *et al.* Reconstruction of the Frank vectorcardiogram from standard electrocardiographic leads: diagnostic comparison of different methods. Eur Heart J. 1990;11:1083-92.
39. Man SC, Maan AC, Kim E, *et al.* Reconstruction of standard 12-lead electrocardiograms from 12-lead electrocardiograms recorded with the Mason-Likar electrode configuration. J Electrocardiol. 2008;41:211-9.
40. Lundin P, Eriksson SV, Erhardt L, *et al.* Continuous vectorcardiography in patients with chest pain indicative of acute ischemic heart disease. Cardiology. 1992;81:145-56.
41. Naslund U, Haggmark S, Johansson G, *et al.* Quantification of myocardium at risk and detection of reperfusion by dynamic vectorcardiographic ST segment monitoring in a pig occlusion-reperfusion model. Cardiovasc Res. 1993;27:2170-8.
42. Draisma HH, Schalij MJ, van der Wall EE, *et al.* Elucidation of the spatial ventricular gradient and its link with dispersion of repolarization. Heart Rhythm. 2006;3:1092-9.
43. Burger HC. A theoretical elucidation of the notion ventricular gradient. Am Heart J. 1957;53:240-6.
44. Warren SG and Wagner GS. The STAFF studies of the first 5 minutes of percutaneous coronary angioplasty balloon occlusion in man. J Electrocardiol. 2014;47:402-7.

PART I.
ECG changes during hyperacute myocardial ischemia

Chapter

2



Difference vectors to describe dynamics of the ST segment and the ventricular gradient in acute ischemia

C. Cato ter Haar
Arie C. Maan
Stafford G. Warren
Michael Ringborn
B. Milan Horáček
Martin J. Schalij
Cees A. Swenne

adapted from:
Journal of Electrocardiology
2013 Jul-Aug;46:302-311

ABSTRACT

Background

The ECG is important in the diagnosis and triage of the acute coronary syndrome (ACS), especially in the hyperacute phase, the "golden hours", during which myocardial salvage possibilities are largest. An important triaging decision to be taken is whether or not a patient requires primary PCI, for which, as mentioned in the guidelines, the presence of an ST elevation (STE) pattern in the ECG is a major criterion. However, pre-existing non-zero ST amplitudes (diagnostic, but also non-diagnostic) can obscure or even preclude this diagnosis.

Methods

In this study, we investigated the potential diagnostic possibilities of ischemia detection by means of changes in the ST vector, ΔST, and changes in the ventricular gradient (VG) vector (QRST integral), ΔVG. We studied the vectorcardiograms (VCGs) synthesized of the ECGs of 84 patients who underwent elective PTCA. Mean ± SD balloon occlusion times were 260 ± 76 s. The ECG ischemia diagnosis (ST elevation, STE, or non-ST-elevation, NSTE), magnitudes and orientations of the ST and VG vectors, and the differences ΔST and ΔVG with the baseline ECG were measured after 3 min of balloon occlusion.

Results

Planar angles between the ΔST and ΔVG vectors were 14.9 ± 14.0°. Linear regression of ΔVG on ΔST yielded ΔVG = 324·ΔST ($r = 0.85$; $P < 0.0001$, ΔST in mV). We adopted ΔST > 0.05 mV, and the corresponding ΔVG > 16.2 mV·ms as ischemia thresholds. The classical criteria characterized the ECGs of 46/84 (55%) patients after 3 min of occlusion as STE ECGs. Combined application of the ΔST and ΔVG criteria identified 73/84 (87%) of the patients as ischemic.

Conclusion

Differential diagnosis by ΔST and ΔVG (requiring an earlier made non-ischemic baseline ECG) could dramatically improve ECG guided detection of patients who urgently require catheter intervention.

INTRODUCTION

Acute ischemia causes shortening of action potentials, decrease of action potential amplitude and decrease of maximum diastolic potential.[1] These cellular changes in the ischemic region of the heart cause systolic and diastolic injury currents[2] that flow between the ischemic and the surrounding, uncompromised tissue. Both the systolic and diastolic injury currents influence the ST segment in the ECG. Systolic injury current causes primary ST changes, while diastolic injury current causes TQ voltage changes that lead to compensatory ST changes as a consequence of the baseline shift.[2] Moreover, the changes in the action potential morphology imply changes throughout the QRS-T complex, which become evident in changes in the spatial ventricular gradient (VG, spatial QRST integral).[3]

The ECG is of major importance in diagnosis of and triaging in acute coronary syndrome (ACS), especially in the hyperacute phase. According to the guidelines, an important triaging decision concerning the initial treatment is based on the presence of a new ST-elevation (STE) pattern in the ECG. In that case, the current guidelines[4] mention primary percutaneous coronary intervention (PCI) as the therapy of first choice (and thrombolytic therapy when there is no, or delayed, access to PCI). In case of acute coronary syndromes without persistent ST elevation (non-ST elevation, NSTE) the current guidelines[5] recommend antithrombotic (anticoagulant, antiplatelet) therapy rather than emergency PCI. The guidelines[4,5] mention, however, situations in which the ECG is non-diagnostic while there is still an urgent indication for PCI (like the ST depression without ST elevation that can be seen in left main disease). The guidelines[4] read: "In any case, ongoing suspicion of myocardial ischemia — despite medical therapy — is an indication for emergency coronary angiography with a view to revascularization, even in patients without diagnostic ST-segment elevation." The percentage of patients with NSTE admission ECGs that require PCI may be considerable: Koyama and colleagues[6] found a completely occluded (TIMI flow grade 0) culprit artery in 47% of patients with an NSTE admission ECG (vs. 57% in patients with a STE admission ECG).

The concept of an ischemia difference vector

The diagnostic possibilities of the ECG are inherently limited by the cancelation effect, which may explain how ST changes can remain limited with relatively large areas at risk, *e.g.*, in case of left main disease. There are, however, more reasons for the limited performance of the ECG in the setting of ACS. Non-ischemic ECGs with non-diagnostic ST segments often have small, non-zero, ST amplitudes (in vectorcardiographic terms a small, non-diagnostic ST vector). When, in such ECGs, ischemia alters the ST segment, and the vector that represents the contribution by ischemia makes an acute angle with the pre-existent non-diagnostic ST vector, the resulting ST vector will initially become smaller than the pre-existent vector. At the same time, the direction of the ST vector will not faithfully represent the direction of the ischemic vector. Only when the ischemic component continues to increase, the resulting ST vector becomes diagnostic and the direction will more and more assume the genuine direction of the ischemia vector. Hence it would be logic to measure the ischemic change of the ST vector with respect to its baseline value instead of the ST vector itself. The concept of an ST difference vector was first published by Lundin *et al.*,[7] and another Swedish research group has continued to explore the usefulness of this concept (first publication by Näslund *et al.*)[8].

Similarly, an ischemia difference vector can be defined for the VG. Baseline values of the VG are by definition non-zero[3] and differ considerably between individuals.[9] This implies that when the VG would be used in ischemia diagnosis, subtraction of the baseline value is mandatory before a reasonable estimate of the ischemia contribution can be made. See Figure 1.

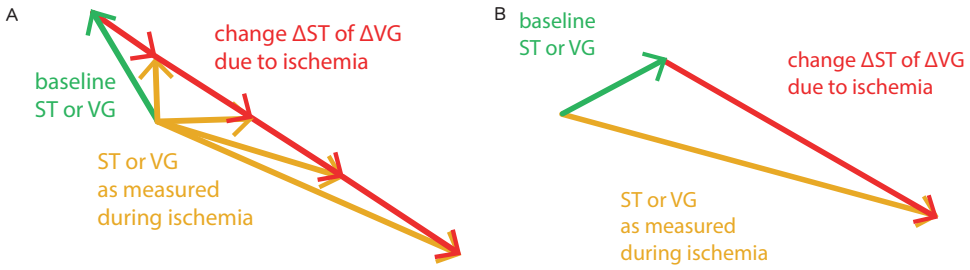


FIGURE 1. A. Concept of the ischemia difference vector.
ST = the heart vector as measured at a given time instant (*e.g.*, at J + 60 ms) in the ST segment; VG = ventricular gradient vector (integral of the heart vector over the QRST interval). Green: non-ischemic baseline vector (in many non-ischemic ECGs, especially in normal ECGs, the ST amplitude is small, but nevertheless often not really zero; in non-ischemic ECGs the VG is by definition non-zero). Yellow: ST or VG vector as measured during ischemia. Red: the difference vector/ischemia vector (change in the ST vector, ΔST, or change in the VG vector, ΔVG). Due to the sharp angle between the baseline value and the ischemia difference vector, the resulting vector measured during ischemia assumes a different direction than the ischemia vector itself; also, the size of the measured vector is different from the ischemia vector itself. NOTA BENE: this figure is conceptual, only meant to illustrate the meaning of what is, in the current text, denoted by a baseline vector, an ischemia difference vector and a vector during ischemia. It is not suggested that the ST and VG vectors have the same size or the same direction, nor that, with increasing ischemia, the ischemia difference vector changes only in size and not in direction. B. Concept of the ischemia difference vector. Different from panel A, the baseline and ischemia difference vectors make an obtuse angle. This gives rise to a larger vector measured during ischemia than the ischemia contribution itself. Thus, ST segments can exhibit amplitudes that suggest a larger than actual ischemic contribution.

Importance and availability of an individual baseline ECG

Ischemia detection on the basis of ST amplitudes in the ECG requires that these ST changes are "new, or presumably new" (guidelines,[4] Table 3), and, hence, ST interpretation in patients with a pre-existent non-zero ST segment (*e.g.*, due to left ventricular hypertrophy) is difficult. We realize that in many cases of suspected ACS the hyperacute ECG made within 10 min after first medical contact will have to be judged without a non-ischemic reference ECG at hand. However, with increasing technical possibilities and the increasing use of electronic patient files, we envisage that such a comparison becomes increasingly more often possible in the near future. With this in mind, exploration of the potential clinical use of an ischemia difference vector, computed by subtraction of the baseline vector from a vector during ischemia, becomes interesting.

Also, exploration of the VG becomes of interest within this perspective. Because of its non-zero[3] and highly individual[9] baseline value, the VG has never been used in diagnosis and triage in acute coronary syndrome. However, individual comparison of the VG in an ischemic ECG and a baseline ECG might be interesting, because the changes in the VG during ischemia are caused by action potential morphology changes in the ischemic area, rather than the ST changes, that are strongly based on the changes in the phase 4 resting

potential in the ischemic area. Moreover, VG is independent of the ventricular depolarization order.[3] Thus, ST changes and VG changes are induced by different electrophysiological processes that are, however, all related to ischemia of a compromised part of the ventricular myocardium.

In the current study we sought to explore the potential clinical value of ischemia diagnosis based on ST and VG difference vectors by analyzing the ECG changes of patients during elective percutaneous transluminal coronary angioplasty (PTCA).

METHODS

Patients and study data

We analyzed ECGs from the STAFF III database, a collection of ECGs recorded in the setting of elective PTCA procedures performed in 1995 and 1996. These ECGs are unique because of the relatively long balloon inflation times. As such, the PTCA procedure is a model of the hyperacute phase of ACS in humans. The data in the STAFF III database were collected before coronary stenting was widely available in the USA.

For the PTCA study, patients were admitted to the Charleston Area Medical Center, West Virginia, USA. The PTCA study was approved by the local investigational review board. Informed consent was obtained from each patient prior to enrollment. Patients were clinically stable during the PTCA study protocol. Nine-lead ECGs (I, II, III, V1–V6; Mason–Likar electrode positions) were recorded by Siemens-Elema electrocardiograph (Siemens-Elema AB, Solna, Sweden), sampling rate 1 kHz, amplitude resolution 0.6 μV. A reference ECG recording with a duration of about 3 min was made in the catheterization room prior to the PTCA procedure. During the PTCA procedure ECGs were recorded continuously.

In a subset of patients, sestamibi area at risk (AAR) assessments were done. An extensive description of the measurement procedure can be found in the recent publication of Romero *et al.*[10]

ECG processing

We preprocessed these ECGs by low-pass (100 Hz) filtering (to remove fluoroscopy-related interference) and by coarse baseline removal.[11] Further ECG processing was done in BEATS,[12] our vectorcardiographically oriented ECG analysis system. BEATS first synthesizes a vectorcardiogram (VCG, adhering to the AHA conventions for the direction of the axes and for the definition of azimuth and elevation,[13] and then interactively detects beats, defines the isoelectric points of each beat, fine-corrects the baseline by piecewise linear regression through these points, and determines landmarks in time (onset QRS, J point, peak and end of the T wave) in each beat. Inherently to the recording conditions, ECGs had sometimes abundant artifacts: beats were manually deselected when signal quality was low. Also, incidental non-sinus beats were removed. In the remaining beats we computed the ST vector (magnitude, azimuth and elevation) at J + 60 ms, and the spatial QRS, T and QRST integrals. Of note: these integrals are also vectors; they are expressed in mV·ms. The QRST integral is the VG. See Figure 2 for a graphical illustration of the computation of the ST and VG vectors.

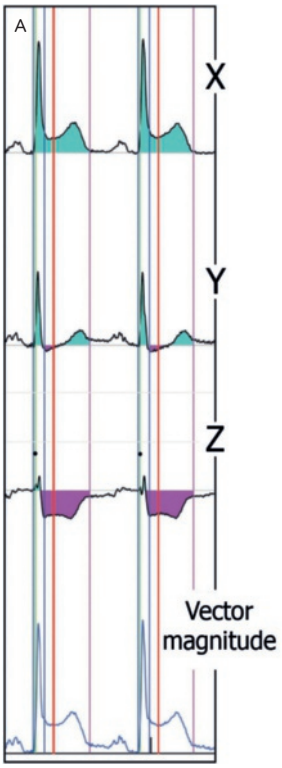
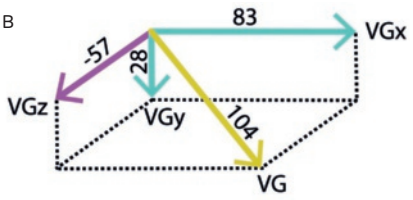


FIGURE 2. Graphical illustration of the computation of the ST and VG vectors. The example ECG was recorded during balloon occlusion.

Panel A depicts the synthesized VCG: X = X lead (lead vector points from right to left, this lead usually resembles leads I and V6 in the 12-lead ECG); Y = Y lead (lead vector points from superior to inferior, this lead usually resembles lead aVF in the 12-lead ECG); Z = Z lead (lead vector points from anterior to posterior, this lead usually resembles the inverted lead V2 in the 12-lead VCG). Vector magnitude = size of the heart vector (square root of the sum of the squared amplitudes in the X, Y and Z leads). Time markers indicate onset QRS, J point, J + 60-ms point and T end. The X, Y and Z amplitudes at the (red) J + 60-ms marker constitute the X, Y and Z components of the ST vector. The X, Y, and Z components of the VG vector are computed as the areas under the curve over the QRST complex, positive amplitudes (colored green) contribute positively and negative areas (colored purple) contribute negatively to the area. It is evident from the figure, that the net QRST areas of the X and the Y leads are positive, while the net QRST area of the Z lead is negative, the latter due to the ST depression and the negative T wave.

B. Vectorial composition of the VG vector. The length of the X, Y and Z components VGx, VGy and VGz equals the QRST integrals in the X, Y and Z leads as described in the left panel. Components VGx and VGy point in the positive directions of the X and the Y axes (from right to left, and from superior to inferior, respectively), because the QRST integrals in the X and Y leads are positive. Component VGz points in the negative direction of the Z axis (from posterior to anterior) because the QRST integral in the Z lead is negative. Vectorial composition of VGx, VGy and VGz yields the resultant VG vector (yellow).



Data selection

To facilitate reliable identification of the ECG episodes of interest we plotted, beat-by-beat, versus time: ST-vector magnitude, QRS width, QTpeak interval, QTend interval, inter-beat interval, QRS integral, T integral, and QRST integral. For the current study we selected a baseline ECG episode and an occlusion ECG episode. As baseline ECG episode we selected a stable 30-s episode in the reference recording, preferably at the end. As occlusion ECG episode we selected the period during the first balloon inflation as indicated in the database annotation file and visually checked with the above-mentioned plots. In addition to the noise- and artifact-related beat data that were already removed during BEATS processing we also removed data associated with dye injections (dye injections during balloon inflation cause — very briefly, though — ischemia in the complete perfusion area of the involved coronary artery and should, hence, be left out of consideration). Reperfusion data were not studied.

At this point the ECGs of all patients were fully known and, when necessary, the decision could be taken to exclude a patient because of the following ECG-related problems: predominant arrhythmias (*e.g.*, atrial fibrillation), predominant low-quality ECG signal, ECG electrode misplacement or abundant dye injections throughout the occlusion episode.

Data analysis

As baseline values we computed the averaged ST and VG vectors in the baseline ECG. Dynamic ST and VG vectors during ischemia were computed as 10-beat moving averages. Dynamic ST and VG difference vectors during ischemia, ΔST and ΔVG, were computed by subtracting the baseline ST and VG vectors from the dynamic ST and VG vectors during ischemia. As occlusion durations differed considerably, we did various calculations with the ST, VG, ΔST and ΔVG values after 3 min of occlusion (or with the terminal values when occlusion lasted somewhat less than 3 min, which was the case in a minority of patients).

To test if the difference vectors ΔST and ΔVG point in the same direction, and to test if this is not as much the case for the absolute ST and VG vectors, we calculated for each patient the planar angle between the ST and VG orientations after 3 min of occlusion and the planar angle between the ΔST and ΔVG orientations after 3 min of occlusion, and compared these angles by a t test.

To investigate the relation between the 3-minute ΔST and ΔVG magnitudes we performed a linear regression forced through the origin. Adopting a cutoff value of 0.05 mV for ΔST magnitude to detect ischemia,[14] the regression formula generated a ΔVG magnitude cutoff value for the detection of ischemia as well. Thus, we determined which patients had an ECG positive for ischemia on the basis of their ST difference vector magnitude alone, their VG difference vector magnitude alone, or one of both.

In addition, we compared the diagnostic performance of ΔST and ΔVG with the standard ECG ischemia diagnosis (STE, NSTE) after 3 min of ischemia. Ten-second ECG segments from the baseline ECGs and from the occlusion ECGs after 3 min of ischemia were transferred to the LUMC departmental ECG management system and analyzed by the University of Glasgow ECG Analysis Program.[15] Thus, an ECG diagnosis was generated, and STE/NSTE classification was established of the baseline and ischemic ECGs, by using the measurement matrix data of the Glasgow program. STE was diagnosed as an elevation at the J point of ≥ 0.2 mV in two or more contiguous leads in leads V1 or V2, and of ≥ 0.1 mV in other contiguous leads. Contiguity in the frontal plane is defined in the lead sequence aVL, I, inverted aVR, II, aVF, III. Also, a depression of ≥ 0.1 mV in leads V2 or V3 was counted as STE. When the ECG did not qualify as STE, it qualified as NSTE. The ECGs after 3 min of occlusion were, analogous to the guidelines of the hyperacute phase of ACS, considered as positive for "PCI-requiring ischemia" if their ECG after 3 min of occlusion had STE, while the baseline ECG had no STE. The percentages of the diagnostic performance of the ST and VG difference vectors combined was compared to the diagnostic performance of the STE/NSTE classification with a z test.

Finally, to test the possible relationship between the absolute and difference ST and VG vectors and the amount of ischemic tissue, we correlated, in a subset of patients in whom technetium sestamibi scans were done, the assessed AAR, expressed as a percentage of the left ventricular mass, with the ST, VG, ΔST and ΔVG vectors measured after 3 min of occlusion. Sestamibi assessment in the STAFF III database was done in 41 patients; we only analyzed the subset of patients in which the assessed AAR corresponded to the site of occlusion of the first balloon occlusion in a patient.

RESULTS

Study group

The STAFF database comprises 104 patients. After exclusion of patients because of predominant arrhythmias (*e.g.*, atrial fibrillation), predominant low-quality ECG signal, ECG electrode misplacement or abundant dye injections throughout the occlusion episode, 84 patients constituted our study group. Table 1 shows the group characteristics. Table 2 gives an overview of the positioning of the balloon in the coronary artery tree during the initial occlusion in each patient. Mean ± SD duration of the initial inflation was 260 ± 76 s, in 13 (15%) of 84 patients the duration of the initial inflation was shorter than 180 s (mean ± SD 145 ± 29 s).

	Number	%
N	84	
Sex (male/female)	54/30	64/36
Age (mean ± SD)	60 ± 11	
Previous infarction	32	38
Aberrant conduction	3	3.6
STE baseline ECG	2	2.4

TABLE 1. Patient characteristics of the study group.

Occlusion site	Number	%
Left main artery	2	2
Proximal LAD	14	17
Proximal–mid LAD	3	4
Mid LAD	6	7
LAD diagonal	2	2
Proximal RCA	17	20
Proximal–mid RCA	2	2
Mid RCA	12	14
Distal RCA	10	12
Proximal LCx	7	8
Mid LCx	4	5
Distal LCx	5	6

LAD = left anterior descending
RCA = right coronary artery
LCx = left circumflex

TABLE 2. Balloon positions during the studied occlusions.

Spatial orientation of the ischemia difference vectors ΔST and ΔVG

The concepts described in the Introduction, more specifically the consequences of pre-existent ST and VG vectors being modified by increasing ST and VG ischemia difference vectors with a different spatial orientation are clearly illustrated by one specific patient in our study group. According to the Sokolow–Lyon[16] and the Cornell voltage[17] criteria this patient had the ECG baseline diagnosis of left ventricular hypertrophy (LVH). The pre-existent, baseline non-zero ST amplitudes in the ECG leads hamper, during ischemia, straightforward interpretation of the ST segment. See Figure 3.

The planar angles between the ST and VG vectors, and between the ΔST and ΔVG vectors during ischemia, have been plotted in panels A and B of Figure 5, respectively. Panel A shows that after 1.5 min of occlusion, the ST and VG vectors in this patient nearly pointed in opposite directions (angle close to 180°). With time, due to increasing ischemia intensity, the orientation of both the ST and the VG vectors changed, and the angle decreased. Panel B shows that the ischemia difference vectors ΔST and ΔVG assumed almost a similar spatial orientation throughout the entire occlusion period (angles between the ΔST and ΔVG vectors remained small). In other words, the directions in which the ischemic injury currents modify the ST vector are nearly the same as the directions in which the ischemic action potential morphology changes modify the VG vector.

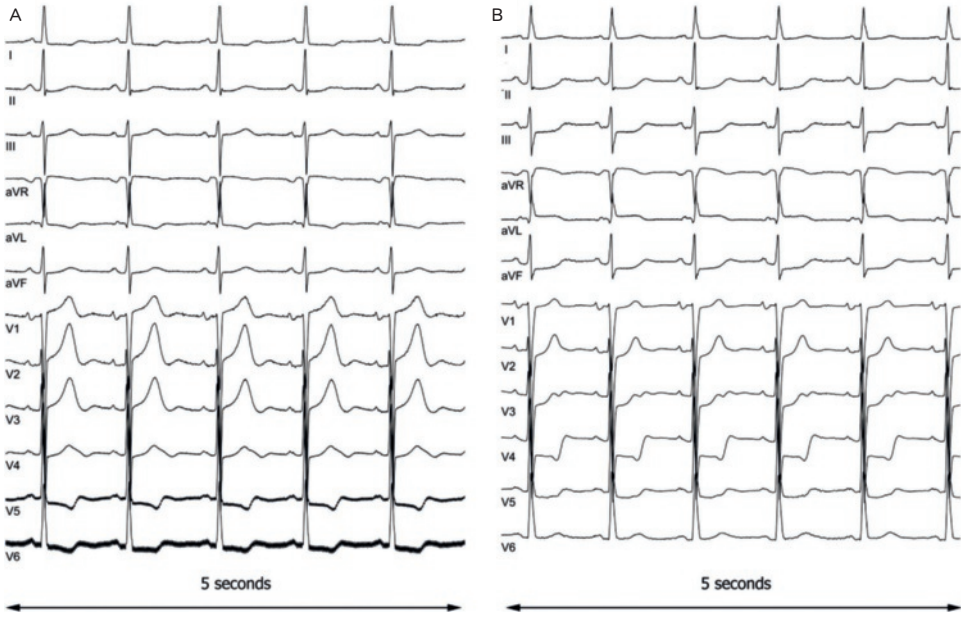


FIGURE 3. The 12-lead ECGs of the patient with LVH discussed in the text.
A. Reference ECG. B. ECG recorded during PTCA after 3 min of occlusion. The magnitudes of the ST and ΔST vectors and of the VG and ΔVG vectors during balloon occlusion of the proximal left circumflex artery in this patient have been plotted in panel A and B of Figure 4, respectively. Panel A of Figure 4 shows that the baseline ST-vector magnitude around 0.18 mV (1.8 mm) initially decreased until, about 1.5 min after occlusion started, a minimum was reached. Then, the ST-vector magnitude increased again. In fact, this might be caused by the effect as illustrated in Figure 1A (acute angle between the directions of the baseline and ischemia vectors). In contrast, the ΔST vector increased gradually throughout the entire occlusion period. This corresponds to the electrocardiographic manifestation that would be expected from a gradually increasing injury current with increasing ischemia. Panel B of Figure 4 shows that the VG magnitude showed little change in the initial ischemia period; then it started to gradually increase. In contrast, the ΔVG vector magnitude increased gradually throughout the entire occlusion period.

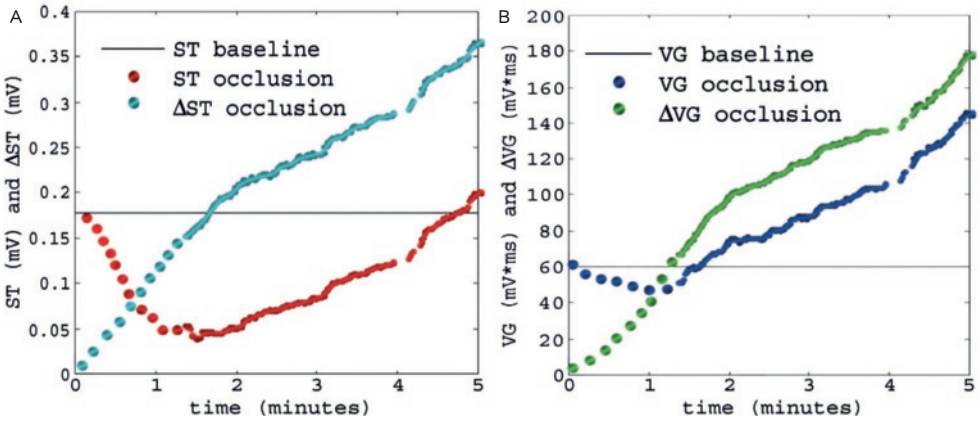


FIGURE 4. Five-minute during balloon occlusion of the proximal left circumflex artery in the patient with left ventricular hypertrophy discussed in the text. A. Magnitude of the ST and ΔST vectors. B. Magnitude of the VG and ΔVG vectors. Baseline values have been indicated as horizontal lines. Widely separated dots during the initial ischemia period indicate a period with manually inserted data (the ECG was unreliable due to dye injections).

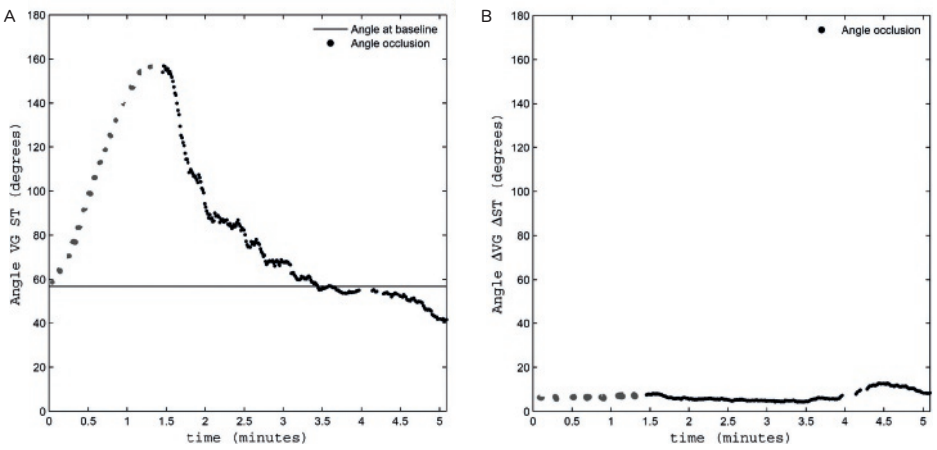


FIGURE 5. Five-minute during balloon occlusion of the proximal left circumflex artery in the patient with left ventricular hypertrophy discussed in the text. A. Angle between the ST and VG vectors. B. Angle between the ΔST and ΔVG vectors. Widely separated dots during the initial ischemia period indicate a period with manually inserted data (the ECG was unreliable due to dye injections).

Figure 6 shows how the spatial orientations of the ST and VG vectors and of the ΔST and ΔVG vectors changed during balloon occlusion. Panel A shows that, in the course of ischemia, the spatial orientations of the ST and VG vectors were not stable at all: the figure shows two long trajectories that differ considerably from each other. The dynamics in the ST and VG vectors would suggest that the direction/localization of the ischemia is highly dynamic. Also, the discrepancy between the ST and VG vector orientations would suggest a discrepancy in the localization of the ischemia. However, when looking at the difference ischemia vectors in panel B of Figure 6, it becomes obvious that the ΔST and ΔVG vectors not only pointed in nearly the same direction (as was already obvious in Figure 5B), but that this direction remained the same irrespective the stage of ischemia (obviously, by their larger marker size, the measurements at the end of ischemia cover the earlier measurements). Hence, in this patient, various stages of ischemia induced changes in the ST and in VG vectors that have a relatively constant and similar orientation. This orientation, in the posterior and partly superior directions, corresponded reasonably well with what can be expected during a proximal left circumflex artery occlusion.

For the complete study group, the mean ± SD angle between the absolute ST and VG vectors after 3 min of occlusion was 50.6° ± 33.7°. The mean ± SD angle between the ΔST and ΔVG vectors after 3 min of occlusion was 14.9° ± 14.0°, which was significantly ($P <$ 0.0001) smaller.

Ischemia thresholds of the difference vectors ΔST and ΔVG

Figure 7 is a scatterplot of the 3-min ΔST and ΔVG magnitudes. The straight line represents the linear regression forced through the origin: ΔVG = 324 · ΔST (ΔVG in mV·ms, ΔST in mV). The ΔST and ΔVG magnitudes correlated significantly (r = 0.84; $P <$ 0.0001). Adopting a cutoff value of 0.05 mV for ΔST magnitude to detect ischemia,[14] the associated ΔVG magnitude cutoff value was 16.2 mV·ms. Hence, either a minimal ΔST magnitude of 0.05 mV or a minimal ΔVG magnitude of 16.2 mV·ms would signify the presence of ischemia in hyperacute complete coronary occlusion.

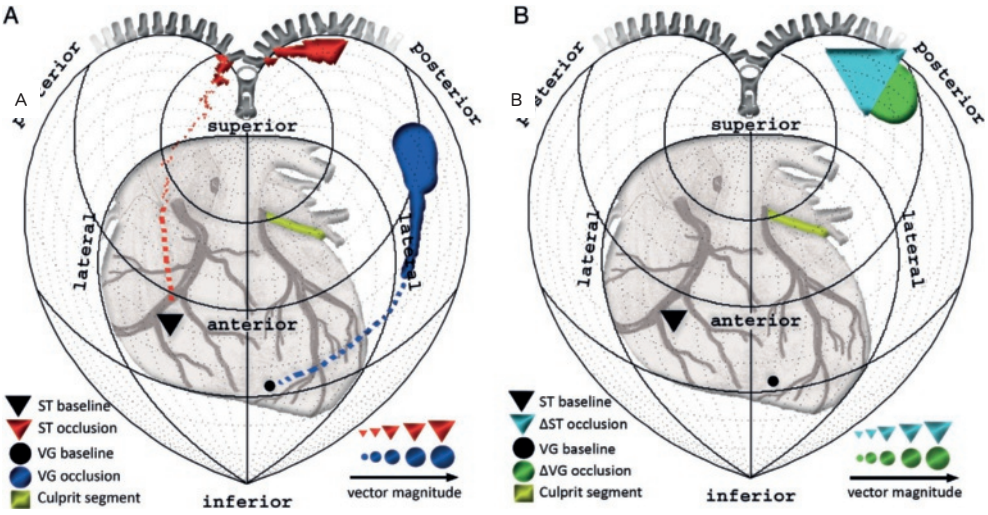


FIGURE 6. Spatial orientations and vector magnitudes during the 5-min balloon occlusion of the proximal left circumflex artery in the patient with left ventricular hypertrophy discussed in the text. Vector orientations (azimuth and elevation) are depicted in cordiform Werner projections, here with a posterior "cut" from superior to inferior, as symbolized by the zipper. **A.** ST and VG vectors. **B.** ΔST and ΔVG vectors. Vector magnitudes are expressed in the marker size. Widely separated dots during the initial ischemia period indicate a period with manually inserted data (the ECG was unreliable due to dye injections).

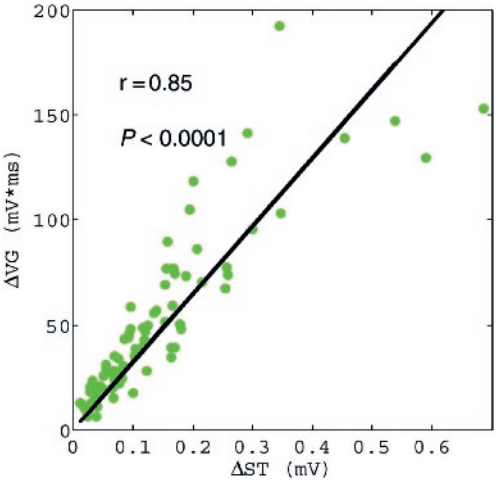


FIGURE 7. Scatterplot of ΔST versus ΔVG after 3 min of balloon occlusion in the study group. The straight line represents the linear regression forced through the origin between ΔST and ΔVG. The regression equation is ΔVG = 324 · ΔST (ΔVG in mV·ms, ΔST in mV).

Diagnostic performance of the ΔST and ΔVG magnitude ischemia thresholds

Table 3 shows the sensitivities of the conventional 12-lead ECG ischemia diagnosis (obtained by using the measurement matrix of the Glasgow ECG analysis program), the ΔST threshold criterion, the ΔVG threshold criterion and the criterion of the ischemia difference vectors thresholds combined (one or both of the thresholds should be reached), respectively. Table 4 shows the more detailed results of this comparison.

	TP (*N*)	TP (%)
STE	46	54.76
ΔST+	68	80.95
ΔVG+	72	85.71
ΔST+ and/or ΔVG+	73	86.90

TABLE 3. Sensitivity of conventional ECG ischemia diagnosis and ischemia diagnosis by ΔST and ΔVG vectors after 3 min of balloon occlusion.
TP = true positive; STE = new ST-elevation ECG.

	STE	NSTE	Σ
ΔST+	45	23	68
ΔST−	1	15	16
Σ	46	38	84
ΔVG+	46	26	72
ΔVG−	0	12	12
Σ	46	38	84
ΔST+ and/or ΔVG+	46	27	73
ΔST− and ΔVG−	0	11	11
Σ	46	38	84

TABLE 4. Comparison of conventional ECG ischemia diagnosis with ischemia diagnosis by ΔST and ΔVG vectors after 3 min of balloon occlusion.
STE = new ST-elevation ECG
NSTE = no new ST-elevation ECG

In 46 (55%) of 84 patients, the ECG after 3 min of balloon occlusion showed a pattern of new STE. Of note, the ECG after 3 min of occlusion of the LVH patient mentioned above was classified as NSTE (large depressions in V3 and V4, but non-diagnostic depressions in V1 and V2, see Figure 3). In the 13 patients who had occlusions < 3 min, 11 (85%) had a new STE ischemic ECG, demonstrating that the patients with the briefer occlusion were not the reason of the limited percentage (55%) of patients who had a new STE ischemic ECG. Regarding the ischemia difference vectors, 68 (81%) of 84 patients reached the ischemia threshold of 0.05 mV for the ΔST magnitude and 72 (86%) of 84 reached the ischemia threshold 16.2 mV·ms for the ΔVG magnitude; 73 (87%) of 84 reached both or at least one of these thresholds; this percentage is significantly ($P < 0.0001$) larger than the 55% positive diagnoses with the conventional ECG criteria.

Relation with area at risk

We further analyzed a subset of 31 patients in whom sestamibi assessments of the AAR was done. The occlusion sites were as follows: LAD/LCx/RCA in 8/6/17 patients, respectively. The AAR was expressed as a percentage of the left ventricular mass. For this subset the mean ± SD AAR was 18.5% ± 15.8%, the median AAR was 14.0% and the range was 0.1%–51.3%. Figure 8 shows scatterplots of ST, ΔST, VG and ΔVG magnitudes after 3 min of occlusion versus AAR. All four correlations are statistically significant ($P < 0.0001$), but there is no relevant difference between either the correlations with ST and with ΔST, or between the correlations with VG and ΔVG.

We arbitrarily defined the median AAR value (14%) as the separation between small and large areas (deemed to become small and large infarctions, respectively, might ischemia continue). ROC analysis revealed areas under the curve of 0.80, 0.85, 0.87 and 0.89 for the ST, ΔST, VG and ΔVG magnitudes after 3 min of occlusion, respectively ($P < 0.0001$).

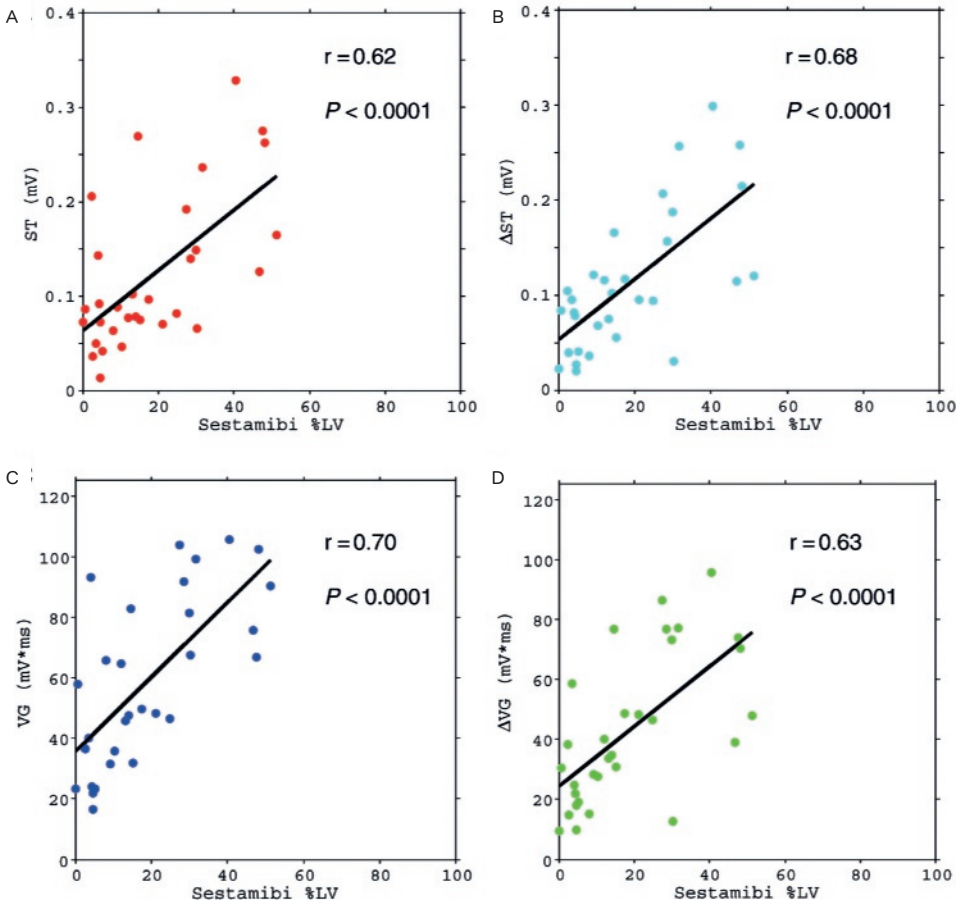


FIGURE 8. Scatter plots of magnitudes of ST **A.** ΔST **B.**, VG **C.** and ΔVG **D.** after 3 min of occlusion, versus the area at risk. The area at risk was expressed in the sestamibi-assessed percentage of involved LV mass. These measurements were done in 31 patients.

DISCUSSION

To our knowledge, our study is the first to characterize differential vectorcardiographic diagnosis not only with changes in the ST vector but also with changes in the VG vector. Additionally, it is the first study that compares ischemia diagnosis by ΔST and ΔVG magnitude with the conventional 12-lead ECG diagnosis in terms of STE or NSTE.

We showed, in a group of 84 patients undergoing elective PTCA for ischemic coronary heart disease that, after 3 min of balloon occlusion the ECG changes were above an ischemic threshold in 81% to 87% of the patients when measuring the change in the ST vector (ΔST), the change in the ventricular gradient (ΔVG), or both or either ΔST or ΔVG, while conventional guideline-based ECG diagnosis of the ischemic ECG was only positive for occlusion-related ischemia (*i.e.*, the ischemic ECG met the STE criteria) in 55% of the cases (Table 3).

Ideally, ECGs during ischemia caused by complete coronary occlusion should lead to a triaging decision that indicates urgent catheter-based intervention to restore perfusion,[4] as is the case in patients with an STE ECG. Obviously, patients with NSTE ECGs may also get an indication for catheter intervention; however, such patients should then pass more diagnostic tests or be considered urgent by the responsible physician.[5] This might take extra time and thus might lead to more necrotic myocardium, and would thus have a negative impact on the prognosis of these patients.

With complete occlusion, NSTE ECGs are nearly as often (47%) seen as STE ECGs (57%)[6]; this raises questions regarding the clinical usefulness of the separation of ECGs into these two diagnostic categories. In our study group, 38 (45%) of 84 patients had NSTE ECGs after 3 min of complete occlusion (Table 3). Of these 38 patients with NSTE ECGs, 23 (61%) had changes in the ST vector > 0.05 mV, 26 (68%) had changes in the VG > 16.2 mV·ms and 27 (71%) had such changes in either one or both. These figures illustrate the potential clinical value of differential vectorcardiographic ECG analysis in ischemia detection.

Our study also indicates that ΔVG could meaningfully contribute to ischemia detection. It is striking, that the planar angle between the ΔST and ΔVG vectors after 3 min of occlusion was only 14.9° ± 14.0°. Hence, the spatial orientation of these ischemia difference vectors is almost the same, and this increases the confidence that the location of the common cause of these difference vectors, *i.e.*, the ischemic area distal from the coronary occlusion site, is reflected in the spatial orientations of the ΔST and ΔVG vectors. Even in an extreme case like the LVH patient presented in the Results section, the spatial orientation of the ΔST and ΔVG vectors remained most of the time interval during occlusion < 10° (Figure 5).

An extra argument to consider ΔVG as a potentially important measure for ischemia is that its magnitude correlated well (r = 0.85, $P < 0.0001$) with the magnitude of ΔST. This relatively strong linear relationship between the magnitude of ΔST and ΔVG has facilitated to define the ΔVG magnitude threshold of 16.2 mV·ms on the basis of the ΔST threshold of 0.05 mV. Table 3 shows that this ΔVG ischemia threshold is rather superior than inferior to the ΔST ischemia threshold in detecting ischemia after 3 min of complete occlusion.

A final argument to consider the magnitude ΔVG as an potentially important measure for ischemia is that, in spite of the limited linear correlation with AAR, its magnitude had the largest area under the curve of the ST, ΔST, VG and ΔVG magnitudes, namely 0.89 ($P < 0.0001$).

The limited correlations of the ST, ΔST, VG and ΔVG magnitudes with the AAR are, in our view, the logical consequence of the genesis of the ECG. While working with the ECG, it has to be accepted that variable amounts of cancellation can cause, *e.g.*, limited ST changes in relatively large ischemic areas and reverse.

We explored the concept of ischemia difference vectors, defined as the ischemia-induced changes in the ST vector and in the VG vector with respect to their baseline values (Figure 1) in an attempt to resolve the problem of non-zero baseline values. Non-zero ST vectors can, by adding them to the ischemic changes, enhance or mask ischemia. Diagnostic non-zero ST vectors are even prohibitive for ST-guided ischemia diagnosis,[4,5] while the VG vector in normal, non-ischemic ECGs is by definition non-zero and, hence, cannot straightforwardly be used in ischemia diagnosis.[3,9] Adding the ventricular gradient to the repertoire of diagnostic algorithms is potentially important, because the VG conveys information about other physiological changes (action potential morphology changes in the ischemic area) than the ST segment does (mainly changes in the phase 4 resting potential in the ischemic area).

If the ECG diagnosis of acute ischemia requiring emergency PCI could be improved in patients with NSTE ECGs, appropriate triage to the cardiac catheterization laboratory for coronary intervention during the "golden hours" could result in significant myocardial salvage.

The here proposed calculations of the ST and VG difference vectors can relatively easy be implemented in existing commercial ECG analysis software. Every ECG analysis system computes an average beat with the major landmarks in time like the onset QRS, J point and end of T instants. Genesis of the vectorcardiogram from the electrocardiogram can be done by simple matrix multiplication, after which the ST and VG vectors can readily be computed. Subtracting the reference ECG results from the index ECG results gives the difference vectors. Regarding the practicality of this approach, general availability would depend on the willingness of the ECG equipment manufacturers to incorporate vectorial ECG variables in their standard ECG measurement list and on the willingness of health authorities to further stimulate and integrate electronic patient databases of which the ECG should be a standard element. In the acute situation, the ambulance ECG made at first medical contact could be teletransmitted to a regionally coordinating hospital (as is already current practice in several places) where serial comparison and authorized decision making should occur.

Our study and other studies regarding serial ECG analysis underscore the importance of the availability of a personal reference ECG for every individual. With technically and logistically increasing possibilities, it is likely that a reference/baseline ECG will be available more often in the future, which renders this form of ECG diagnosis more and more realistic. It is not known what percent of patients presenting with ACS currently have a prior obtainable ECG, and this percentage may vary from one institution or country to another. Until computerized records are readily available between all medical facilities, carrying a USB stick, a wallet or purse-sized laminated copy of one's last ECG, could facilitate the accurate diagnosis of acute ischemia. It might even be considered to strategically make reference ECGs in the population for preventive purposes.

Limitations

The STAFF III database comprises patients with elective PTCA. To a certain extent this is an advantage, because we can be sure of the fact that all patients had ischemia on the basis of a complete occlusion. Hence, in ischemia detection in this database, we can only observe true-positive and false-negative cases, and thus determine the sensitivity of a new ischemia detection method. As a consequence, specificity of ischemia detection on the basis of ΔST and of ΔVG could not be studied. After the positive result of this study regarding sensitivity, a new study also involving negative cases is a necessary next step.

It is also important to realize that in real life the situation can greatly differ from that in the elective procedures as observed in the STAFF III database. Spontaneous occlusions can be incomplete and dynamic, and often the time between the first ECG and the starting symptoms of what might be an ACS is longer than the few minutes that we can observe in the STAFF III patients. Hence, only real-life testing of serial ECG diagnosis in the setting of emerging ACS can determine its utility in the clinical setting.

REFERENCES

1. Downar E, Janse MJ and Durrer D. The effect of acute coronary artery occlusion on subepicardial transmembrane potentials in the intact porcine heart. Circulation. 1977;56:217-24.
2. Mirvis D, Goldberger, AL. Electrocardiography Braunwald's Heart Disease. 7th ed.: Elsevier Saunders; 2005: 25.
3. Draisma HH, Schalij MJ, van der Wall EE, *et al.* Elucidation of the spatial ventricular gradient and its link with dispersion of repolarization. Heart Rhythm. 2006;3:1092-9.
4. Steg P, James S, Atar D, *et al.* ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012;33:2569-619.
5. Hamm C, Bassand J, Agewall S, *et al.* ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011;32:2999-3054.
6. Koyama Y, Hansen PS, Hanratty CG, *et al.* Prevalence of coronary occlusion and outcome of an immediate invasive strategy in suspected acute myocardial infarction with and without ST-segment elevation. Am J Cardiol. 2002;90:579-84.
7. Lundin P, Eriksson SV, Erhardt L, *et al.* Continuous vectorcardiography in patients with chest pain indicative of acute ischemic heart disease. Cardiology. 1992;81:145-56.
8. Naslund U, Haggmark S, Johansson G, *et al.* Quantification of myocardium at risk and detection of reperfusion by dynamic vectorcardiographic ST segment monitoring in a pig occlusion-reperfusion model. Cardiovasc Res. 1993;27:2170-8.
9. Scherptong RW, Henkens IR, Man SC, *et al.* Normal limits of the spatial QRS-T angle and ventricular gradient in 12-lead electrocardiograms of young adults: dependence on sex and heart rate. J Electrocardiol. 2008;41:648-55.
10. Romero D, Ringborn M, Laguna P, *et al.* Detection and quantification of acute myocardial ischemia by morphologic evaluation of QRS changes by an angle-based method. J Electrocardiol. 2013;46:204-14.
11. Shusterman V, Shah SI, Beigel A, *et al.* Enhancing the precision of ECG baseline correction: selective filtering and removal of residual error. Comput Biomed Res. 2000;33:144-60.
12. Man S, Maan A, van der Wall E, *et al.* BEATS: an interactive Research Oriented ECG Analysis System. Comput Cardiol. 2010:1007-1010.
13. Report of committee on electrocardiography, American Heart Association. Recommendations for standardization of leads and of specifications for instruments in electrocardiography and vectorcardiography. Circulation. 1967;35:583-602.
14. Jensen SM, Johansson G, Osterman G, *et al.* On-line computerized vectorcardiography monitoring of myocardial ischemia during coronary angioplasty: comparison with 12-lead electrocardiography. Coron Artery Dis. 1994;5:507-14.
15. Macfarlane PW, Devine B, Latif S, *et al.* Methodology of ECG interpretation in the Glasgow program. Methods Inf Med. 1990;29:354-61.
16. Sokolow M and Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. Am Heart J. 1949;37:161-86.
17. Carey MG and Pelter MM. Cornell voltage criteria. Am J Crit Care. 2008;17:273-4.

Chapter

3

Directionality and proportionality of the ST and ventricular gradient difference vectors during acute ischemia

C. Cato ter Haar
Arie C. Maan
Martin J. Schalij
Cees A. Swenne

adapted from:
Journal of Electrocardiology
2014 Jul-Aug;47:500-504

ABSTRACT

Background

The ECG is important in diagnosis and triage in the initial phase of the acute coronary syndrome (ACS). The primary goal of making an ECG at first medical contact should be the reliable detection of cardiac ischemia, thus facilitating a correct triage by corroborating the diagnosis of ACS. Ischemia detection by ST amplitude analysis is limited to situations in which there is an identifiable J point. The ventricular gradient (VG) is independent of conduction and might be an alternative ECG-based variable for ischemia detection.

Methods

We studied vectorcardiograms (VCGs) synthesized of the ECGs of 67 patients who underwent elective PTCA with prolonged balloon occlusions (mean ± SD occlusion duration 214 ± 77 s), and computed, during occlusions, the changes of the ST and VG vectors with respect to baseline, ΔST and ΔVG, and the angle between these vectors, ∠(ΔST, ΔVG). We then analyzed directionality and proportionality of ΔST and ΔVG by performing linear regressions of ∠(ΔST, ΔVG) on time after occlusion, and of ΔVG on ΔST, respectively.

Results

Linear regression of ∠(ΔST, ΔVG) on time after occlusion yielded a slope of 1.55*10− 3 °/s and an intercept of 11.96°; r2 < 0.001 (NS). Linear regression of ΔVG on ΔST on all data yielded a slope of 253 mV and an intercept of 14.4 mV·ms; r2 = 0.75 (P < 0.001). Broken stick linear regression (breakpoint ΔST = 0.255 mV) yielded slopes of 330 mV and 160 mV, intercepts of 5.6 mV·ms and 47.2 mV·ms, and r2 values of 0.66 (P < 0.001) and 0.63 (P < 0.001) for the smaller and larger ΔST values, respectively.

Conclusion

Our study suggests that, because of the directionality and proportionality between ΔST and ΔVG, the change in the ventricular gradient, ΔVG, between a reference ECG and an ischemic ECG is a meaningful measure of ischemia.

INTRODUCTION

If a patient presents with symptoms that might be caused by Acute Coronary Syndrome (ACS), establishing that diagnosis is of utmost importance for adequate triaging and treatment. At first medical contact, often occurring during the "Golden Hour" (the first hour after symptom onset), the diagnostic options are limited to history taking, physical examination and ECG recording and analysis. At that point in time, cardiac ultrasound is unavailable, and biomarker analysis (that measures necrosis rather than ischemia) cannot contribute to diagnosis in this early phase.[1,2]

The current ECG diagnosis of acute ischemia rests mainly on ST segment interpretation. Patients are thus triaged into two strata: those with an ST elevation (STE) ECG and those with a non-ST elevation (NSTE) ECG. First-choice therapy is percutaneous coronary intervention (PCI) in STE-ACS patients and antithrombotic treatment in NSTE-ACS patients. Some publications suggest, suppose or state that STE and NSTE ECGs are caused by complete, prolonged and by incomplete, temporal occlusions of a coronary artery segment, respectively.[3-5] The current guidelines state that NSTE ECGs can occur with complete and with incomplete occlusion.[6] The guidelines of STEACS do not state this difference.[7] However, research has shown that complete and incomplete occlusion can produce STE as well as NSTE ECGs. Koyama and colleagues found a completely occluded coronary artery in 47% of NSTE-ACS patients,[8] and Man and colleagues found NSTE ECGs in 29% of ACS patients with a completely occluded coronary artery.[9] In ECG recordings made during elective PTCA with prolonged balloon inflations, Ter Haar and colleagues found, after three minutes of occlusion, NSTE ECGs in 45% of the patients.[10] Together, these studies suggest that the ECG cannot reliably discriminate completely and incompletely occluded coronary arteries.

Therefore, the primary goal of ECG diagnosis at first medical contact should be the reliable detection of cardiac ischemia, thus corroborating the diagnosis of ACS, potentially an indication for acute cardiac catheterization followed by revascularization (PCI, or CABG) when appropriate. We investigate an approach in which sufficient sensitivity and specificity are aimed at by serial vectorcardiographic analysis, in which the acute ischemic ST vector is individually compared with a non-ischemic reference ST vector obtained from an earlier recording.[10] The ST vector magnitude and magnitude change are measured irrespective of its direction (depending on the individual coronary anatomy and pathology and the localization of the culprit site in the coronary artery tree, the resulting ischemic area and the associated ST vector direction can be situated virtually everywhere in the heart and assume virtually every direction)[9,10] and the ischemia detection threshold should be lower than the conventional threshold of 0.1 mV.[11]

Ischemia detection by ST amplitude analysis is limited to situations in which there is a measurable ST amplitude in the reference ECG as well as in the ECG during acute ischemia. If pre-existing or acutely occurring ventricular conduction disturbances preclude identification of the J point, an alternative vectorcardiographic ECG measure for ischemia could be the ventricular gradient (VG). The VG is a promising ECG feature for ischemia detection because it is determined by the action potential morphology distribution in the heart and is independent of the ventricular depolarization order.[12]

Our initial exploration of ECG recordings made during elective PTCA with prolonged balloon inflations gave an impression that, in patients with measurable reference and ischemic ST amplitudes, ischemic ST and VG changes are proportional and have a similar 3D orientation.[10,11] Proportionality of ST and VG is highly interesting because it would mean that it is possible to compute an equivalent/surrogate ST change on the basis of a VG change in cases of pre-existing or acute ischemic conduction disturbances. This prompted us to explore this phenomenon further in the same dataset.

METHODS

Patients and study data

We analyzed ECGs from the STAFF III database, a collection of ECGs recorded in the setting of elective PTCA procedures with relatively long balloon inflation times. As such, the PTCA procedure is a model of the hyperacute phase of ACS in humans. A non-ischemic reference ECG was recorded in the catheterization room prior to the PTCA procedure. During the PTCA procedure the ECG was recorded continuously. Further details about this database and data recording can be found in Pettersson *et al.*[13] Further details about data selection and ECG processing can be found in the paper by Ter Haar *et al.*[10]

ECG processing

Briefly, ECG processing was done in BEATS,[14] our interactive vectorcardiographically-oriented beat-to-beat ECG analysis system. BEATS first synthesizes a vectorcardiogram (VCG), and then detects beats and determines in each beat the relevant landmarks in time (onset QRS, J point, and end of the T wave). Noisy beats and incidental non-sinus beats were manually deselected. In the remaining beats, BEATS computed the ST vector (magnitude, azimuth and elevation) at J + 60 ms, and the 3-dimensional QRST integral, which is the VG.[12]

Data selection

The data selection procedure was done as previously described.[10] Briefly, baseline and occlusion ECG episodes were selected from the reference ECG made before and during the continuously recorded ECG throughout the PTCA procedure, respectively. Then, data associated with dye injections were removed. Finally, patients were excluded if they had predominant arrhythmias (*e.g.*, atrial fibrillation), predominantly low-quality ECG signal, ECG electrode misplacement or frequent dye injections throughout the occlusion episode. Additionally, in the current study, we excluded three patients because of a striking difference in heart rate between the baseline and occlusion ECGs.

Data analysis

As baseline values we computed the averaged ST and VG vectors in the baseline ECG. Dynamic ST and VG vectors during ischemia were computed as 10-beat moving averages. Dynamic ST and VG difference vectors during ischemia, ΔST and ΔVG, were computed by subtracting the baseline ST and VG vectors from the dynamic ST and VG vectors during ischemia.

To investigate directionality (whether the difference vectors ΔST and ΔVG point in the same direction), we calculated for all observations in every patient the angle between the ΔST and ΔVG orientations, ∠(ΔST, ΔVG). As the orientations of small ΔST and ΔVG vectors are very sensitive to noise, we removed data if ΔST and/or ΔVG vector magnitudes were smaller than 0.05 mV and 16.2 mV·ms, respectively. These threshold values were chosen because the ΔST threshold of 0.05 mV is half of the traditional ischemia threshold in electrocardiography and may have sufficient sensitivity for ischemia detection in ACS with differential ECG analysis;[11,15] the ΔVG threshold of 16.2 mV·ms corresponds to this ΔST threshold.[11] This necessary measure of removing small deviations from baseline caused the exclusion of 14 additional patients, whose ST and VG changes remained completely under these thresholds. To test for directionality, we finally performed a linear regression of ∠(ΔST, ΔVG) on time after occlusion on the collective data.

To investigate, in the same patient selection, proportionality (whether there is proportionality of the ΔST and ΔVG vector magnitudes), we performed a linear regression of ΔVG on ΔST on the collective data.

Finally, means and standard deviations of all regression constants were computed in the three groups of patients as formed by the coronary artery in which the balloon occlusion had occurred.

RESULTS

Study group

The STAFF database comprises 104 patients. After exclusion of patients because of predominant arrhythmias (e.g., atrial fibrillation), predominantly low-quality ECG signal, ECG electrode misplacement, frequent dye injections throughout the occlusion episode, a striking difference in heart rate between the baseline and occlusion ECGs or sub threshold ΔST and/or ΔVG values, 67 patients constituted the study group. Table 1 shows the group characteristics. Table 2 gives an overview of the positioning of the balloon in the coronary artery tree during the initial occlusion in each patient. Mean ± SD duration of balloon occlusion was 214 ± 77 s.

Baseline values

Mean ± SD baseline values of the ST vector magnitude were 0.07 ± 0.04 mV. The ST vector magnitude ranged from 0.02 to 0.21 mV; nine patients had an ST vector magnitude > 0.10 mV, one of these patients had an ST vector magnitude > 0.20 mV. Mean ± SD baseline values of the VG vector magnitude were 49.9 ± 20.9 mV·ms. The VG vector magnitude ranged from 11.9 to 129.8 mV·ms; two patients had a VG vector magnitude > 100.0 mV·ms.

	Number	%
N	67	
Sex (male/female)	45/22	67/33
Age (mean ± SD)	61 ± 12	
Previous infarction	24	36
Aberrant conduction	3	4

TABLE 1. Patient characteristics of the study group.

Occlusion site	Number	%
Left main artery	2	3
Proximal LAD	13	19
Proximal–mid LAD	3	5
Mid LAD	4	6
LAD diagonal	1	2
Proximal RCA	15	22
Proximal–mid RCA	1	2
Mid RCA	10	15
Distal RCA	7	10
Proximal LCx	5	7
Mid LCx	1	2
Distal LCx	5	7

TABLE 2. Balloon positions during the studied occlusions.
LAD = Left Anterior Descending
RCA = Right Coronary Artery
LCx = Left Circumflex.

Directionality of ΔST and ΔVG

Figure 1 shows the collective ∠(ΔST, ΔVG) values of the study group. The same Figure also shows the regression line of ∠(ΔST, ΔVG) on time on the collective data. Collective linear regression ∠(ΔST, ΔVG) = a · time + b yielded a slope a of 1.55*10− 3 °/s (95% CI − 2.89*10− 4 °/s, 3.38*10− 3 °/s) and an intercept b of 11.96° (95% CI 11.54°, 12.37°); r2 = 0.0003 (NS).

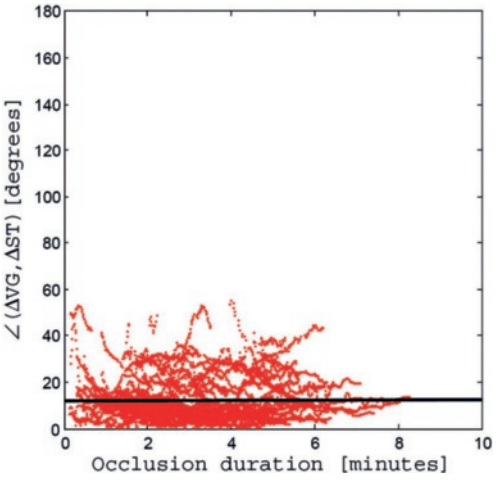


FIGURE 1. Angles between ΔVG and ΔST during balloon occlusion; pooled data. Fragments of missing data are caused by rejected beats due to inferior signal quality. The black line is the linear regression line through all data. See Results section for regression values.

Proportionality of ΔST and ΔVG

Figure 2 shows the collective data pairs ∠(ΔST, ΔVG). The same Figure also shows the regression line of ΔVG on ΔST on the collective data. Collective linear regression ΔVG = a · ΔST + b yielded a slope of 253 mV (% CI 250 mV, 256 mV) and an intercept of 14.4 mV·ms (95% CI 13.9 mV·ms, 14.9 mV·ms); r2 = 0.75 ($P < 0.001$). Because of the non-zero intercept, an additional piecewise linear regression (broken stick method)[16] was done. The resulting breakpoint was ΔST = 0.255 mV. The linear regression in the ΔST values below the breakpoint yielded a slope of 330 mV (% CI 325 mV, 334 mV) and an intercept of 5.6 mV·ms (95% CI 5.0 mV·ms, 6.2 mV·ms); r2 = 0.66 ($P < 0.001$). The linear regression in the ΔST values above the breakpoint yielded a slope of 160 mV (% CI 153 mV, 168 mV) and an intercept of 47.2 mV·ms (95% CI 44.3 mV·ms, 50.1 mV·ms); r2 = 0.63 ($P < 0.001$).

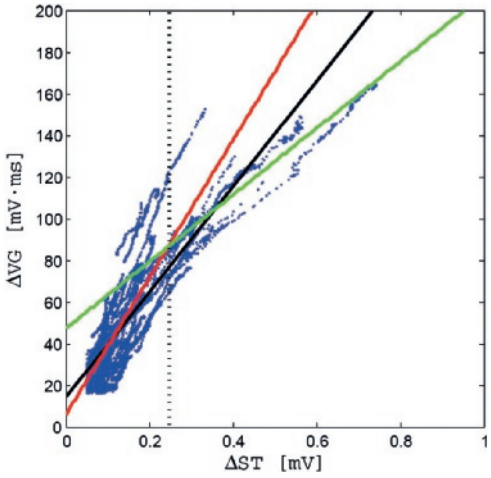


FIGURE 2. Pooled ΔST, ΔVG measurements (blue data points). Fragments of missing data are caused by rejected beats due to inferior signal quality. The black line is the linear regression line through all data. The red and green lines are the result of the broken-stick piecewise linear regression procedure. The red line fits the data at the left of the breakpoint (dashed vertical line at ΔST = 0.255 mV). The green line fits the data at the right of the breakpoint. See Results section for regression values.

Proportionality and directionality in the patient groups with LAD, RCA, LCx occlusions

Table 3 shows the means and standard deviations of all regression constants in the three groups of patients as formed by the coronary artery in which the balloon occlusion had occurred. No significant differences between groups were found.

N = 65	LAD (*N* = 21)	RCA (*N* = 33)	LCx (*N* = 11)
Angle a (°/min)	2.6 ± 18.1	−1.9 ± 8.1	−2.1 ± 11.7
Angle b (°)	8.0 ± 25.0	21.2 ± 24.9	7.9 ± 19.6
Delta a (mV)	375 ± 152	354 ± 209	462 ± 196
Delta b (mV·ms)	6.5 ± 21.2	−0.2 ± 20.8	−5.5 ± 19.5

TABLE 3. Mean and SD values of the coefficients of the linear regressions of the angle between the ΔST and ΔVG vectors on time (Angle) and of the linear regressions of the magnitudes of ΔVG on ΔST (Delta). Data are grouped per coronary artery in which the balloon occlusion was performed. The two patients with a left main occlusion were excluded from this table. LAD = Left Anterior Descending; RCA = Right Coronary Artery; LCx = Left Circumflex; a = slope; b = intercept. All differences between the data from the three major coronary arteries groups are non-significant.

DISCUSSION

In non-ischemic ECGs, the ST segment is often close to the baseline; and ischemia causes deviations of the ST segment from the baseline. This was also the general finding in the study group: the mean baseline ST vector magnitude was relatively small (0.07 mV), and the changes in the ST vector due to ischemia (see Figure 2) were generally much larger than the baseline values. The VG behaves differently: according to expectation[12,17] baseline VG magnitudes were essentially different from zero (mean 49.9 mV·ms), and individual values differed widely, as shown by the SD (20.9 mV·ms) and the range of the data (11.9 to 129.8 mV·ms). The changes in the VG due to ischemia had the same order of magnitude (see Figure 2) as the baseline values, and, depending on the direction of the ischemic VG change, the magnitude of the ischemic VG may become smaller or larger than the baseline VG (see Figure 1 in the paper by Ter Haar *et al.*)[10]. Hence, in the VG, ischemic changes must necessarily be estimated by comparing the ischemic ECG with a non-ischemic baseline ECG. There may, however, also be good reasons to interpret the ST deviation in an ischemic ECG in a similar way: the average ST vector magnitude of 0.07 mV was not far below the value of 0.10 mV, which is considered to be the diagnostic threshold for ischemia in several ECG leads. Nine patients had even baseline ST vector magnitudes > 0.10 mV. Hence, estimating ischemic ST changes by comparing the ischemic ECG with a non-ischemic baseline ECG could potentially be a superior strategy.

This study shows that ischemia-induced changes in the ST and VG vectors assume grossly the same direction. The angles are always acute, most of the time even < 30°. The slope of the regression line is not significantly different from 0 and the intercept of $\angle(\Delta ST, \Delta VG)$ is rather small (11.96°). In addition, the broken-stick piecewise linear regression of the relationship between the magnitudes of ΔST and ΔVG reveals that there is a different proportionality constant for smaller and larger ΔST values (breakpoint was 0.255 mV): the slope of the linear regression line is steeper for smaller ΔST than for larger values.

Our results show that ST and VG changes are positively associated, this holds for the regression results in the pooled data as well as for the individual data (see also Figure 2). Such a positive association between ST and VG changes is according to expectation. Ischemia alters the entire action potential morphology and the maximal diastolic potential.[18] This leads to injury currents throughout the entire cardiac cycle, necessarily affecting the ST amplitude directly (*i.e.*, due to the phase 2 injury current) as well as indirectly (*i.e.*, due to the ECG baseline correction as a consequence of the phase 4 injury current).[19] At the same time, these action potential morphology changes in the ischemic area generate alterations in the entire QRST complex, thus changing the QRST integral (*i.e.*, the VG). Such alterations occur within minutes after onset of ischemia[20] and affect the QRS complex, the ST segment and the T wave in various combinations,[21] all depending on individual conditions (coronary anatomy and pre-existing pathology, collateral circulation, absence or presence of ischemic preconditioning, site of occlusion).[22,23]

Comparison of the slope of the regressions of ΔVG on ΔST for smaller and for larger values of ΔST suggests that ΔVG is more sensitive for smaller values of ΔST. These data may partly represent situations in which changes in the QRS complex and/or in the T wave are predominating changes in the ST amplitude.

The small acute angle between ΔVG and ΔST indicates that the VG and ST vectors both change in the same direction under the influence of ischemia. This is also according to expectation. A major component of the ST changes during ischemia is the phase 4 injury current, flowing through the gap junctions from the ischemic area (less negative phase 4 potential) to the non-ischemic area (more negative phase 4 potential). This induces a DC baseline shift during phase 4. Baseline removal algorithms in the electrocardiograph correct for this shift, thus inducing an ST amplitude shift that points in the direction of the ischemic area. The VG vector points in the direction of the briefest action potentials in the heart.[12] In normal hearts epicardial cells have briefer action potentials than endocardial cells, and apical cells have briefer action potential durations than cells at the base of the heart. As a consequence the VG in normal hearts points in the direction of the apex. When the action potential amplitude and duration decrease during ischemia this will, by definition, change the VG in the direction of the ischemic area. Hence, we may expect that ST and VG vector changes due to ischemia both point in (about) the same direction. The fact that there were no differences between the results of the three major coronary arteries suggests that the relations between the ST and VG vector changes during ischemia are independent of the anatomical localization of the area at risk.

The positive association of ΔVG and ΔST, in combination with the small acute angle between these vectors, underscores the potential value of ΔVG as an alternative index of ischemia in case ΔST cannot be measured in either the reference ECG or the acute ischemic ECG, or both. Invariably, the impossibility to measure ΔST is caused by a conduction disturbance that precludes identification of the J point. By its nature, the VG is independent of conduction, and because of that property, meaningful VG measurements can be done in QRST complexes in which there is no distinct separation between the QRS complex and the T wave.

Our study is limited by the fact that there are no ECGs in the study group where the J point could not be identified. Additionally, in the real world, a previously made reference ECG is more remote from the acute ECG, and, hence, spontaneous variability under influence of hour of the day, heart rate differences, medication differences, inaccuracies in electrode positions, etc. may confound the differential measurement.

In conclusion, our study suggests that the change in the ventricular gradient, ΔVG, between a reference ECG and an ischemic ECG is a meaningful measure of ischemia. This should be corroborated in further studies in patients with conduction disturbances and unidentifiable ST segments and in a real-world situation in which the non-ischemic reference ECGs are more remote in time from the acute ischemic ECGs.

REFERENCES

1. Stengaard C, Sorensen JT, Ladefoged SA, *et al.* Quantitative point-of-care troponin T measurement for diagnosis and prognosis in patients with a suspected acute myocardial infarction. Am J Cardiol. 2013;112:1361-6.
2. van der Laarse A, Cobbaert CM, Gorgels AP, *et al.* Will future troponin measurement overrule the ECG as the primary diagnostic tool in patients with acute coronary syndrome? J Electrocardiol. 2013;46:312-7.
3. Cohn JN. The message is clear: prevent as well as treat acute myocardial infarction. Circulation. 2013;128:2554-6.
4. Daga LC, Kaul U and Mansoor A. Approach to STEMI and NSTEMI. J Assoc Physicians India. 2011;59 Suppl:19-25.
5. Knot J, Kala P, Rokyta R, *et al.* Comparison of outcomes in ST-segment depression and ST-segment elevation myocardial infarction patients treated with emergency PCI: data from a multicentre registry. Cardiovasc J Afr. 2012;23:495-500.
6. Hamm C, Bassand J, Agewall S, *et al.* ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011;32:2999-3054.
7. Steg P, James S, Atar D, *et al.* ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012;33:2569-619.
8. Koyama Y, Hansen PS, Hanratty CG, *et al.* Prevalence of coronary occlusion and outcome of an immediate invasive strategy in suspected acute myocardial infarction with and without ST-segment elevation. Am J Cardiol. 2002;90:579-84.
9. Man S, Rahmattulla C, Maan AC, *et al.* Acute coronary syndrome with a totally occluded culprit artery: relation of the ST injury vector with ST-elevation and non-ST elevation ECGs. J Electrocardiol. 2014;47:183-90.
10. ter Haar CC, Maan AC, Warren SG, *et al.* Difference vectors to describe dynamics of the ST segment and the ventricular gradient in acute ischemia. J Electrocardiol. 2013;46:302-11.
11. ter Haar CC, Maan AC, Schalij MJ, *et al.* Improved electrocardiographic detection of hyperacute ischemia by difference vector analysis. Comput in Cardiol. 2013:9-12.
12. Draisma HH, Schalij MJ, van der Wall EE, *et al.* Elucidation of the spatial ventricular gradient and its link with dispersion of repolarization. Heart Rhythm. 2006;3:1092-9.
13. Pettersson J, Pahlm O, Carro E, *et al.* Changes in high-frequency QRS components are more sensitive than ST-segment deviation for detecting acute coronary artery occlusion. J Am Coll Cardiol. 2000;36:1827-34.
14. Man S, Maan A, van der Wall E, *et al.* BEATS: an interactive Research Oriented ECG Analysis System. Comput Cardiol. 2010:1007-1010.
15. Jensen SM, Johansson G, Osterman G, *et al.* On-line computerized vectorcardiography monitoring of myocardial ischemia during coronary angioplasty: comparison with 12-lead electrocardiography. Coron Artery Dis. 1994;5:507-14.
16. Yang L and Gao S. Bivariate random change point models for longitudinal outcomes. Stat Med. 2013;32:1038-53.
17. Scherptong RW, Henkens IR, Man SC, *et al.* Normal limits of the spatial QRS-T angle and ventricular gradient in 12-lead electrocardiograms of young adults: dependence on sex and heart rate. J Electrocardiol. 2008;41:648-55.
18. Downar E, Janse MJ and Durrer D. The effect of acute coronary artery occlusion on subepicardial transmembrane potentials in the intact porcine heart. Circulation. 1977;56:217-24.
19. Mirvis D, Goldberger, AL. Electrocardiography Braunwald's Heart Disease. 7th ed.: Elsevier Saunders; 2005: 25.
20. Sodi Pallares D. New bases of electrocardiography. St. Louis: The C.V. Mosby Co.; 1956.
21. Birnbaum Y, Sclarovsky S, Blum A, *et al.* Prognostic significance of the initial electrocardiographic pattern in a first acute anterior wall myocardial infarction. Chest. 1993;103:1681-7.
22. Floyd JS, Maynard C, Weston P, *et al.* Effects of ischemic preconditioning and arterial collateral flow on ST-segment elevation and QRS complex prolongation in a canine model of acute coronary occlusion. J Electrocardiol. 2009;42:19-26.
23. Weston P, Johanson P, Schwartz LM, *et al.* The value of both ST-segment and QRS complex changes during acute coronary occlusion for prediction of reperfusion-induced myocardial salvage in a canine model. J Electrocardiol. 2007;40:18-25.

Chapter

4

Improved Electrocardiographic Detection of Hyperacute Ischemia by Difference Vector Analysis

C. Cato ter Haar
Arie C. Maan
Martin J. Schalij
Cees A. Swenne

adapted from:
Computing in Cardiology
2013;40:9-12

ABSTRACT

Background

The ECG is important for diagnosis and triage in the hyperacute phase of acute coronary syndrome (ACS), especially during the "golden hours", when myocardial salvage possibilities are largest. An important triaging decision is whether or not a patient requires primary PCI, for which the guidelines mention ST elevation (STE) in the ECG as major criterion. This criterion has, however, a low sensitivity and specificity.

Methods

We investigated the diagnostic possibilities of ischemia detection by means of changes in the ST vector, ΔST, and/or changes in the VG (QRST-integral) vector, ΔVG. We studied vectorcardiograms (VCGs) synthesized from the ECGs of 84 patients who underwent elective PTCA. Mean ± SD balloon occlusion times were 260 ± 76 s. ECG ischemia diagnosis (STE or non-STE (NSTE), and the differences ΔST and ΔVG with the baseline ECG were measured after 3 min. of occlusion.

Results

Linear regression of ΔVG on ΔST yielded ΔVG = 324•ΔST ($r = 0.85$; $P < 0.0001$, ΔST in mV). With ΔST thresholds of 0.025, 0.050, 0.075 and 0.100 mV and corresponding ΔVG thresholds of 8.1, 16.2, 24.3 or 32.4 mV·ms, respectively, we determined the sensitivity for ischemia detection, that varied from 55% for the STE criterion to 87 or even 99% for the one but most and the most sensitive ΔST and ΔVG criteria, respectively.

Conclusion

Differential diagnosis by ΔST and ΔVG (requiring an earlier made non-ischemic baseline ECG) could dramatically improve ECG guided detection of patients who urgently require catheter intervention.

INTRODUCTION

Ischemia affects action potential morphology and maximum diastolic potential,[1] thus causing systolic and diastolic injury currents[2] between ischemic and surrounding healthy tissue, changing the ECG throughout the QRST interval. Amongst others, this manifests as alterations in the ST segment and in the spatial ventricular gradient (VG, spatial QRST integral).[3]

In the hyperacute phase of acute coronary syndrome (ACS), the ECG is of major importance in diagnosis of ischemia and in triaging. According to the current guidelines,[4] first-choice therapy in patients with a new ST elevation (STE) pattern in the ECG is primary percutaneous coronary intervention (PCI). In case of acute coronary syndromes without ST-elevation (non-ST elevation, NSTE) the current guidelines[5] recommend antithrombotic (anticoagulant, antiplatelet) therapy rather than PCI. However, there are situations in which the ECG is non-diagnostic while there is still an urgent indication for PCI (like the ST depression without ST elevation that can be seen in left main disease). Consequently, the guidelines[4] read: "In any case, ongoing suspicion of myocardial ischemia— despite medical therapy—is an indication for emergency coronary angiography with a view to revascularization, even in patients without diagnostic ST-segment elevation." The percentage of patients with NSTE admission ECGs that require PCI may be considerable: Koyama and colleagues[6] found a completely occluded culprit artery in 47% of patients with an NSTE admission ECG (vs. 57% in patients with a STE admission ECG). These numbers clearly illustrate that there is a need to investigate if and how these ECG triaging criteria can be improved.

Reasons why the performance of the ECG criteria in separating patients who urgently need PCI from those who do not is limited, are various. Cancelation, inherent to electrocardiography, may explain how ST-changes can remain limited with relatively large areas at risk (AARs), *e.g.*, in case of left main disease. A pre-existing non-zero ST deviation, even when not diagnostic, may either mask or exaggerate new ST changes during acute ischemia, depending on (in vectorcardiographic terms) the direction of the ischemia vector in relation to the pre-existing ST vector. Hence, it would be logical to measure and interpret the ischemic change of the ST vector with respect to its baseline value (measured in a preceding non-ischemic ECG of the same patient), instead of the ST vector in the ischemic ECG alone. The concept of such an ST difference vector was first published by Lundin *et al.*,[7] and another Swedish research group has continued to explore the usefulness of this concept (first publication by Näslund *et al.*),[8] but its performance as compared with the conventional STE and NSTE ECG ischemia criteria has not been investigated so far.

For the computation of an ST difference vector in suspected ACS, access to a previously made non-ischemic ECG of the same patient is needed. We realize that this is often not possible; however, with increasing technical possibilities and the increasing use of electronic patient files, we envisage that such a comparison becomes increasingly more feasible in the near future.

Availability of a baseline ECG would also facilitate computation of an ischemic VG difference vector. Because of its non-zero[3] and highly individual[9] baseline value, the VG has until now never been used in diagnosis and triage in acute coronary syndrome. Individual comparison of the VG in an ischemic ECG and a baseline ECG is of interest because the changes in the VG during ischemia are caused by action potential morphology changes in the ischemic area, rather than the ST changes, that are strongly based on the changes in the phase 4 resting potential in the ischemic area. Moreover, VG is independent of the ventricular depolarization order.[3] Thus, ST changes and VG changes are induced by different electrophysiological processes that are, however, all related to the compromised myocardium.

In the current study, we explored the potential clinical use of ischemic ST and VG difference vectors by analyzing the ECG changes of patients during elective percutaneous transluminal coronary angioplasty (PTCA).

METHODS

We analyzed ECGs from the STAFF III database, a collection of ECGs recorded in the setting of elective PTCA procedures performed in 1995 and 1996. These ECGs are unique because of the relatively long balloon inflation times. As such, the PTCA procedure is a model of the hyperacute phase of ACS in humans. Patients were admitted to the Charleston Area Medical Center, West Virginia, USA. Nine-lead ECGs (I, II, III, V1-V6; Mason-Likar electrode positions) were recorded at a sampling rate of 1 kHz and an amplitude resolution of 0.6 μV. A 5-minute reference ECG was made in the catheterization room prior to the PTCA procedure. ECGs were continuously recorded during PTCA. Patients were excluded when they had predominant arrhythmias (*e.g.*, atrial fibrillation), predominant low quality ECG signal, ECG electrode misplacement, or abundant dye injections throughout the balloon occlusion episode.

ECG processing

After 100 Hz low-pass filtering to remove fluorescopyrelated interference and after coarse baseline removal[10] the ECGs were processed by BEATS,[11] our vectorcardiographically-oriented ECG analysis system. BEATS synthesizes a vectorcardiogram (VCG) and then interactively detects beats, defines their isoelectric points, fine-corrects the baseline by piecewise linear regression through these points, and determines landmarks in time (onset QRS, J point, peak and end of the T wave). Heart beats with low quality, incidental non-sinus beats and beats during dye injections were manually removed. In the remaining beats we computed the ST vector (magnitude, azimuth and elevation)[12] at J+60 ms, and the spatial QRST integral (a vector expressed in mV·ms), which is, by definition, the VG.

For the current study we selected a baseline and an occlusion ECG episode. As baseline we selected a stable 30-seconds episode at the end of the reference recording. As occlusion ECG we selected the period during the first balloon inflation. Reperfusion data were not studied.

Data analysis

As baseline values we computed the averaged ST and VG vectors in the baseline ECG. Dynamic ST and VG vectors during ischemia were computed as 10-beat moving averages. Dynamic ST and VG difference vectors during ischemia, ΔST and ΔVG, were computed by subtracting the baseline ST and VG vectors from these dynamic ST and VG vectors. As occlusion durations differed considerably, we report here ΔST and ΔVG values after 3 minutes of occlusion.

To investigate the relation between the 3-minute ΔST and ΔVG magnitudes we performed a linear regression forced through the origin. We adopted four cut-off values for the ΔST magnitude to detect ischemia: 0.025 mV, 0.050 mV, 0.075 mV and 0.100 mV, respectively. The cut-off value of 0.050 mV has been proposed in the setting of differential ST segment analysis,[13] while the value of 0.100 mV is usually applied in conventional ischemia diagnosis. Linear regression of ΔVG on ΔST yielded corresponding ΔVG cut-off values. Thus, we determined which patients had an ECG positive for ischemia on the basis of their ST difference vector magnitude alone, their VG difference vector magnitude alone, or in either one or both.

In addition, we compared the diagnostic performance of ΔST and ΔVG with the standard ECG ischemia diagnosis (STE, NSTE) after 3 minutes of ischemia. Ten-second ECG segments from the baseline ECGs and from the occlusion ECGs after 3 minutes of ischemia were transferred to our departmental ECG management system and analyzed by the University of Glasgow ECG Analysis Program.[14] Thus, an ECG diagnosis was generated, and STE / NSTE classification was established of the baseline and ischemic ECGs, by using the measurement matrix data of the Glasgow program. STE was diagnosed as an elevation at the J-point of ≥ 0.2 mV in two or more contiguous leads in leads V1 or V2, and of ≥ 0.1 mV in other contiguous leads. Contiguity in the frontal plane is defined in the lead sequence aVL, I, inverted aVR, II, aVF, III. Also, a depression of ≥ 0.1 mV in leads V2 or V3 was counted as STE. When the ECG did not qualify as STE, it qualified as NSTE.

RESULTS

The STAFF database comprises 104 patients; after exclusion, 84 patients (54/30 male/female, mean ± SD age 60 ± 11years) constituted our study group. Three patients had aberrant conduction and two had a pre-existing STE ECG. Occlusion sites of the first inflation were: left main in 2, LAD in 25, LCx in 16, and RCA in 41 patients. Mean ± SD duration of the initial inflation was 260 ± 76 seconds; in 13 of 84 patients (15%) the duration of the initial inflation was shorter than 180 seconds (mean ± SD 145 ± 29 seconds). In those 13 patients, ΔST and ΔVG were measured at the end of balloon inflation.

Ischemia thresholds

Figure 1 is a scatterplot of 3-minute ΔST and ΔVG magnitudes. The equation of the linear regression forced through the origin was ΔVG = 324·ΔST (ΔVG mV·ms, ΔST mV). ΔST and ΔVG magnitudes correlated significantly ($r = 0.84$; $P < 0.0001$). The ΔVG magnitude cut-off values that correspond to the ΔST cutoff values 0.025, 0.050, 0.075 and 0.100 mV are 8.1, 16.2, 24.3 or 32.4 mV·ms, respectively. Hence, either a minimal ΔST magnitude of 0.025/0.050/0.075/0.100 mV or a minimal ΔVG magnitude of 8.1, 16.2, 24.3 or 32.4 mV·ms would signify the presence of ischemia in hyperacute complete coronary occlusion.

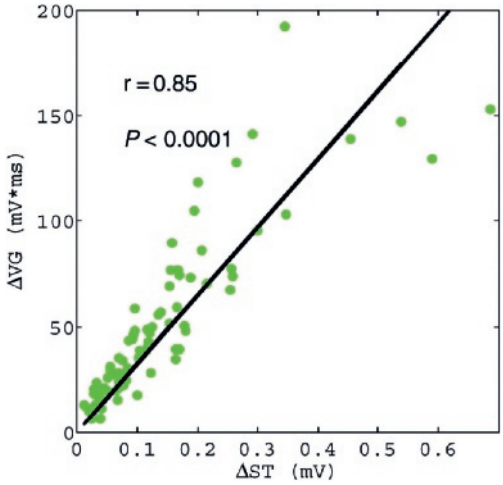


FIGURE 1. Scatterplot of ΔST versus ΔVG after 3 minutes of balloon occlusion with linear regression forced through the origin:
ΔVG = 324 • ΔST
(ΔVG in mV·ms, ΔST in mV, r = 0.84; P < 0.0001).

Diagnostic performance

Table 1 shows the sensitivities of the conventional 12- lead ECG ischemia diagnosis, the four ΔST and the four ΔVG four combined threshold criteria (one or both of the thresholds should be reached), respectively.

In 46/84 (55%) of the patients, the ischemic ECG showed a pattern of new STE. Eleven of the 13 (85%) patients who had occlusions <3 minutes had a new STE ECG, demonstrating that the patients with the briefer occlusions were not the reason of the limited percentage (55%) of patients who had a new STE ischemic ECG. ΔVG performed slightly better than ΔST, and the combination of ΔVG and ΔST performed slightly better than ΔVG alone for all threshold categories.

	New STE			
N				46
%				5
	ΔST (mV)			
Δ	0.025	0.050	0.075	0.100
N	77	68	54	45
%	92	81	64	54
	ΔVG (mV·ms)			
Δ	8.1	16.2	24.3	32.4
N	82	72	61	50
%	98	86	73	60
	Combined ΔST and ΔVG			
Δ	*see above for Δ values*			
N	83	73	62	52
%	99	87	74	62

TABLE 1. Sensitivity to detect ischemia after 3 minutes of total occlusion by the conventional ECG criteria ("New STE"), by the ST difference vector ΔST, by the VG difference vector ΔVG and by their combination.

DISCUSSION

In the current study, we compared conventional ECG ischemia diagnosis with ST and VG difference vector diagnosis. Measured during PTCA, the cause of ischemia was a complete coronary occlusion in all patients. If a similar complete occlusion had spontaneously occurred in these patients, this should have led to the triaging decision of cardiac catheterization. In the guidelines this decision is taken for patients with STE ECGs. Patients with NSTE ECGs may also get an indication for PCI; however, such patients should then pass more diagnostic tests or be considered urgent by the responsible physician.[5] This might take extra time and thus might lead to more necrotic myocardium, and would thus have a negative impact on the prognosis of these patients. In our study, only 55% of the patients had a STE ECG after 3 minutes of occlusion, 45% of the ECGs remained NSTE.

The difference vector magnitudes performed better: at the conventional STE threshold (ΔST > 0.100 mV; corresponding ΔVG > 32.4 mV·ms), this combination could identify 62% of the cases. With ΔST > 0.050 mV and ΔVG > 16.2 mV·ms, 87% of the cases was detected. As mentioned in the Methods section, the ΔST threshold of 0.050 mV was earlier proposed in the setting of differential ST segment analysis.[13] A further decrease to ΔST > 0.025 mV and ΔVG > 8.1 mV·ms allowed identification of nearly all ischemic ECGs.

Our study demonstrates that appropriate sensitivity of ECG-based ischemia detection during complete coronary occlusion requires a much lower ST threshold than currently applied in clinical routine. However, the lower the ST threshold, the more pre-existing non-zero ST amplitudes would hamper such a diagnosis. When a non-ischemic reference ECG of the same patient is at disposition, differential vectorcardiographic analysis can potentially solve this problem.

The good linear relationship (r = 0.84) between the ΔST and ΔVG suggests that a potential solution for patients with pre-existing conduction disturbances can be found in difference vector analysis of the ventricular gradient (as mentioned earlier, VG is independent of the ventricular depolarization order). Again, a requirement is that a non-ischemic reference ECG of the patient is at disposition.

As the STAFF III database contains no false positive cases, our study offers no insight in the specificity of ischemia detection by ECG difference vector analysis. Further research should be done to assess spontaneous short and long term intra-subject ST and VG variability and the effects of medication on ST and VG. Also, intra-individual ST and VG changes with ACS-alike symptoms (*e.g.*, pulmonary embolism) should be assessed.

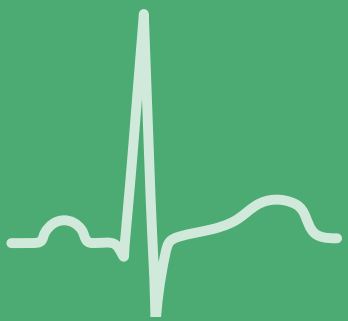
During the first two hours of ACS, when most of the myocardial AAR is still salvageable and when point-of-care biomarker tests are not yet conclusive because of the still limited amount of necrosis, the ECG is nearly the sole objective source of information. Because the limited diagnostic performance of the current ECG criteria for ischemia detection hampers hyperacute ACS triaging, continuing efforts should be done to improve ECG-based ischemia detection.

REFERENCES

1. Downar E, Janse MJ and Durrer D. The effect of acute coronary artery occlusion on subepicardial transmembrane potentials in the intact porcine heart. Circulation. 1977;56:217-24.
2. Mirvis D, Goldberger, AL. Electrocardiography Braunwald's Heart Disease. 7th ed.: Elsevier Saunders; 2005:25.
3. Draisma HH, Schalij MJ, van der Wall EE, *et al.* Elucidation of the spatial ventricular gradient and its link with dispersion of repolarization. Heart Rhythm. 2006;3:1092-9.
4. Steg P, James S, Atar D, *et al.* ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012;33:2569-619.
5. Hamm C, Bassand J, Agewall S, *et al.* ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011;32:2999-3054.
6. Koyama Y, Hansen PS, Hanratty CG, *et al.* Prevalence of coronary occlusion and outcome of an immediate invasive strategy in suspected acute myocardial infarction with and without ST-segment elevation. Am J Cardiol. 2002;90:579-84.
7. Lundin P, Eriksson SV, Erhardt L, *et al.* Continuous vectorcardiography in patients with chest pain indicative of acute ischemic heart disease. Cardiology. 1992;81:145-56.
8. Naslund U, Haggmark S, Johansson G, *et al.* Quantification of myocardium at risk and detection of reperfusion by dynamic vectorcardiographic ST segment monitoring in a pig occlusion-reperfusion model. Cardiovasc Res. 1993;27:2170-8.
9. Scherptong RW, Henkens IR, Man SC, *et al.* Normal limits of the spatial QRS-T angle and ventricular gradient in 12-lead electrocardiograms of young adults: dependence on sex and heart rate. J Electrocardiol. 2008;41:648-55.
10. Shusterman V, Shah SI, Beigel A, *et al.* Enhancing the precision of ECG baseline correction: selective filtering and removal of residual error. Comput Biomed Res. 2000;33:144-60.
11. Man S, Maan A, van der Wall E, *et al.* BEATS: an interactive Research Oriented ECG Analysis System. Comput Cardiol. 2010:1007-1010.
12. Report of committee on electrocardiography, American Heart Association. Recommendations for standardization of leads and of specifications for instruments in electrocardiography and vectorcardiography. Circulation. 1967;35:583-602.
13. Jensen SM, Johansson G, Osterman G, *et al.* On-line computerized vectorcardiography monitoring of myocardial ischemia during coronary angioplasty: comparison with 12-lead electrocardiography. Coron Artery Dis. 1994;5:507-14.
14. Macfarlane PW, Devine B, Latif S, *et al.* Methodology of ECG interpretation in the Glasgow program. Methods Inf Med. 1990;29:354-61.

Chapter

5



Subtraction electrocardiography: Detection of ischemia-induced ST displacement without the need to identify the J point

C. Cato ter Haar
Sumche Man
Arie C. Maan
Martin J. Schalij
Cees A. Swenne

adapted from:
Journal of Electrocardiology
2016 May-Jun;49:316-322

ABSTRACT

Background

When triaging a patient with acute chest pain at first medical contact, an electrocardiogram (ECG) is routinely made and inspected for signs of myocardial ischemia. The guidelines recommend comparison of the acute and an earlier-made ECG, when available. No concrete recommendations for this comparison exist, neither is known how to handle J-point identification difficulties. Here we present a J-point independent method for such a comparison.

Methods

After conversion to vectorcardiograms, baseline and acute ischemic ECGs after 3 minutes of balloon occlusion during elective PCI were compared in 81 patients of the STAFF III ECG database. Baseline vectorcardiograms were subtracted from ischemic vectorcardiograms using either the QRS onsets or the J points as synchronization instants, yielding vector magnitude difference signals, ΔH. Output variables for the J-point synchronized differences were ΔH at the actual J point and at 20, 40, 60 and 80 ms thereafter. Output variables for the onset-QRS synchronized differences were the ΔH at 80, 100, 120, 140 and 160 ms after onset QRS. Finally, linear regressions of all combinations of $\Delta H_{J + ...}$ versus $\Delta H_{QRS + ...}$ were made, and the best combination was identified.

Results

The highest correlation, 0.93 ($p < 0.01$), was found between ΔH 40 ms after the J point and 160 ms after the onset of the QRS complex. With a ΔH ischemia threshold of 0.05 mV, 66/81 (J-point synchronized differences) and 68/81 (onset-QRS synchronized differences) subjects were above the ischemia threshold, corresponding to sensitivities of 81% and 84%, respectively.

Conclusion

Our current study opens an alternative way to detect cardiac ischemia without the need for human expertise for determination of the J point by measuring the difference vector magnitude at 160 ms after the onset of the QRS complex.

INTRODUCTION

When triaging a patient with acute chest pain at first medical contact, an electrocardiogram (ECG) is routinely made and inspected for signs of myocardial ischemia, to support clinical decision making. Usually, and according to the guidelines,[1] the ECG is inspected on signs of ST elevation or depression often measured at the J point or at fixed distance, *e.g.*, 60 ms, thereafter.[2,3] ST deviations in ischemia are classically explained as a consequence of diastolic, phase 4, injury current in combination with systolic injury current.[4] In practice, the interpretation of ST deviations in ischemia is often complicated by pre-existing non-zero ST amplitudes and/or conduction disturbances and by ischemia-induced delayed conduction and/or early repolarization, sometimes leading to various expressions of a J wave, like notches and slurs, and to an obscured or unidentifiable J point.[5-7] Serial comparison of the acute ECG with a previous ECG of the same patient that was made under conditions that were not suspect for acute ischemia can reveal whether the observed ST deviations and conduction disturbances are new. Serial ECG analysis could also reveal the actual ischemia-induced ST deviation by subtracting the pre-existing from the acute ST amplitude. Vectorcardiographically, this would result in the establishment of the ST difference vector ("injury vector") that gives the net displacement of the ST segment as a consequence of ischemia.[8,9]

The guidelines[1] do not prescribe specific algorithms for serial ECG comparison and what to do when problems arise. For example, ischemia can broaden the QRS complex; in such a case, serial comparison of J-point amplitudes or amplitudes at a fixed distance after the J point would imply that the compared acute and pre-existing amplitudes are relatively shifted in the cardiac cycle, making such a comparison somewhat awkward. An even more serious problem arises if it is not possible to identify the J point at all, or if discussion about the position of the J point remains. In the current study, we investigate the possibility of determining an ST difference vector that is J point independent.

METHODS

For this study, we compared baseline ECGs with acute ischemic ECGs during elective percutaneous coronary intervention (PCI). These data belong to the STAFF III database.[10,11] Data processing details can be found in an earlier publication of our group.[8] Briefly, 10-second ECG episodes were selected from the baseline ECG and from the ECG recording made continuously during PCI, the latter after 3 minutes of balloon occlusion. ECGs were analyzed by using the LEADS program.[12] Vectorcardiograms (VCGs) were mathematically synthesized from the standard 12-lead ECGs by matrix multiplication. The vectorcardiographic representation of the averaged beat was output in the form of the 500 Hz sampled X, Y and Z leads. Then, in each patient, the baseline VCG was vectorially subtracted from the ischemic VCG using either the onset of the QRS complex or the J point as synchronization instants. Finally, the vector magnitude signal of the difference between the baseline and the ischemic VCG was computed for both subtraction-synchronization instants. In the following, this difference vector magnitude is denoted as ΔH (the symbol H refers to the heart vector).

Output variables for the J-point synchronized differences were the difference vector magnitudes at the actual J point and at 20, 40, 60 and 80 ms thereafter: ΔH_{J+0}, ΔH_{J+20}, ..., ΔH_{J+80}. Output variables for the onset-QRS synchronized differences were the difference vector magnitudes at 80, 100, 120, 140 and 160 ms after onset QRS: ΔH_{QRS+80}, $\Delta H_{QRS+100}$, ..., $\Delta H_{QRS+160}$. Finally, linear regressions of all combinations of $\Delta H_{J+...}$ versus $\Delta H_{QRS+...}$ were made, and the combination with the highest correlation was identified.

RESULTS

The study group consisted of 81 patients. Patient characteristics are described in Table 1.

	Number	%
N	81	
Sex (male/female)	52/29	64/36
Mean ± SD age (years)	60 ± 12	
Aberrant conduction[a]	4	5
Previous infarction[b]	26	32
STEMI occlusion ECG[c]	58	70

TABLE 1. Patient characteristics.
a Number of patients with aberrant conduction in the baseline ECG.
b Number of patients with a baseline ECG suggestive of previous myocardial infarction.
c Number of patients in whom the occlusion ECG shows a STEMI pattern[16] (ST elevation of ≥ 0.1 mV in two adjacent limb or precordial leads, except for leads V2 and V3 in which the threshold is 0.2 mV; including "STEMI equivalent": less than or equal to − 0.05 mV in V2 and V3).Sensitivity to detect ischemia after 3 minutes of total occlusion by the conventional ECG criteria ("New STE"), by the ST difference vector ΔST, by the VG difference vector ΔVG and by their combination.

Figure 1 gives an example of the signal processing steps in one patient. Panels A and B depict the baseline and ischemic vectorcardiograms (VCGs). Panels C and D show J-point synchronized and onset-QRS synchronized difference vectorcardiograms (baseline VCG subtracted from ischemic VCG); panels E and F depict the corresponding difference vector magnitude signals.

Figure 2 gives examples of J-point synchronized and onset-QRS synchronized difference vector magnitude signals. Three major patterns of the difference vector magnitude signal were observed. Upper panels A and B depict a pattern that is characterized by a fairly horizontal or slightly up- or down-sloping signal during the ST segment. Middle panels C and D depict a saddle-shaped pattern. Lower panels E and F show a less-frequently-occurring steeply down-sloping pattern of the difference vector magnitude signal during the ST segment. All three patterns occurred with and without ischemia-induced QRS widening. Ischemia-induced QRS widening (*e.g.*, 18 ms in panels C and D, and 20 ms in panels E and F) gave rise to striking differences over the QRS complex between the J-point and onset-QRS synchronized subtraction signal. The subtraction signal over the ST segment remained, however, relatively unaffected by the subtraction-synchronization instant.

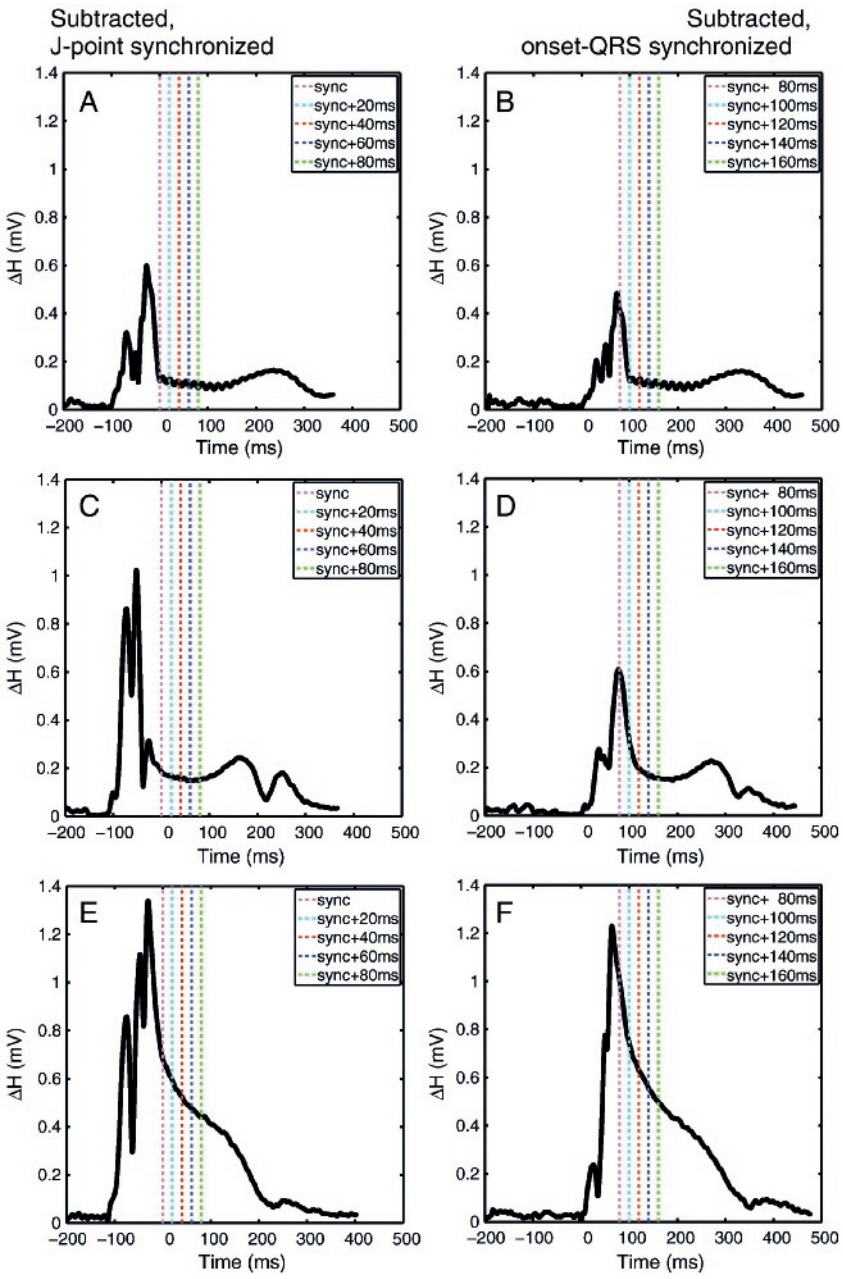


FIGURE 1. Example of J-point synchronized and onset-QRS synchronized subtraction of a baseline VCG from an ischemic VCG in a patient (subject #11 in the STAFF III database). Panels A and B: baseline and ischemic VCG. Panels C and E: J-point synchronized subtraction. Panels D and F: onset-QRS synchronized subtraction. Panels C and D: lead-dependent baseline-ischemia amplitude-difference (ΔVCG) signal. Panels E and F: baseline-ischemia difference-vector-magnitude (ΔH) signal.

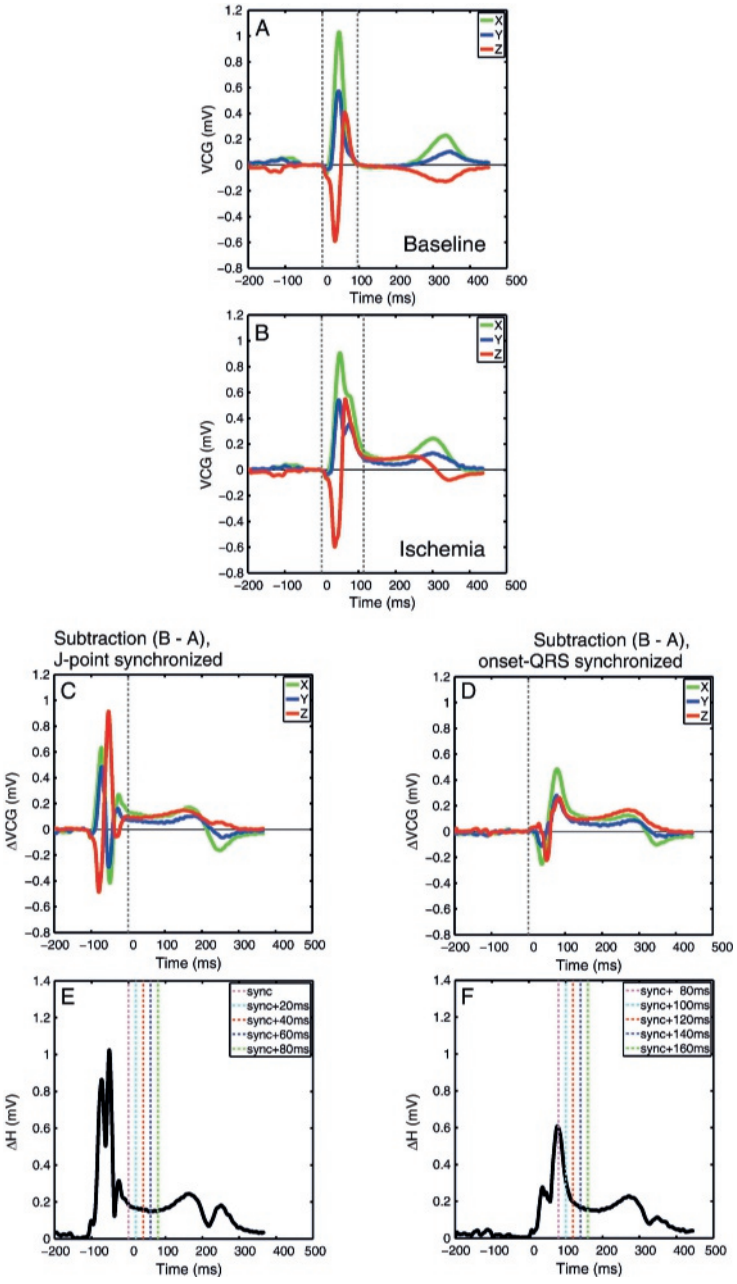


FIGURE 2. Three typical difference vector magnitude (ΔH) patterns in the ST segment as met in the study population. Panels A and B (subject #84 in the STAFF III database): fairly horizontal or slightly up- or down-sloping. Panels C and D (subject #11 in the STAFF III database): saddle shaped. Panels E and F (subject #44 in the STAFF III database): steeply down-sloping. All three patterns can occur with or without ischemia-induced QRS widening. It is a general observation that ischemia-induced QRS widening (*e.g.*, 18 ms between panels C and D, and 20 ms between panels E and F) gives rise to striking differences between the J-point and onset-QRS synchronized subtraction signal over the QRS complex. The subtraction signal over the ST segment remains, however, relatively unaffected by the subtraction-synchronization instant.

Figure 3 shows the baseline (panel A) and ischemic (panel B) ECGs of the patient of whom the difference vector magnitude signals are depicted in panels E and F of Figure 2. Of note, the QRS complex and the T wave, who are clearly separated in the baseline ECG, have merged completely in several leads in the ischemic ECG, and no distinct ST segment can be discerned. This phenomenon occurred in about 10% of the study population; a precise number is difficult to determine because in part of these subjects this phenomenon is present, but less outspoken. In subjects presenting with an unstable difference vector magnitude signal in the ST range, it is evident that the time lag after the synchronization point at which the difference vector magnitude is determined is of much influence on the measurement result.

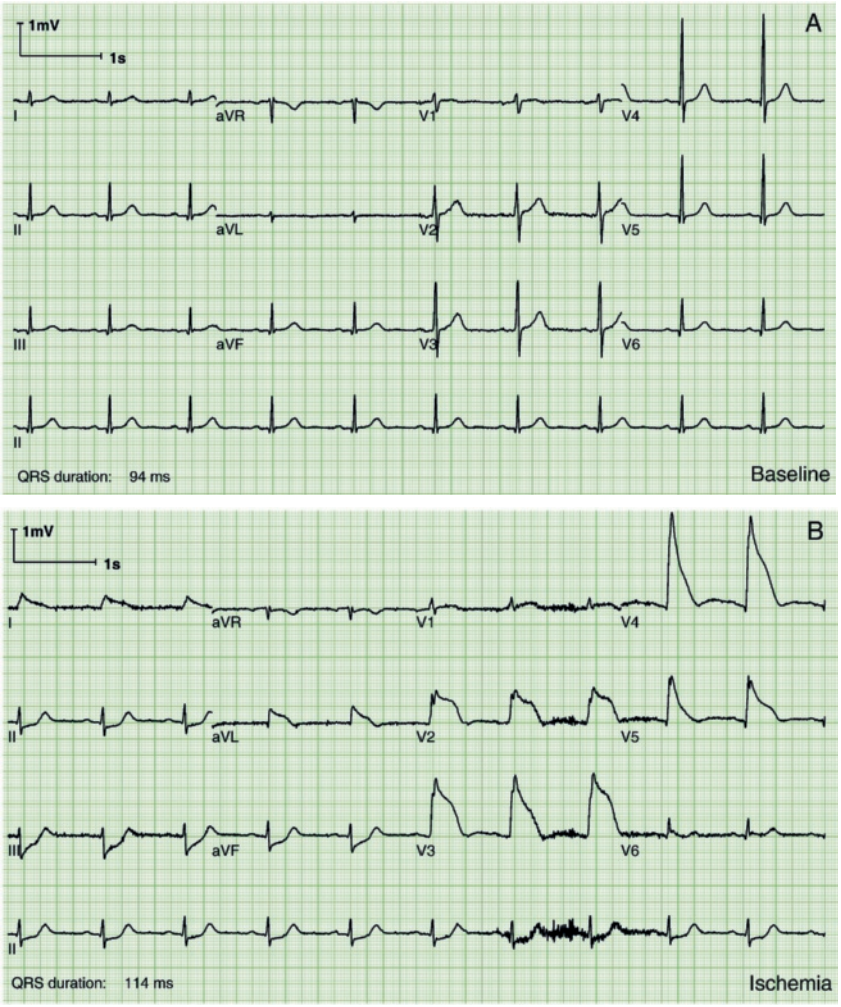


FIGURE 3. Baseline and ischemic ECG in subject #44 in the STAFF III database. The J-point and onset-QRS synchronized subtraction signals of this patient are shown in panels E and F of Figure 2. In this patient, the QRS complex and the T wave, who are distinctly separated in the baseline ECG, have merged completely in several leads in the ischemic ECG, and no distinct ST segment can be discerned. This type of ischemic ECG change and the associated difference-signal pattern as seen in panels E and F of Figure 2 occurred in about 10% of the study group.

Figure 4 depicts the difference vector magnitudes averaged for the study group as a function of the time lag after the subtraction-synchronization point. J-point synchronized subtraction data are displayed at the J point and at 20, 40, 60 and 80 ms thereafter. Onset-QRS synchronized subtraction data are displayed at onset QRS plus 80, 100, 120, 140 and 160 ms. The J-point synchronized subtraction-data curve flattened at 40 ms after the J point. The onset-QRS synchronized subtraction-data curve flattened at 140 ms after the onset of the QRS complex. The average amplitudes in the terminal parts of both curves were almost identical. *E.g.*, at a time lag of 40 ms after the J point, the mean ± SD difference vector magnitude was 0.14 ± 0.12 mV, and at a time lag of 140 ms after the onset of the QRS complex the mean ± SD difference vector magnitude was 0.15 ± 0.15 mV.

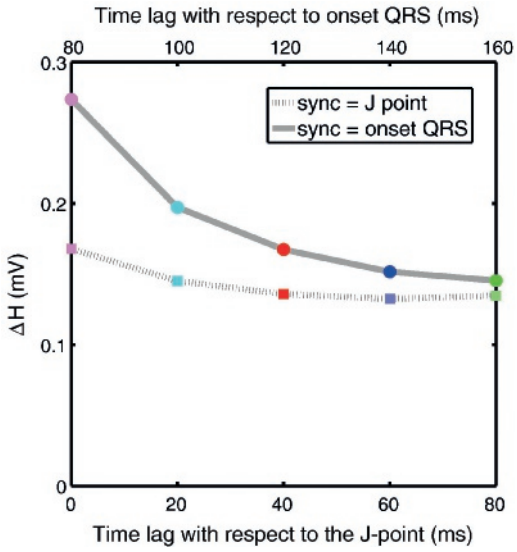


FIGURE 4. Average difference vector magnitudes (ΔH) in the study group as a function of the time lag with respect to the subtraction-synchronization points. The marker colors correspond to those used for the dashed lines in Figure 2 and in panels E and F of Figure 1 that denote the time lag with respect to the subtraction-synchronization points.

The highest correlation between $\Delta H_{J+\dots}$ and $\Delta H_{QRS+\dots}$, 0.93 ($P < 0.01$), was found between the measurements 40 ms after the J point, ΔH_{J+40}, and 160 ms after the onset of the QRS complex, $\Delta H_{QRS+160}$. Figure 5 shows the corresponding scatterplot. In previous publications[8,9] we have suggested a difference-vector-magnitude ischemia threshold of 0.05 mV. In the current study, with the measurements made at a time lag of 40 ms after the J point and at a time lag of 160 ms after the onset of the QRS complex, 66/81 and 68/81 subjects were above the ischemia threshold, corresponding to sensitivities of 81% and 84%, respectively.

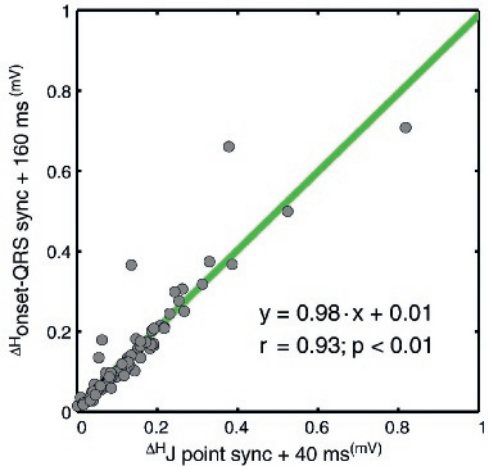


FIGURE 5 Scatterplot and linear regression results of the difference vector magnitudes (ΔH) measured in the study group at 40 ms after the J point (X axis) and at 160 ms after the onset of the QRS complex (Y axis).

DISCUSSION

We vectorially subtracted baseline ECGs from acute ischemic ECGs (see Figure 1) in 81 patients who underwent elective PCI, and studied the behavior of the difference vector magnitude signals. Subtractions were done in two ways: synchronized on the J points or synchronized on the onsets of the QRS complexes in the baseline and ischemic ECGs.

According to current insight, ischemia-induced differences in the J-point amplitudes are primarily caused by the baseline displacement due to the ischemia-induced phase-4 injury current that flows from partly depolarized ischemic tissue to the fully polarized surrounding healthy tissue. Additionally, other ischemia-related effects contribute to the J-point amplitude difference. Ischemia alters the entire action potential morphology of the involved myocytes, hence, there are also injury currents flowing at the J-point instant (see Figures 12-31 and 12-32 in Braunwald's Heart Disease)[4]. Possible pre-existing or ischemia-induced delayed conduction and/or early repolarization hamper detection of the J point and affect its amplitude.[5-7] It is unlikely that the above-mentioned contributions to the J-point displacement can be unraveled; this is an intrinsic difficulty for the interpretation of ischemic ECGs.

A basic question is how to measure the ST displacement: at the J point or at a fixed time lag thereafter. Subtraction of the baseline ECG from the ischemic ECG is a logical first step, because that corrects for possible pre-existent non-zero amplitudes. Where to measure exactly, has ever been a point of discussion. The guidelines[1] suggest that measurements be made at the very J point, but several authors have suggested a fixed time interval thereafter, *e.g.*, after a time lag of 40 or 60 ms.[2,3] We were curious to see how critical the measurement instant is for the ST displacement. This appeared not to be very relevant, as is evident from the average J-point synchronized difference vector magnitude displayed in Figure 4. The insensitivity of the ST displacement for the exact measurement instant is caused by the limited dynamics of the difference vector magnitude signal in the ST segment (see Figure

2 panels A and C), except for a minority of cases (see, *e.g.*, Figure 2 panel E). The phase-4 injury-current induced baseline shift likely generates a constant difference vector magnitude signal throughout, while the dynamics in the difference vector magnitude signal are caused by injury currents that occur during the action potential itself. See Figure 2, Figure 4.

Strikingly, there was little difference between the ST displacement when assessed either by J-point synchronized or by onset-QRS synchronized subtraction. In our study population, measurements made at a time lag of 40 ms after the J point (ΔH_{J+40}) and at a time lag of 140 ms after the onset of the QRS complex ($\Delta H_{QRS+140}$) were almost similar: the slope of the regression line, 0.98, equals almost 1, the intercept of the regression line, 0.01, equals almost 0, and the correlation, 0.93, is very high (see Figure 5). While the synchronization instant for subtraction (the J point or the onset of the QRS complex) can give rise to differences in the QRS and/or T range (compare panels C and D and panels E and F in Figure 2), the differences in the ST range remain limited.

The J point is classically defined as the time instant at which an ECG tracing changes slope abruptly at the end of the S wave.[13] In a 12-lead ECG, theoretically, 12 different lead-dependent J points could be identified; the global J point is the latest of the lead-dependent J points.[14,15] Determination of the J point can be problematic, especially in ischemic ECGs. In our view, accurate establishment of the J point requires a superimposed magnified display of all ECG leads, a form of ECG rendering that is not routinely available in the clinic. Irrespective the available ECG display modality, the ECG analyst is faced with a difficult task. Small amounts of noise can already mask a J point. Moreover, delayed conduction as well as early repolarization, manifesting as notches, slurs or J waves[5-7] are further complicating this task. These phenomena have reopened the discussion about where exactly in the ECG ST elevation should be measured.[7] Our study suggests that a solution can be found in a measurement at a fixed distance, 160 ms, after the onset of the QRS complex. This yields a sensitivity of 84% at an ischemia threshold of 0.05 mV for the difference vector magnitude in our study group. This means that still 16% of the cases are missed, but it is a considerable improvement with respect to the 70% sensitivity yielded by the STEMI criteria (Table 1).

Experienced electrocardiographers often visually recognize ischemia by inspecting the entire QRST morphology, instead of, or in addition to, focusing on the J amplitudes only. Obviously, this strategy is not only chosen because of the difficulty of identifying the J point and performing precise J-point amplitude measurements in a conventional ECG tracing, but also because the ischemia-induced action potential changes cause ECG changes throughout the entire QRST wave shape. The findings in our study correspond to this practice. An important advantage of a J-point independent method for ischemia detection by subtraction electrocardiography would be that it can be implemented in automated ECG analysis algorithms. This would make the diagnosis more objective and widely available, also in circumstances where there is a lack of experienced electrocardiographers.

Much is still to be investigated, among others, first-medical-contact ECGs should be studied. When myocardial ischemia is present, the occlusion will not always be complete and will generally have existed for a longer period than 3 minutes, in contrast to our current study

group. Also, to determine specificity, ECGs made in patients with chest pain due to other causes, should be investigated. Finally, it is relevant to include in such validation studies the performance of experienced electrocardiographers. Sometimes, experts can extract more information from the ECG by global visual inspection rather than by following strict decision rules. An example of this phenomenon has been described in a recent study, where culprit artery assessment in acute ischemic ECGs was correct in 43/53 cases by global visual inspection, and only 38/53 cases by a computer algorithm in which the expert decisions had been formalized. However, an alternative computer algorithm based on a physiological model outperformed the experts (47/53 correct).[17]

Admittedly, subtraction electrocardiography requires a baseline ECG; that is not standard available. However, we believe that with increasing pervasion of digital technology and databases, this will become less an obstacle in the near future.

In conclusion, our current study opens an alternative way to detect cardiac ischemia without the need for human expertise for determination of the J point, by measuring the difference vector magnitude at 160 ms after the onset of the QRS complex.

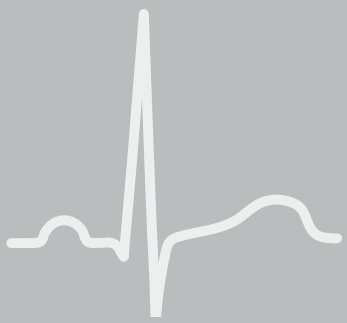
REFERENCES

1. Steg P, James S, Atar D, *et al.* ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012;33:2569-619.
2. Garcia J, Wagner G, Sommo L, *et al.* Identification of the occluded artery in patients with myocardial ischemia induced by prolonged percutaneous transluminal coronary angioplasty using traditional vs transformed ECG-based indexes. Comput Biomed Res. 1999;32:470-82.
3. Tan CC, Hiew TM and Chia BL. Right chest electrocardiographic patterns in normal subjects. Chest. 1990;97:572-5.
4. Mirvis D, Goldberger, AL. Electrocardiography Braunwald's Heart Disease. 7th ed.: Elsevier Saunders; 2005: 25.
5. Deshpande A and Birnbaum Y. ST-segment elevation: Distinguishing ST elevation myocardial infarction from ST elevation secondary to nonischemic etiologies. World J Cardiol. 2014;6:1067-79.
6. Shinde R, Shinde S, Makhale C, *et al.* Occurrence of "J waves" in 12-lead ECG as a marker of acute ischemia and their cellular basis. Pacing Clin Electrophysiol. 2007;30:817-9.
7. Macfarlane PW, Antzelevitch C, Haissaguerre M, *et al.* The Early Repolarization Pattern: A Consensus Paper. J Am Coll Cardiol. 2015;66:470-7.
8. ter Haar CC, Maan AC, Warren SG, *et al.* Difference vectors to describe dynamics of the ST segment and the ventricular gradient in acute ischemia. J Electrocardiol. 2013;46:302-11.
9. ter Haar CC, Maan AC, Schalij MJ, *et al.* Improved electrocardiographic detection of hyperacute ischemia by difference vector analysis. Comput in Cardiol. 2013:9-12.
10. Laguna P and Sornmo L. The STAFF III ECG database and its significance for methodological development and evaluation. J Electrocardiol. 2014;47:408-17.
11. Warren SG and Wagner GS. The STAFF studies of the first 5 minutes of percutaneous coronary angioplasty balloon occlusion in man. J Electrocardiol. 2014;47:402-7.
12. Draisma HHM, Swenne CA, van de Vooren H, *et al.* LEADS: An Interactive Research Oriented ECG/VCG Analysis System. Computers in Cardiology. 2005:515-518.
13. Barr RC and Van Oosterom A. A Genesis of the electrocardiogram Comprehensive Electrocardiology. 4th ed. London: Springer; 2011: 183.
14. Kligfield P, Gettes LS, Bailey JJ, *et al.* Recommendations for the standardization and interpretation of the electrocardiogram: part I: The electrocardiogram and its technology: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. Circulation. 2007;115:1306-24.
15. Rautaharju PM, Surawicz B, Gettes LS, *et al.* AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval. Circulation. 2009;119:e241-50.
16. Man S, Rahmattulla C, Maan AC, *et al.* Acute coronary syndrome with a totally occluded culprit artery: relation of the ST injury vector with ST-elevation and non-ST elevation ECGs. J Electrocardiol. 2014;47:183-90.
17. Kamphuis VP, Wagner GS, Pahlm O, *et al.* Comparison of model-based and expert-rule based electrocardiographic identification of the culprit artery in patients with acute coronary syndrome. J Electrocardiol. 2015;48:483-9.

PART II.
Non-ischemic ECG changes and variations

Chapter

6



Intra-individual ECG changes over 25 years: How long can elective ECGs be used as reference for acute ischemia detection?

Marjolein C. de Jongh
C. Cato ter Haar
Sumche Man
Roderick W. Treskes
Arie C. Maan
Martin J. Schalij
Cees A. Swenne

adapted from:
Journal of Electrocardiology
2015 Jul-Aug;48:490-497

ABSTRACT

Background

The guidelines advocate, in patients with chest pain, comparison of the acute ECG with a previously made, non-ischemic ECG that serves as a reference, to corroborate the working diagnosis of acute coronary syndrome (ACS). Our approach of this serial comparison is to compute the differences between the ST vectors at the J point and 60 ms thereafter ($\Delta ST_{(J+0)}$, $\Delta ST_{(J+60)}$) and between the ventricular gradient (VG) vectors (ΔVG). In the current study, we investigate if reference ECGs remain valid in time.

Methods

We studied 6 elective non-ischemic ECGs (ECG_0, ECG_1, ..., ECG_5), 5 years apart, in 88 patients. Within each patient, serial comparisons were done 1) between all successive ECGs, and 2) between each of ECG_1, ECG_2, ..., ECG_5 and ECG_0, computing, in addition to $\Delta ST_{(J+0)}$, $\Delta ST_{(J+60)}$ and ΔVG, the difference in heart rates, ΔHR. Additionally, relevant clinical events and the diagnoses associated with each ECG were collected. Linear regression was used to assess trends in $\Delta ST_{(J+0)}$, $\Delta ST_{(J+60)}$ and ΔVG; multiple linear regression was used to assess the influence of the clinical events and diagnoses on $\Delta ST_{(J+0)}$, $\Delta ST_{(J+60)}$ and ΔVG.

Results

There were no trends in the differences between successive ECGs. Positive trends were seen with increasing time lapses between ECGs: $\Delta ST_{(J+0)}$, $\Delta ST_{(J+60)}$ and ΔVG increased per year by 0.65 μV, 1.45 μV and 3.69 mV·ms, respectively. Extrapolation to a time lapse of 0 yielded 50.92 μV, 36.63 μV and 20.91 mV·ms for the short-term reproducibility of $\Delta ST_{(J+0)}$, $\Delta ST_{(J+60)}$ and ΔVG, respectively. Multiple linear regression revealed that clinical variables could explain only 10%, 17% and 13% of the variability in $\Delta ST_{(J+0)}$, $\Delta ST_{(J+60)}$ and ΔVG, respectively.

Conclusion

With a view on ischemia detection thresholds in the order of magnitude of 58 μV for ΔST and 26 mV·ms for ΔVG, our study suggests that it is important to have a recent ECG available for the detection of myocardial ischemia, as an "aged" ECG may have lost its validity as a reference.

INTRODUCTION

Detection of myocardial ischemia in ECGs made at first medical contact in patients with chest pain, remains a challenge. The differential diagnosis of chest pain is extensive. In addition to the working diagnosis acute coronary syndrome (ACS), several other diagnostic options are medical emergencies, and several pathologies that cause chest pain can give rise to ECG changes mimicking ischemia. In many cases of ACS, the acute triaging decision would involve transportation of the patient to a medical center with facilities for percutaneous coronary intervention (PCI). To minimize the door-to-balloon time as much as possible, a catheterization room should be activated already during transportation of the patient. Missing the diagnosis of ACS implies delayed adequate treatment and is detrimental for the prognosis of the patient; a false positive diagnosis of ACS would at least involve false positive activation of a catheterization room with its associated cost.

ECG diagnosis of acute ischemia relies strongly on interpretation of the ST amplitude at the J point. Known pitfalls are the presence of pre-existent non-zero ST amplitudes, *e.g.*, as often seen in hypertrophy, in conduction disturbances and in leads V2-V3 in normal ECGs. Also, due to the cancellation effect, limited ST changes may happen in serious conditions associated with massive ischemia, as in left main occlusion. Hence, on one hand, presence of pre-existing non-zero ST amplitudes force an increase of the ischemia detection threshold (to prevent false positive detections); on the other hand, serious conditions with limited ST changes would require a decrease of the ischemia detection threshold (to prevent false negative detections). The current STEMI criteria (STEMI = ST-elevation myocardial infarction)[1,2] have been defined in such a way that they are high specific.[3]

Another problem in ischemia detection is the direction of the ST deviation. The current STEMI criteria strongly favor LAD occlusions because, in terms of vectorcardiography, the direction of the ischemia vector is in this situation such that it causes ST elevation in some of the standard 12 ECG leads. Ischemia vectors associated with LCX or RCA occlusions oftentimes cause depressions in the standard leads and are then by definition missed by the STEMI criteria[4] (except for depressions in V2-V3 that are covered by the so-called "STEMI-equivalent criteria"),[5] *e.g.*, in a group of 300 patients triaged for primary PCI because of suspected ACS and showing a completely occluded culprit artery on the coronary angiogram, 86 patients did not meet the STEMI criteria.[4]

Abandoning the direction of the ST deviation as a criterion for the presence of acute ischemia implies that depression should be considered equivalent to elevation. In that case, only the size of the ischemia vector, and not the direction, is of interest. A solution for pre-existent ST deviations that hamper lowering the ischemia detection threshold to reach sufficient sensitivity can be found in performing difference measurements, *i.e.*, serial comparison of the acute ECG and a previously made non-ischemic ECG, which serves as a reference ECG. Thus, using the patient as his/her own reference, small, ischemia-induced changes in the ST vector can be detected irrespective of the pre-existent value. We have demonstrated this principle in acute ischemic ECGs during elective PCI[6,7] (see Figures 3 and 4 from the first of these two publications,[6] illustrating this for a patient with left ventricular

hypertrophy). Similarly, changes in the ventricular gradient (VG) vector can be used to detect ischemia, particularly in ECGs where, due to conduction disturbances, the J point cannot be identified.[6,7] The VG, computed as the 3-dimensional integral of the ECG over the QT interval, equals the integral of the action potential morphology gradients in the heart, is supposedly independent of the conduction in the heart, and changes with ischemia because of the changes in the action potential morphology in the ischemic area.[8]

Comparison of an acute ECG of a patient suspected of ACS with a previous ECG of the same patient, if available, is advocated by the guidelines[1,2,5] without further specification regarding the ECG variables/characteristics to be compared or regarding the validity of the previous ECG as a non-ischemic reference. It seems ideal to have a reference ECG available that is recorded with identical electrode positions and just prior to the ischemic ECG. In practice, previous ECGs, if present at all, have a certain age that renders them less valid or even invalid as a reference ECG: in the meantime the ECG of a person may have changed due to variations or errors in electrode placement, food and fluid intake, emotional stress, increasing age, or changes in weight, filling status, body temperature or cardiac dimensions (*e.g.*, due to physical training).[9-11] Additionally, factors like developing disease or medication affect the ECG. Thus, ST and VG vector differences between a recent and a previous ECG occur that are unrelated to acute ischemia interfere with the ischemia detection algorithm.

In an earlier study,[6] we have proposed that acute ischemia can be detected with sufficient sensitivity by 50 μV changes in the ST vector or by 17 mV·ms changes in the VG vector. In a later study,[12] we have determined, by ROC analysis, slightly different thresholds: 58 μV for ST changes and 26 mV·ms for VG changes. If similar or even larger differences over time also occur without the presence of ischemia, the older ECGs are no longer useful as a reference ECG for ischemia detection. Our current study aims to investigate how much the J and VG vectors in non-ischemic ECGs change in a serial ECGs made in patients over a 25 year period, in order to determine how recent a previous ECG should be to be acceptable as a reference ECG for ischemia detection.

MATERIAL AND METHODS

Data were selected from our Departmental ECG database, comprising more than 800,000 ECGs. Only electively ECGs made in the outpatient clinic were selected; ECGs made during a hospital admission or at the emergency department were excluded. Six successive 5-year periods were defined, beginning 1985–1989, and ending 2010–2014. A computerized algorithm selected all patients who had at least one elective ECG made in each of these 5-year periods. Only ECGs of sufficient technical quality and with regular sinus rhythm were included. When more than one ECG was available in one period, the ECG best positioned in time (*i.e.*, equalising the time-intervals to the preceding and following ECGs as much as possible) was selected. Thus, we collected, per patient, a set of six ECGs (ECG_0, ..., ECG_5), about evenly spaced in time, about five years apart, and spanning (from ECG_0 to ECG_5) a period of about 25 years.

Coding of diagnoses and clinical events

In the following we refer to the five successive 5-year periods in between ECG_0-ECG_1, ECG_1-ECG_2, ..., ECG_4-ECG_5, as pentads 1–5. The medical context of each pentad was coded according to the associated clinical data as retrieved from the digital patient file. The following characteristics were noted for each pentad: a) diagnosis/diagnoses valid at the time the initial ECG of the current pentad was made; b) the clinical events that occurred between the initial and the terminal ECG of the current pentad, and c) new diagnosis/diagnoses established between the initial and the terminal ECG of the current pentad.

ECG interpretation

To characterize the ECGs clinically, the initial ECGs of pentad 1 and the terminal ECGs of pentad 5 were analysed by the Glasgow ECG Analysis Program.[13] The following abnormalities were noted: sinus tachycardia or bradycardia, abnormal P wave, abnormal AV conduction, abnormal frontal QRS axis, prolonged QRS duration, high QRS amplitude, abnormal ST segment, abnormal T wave, long QT, abnormal or borderline abnormal ECG.

ECG analysis, separate ECGs

All ECGs were analyzed by our vectorcardiographically-oriented research tool LEADS,[14] using the Kors matrix for vectorcardiogram (VCG) synthesis. After computation of an averaged beat, the automatically determined default onset-QRS, J-point and end-T settings were manually verified by three observers (MCdJ, SM, CAS) and when necessary corrected. The onset-QRS was defined as the first visible deflection of any lead from the baseline, the J point was localized at the end of the QRS-complex as determined according to the procedure mentioned in the Minnesota code,[15] and the end of the T wave was defined in the vector magnitude signal as the time instant where the tangent to the point with the steepest slope of the descending limb of the T wave intersects the baseline. Finally, four variables were computed: the ST vectors at the J point, $ST_{(J+0)}$, and at 60 ms after the J point, $ST_{(J+60)}$, the ventricular gradient vector, VG, and the heart rate, HR. The VG equals the spatial integral of the ECG over the QT interval, its x-, y-, and z-components are measured by computing the area under the ECG curve in the X-, the Y-, and the Z-lead, respectively (graphically illustrated in Figure 2 of a publication by Ter Haar *et al.*)[6]. See Draisma *et al.*[8] for an in-depth discussion of the concept of the VG.

Serial comparison of ECGs

Within each patient, two different modalities of serial ECG comparisons were done: 1) serial comparison between successive ECGs 5 years apart, and 2) serial comparison between each of ECG_1, ECG_2, ..., ECG_5 and the first ECG of each patient, ECG0. In the ECGs under comparison, we computed the vectorial differences between $ST_{(J+0)}$, $ST_{(J+60)}$ and VG and retained the absolute values of these vectorial differences, denoted as $\Delta ST_{(J+0)}$, $\Delta ST_{(J+60)}$ and ΔVG. Because the VG is heart rate dependent,[16] differences in heart rate between two ECGs under comparison may explain part of the differences in VG. For that reason we retained, for the serial comparisons, also the absolute difference in heart rate between the two ECGs, ΔHR.

Statistics

Data are described as numbers, percentages, means and standard deviations. Trends over 25 years were detected by linear regression. Comparisons between data series were made by paired t-tests. Comparisons between proportions were made by McNemar's test. We adopted $P = 0.05$ as the level of significance.

To detect possible influences of the diagnosis and clinical events on ECG changes, we pooled all pentad-related ECG comparisons (all patients, five pentads per patient) and performed multiple linear regressions (forward entry method; $P_{in} = 0.05$; $P_{out} = 0.10$) of ΔST(J + 0), of ΔST(J + 60) and of ΔVG on the presence of any of the diagnostic statements (categorical variables), the occurrence of any of the clinically events (categorical variables), and the heart rate differences between the ECGs under comparison (numerical variables).

RESULTS

A total of 88 patients (58/30 male/female, mean ± SD age 40.0 ± 12.4 years at the time ECG_0 was made) fitted all selection conditions and constituted the study group. ECG_5 was made 25.2 ± 1.1 year after ECG_0. Body mass index increased from 24.2 ± 3.4 to 27.0 ± 5.0 kg · m− 2 ($P < 0.01$) during the time span between ECG_0 and ECG_5.

Clinical Diagnosis and Events

The major diagnostic categories at the time ECG_0 and ECG_5 were made are listed in Table 1. The most prevalent diagnosis at the time of ECG_0 was congenital heart disease: a known category of patients that has lifelong medical checkups. According to expectation, the prevalence of most diagnoses increased significantly over 25 years. The totals of the events that occurred during the 25 years of follow-up are listed in Table 2. Most common events were valvular heart surgery, PCI, CABG and acute coronary syndrome.

	T_{ECG0}		T_{ECG5}		*P*
Diagnosis	*N*	%	*N*	%	
Congenital	31	35.2	31	35.2	NA
Valvular Heart Disease	16	18.2	14	15.9	NS
Systemic Hypertension	29	33.0	37	42.0	< 0.05
Pulmonary Hypertension	0	0	6	6.8	< 0.05
Non-ischemic Myopathy	4	4.5	25	28.4	< 0.05
Stable Angina	8	9.1	18	20.4	< 0.05
Myocardial Infarction	14	15.9	26	29.5	< 0.05
Heart Failure	0	0	3	3.4	NS
Conduction Disorders	19	21.6	34	38.6	< 0.05
Arrhythmia/channelopathy	4	4.5	20	22.7	< 0.05
Diabetes mellitus	2	13.6	19	21.6	< 0.05
Total	137		233		

TABLE 1. Diagnoses at the time of ECG0 (T_{ECG0}) and ECG5 (T_{ECG5}). More than one diagnosis may apply to a single patient; this explains that the total numbers of diagnoses (137 and 233) exceed the number of patients (88). The diagnosis valvular heart disease applies only when it is functionally relevant (at least mild valvular dysfunction). The diagnosis myocardial infarction includes multiple infarctions in one patient.
NA = not applicable
NS = not significant

Clinical event	Incidence
Heart surgery	4
Pacemaker implantation	1
Ablation	4
ICD implantation	6
CRTD	0
Valvular heart surgery	35
PCI	45
CABG	21
Acute coronary syndrome	24
Endocarditis/pericarditis	2
Heart tamponade	2

TABLE 2. List of clinical events coded in the current study. More than one event may apply in the same patient. The 24 acute coronary syndrome (ACS) events occurred in 16 patients; 11 patients had 1 ACS event, 3 patients had 2 events, 1 patient had 3 events, and 1 patient had 4 events.
ICD = implantable defibrillator/cardioverter
CRTD = cardiac resynchronization therapy combined with defibrillator; PCI = percutaneous coronary intervention
CABG = coronary artery bypass grafting.

ECG interpretation

According to the Glasgow ECG interpretation program, 38/88 (43%) of the initial ECGs (ECG_0) were classified as abnormal or borderline abnormal. After 25 years, significantly ($P < 0.05$) more ECGs (57/88 [65%]) were abnormal. An overview of ECG abnormalities is given in Table 3.

	ECG_0		ECG_5		*P*
Category of ECG abnormality	*N*	%	*N*	%	
Sinus tachycardia/bradycardia	21	23.9	23	26.1	NS
Abnormal P wave	7	8.0	9	10.2	NS
Abnormal AV conduction	2	2.3	15	17.0	< 0.05
Abnormal frontal QRS axis	12	13.6	17	19.3	NS
Prolonged QRS duration	14	15.9	31	35.2	< 0.05
High QRS amplitude	9	10.2	5	5.7	NS
Abnormal ST segment	24	27.3	26	29.5	NS
Abnormal T wave	21	23.9	31	35.2	NS
Long QT	2	2.3	4	4.5	NS
Abnormal or borderline abnormal ECG	38	43.2	57	64.8	< 0.05
Total	150		218		

TABLE 3. Major categories of abnormalities in ECG_0 and ECG_5 according to the Glasgow ECG interpretation program. More than one ECG abnormality may occur in a single patient; this explains that the total numbers of ECG abnormalities (150 and 218) exceed the number of patients (88).

ECG analysis

Descriptive statistics of the differences $\Delta ST_{(J+0)}$, $\Delta ST_{(J+60)}$, ΔVG and ΔHR between successive ECGs, denoted as 0–1 (ECG_0 and ECG_1), 1–2 (ECG_1 and ECG_2), ..., 4–5 (ECG_4 and ECG_5) are shown in Table 4. Descriptive statistics of the differences $\Delta ST_{(J+0)}$, $\Delta ST_{(J+60)}$ and ΔVG between ECG_0 and each of the following ECGs, denoted as 0–1 (ECG_0 and ECG_1), 0–2 (ECG_0 and ECG_2), ..., 0–5 (ECG_0 and ECG_5) are shown in Table 5. Scatterplots of these differences are given in Figure 1.

$\Delta ST_{(J+0)}$	0-1	1-2	2-3	3-4	4-5
Mean (μV)	53.4	49.9	49.1	53.0	52.5
SD (μV)	35.9	30.1	29.3	31.5	34.9
Min (μV)	10.2	8.9	8.0	15.7	9.7
Max (μV)	237.5	179.1	131.4	156.0	199.4
$\Delta ST_{(J+60)}$	0-1	1-2	2-3	3-4	4-5
Mean (μV)	41.8	45.9	44.9	43.6	44.2
SD (μV)	27.9	45.3	33.1	30.5	41.7
Min (μV)	7.9	7.5	3.4	8.2	6.7
Max (μV)	154.6	384.1	264.4	134.9	251.0
ΔVG	0-1	1-2	2-3	3-4	4-5
Mean (mV·ms)	26.2*	21.2	20.3	21.7	23.5
SD (mV·ms)	17.3	12.6	13.1	13.4	18.4
Min (mV·ms)	5.4	4.7	2.3	1.2	3.0
Max (mV·ms)	87.5	60.2	70.2	70.4	128.7
ΔHR	0-1	1-2	2-3	3-4	4-5
Mean (bpm)	9.2	8.3	9.2	10.3	9.9
SD (bpm)	7.8	8.2	8.2	8.9	8.6
Min (bpm)	0.2	0.0	0.1	0.0	0.3
Max (bpm)	36.6	55.1	50.1	48.4	37.7

TABLE 4. Descriptive statistics of the differences $\Delta ST_{(J+0)}$, $\Delta ST_{(J+60)}$, ΔVG and ΔHR between successive ECGs (time lapse 5 years), denoted as 0–1 (ECG_0 and ECG_1), 1–2 (ECG_1 and ECG_2), ..., 4–5 (ECG_4 and ECG_5). Asterisks mark the mean values that are above the threshold as found in the companion paper by Treskes *et al*.[12] (58 μV for ΔST and 26 mV·ms for ΔVG).

$\Delta ST_{(J+0)}$	0-1	0-2	0-3	0-4	0-5
Mean (μV)	53.4	55.9	63.9*	65.0*	65.1*
SD (μV)	35.9	34.1	36.7	33.3	38.9
Min (μV)	10.2	7.6	11.6	11.3	8.8
Max (μV)	237.5	213.8	178.3	155.2	163.4
$\Delta ST_{(J+60)}$	0-1	0-2	0-3	0-4	0-5
Mean (μV)	41.8	52.3	61.0*	65.4*	71.5*
SD (μV)	27.9	46.3	33.8	38.6	43.1
Min (μV)	7.9	4.6	6.1	11.2	12.8
Max (μV)	154.6	396.7	149.6	188.7	259.5
ΔVG	0-1	0-2	0-3	0-4	0-5
Mean (mV·ms)	26.2*	26.7*	31.3*	35.2*	40.5*
SD (mV·ms)	17.3	15.9	17.5	19.0	20.0
Min (mV·ms)	5.4	3.9	5.3	4.7	6.9
Max (mV·ms)	87.5	91.2	90.5	88.4	93.6
ΔHR	0-1	0-2	0-3	0-4	0-4
Mean (bpm)	9.2	8.8	10.9	11.0	11.5
SD (bpm)	7.8	7.0	7.6	8.0	8.8
Min (bpm)	0.2	0.3	0.1	0.1	0.1
Max (bpm)	36.6	33.3	37.4	34.0	37.9

TABLE 5. Descriptive statistics of the differences $\Delta ST_{(J+0)}$, $\Delta ST_{(J+60)}$, ΔVG and ΔHR between ECG_0 and each of the following ECGs, denoted as 0–1 (ECG_0 and ECG_1, time lapse 5 years), 0–2 (ECG_0 and ECG_2, time lapse 10 years), ..., 0–5 (ECG_0 and ECG_5, time laps 25 years). Asterisks mark the mean values that are above the threshold as found in the companion paper by Treskes *et al*.[12] (58 μV for ΔST and of 26 mV·ms for ΔVG).

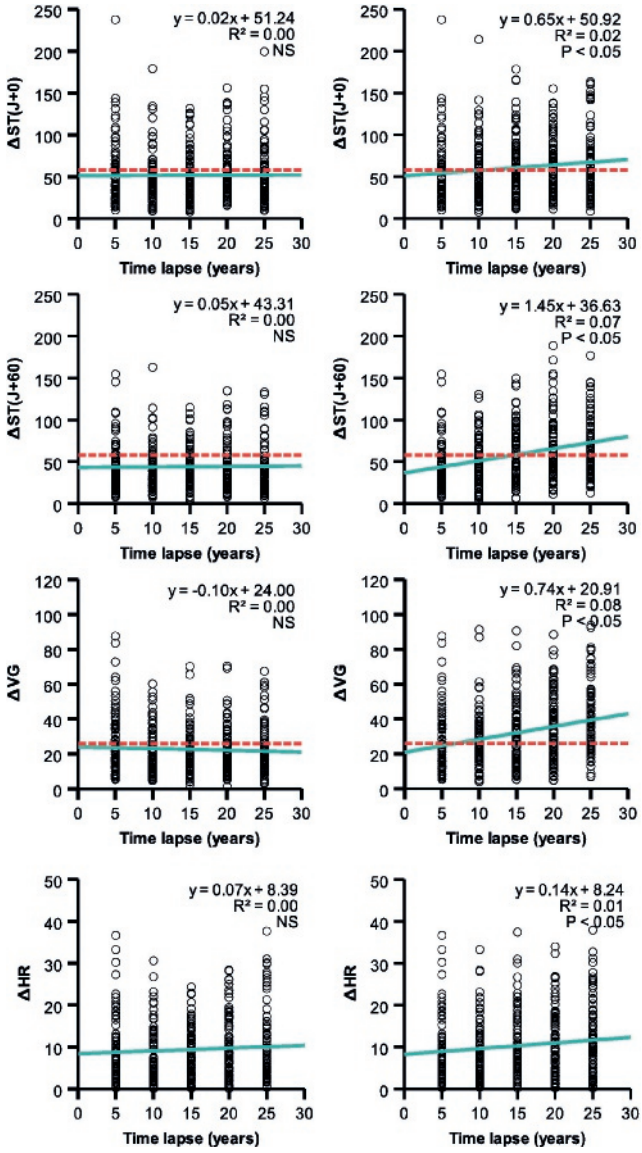


FIGURE 1. Left panels: scatterplots of the differences $\Delta ST_{(J+0)}$, $\Delta ST_{(J+60)}$, ΔVG and ΔHR between successive ECGs, denoted as 0–1 (ECG_0 and ECG_1), 1–2 (ECG_1 and ECG_2), ..., 4–5 (ECG_4 and ECG_5). Right panels: scatterplots of the differences $\Delta ST_{(J+0)}$, $\Delta ST_{(J+60)}$ and ΔVG between ECG_0 and each of the following ECGs, denoted as 0–1 (ECG_0 and ECG_1), 0–2 (ECG_0 and ECG_2), ..., 0–5 (ECG_0 and ECG_5). For the sake of clarity some outliers were clipped (left panels: four data points in $\Delta ST_{(J+60)}$, one data point in ΔVG and five data points in ΔHR; right panels: two data points in $\Delta ST_{(J+60)}$; see Table 4, Table 5 for the data ranges). Dashed horizontal red lines: threshold as determined in the companion paper by Treskes *et al.*[12] (58 μV for ΔST and of 26 mV·ms for ΔVG). Solid blue lines: linear regressions.

The standard deviations and the ranges of $\Delta ST_{(J+0)}$, $\Delta ST_{(J+60)}$, ΔVG and ΔHR were remarkably large, for the differences between successive ECGs (see Table 4 and the left panels of Figure 1) as well as between ECG_0 and either of the following ECGs (see Table 5 and the right panels of Figure 1). There were no trends in the differences between successive ECGs (see results of the linear regressions in the left panels of Figure 1). Positive trends were seen with increasing time lapses between ECGs (see results of the linear regressions in the right panels of Figure 1). Overall, the mean $\Delta ST_{(J+0)}$, $\Delta ST_{(J+60)}$, ΔVG and ΔHR increased per year by 0.65 μV, 1.45 μV, 3.69 mV·ms and 0.14 bpm, respectively.

The results of the multiple linear regression models for the dependent variables $\Delta ST_{(J+0)}$, $\Delta ST_{(J+60)}$ and ΔVG are given in Table 6. As can be seen from the adjusted R square values, these models were only able to explain a small part of the variability of the dependent variables. Fourteen independent variables were selected by the forward entry procedures in any regression model. Four independent variables figure in two models; only the heart rate difference between the first and last ECG in a pentad was selected in all three models.

Independent variable	$\Delta ST_{(J+0)}$	*P*	$\Delta ST_{(J+60)}$	*P*	ΔVG	*P*
(Constant)	45.76	< 0.01	45.30	< 0.01	29.30	< 0.01
Congenital heart disease					−4.53	0.01
Valvular heart disease			10.11	0.04		
Pulmonary hypertension			70.95	< 0.01		
Non-ischemic myopathy	21.72	< 0.01			7.24	0.01
Heart failure	54.13	0.02				
Conduction disorder			16.92	< 0.01		
Arrhythmia	−22.49	< 0.01				
Diabetes mellitus	−8.19	0.04				
New pulmonary hypertension			63.32	< 0.01	11.84	0.05
New conduction disorder	18.58	0.03	24.33	0.01		
Valvular heart surgery in the interim					12.39	< 0.01
Other heart surgery in the interim			−34.57	0.04		
ΔHR (bpm)	0.66	< 0.01	0.71	< 0.01	0.36	< 0.01
R square adjusted	0.1		0.17		0.13	

TABLE 6. Multiple linear regression models for the dependent variables $\Delta ST_{(J+0)}$, $\Delta ST_{(J+60)}$ and ΔVG; constructed with forward entering of the independent variables, *P*in = 0.05, *P*out = 0.10. Age and the listed diagnoses relate to the time of the first ECG made in a pentad, except for "new" diagnoses that have emerged between the first and second ECG of a pentad. Clinical events between the first and second ECG of a pentad have been labeled as "in the interim". ΔHR = absolute value of the heart rate difference between the first and second ECG of a pentad.

DISCUSSION

Purpose of this study was to investigate ECG changes in time, to assess if an elective ECG can be used as a reference ECG for serial comparison with an acute ECG in order to detect myocardial ischemia. ECGs were studied in a clinical population that was followed over 25 years; only elective ECGs of these patients were included, ECGs made in acute conditions were excluded from the study. We assessed the short term reproducibility and the long term changes in the elective ECGs, with the purpose to determine if these ECGs were sufficiently stable in order to be used as reference ECGs. When the differences between ECGs seen in this data set would have the same order of magnitude as the differences to be detected when comparing a reference ECG and an acute ischemic ECG, the specificity of the ischemia detection algorithm would be too low, rendering differential detection of ischemia unfeasible.

In 88 patients that could be followed over a 25-year period, we selected repeat ECGs five years apart. Thus we could study 440 5-year differences between ECG. We could also study,

within each patient, a 5-, 10-, 15-, 20- and 25-year difference with the initial ECG. We aimed specifically at differences in three vectorcardiographic ECG variables: the ST vectors at the J point and 60 ms after the J point, and the ventricular gradient.

Our results suggest that larger part of the within-subject ECGs differences are inherent to the day-by-day reproducibility rather than by time. We could also demonstrate a trend of increasing differences with time. Multiple linear regression revealed some diagnoses and clinical events that contributed to the differences between ECGs, but the percentage explained variance was low. In the following the results of our study are discussed in detail.

Study group composition

Two leading principles have determined the principal selection criteria that were applied to identify the study group in our cardiologic patient population:

1. Only ECGs in a stable clinical condition were included because ECGs made in acute conditions cannot serve as future reference ECGs for serial comparison in case of suspected ACS.
2. In order to study long-term ECG dynamics, only patients were selected who had every five years at least one ECG in a stable clinical condition, going 25 years back in time.

These selection criteria will have influenced the composition of our study group (see Table 1). According to expectation, a considerable part (35.2%) of the patients had congenital heart disease; as this is a patient group that is under lifelong supervision of pediatric cardiologists and cardiologists specialized in congenital heart diseases.

Except for valvular heart disease and heart failure there was a significant increase in the prevalence of diagnoses in our study group after 25 years (see Table 1). Numerically, the number of patients suffering from valvular heart disease was less after 25 years; this is due to the fact that only functional valvular heart disease was coded: when after valvular surgery normal valvular function was restored the patient was no longer coded as having valvular heart disease.
A total of 24 new infarctions occurred in our study group during the 25-years observation period. Of these, 12 were repeat infarctions and 12 were first infarctions which brought the total number of infarctions from 14 to 26 (see Table 1). The average yearly occurrence rate of myocardial infarctions in our study group was 24 cases/(88 patients · 25 years) = 1.1%. This is more than the infarction rate in the population, which is about 0.2%.[17]

Table 3 shows that considerable part, 43.2%, of the ECGs was abnormal or borderline abnormal in the beginning of the observation period, this increased to 64.8% after 25 years. Our intake criterion that ECGs had to show regular sinus rhythm may have introduced selection bias: patients with pacemaker rhythm and permanent atrial fibrillation were not incorporated in this study and patients with paroxysmal atrial fibrillation were excluded if atrial fibrillation was manifest in any ECG selected for potential analysis. Prolonged QRS duration which could potentially mask the J-point and, thus, hamper the computation of ΔST occurred in 15.9% of the initial ECGs and in 35.2% of the final ECGs in the 25-year period. However, in practice, J-points were identifiable in any of the studied patients.

Factors influencing short term reproducibility and long term changes in $\Delta ST_{(J+0)}$, $\Delta ST_{(J+60)}$, ΔVG and ΔHR

Various factors will have contributed to the intra-individual ECG differences that we have observed in our study. Factors that affect ECG reproducibility are, *e.g.*, inconsistency in electrode placement (small variations in electrode positioning or unintended electrode malpositioning), food and fluid intake, emotional stress, increasing age, changes in weight, filling status, body temperature, cardiac dimensions (*e.g.*, due to physical training).[9-11] Except for cardiac dimensions and weight changes, all before mentioned factors can play a role even when there is only one day between two successive ECG recordings.

It is not clear how much such factors would influence the reproducibility of the specific variables under study, ΔST and ΔVG. Ideally, ST amplitudes are close to zero, and it is not likely that the before mentioned factors influence this. This may be different for the ventricular gradient. In a previous study we have demonstrated, in exercise ECGs, that the ventricular gradient during the exercise phase differs from the ventricular gradient during the recovery phase, when measured at equal heart rates.[18] This is due to the differences in circulating catecholamines and sympathetic and parasympathetic tone measured in these different physiological situations, similar differences may also occur during routine ECG recordings when patients are not given ample time to accommodate to a complete resting state.

Factors influencing short term reproducibility as discussed above remain operational on the long term as well. Additional factors that may require time to develop may add to this and enhance the differences measured with serial ECG comparison. Such factors are, amongst others, increasing age, developing disease, modelling of the heart due to developing disease or to training or inactivity and institution/modification of pharmacological therapy. Some of these factors may influence the J-amplitude, thus increasing ΔST (one example is the non-zero J-amplitudes seen in ventricular hypertrophy). Any factor that changes the QRST waveform changes, by definition, the ventricular gradient as this equals the integral of the heart vector over the QT interval. Anyway, heart rate differences between two compared ECGs will increase ΔVG, as VG is known to depend on heart rate.[16]

As evident from Table 4 and from the left panels of Figure 1, the 5-year differences $\Delta ST_{(J+0)}$, $\Delta ST_{(J+60)}$, ΔVG and ΔHR show a remarkable standard deviation and range. It is striking that the average heart rate difference between two successive study ECGs has the order of magnitude of 10 bpm. This may have contributed considerably to the ΔVG values, of which the means are well above 20 mV·ms. The average of $\Delta ST_{(J+0)}$ is consistently around 50 μV. We have considered the positioning of the J-point as a possible cause of this difference. The J-point was consistently put at the end of the QRS-complex, which is found by taking the last-occurring lead-dependent J-point candidates. In case of two J-point candidates in one lead, the Minnesota Code[15] dictates to select the first-occurring as the lead-dependent J-point candidate for end-QRS. In certain cases this may lead to a relatively short QRS-complex estimate. This is a potential criticism on the Minnesota procedure that determines the end of the QRS-complex.[19] If this effect would play a role one would expect a more stable ST-vector measurement when it is measured somewhat later (in our case 60 ms) in the ST-segment. Indeed, mean $\Delta ST_{(J+60)}$ was somewhat smaller but still these differences were quite large.

As evident from Table 5 and from the right panels of Figure 1, $\Delta ST_{(J+0)}$, $\Delta ST_{(J+60)}$, ΔVG and ΔHR increase with increasing distance between ECGs from 5 to 25 years. With the aid of the linear regression formulae backward extrapolations to a time difference of zero can be made. This yields estimates for the short term reproducibility: $\Delta ST_{(J+0)}$ = 50.92 μV, $\Delta ST_{(J+60)}$ = 36.63 μV and ΔVG = 20.91 mV·ms. The results suggest somewhat stronger that ST measurement 60 ms after end QRS would be more stable and possibly preferable. In that case we would have an average increase of $\Delta ST_{(J+60)}$ of 1.45 μV per year. Likewise we can estimate the short term reproducibility of the ventricular gradient and the heart rate: ΔVG = 20.91 mV·ms and ΔHR = 8.40 bpm and we can estimate the yearly increase of ΔVG and of ΔHR: 0.74 mV·ms and 0.14 bpm, respectively.

The increases in the average values of $\Delta ST_{(J+0)}$, of $\Delta ST_{(J+60)}$ and of ΔVG of 0.65 μV, 1.45 μV and 20.91 mV·ms per year, respectively (Figure 1, right panels), lump several effects together: ECG changes with age, due to progression of the disease process, and due to clinical events in part of the group all add in these numbers. Of course, this is a group of patients of mixed pathology, and changes in some patients are relatively small and in other patients relatively large (this is evident from the right panel plots in Figure 1, where some patients have, after 25 years, almost negligibly small values of $\Delta ST_{(J+0)}$, of $\Delta ST_{(J+60)}$ and of ΔVG, while others have very large changes). This suggests that age changes per se are relatively small. It is, indeed, known that J amplitude changes with age in normal subjects are minor.[10]

Multiple linear regression of ΔHR, the diagnoses at the beginning of a pentad, the clinical events that occurred in a pentad and the new diagnoses that arose during a pentad on $\Delta ST_{(J+0)}$, $\Delta ST_{(J+60)}$ and ΔVG showed that only a very limited part of the variability in $\Delta ST_{(J+0)}$, $\Delta ST_{(J+60)}$ and ΔVG could be explained by the independent variables (R square adjusted 0.10, 0.17 and 0.13, respectively). The strongest influences seen were pulmonary hypertension at the onset of a pentad or pulmonary hypertension as a new diagnosis during a pentad, which increased $\Delta ST_{(J+60)}$ by approximately 70 μV. This finding reflects the ST-segment changes usually seen in right ventricular pressure overload.[20]

Ischemia detection thresholds

In a recent companion study,[12] we assessed the diagnostic performance of a serial analysis algorithm with two databases: one with two ECGs per patient preceding and during acute ischemia in elective PCI (cases), and one with two elective non-ischemic ECGs per patient, one year apart (controls). ROC analysis revealed ischemia detection thresholds of 58 μV for $\Delta ST_{(J+0)}$ and of 26 mV·ms for ΔVG. These thresholds should be seen in the light of a mean ± SD 1-year reproducibility that we measured in the companion study: 33 ± 22 μV for $\Delta ST_{(J+0)}$, 30 ± 22 μV for $\Delta ST_{(J+60)}$, and 14 ± 8 mV·ms for ΔVG. In our current study, the short-term reproducibility's (estimated by extrapolation back in time to a zero time lap between successive ECGs) were larger: 51 μV for $\Delta ST_{(J+0)}$, 37 μV for $\Delta ST_{(J+60)}$, and 21 mV·ms for ΔVG (values for SD with time-lap zero are not available). The smaller mean values of $\Delta ST_{(J+0)}$, $\Delta ST_{(J+60)}$ and ΔVG in the companion study can readily be explained by the fact that, in that study, only stable patients were included, without intervening events between successive ECGs. Hence, in a medically more dynamic population like the population in the current

study, reproducibility of ECGs is worse, and changes between successive ECGs in terms of ST and VG vectors are larger. Strikingly, the stability of the ST vector when measured 60 ms after the J point is better than the stability of the ST vector measured at the J point.

Limitations

It is a major limitation of this study that it contains only controls (elective ECGs without acute ischemia). Another limitation is the selection bias that may have occurred because of the selection criteria (notably the requirement that only patients were included of whom our ECG database contained ECGs over a period of 25 years). Table 1 shows that the most common diagnosis is congenital heart disease; this patient group is by definition having periodic checkups, including ECGs. Part of these patients is known to have progressive remodeling of either the left or right ventricle, thus altering the ECG. Also surgery may affect the ECG. At the other side of the spectrum, subjects without apparent cardiovascular heart disease, in whom the long-term ECG changes are known to be relatively small[10] are not represented in our study group.

CONCLUSION

Our study demonstrates that the ST vectors (at the J point and 60 ms after the J point) and the VG vectors in elective, non-ischemic ECGs of a group of cardiology patients change considerably and, with time, the differences between the current and past ECG increase. From our data we can conclude that, in a medically-dynamic cardiology population, ECGs that can be used as a reference for ischemia detection remain only valid for a limited period of time. In clinical practice, this seems not to be a serious limitation, because most patients who are under permanent cardiologic supervision will have a yearly visit, and a yearly ECG made.

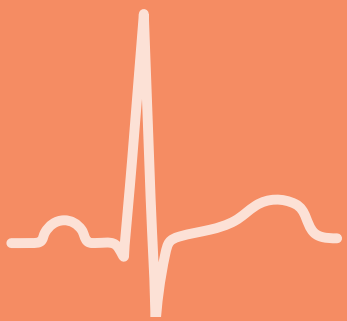
ECGs that are routinely made before a patient sees his cardiologist are of importance for the visit itself, but, additionally, these ECGs can play an important role in the detection of acute ischemia, in case the patient develops symptoms suggestive for acute coronary syndrome. If comparison of the acute ECG with a preceding elective ECG is supposed to help in establishing the working diagnosis of acute coronary syndrome, as the guidelines state, our study suggests that it is important to have a recent ECG available, as an "aged" ECG may have lost its validity as a reference.

REFERENCES

1. Steg P, James S, Atar D, *et al.* ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012;33:2569-619.
2. O'Gara PT, Kushner FG, Ascheim DD, *et al.* 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. Circulation. 2013;127:e362-425.
3. Rokos IC, French WJ, Mattu A, *et al.* Appropriate cardiac cath lab activation: optimizing electrocardiogram interpretation and clinical decision-making for acute ST-elevation myocardial infarction. Am Heart J. 2010;160:995-1003, 1003 e1-8.
4. Man S, Rahmattulla C, Maan AC, *et al.* Acute coronary syndrome with a totally occluded culprit artery: relation of the ST injury vector with ST-elevation and non-ST elevation ECGs. J Electrocardiol. 2014;47:183-90.
5. Thygesen K, Alpert JS, Jaffe AS, *et al.* Third universal definition of myocardial infarction. Circulation. 2012;126:2020-35.
6. ter Haar CC, Maan AC, Warren SG, *et al.* Difference vectors to describe dynamics of the ST segment and the ventricular gradient in acute ischemia. J Electrocardiol. 2013;46:302-11.
7. ter Haar CC, Maan AC, Schalij MJ, *et al.* Directionality and proportionality of the ST and ventricular gradient difference vectors during acute ischemia. J Electrocardiol. 2014;47:500-4.
8. Draisma HH, Schalij MJ, van der Wall EE, *et al.* Elucidation of the spatial ventricular gradient and its link with dispersion of repolarization. Heart Rhythm. 2006;3:1092-9.
9. Frederiks J, Swenne CA, Kors JA, *et al.* Within-subject electrocardiographic differences at equal heart rates: role of the autonomic nervous system. Pflugers Arch. 2001;441:717-24.
10. Rijnbeek PR, van Herpen G, Bots ML, *et al.* Normal values of the electrocardiogram for ages 16-90 years. J Electrocardiol. 2014;47:914-21.
11. Schijvenaars BJ, van Herpen G and Kors JA. Intraindividual variability in electrocardiograms. J Electrocardiol. 2008;41:190-6.
12. Treskes RW, ter Haar CC, Man S, *et al.* Performance of ST and ventricular gradient difference vectors in electrocardiographic detection of acute myocardial ischemia. J Electrocardiol. 2015;48:498-504.
13. Macfarlane PW, Devine B, Latif S, *et al.* Methodology of ECG interpretation in the Glasgow program. Methods Inf Med. 1990;29:354-61.
14. Draisma HHM, Swenne CA, van de Vooren H, *et al.* LEADS: An Interactive Research Oriented ECG/VCG Analysis System. Computers in Cardiology. 2005:515-518.
15. Prineas R, Crow R and Zhang Z. The Minnesota code manual of electrocardiograhic findings. 2nd ed: Springer; 2010.
16. Scherptong RW, Henkens IR, Man SC, *et al.* Normal limits of the spatial QRS-T angle and ventricular gradient in 12-lead electrocardiograms of young adults: dependence on sex and heart rate. J Electrocardiol. 2008;41:648-55.
17. Yeh RW, Sidney S, Chandra M, *et al.* Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med. 2010;362:2155-65.
18. Draisma H, Hooft van Huysduynen B, Swenne C, *et al.* Increased dispersion of ventricular repolarization during recovery from exercise. Comput Cardiol. 2005:85.
19. Melgaard J, Struijk J, Kanters J, *et al.* Automatic J-point location in subjects with electrocardiographic early repolarization. Comput Cardiol. 2014:585.
20. Kamphuis VP, Wagner GS, Pahlm O, *et al.* Comparison of model-based and expert-rule based electrocardiographic identification of the culprit artery in patients with acute coronary syndrome. J Electrocardiol. 2015;48:483-9.

Chapter

7



The prevalence of electrocardiograms exceeding thresholds for ST-elevation myocardial infarction in apparently healthy individuals: the role of ethnicity

C. Cato ter Haar
Jan A. Kors
Ron J.G. Peters
Michael W.T. Tanck
Marieke B. Snijder
Arie C. Maan
Cees A. Swenne
Jonas S.S.G. de Jong
Peter W. Macfarlane
Pieter G. Postema

Submitted

ABSTRACT

Study hypothesis

Early prehospital recognition of conditions such as ST-elevation myocardial infarction (STEMI) has prognostic relevance. Current international electrocardiographic (ECG) STEMI thresholds are predominantly based on Western-European individuals. However, with the awareness that there is ethnic electrocardiographic variability both in health and disease, there is a growing need to re-evaluate diagnostic ST-elevation thresholds for different populations. We hypothesized that fulfilment of ST-elevation thresholds of the STEMI criteria (STE-ECGs) in apparently healthy individuals is ethnicity dependent.

Objective

Determining background variation in ST elevation by quantification of the impact of using non-ethnicity specific ST-elevation thresholds in an apparently healthy population.

Methods

HELIUS is a multi-ethnic cohort study consisting of 10,783 apparently healthy subjects of African Surinamese, Dutch, Ghanaian, Moroccan, South-Asian Surinamese or Turkish ethnic origin. Prevalence of STE-ECGs across ethnicities, sexes and age groups, were assessed with respect to the two international STEMI thresholds: sex- and age-specific and only sex-specific.

Results

Prevalence of STE-ECGs was 2.8%-3.4%, with and without age included in the thresholds. Subgroup analyses showed prevalences of 21.7%-27.5% in young (< 40 years) Ghanaian males (age/sex-sex specific thresholds, respectively) versus 0.0% - 0.0% in older (≥ 40 years) Turkish females. Ethnicity (Sub-Saharan African origin) and other variables (*e.g.*, younger age, male sex, high QRS-voltages and/or antero-lateral early repolarization pattern) were positively associated with STE-ECG occurrence, resulting in subgroups with > 45% STE-ECG.

Conclusions

There is a highly variable prevalence of electrocardiograms with ST elevations exceeding thresholds for STEMI across ethnicities in apparently healthy subjects. This has potential consequences for the urgent evaluation for STEMI in non Western-European individuals.

INTRODUCTION

Background

The prehospital triage of acute chest pain patients remains a clinical challenge requiring rapid and accurate determination of ischemic versus non-ischemic pathology.[1,2] Since the introduction of thrombolysis, possible detrimental effects of inaccurate diagnosis have been documented.[3] Thresholds in ST shifts, formerly proposed to identify eligible thrombolysis candidates, differed between precordial and extremity leads because of higher healthy non-zero precordial J-point amplitudes.[4] This concept was expanded by investigations of differences between sexes[5-7] and between age groups, where young healthy males were found to have highest ST-segment amplitudes.[6-8] These findings prompted refinement of the ST-elevation myocardial infarction (STEMI) thresholds,[9] with sex-specific and later both age- and sex-specific thresholds,[10] respectively adapted in the USA (ACCF/AHA)[1] and European (ESC)[2] guidelines.

Importance

Normal electrocardiogram (ECG) values are not only sex- and age-dependent, differences between ethnicities have also been well established.[6,11-13] For instance, individuals of (Sub-Saharan) African descent are known to have higher pre-existent J-point/ST-segment amplitudes compared to Western Europeans.[12,14] STEMI evaluations in non Western Europeans may thus be less accurate. Indeed, depending on the ethnic origin of the investigated individuals, there appear to be more false-positive or more false-negative referrals for urgent coronary interventions.[15,16] With the increasing diversity of populations world-wide, there is a growing need to re-evaluate thresholds for health and disease such as STEMI, as these may impact on recognition, treatment and outcome. On the one hand, while costly[17] and sometimes risky[18] coronary catheterization should be limited to patients with acute myocardial ischemia metropolitan areas are becoming increased multi ethnic. On the other hand, in more remote often non Western-European areas, hazardous unnecessary prehospital thrombolysis should be prevented.[3,19]

Goals of this investigation

To appreciate electrocardiographic variation in disease, variation in apparently healthy individuals should first be determined. To determine background variability across ethnicities in ECGs exceeding ST-elevation thresholds of the STEMI criteria (STE-ECGs), we studied the performance of non-ethnicity specific STEMI thresholds[1,2] by investigating prevalences of STE-ECGs in the apparently healthy multi-ethnic population from the HEalthy LIfe in an Urban Setting (HELIUS) study.

METHODS

Study design, setting and participants

HELIUS is a multi-ethnic cohort study including inhabitants of Amsterdam, the Netherlands.[20,21] Its general aim is to assess differences in disease prevalence across ethnic groups, unravel their causes, and ultimately enable improvement of health care and prevention strategies. Initial inclusion consisted of nearly 25,000 participants mainly of Dutch, Ghanaian, Moroccan, Surinamese and Turkish ethnic origin. Baseline investigations, used for this specific study, were electively performed in ambulatory subjects and included questionnaires, physical examinations, an ECG and blood sampling. The study was approved by our Medical Ethics Committee prior to data collection and all participants provided written informed consent. A more detailed description of HELIUS has been published previously.[20,21]

Clinical diagnoses

To identify apparently healthy subjects for the current study, medical history was retrieved from the questionnaires combined with physical examination and blood-test results. Arterial disease was defined by self-reported stroke, transient ischemic attack, myocardial infarction, (coronary) bypass surgery and/or percutaneous intervention, and/or use of antithrombotics, anticoagulation therapy and/or nitrates. Subjects were hypertensive when they: reported a history of hypertension, used antihypertensive medication, and/or had current hypertension defined as systolic ≥ 140 mmHg and/or diastolic ≥ 90 mmHg (WHO criteria) each based on a mean of two measurements. Antihypertensive agents can also be used for other conditions, which were therefore also excluded. Diabetes mellitus was based on self-reported diagnosis, fasting glucose (≥ 7 mmol/l), HbA1c (≥ 48 mmol/mol) and/or the use of glucose-lowering medication. Chronic kidney disease was defined as CKD-EPI stage ≥ 3 (eGFR < 60 ml/min/1.73 m2) and/or a KDIGO albumin-to-creatinine ratio ≥ 3 mg/mmol. Possible ECG-modifying medications were determined as self-reported use of any anti-arrhythmic Vaughan-Williams classification medication plus digoxin and/or the daily use of psychotropic medication.

ECG processing and analysis

Standard 12-lead supine digital resting ECGs were recorded (GE MAC5500, 500 samples/second) and processed with the Modular ECG Analysis System (MEANS) program.[22] MEANS determines common P-wave, QRS, and T-wave onsets and offsets for all 12 leads together on one representative averaged beat. All on- and offsets were manually checked and adjusted when necessary. The QRS offset/J point was positioned after a potential end-QRS notch/slur. Various ECG variables were subsequently computed, including heart rate, QRS interval, QTc (Bazett), QRS-complex amplitudes and J-point amplitudes. Additionally, the ST/J-point vector[23,24] was computed after synthesizing vectorcardiographic leads from the 12-lead ECGs.

Additionally, early repolarization pattern (ERP) was fully automatically assessed by the University of Glasgow ECG core lab and defined as following: end-QRS notching or slurring (irrespective of ST elevation) in at least two contiguous leads (lateral ERP [aVL, I], inferior ERP [II, aVF, III], antero-lateral ERP [V4-V6]) with J peak or end QRS slur onset ≥ 0.1 mV.[25,26] High QRS voltages were initially identified using the ESC hypertension guideline for electrocardiographic criteria of left ventricular hypertrophy (LVH).[27] Because these criteria resulted in a high prevalence in our normotensive subjects (Table S1), we report high QRS voltages with broadly used composite LVH-ECG criteria.[28]

Prevalence % (95% CI)	Apparently healthy population *N* = 10,783	Ghanaian, males, < 40 y *n* = 120	Turkish, females, ≥ 40 y *n* = 417
Original Sokolow-Lyon index (A)	4.49 (4.10-4.88)	36.67 (28.04-45.29)	0.48 (-0.18-1.14)
Original Sokolow-Lyon index without V6 (B)	4.45 (4.06-4.84)	36.67 (28.04-45.29)	0.48 (-0.18-1.14)
Modified Sokolow-Lyon index (B)	20.11 (19.36-20.87)	82.50 (75.70-89.30)	0.72 (-0.09-01.53)
Cornell voltage (A)	1.39 (1.17-1.61)	1.67 (-0.62-3.96)	0.48 (-0.18-1.14)
Cornell voltage duration product (B)	2.48 (2.18-2.77)	4.17 (0.59-7.74)	0.96 (0.02-1.89)
R aVL (A, B)	0.76 (0.60-0.92)	2.50 (-0.29-5.29)	0.48 (-0.18-1.14)
ESC hypertension guideline 2013: any of B	21.83 (21.05-22.61)	83.33 (76.67-90.00)	2.16 (0.76-3.55)
High QRS voltage criteria used for this study: any of A	6.33 (5.87-6.79)	38.33 (29.63-47.03)	1.44 (0.30-2.58)

TABLE S1. Prevalence of high QRS voltage ECGs.
Prevalences of ECGs meeting one of the high QRS-voltage criteria in the apparently healthy population and the on age-, sex- and ethnicity based subgroups with respectively the highest and lowest prevalence of electrocardiographic LVH according to the criteria from the ESC hypertension guideline.

- Original Sokolow-Lyon index: S V1 + R V5/V6 > 3.5 mV
- Original Sokolow-Lyon index without V6: S V1 + R V5 > 3.5 mV
- Modified Sokolow-Lyon index: any precordial S + any precordial R > 3.5 mV
- Cornell voltage: R aVL + S V3 > 2.8 mV (males), 2.0mV (females)
- Cornell voltage duration product: (R aVL + S V3 (females + 0.8mV)) · QRS duration > 244 mV·ms; R aVL > 1.1 mV

Abbreviations: y = years old.

ECG abnormalities, used for the exclusion process (see "Exclusion criteria"), were assessed utilizing 3 methods (Minnesota coding, 29 GE Marquette 12SL report, cardiologist interpretation). In case of discrepancies between the three methods, recommendations of international expert groups[10,30] were used for final diagnoses. Using the MEANS measurements, diagnoses were further verified (*e.g.*, an assigned complete right bundle branch block required a measured QRS duration of ≥ 120 ms). The QTc-interval was scored following the description of Viskin (very-long/long/normal/short/very-short).[31] Low QRS voltages were defined as peak-to-peak QRS amplitudes of < 0.5 mV in all limb leads and/or < 1.0 mV in all precordial leads.

Criteria used to recognize STE-ECGs

Since the ACCF/AHA and ESC STEMI thresholds slightly differ, ECGs were classified twice by applying two sets of thresholds on the J-point amplitudes[2,10]:

- Sex-specific STEMI thresholds: 2013 ACCF/AHA STEMI guidelines[1]
  - lead V2-V3: ≥ 0.2 mV [males]
  - lead V2-V3: ≥ 0.15 mV [females]
  - other leads: ≥ 0.1 mV
- Age- and sex-specific STEMI thresholds: 2017 ESC STEMI guidelines[2]
  - lead V2-V3: ≥ 0.25 mV [males < 40 years]
  - lead V2-V3: ≥ 0.20 mV [males ≥40 years]
  - lead V2-V3: ≥ 0.15 mV [females]
  - other leads: ≥ 0.1 mV

Exclusion criteria

Subjects were excluded when questionnaires were incomplete and/or no ECG of sufficient quality was recorded. To allow statistically meaningful analyses, only ethnicities with a sufficient number of subjects were included, resulting in subgroups of African Surinamese (South America with African roots), Dutch (Western Europe), Ghanaian (Western Africa), Moroccan (Northern Africa), South-Asian Surinamese (South Asia) and Turkish (Middle East) ethnic origin. Figure 1 depicts the exclusion process for establishing an apparently healthy population based on clinical diagnoses, medication, and ECG characteristics.

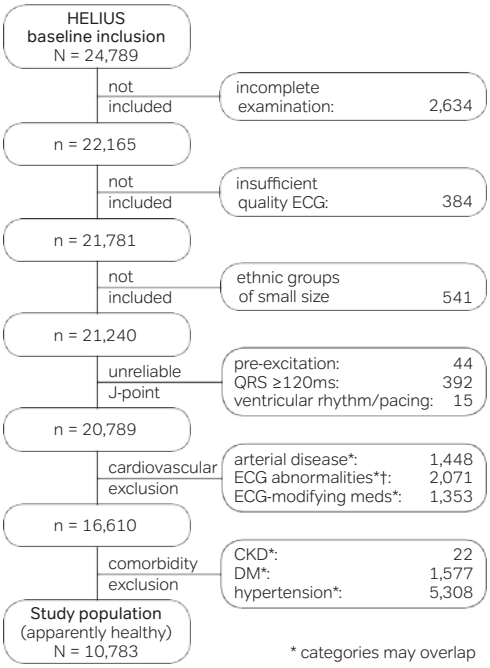


FIGURE 1. Inclusion and exclusion flowchart.
† ECG abnormalities: overt tachycardia (> 110/min), supraventricular arrhythmia, second- or third-degree atrioventricular block, left, right, extreme or indeterminate axis, pathological Q-waves or high R-waves V1/V2, low QRS voltages, T-wave abnormalities, very-long or very-short QTc interval, suspicion of cardiomyopathy and/or other overt ECG abnormalities (*e.g.*, dextrocardia).

Statistical analysis

The prevalence and corresponding Wilson score 95% confidence intervals (95% CIs) of STE-ECGs were computed using sex-specific and age- and sex-specific STEMI thresholds. 95% CIs are noted between parentheses. For initial analyses, the prevalence of STE-ECGs was computed in the total HELIUS population still including subjects with comorbidities (presented in web-only appendix Table S2). For further statistical analyses only apparently healthy subjects were investigated, using age- and sex-specific thresholds. Differences between ethnicities in spatial orientation of the largest ST elevation were explored by plotting interquartile ranges of ST vectors. The distribution of ethnicity- and sex-based subgroups within the STE-ECGs was depicted after correction for the study population distribution regarding ethnicity, sex and the two age groups (</≥ 40 years).

Using logistic regression, associations between a STE-ECG pattern (yes/no), using age- and sex-specific thresholds, and variables influencing J-point amplitudes (ethnicity, age, sex, high QRS voltages, ERP, QRS duration and QTc interval) were tested. Single two-way interactions were tested while correcting for the other variables. Finally, multivariable logistic regression including all significant variables was performed to estimate associations' effect sizes. The Bonferroni corrected significance threshold was 0.001.

RESULTS

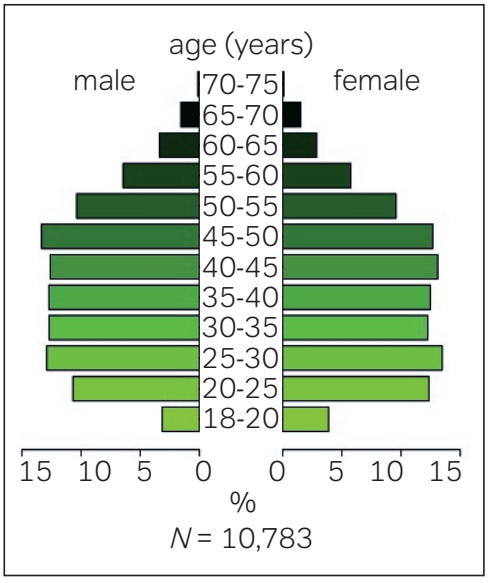


FIGURE S1. Population pyramid.
Age distribution separated by sex. Note the relatively high prevalence of younger subjects.

Apparently healthy population N = 10,783		
Age in years, median (Q1-Q3) [min-max]	38 (28-48) [18-71]	
Sex, male/female	4,079/6,704	
Ethnicity, n (%):		
African Surinamese	1,660	(15%)
Dutch	2,603	(24%)
Ghanaian	870	(8%)
Moroccan	2,384	(22%)
South-Asian Surinamese	1,318	(12%)
Turkish	1,948	(18%)

TABLE 1. Characteristics of the study population.
Abbreviations: Q = quartile.

Study population description

After exclusion 10,783 apparently healthy subjects remained (Figure 1). Study population characteristics are detailed in Table 1 and Figure S1. The median age was 38 (IQR: 20) and the male/female ratio was 4,079/6,704, while the six ethnic subgroups existed of 870-2,603 subjects. A description of exclusions stratified per ethnicity is provided (Table S3).

n (%)	All	Afr. Sur.	Dutch	Ghan.	Moroc.	S.-Asian Sur.	Turkish
Initial inclusion	21,240 (100)	4,060 (19)	4,477 (21)	2,309 (11)	3,860 (18)	2,981 (14)	3,553 (17)
Exclusion for STE-ECG analysis:							
Pre-excitation	44	8	5	5	9	10	7
QRS ≥120ms	392	53	132	25	65	52	65
Ventricular rhythm/pacing	15	3	3	2	2	4	1
None of above:	20,789 (100)	3,996 (19)	4,337 (21)	2,277 (11)	3,784 (18)	2,915 (14)	3,480 (17)
Cardiovascular exclusion:							
Arterial disease*	1,448	310	239	126	152	346	275
ECG abnormalities*	2,071	446	409	231	282	353	350
ECG-mod. medication*	1,353	211	337	79	220	214	292
None of above:	16,610 (100)	3,178 (19)	3,479 (21)	1,882 (11)	3,202 (19)	2,167 (13)	2,702 (16)
Comorbidity exclusion:							
CKD*	22	7	1	1	3	6	4
DM*	1,577	357	85	230	326	340	239
Hypertension*	5,308	1,430	850	966	672	736	654
None of above: Apparently healthy population	10,783 (100)	1,660 (15)	2,603 (24)	870 (8)	2,384 (22)	1,318 (12)	1,948 (18)

TABLE S3. Exclusions stratified per ethnicity.
Abbreviations: S.-Asian Sur.=South-Asian Surinamese, Afr. Sur.=African Surinamese, Ghan.=Ghanaian, Moroc.=Moroccan, ECG-mod. med.=ECG-modulating medication, *=Categories may overlap.

STE-ECG prevalence

The STE-ECG prevalence in the total apparently healthy population was 3.43% (3.10%-3.79%) using the sex-specific thresholds and slightly lower, 2.76% (2.47%-3.09%), when using both age- and sex-specific thresholds. The STE-ECG prevalence using age- and sex-specific thresholds was higher in males, 6.15% (5.46%-6.93%), than females, 0.70% (0.53%-0.93%). Younger (< 40 years) individuals had a higher prevalence, 3.45% (3.01%-3.95%) than older subjects (≥ 40 years): 1.98% (1.63%-2.40%).

Prevalence % (95% CI)	Apparently healthy population *N* = 10,783	CVD-free population *N* = 16,610	Total HELIUS cohort *N* = 20,789
Sex-specific STEMI thresholds	3.43 (3.10-3.79)	3.05 (2.80-3.33)	2.95 (2.73-3.19)
Age- and sex-specific STEMI thresholds	2.76 (2.47-3.09)	2.52% (2.29-2.77)	2.46 (2.26-2.68)

TABLE S2. STE-ECG prevalence in the larger HELIUS population.
Prevalences of STE-ECGs in the larger HELIUS population next to the apparently healthy subjects additionally including subjects with hypertension, CKD and/or diabetes (CVD-free population) and the total HELIUS cohort additionally including subjects with cardiovascular disease (see Figure 1).
Abbreviations: CVD-free = without cardiovascular disease

Additionally, ethnic differences in STE-ECG prevalence were observed (Figure 2, Table S4). Prevalences were highest in Ghanaian and lowest in Turkish subjects. Ghanaian males aged < 40 had the highest STE-ECG prevalence (21.7%-27.5%) while none of the Turkish females aged ≥ 40 had a STE-ECG. Within the STE-ECGs, correction for study population distributions (*e.g.*, males/females) further elaborates this ethnic variability (Figure 3).

Prevalence (%) (95% CI)	All	Afr. Sur.	Dutch	Ghan.	Moroc.	S.-Asian Sur.	Turkish
All	2.76 (2.47 -3.09) *N* = 10,783	4.76 (3.84- 5.89) *n* = 1,660	2.31 (1.79- 2.96) *n* = 2,603	7.01 (5.50- 8.90) *n* = 870	2.18 (1.67- 2.85) *n* = 2,384	1.90 (1.29- 2.79) *n* = 1,318	1.08 (0.71- 1.64) *n* = 1,948
Males	6.15 (5.46- 6.93) *n* = 4,079	11.11 (8.84- 13.87) *n* = 603	4.66 (3.53- 6.12) *n* = 1,030	17.52 (13.48- 22.46) *n* = 274	5.70 (4.30- 7.52) *n* = 807	4.14 (2.77- 6.13) *n* = 556	2.35 (1.51- 3.64) *n* = 809
Females	0.70 (0.53- 0.93) *n* = 6,704	1.14 (0.65- 1.97) *n* = 1,057	0.76 (0.44- 1.33) *n* = 1,573	2.18 (1.28- 3.70 *n* = 596	0.38 (0.17- 0.83) *n* = 1,577	0.26 (0.07- 0.95) *n* = 762	0.18 (0.05- 0.64) *n* = 1,139
< 40 years	3.45 (3.01- 3.95) *n* = 5,776	6.36 (4.82- 8.35) *n* = 739	3.64 (2.72- 4.85) *n* = 1,209	8.01 (5.81- 10.94) *n* = 437	2.56 (1.87- 3.49) *n* = 1487	2.38 (1.49- 3.79) *n* = 713	1.51 (0.96- 2.38) *n* = 1,191
≥ 40 years	1.98 (1.63- 2.40) *n* = 5,007	3.47 (2.47- 4.86) *n* = 921	1.15 (0.71- 1.86) *n* = 1,394	6.00 (4.13- 8.65) *n* = 433	1.56 (0.93- 2.60) *n* = 897	1.32 (0.67- 2.59) *n* = 605	0.40 (0.13- 1.16) *n* = 757
Males, < 40 years	7.71 (6.65- 8.92) *n* = 2,127	14.77 (11.00- 19.56) *n* = 264	7.20 (5.22- 9.85) *n* = 486	21.67 (15.24- 29.85) *n* = 120	6.82 (4.87- 9.47) *n* = 469	5.02 (3.11- 7.99) *n* = 319	3.41 (2.11- 5.47) *n* = 469
Males, ≥ 40 years	4.46 (3.63- 5.47) *n* = 1,952	8.26 (5.78- 11.68) *n* = 339	2.39 (1.40- 4.05) *n* = 544	14.29 (9.63- 20.68) *n* = 154	4.14 (2.48- 6.83) *n* = 338	2.95 (1.44- 5.97) *n* = 237	0.88 (0.30- 2.56) *n* = 340
Females, < 40 years	0.96 (0.69- 1.33) *n* = 3,649	1.68 (0.86- 3.29) *n* = 475	1.24 (0.66- 2.35) *n* = 723	2.84 (1.50- 5.31) *n* = 317	0.59 (0.27- 1.28) *n* = 1,018	0.25 (0.01- 1.42) *n* = 394	0.28 (0.08- 1.00) *n* = 722
Females, ≥ 40 years	0.39 (0.22- 0.69) *n* = 3,055	0.69 (0.27- 1.75) *n* = 582	0.35 (0.12- 1.03) *n* = 850	1.43 (0.56- 3.63) *n* = 279	0.00 (0.00- 0.68) *n* = 559	0.27 (0.01- 1.52) *n* = 368	0.00 (0.00- 0.91) *n* = 417

TABLE S4. STE-ECG prevalence stratified per ethnicity, sex and age.
Prevalences of STE-ECGs (age- and sex- specific STEMI thresholds) stratified per ethnicity, sex and age group. Abbreviations: S.-Asian Sur. = South-Asian Surinamese, Afr. Sur. = African Surinamese, Ghan. = Ghanaian, Moroc. = Moroccan.

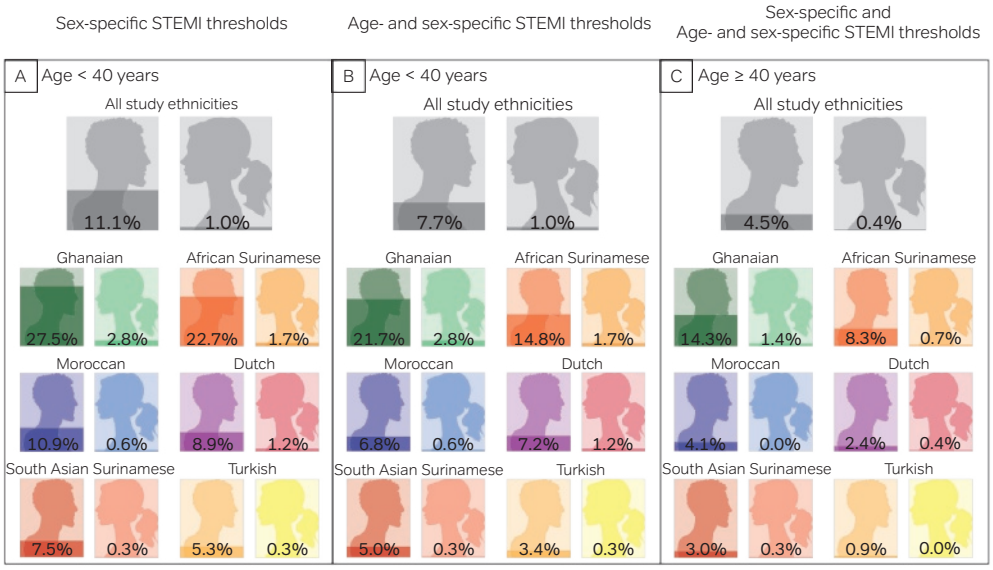


FIGURE 2. STE-ECG prevalence stratified per ethnicity, sex and age group.
Application of the two STEMI thresholds for the different ethnicity, sex and age groups. Note the increase in prevalence when using only sex-specific thresholds. Furthermore, note the higher prevalence with younger age, male sex (despite sex-specific thresholds) and in certain ethnicities.

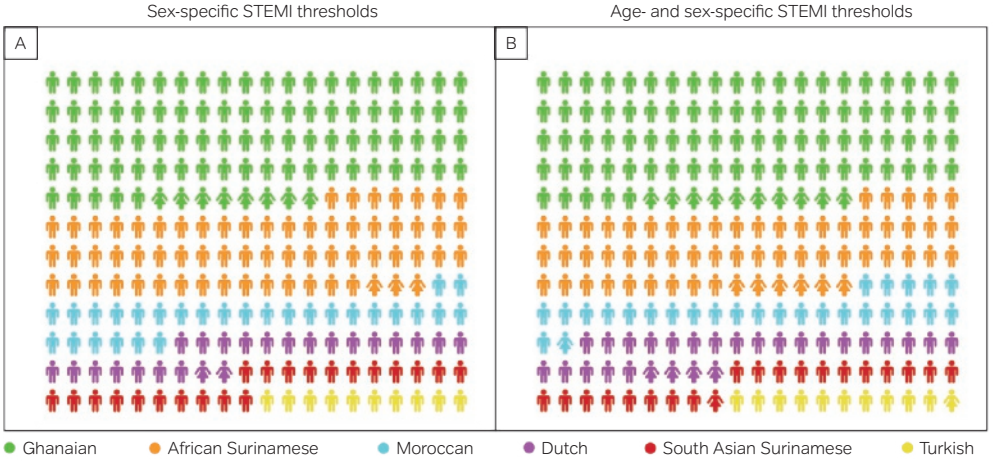


FIGURE 3. Corrected distribution of ethnicity and sex within the STE-ECGs.
Distribution of ethnicity- and sex- based subgroups within the STE-ECGs plotted after correction for the study population distribution regarding ethnicity, sex and the two age groups (cut-off 40 years). Note that subjects originating from Western Africa account for more than half (sex-specific thresholds) up to two thirds (age- and sex-specific thresholds) of all STE-ECGs.

Factors contributing to STE-ECGs

J-point amplitudes and ST-elevation location: The J-point amplitudes of all 12 ECG leads with corresponding STEMI thresholds are depicted in Figure 4-A. The most prevalent leads exceeding STEMI thresholds were V4-V5 (Table S5). 89% of all STE-ECGs included an above threshold V4 J-point amplitude. Highest V4 medians were documented in African Surinamese and Ghanaian males < 40 years, respectively, just above (109 μV) and slightly under (95 μV) the STEMI threshold (Figure S2). To further investigate the location of the largest ST elevation per patient, the spatial orientations of the ST/J-point vectors were two-fold plotted in the cordiform Stab-Werner projection[32] (Figure 4-B and 4-C). No clear difference in spatial ST-vector distribution could be visually observed between ethnicities, pointing to the magnitude and not the location of the ST elevation as an explanation for STE-ECG prevalence differences between ethnicities.

ECG lead combination prevalence (%)	All *N* = 10,783	Afr. Sur. *n* = 1,660	Dutch *n* = 2,603	Ghan. *n* = 870	Moroc. *n* = 2,384	S.-Asian Sur. *n* = 1,318	Turkish *n* = 1,948
aVL & I	0.02	0.00	0.00	0.23	0.00	0.00	0.00
I & -aVR	0.03	0.00	0.00	0.11	0.04	0.00	0.05
-aVR & II	0.07	0.24	0.04	0.11	0.08	0.00	0.00
II & aVF	0.18	0.30	0.23	0.23	0.08	0.15	0.10
aVF & III	0.07	0.06	0.15	0.00	0.04	0.08	0.05
V1 & V2	0.19	0.42	0.04	0.80	0.17	0.00	0.05
V2 & V3	0.45	0.66	0.31	2.07	0.34	0.30	0.00
V3 & V4	0.93	1.99	0.65	3.45	0.46	0.46	0.15
V4 & V5	1.96	3.31	1.77	4.71	1.59	1.21	0.77
V5 & V6	0.26	0.48	0.15	0.46	0.25	0.30	0.10
STE-ECG: One or more of above							
prevalence (95% CI)	2.76% (2.47%-3.09%)	4.76% (3.84%-5.89%)	2.31% (1.79%-2.96%)	7.01% (5.50%-8.90%)	2.18% (1.67%-2.85%)	1.90% (1.29%-2.79%)	1.08% (0.71%-1.64%)
Involvement of lead V4							
% (95% CI)	88.93 (84.86-92.01)	89.87 (81.27-94.78)	91.67 (81.93-96.39)	91.80 (82.21-96.45)	84.62 (72.48-91.99)	84.00 (65.35-93.60)	85.71 (65.36-95.02)

TABLE S5. Electrocardiographic locations of STE-ECGs stratified per ethnicity.
Abbreviations: S.-Asian Sur.=South-Asian Surinamese, Afr. Sur.=African Surinamese, Ghan.=Ghanaian, Moroc.=Moroccan.

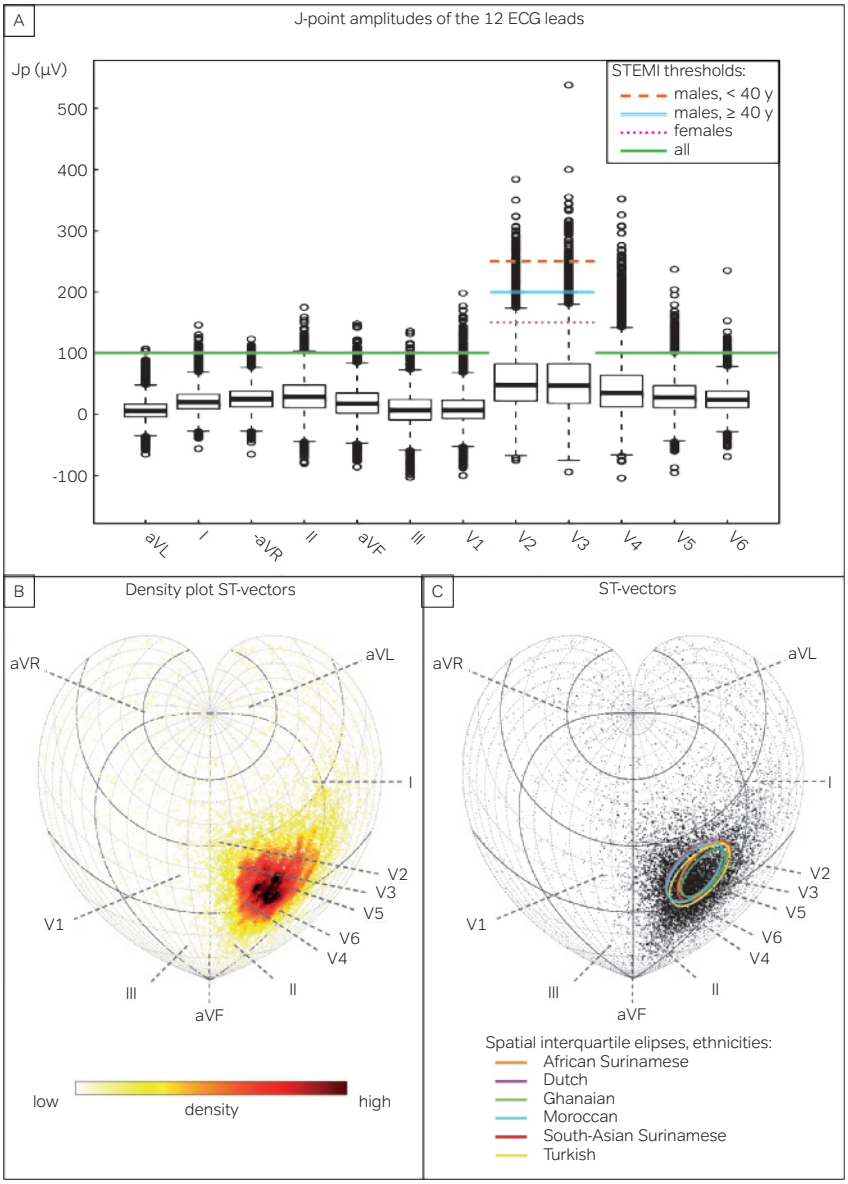


FIGURE 4. J-point amplitudes and ST-elevation location.
Panel A: The colored lines represent the current age- and sex-specific STEMI thresholds for each lead. Black stripes box: Q1, Q2, Q3, whiskers: Q1-1.5·IQR and Q3+1.5·IQR. Boxplots of the J-point amplitudes in the total apparently healthy population (N=10,783). Appreciate the amount of J-point amplitudes above the STEMI threshold in leads V2, V3 and V4.
Panel B and C general: The directions of the 3D ST-vectors of all subjects are shown on a sphere in the 2D-plane by cordiform Stab-Werner projections. Lead vector projections are marked with dashed lines. Panel B: Density plot. Note the precordial orientation of most ST-vectors. Panel C: ST-vector of all subjects in which the marker size represents the size of the ST-vector. Interquartile ellipses of a combination of azimuth and elevation are stratified per ethnicity. Because the direction of small ST-vectors is rather unreliable, small markers with a deviant direction should, in our opinion, not be seen as actual outliers. No evident ethnic difference in spatial ST-vector distribution can be appreciated.
Abbreviations: Jp = J point; y = years old.

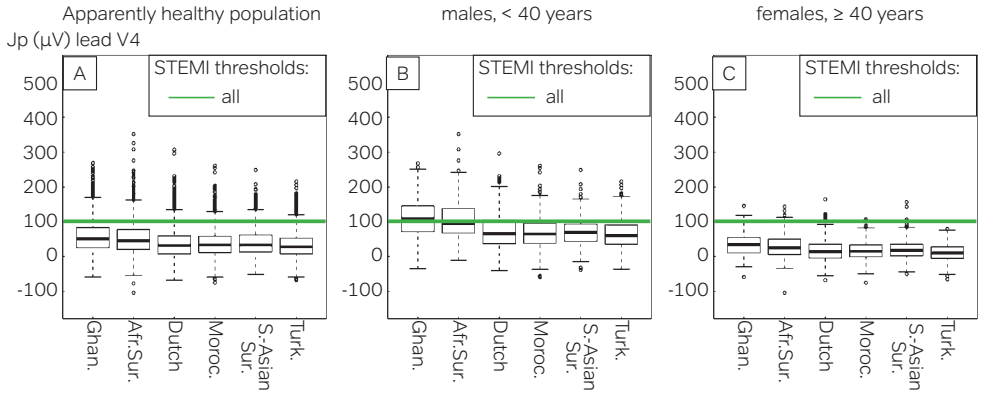


FiGURE S2. J-point amplitude of lead V4.
Panel A: Boxplots of the J-point amplitudes of the 12 ECG leads in the apparently healthy population (*N* = 10,783).
Panel B: Age and sex based subgroup with the highest STE-ECG prevalence (7.71%): males aged younger than 40 (*n* = 2,127).
Panel C: Age and sex based subgroup with the lowest STE-ECG prevalence (0.39%): females 40 years or older (*n* = 3055). The green line represents the current STEMI threshold. Ethnicities are ranked from the highest STE-ECG prevalence (left) to the lowest (right).
Abbreviations: Afr. Sur. = African Surinamese; F = female; Ghan. = Ghanaian; Jp = J point; M = male; Moroc. = Moroccan; S.-Asian Sur. = South-Asian Surinamese; Turk. = Turkish ethnicity.

Associated variables: All tested variables (ethnicity, age, sex, high QRS voltages, ERP, QRS duration and QTc interval) were statistically significantly associated with the occurrence of a STE-ECG, using the age- and sex-specific thresholds (Table S6). None of the two-way interactions was statistically significant. African Surinamese and Ghanaian ethnicity had the highest significant OR for the presence of a STE-ECG, 4.49 (2.66-7.57) and 5.71 (3.25-10.02), respectively. An antero-lateral ERP was significantly associated with a STE-ECG, whether or not in combination with another ERP-location, with ORs of 3.16 (2.11-4.72) and 4.06 (2.85-5.80). The OR for the occurrence of a STE-ECG was 2.80 (2.08-3.76) for high QRS-voltages and 4.06 (2.79-5.90) for male sex. Age and QTc interval were negatively associated with a STE-ECG: OR 0.97 (0.96-0.98) and 0.98 (0.97-0.99) per unit (year, millisecond), respectively. QRS duration was positively associated with a STE-ECG: OR 1.06 (1.05-1.08) per millisecond.

		Odds ratio (95% CI)	*p*-value
Ethnicity:			
	Ghanaian	5.71 (3.25-10.02)	< 0.0001*
	African Surinamese	4.49 (2.66-7.57)	< 0.0001*
	Dutch	2.18 (1.29-3.68)	0.0037
	Moroccan	2.12 (1.24-3.61)	0.0057
	South-Asian Surinamese	1.79 (0.97-3.30)	0.0619
	Turkish	reference	
Sex:			
	Male	4.06 (2.79-5.90)	< 0.0001*
	Female	reference	
Age:			
	Years	0.97 (0.96-0.98)	< 0.0001*
High QRS voltage:			
	High QRS voltages	2.80 (2.08-3.76)	< 0.0001*
	No high QRS voltages	reference	
ERP:			
	Inferior and antero-lateral (*n* = 532)	4.06 (2.85-5.80)	< 0.0001*
	Antero-lateral (*n* = 478)	3.16 (2.11-4.72)	< 0.0001*
	Lateral (*n* = 304)	2.80 (1.49-5.26)	0.0014
	Lateral and antero-lateral (*n* = 65)	1.33 (0.44-4.00)	0.6089
	Lateral, inferior and antero-lateral (*n* = 7)	0.00 (0.00-INF)	0.9791
	Inferior (*n* = 1,166)	1.08 (0.70-1.68)	0.7196
	Lateral and inferior (*n* = 3)	0.00 (0.00-INF)	0.9887
	No early repolarization pattern	reference	
QRS duration:			
	milliseconds, IQR: 14 ms	1.06 (1.05-1.08)	< 0.0001*
QTc interval (Bazett):			
	milliseconds, IQR: 28 ms	0.98 (0.97-0.99)	< 0.0001*

TABLE S6. Electrocardiographic locations of STE-ECGs stratified per ethnicity.
The reference category for the categorical variables was the subgroup with the lowest prevalence of a STE-ECG (age- and sex-specific STEMI thresholds): Turkish ethnicity, female, no high QRS voltages, no ERP.
Abbreviations: * = significant with a significance level of 0.001; IQR = interquartile range.

DISCUSSION

The 12-lead ECG still represents a cornerstone in the accurate prehospital (and also inhospital) emergency triage of patients with symptoms possibly or probably attributable to acute myocardial ischemia, and impacts on resultant survival and morbidity.[10] Diagnostic accuracy and error during these critical initial evaluations follow from balancing ratios of correct versus false positive and false negative test results in history taking, physical examinations and ECG interpretation. Additional investigations to rule in or rule out cardiac ischemia such as echocardiography or cardiac biomarker assessment are often either unavailable (*e.g.*, prehospital) or too time consuming for initial decision making in a STEMI triage system selecting patients for direct thrombolysis or urgent coronary angiography. It is already known that age and sex impact on a STEMI classification,[5-9] but reference values are predominantly derived from populations originating from Western Europe. This has resulted in age- and sex-specific STEMI thresholds in international guidelines and consensus documents, without incorporation of ethnicity.[1,2,10] Our findings, however, confirm that ethnicity is an important element to be considered, while there remain large age- and sex-dependent differences despite age- and sex-specific thresholds. This is relevant in our era with increasing diversity of populations world wide, especially in areas with large multi-ethnic populations (*e.g.*, metropolitan areas) and in parts of the world where riskful thrombolysis is administered more frequently. When current thresholds are used to evaluate health and disease, non Western-European patients with acute chest pain may thus be less accurately evaluated due to either a higher (*e.g.*, males from Sub-Saharan African descent) or lower (*e.g.*, Turkish females) incidence of pre-existent ST elevation. This could putatively result in worse outcome.

Factors contributing to STE-ECGs

J-point amplitudes and ST-elevation location: Since no clear differences were observed in the location of ST elevation (Figure 4), classification of STE-ECGs across ethnicities, sex and age, is predominantly determined by the J-point amplitude magnitude. In this respect, lead V4 appears in our study to be the most vulnerable for exceeding STEMI thresholds. In earlier studies, antero-lateral ST elevation proved to cause most false-positive cathlab activations,[16] which is currently mirrored in higher V2/V3 thresholds but not V4.

Sex, age and ethnicity: Male sex and younger age are well known to be associated with higher J-point amplitudes,[6-8] which is confirmed in this study. In contrast, female sex and older age indeed showed lower prevalences of non-ischemic STE-ECGs. Notably, despite different STEMI thresholds according to age and sex categories, we still noted overt differences in STE-ECGs exceeding STEMI thresholds in our study (*e.g.*, up to 8-fold higher prevalence in young males compared to older females while applying age- and sex-specific thresholds). The observed association of STE-ECGs and ethnic origin, especially Sub-Saharan African origin, was not unexpected.[12,14] However, the magnitude of this ethnic variability surpassed our prior understanding of this phenomenon at both extremes of the spectrum. Ethnicity, especially in combination with age and sex, jeopardizes both current STEMI thresholds for false-positive (particularly in males from Sub-Saharan African descent)

and for false-negative (particularly in Turkish females) outcomes, putatively resulting in over- and under treatment, morbidity and mortality when these individuals present with signs or symptoms of suggestive of acute coronary syndrome (ACS).

High QRS voltage: LVH is a known confounder of ECG interpretation[33,34] and complicates triage,[15,16] typically manifesting with high QRS voltages combined with pronounced ST elevation in right-precordial leads and ST depression in lateral leads.[35] In our study, subjects with high QRS voltages were only included in the absence of (current or previous) hypertension and a strain pattern. Additionally, typical electrocardiographic LVH does usually not affect the lead V4 ST segment, while STE-ECGs in this study are dominated by V4. Our STE-ECGs are therefore unlikely to result from actual LVH in this non-hypertensive population. This supports careful ST elevation assessment in combination with high QRS voltages, even in the absence of typical strain patterns.[36]

QRS duration and QTc interval: Associations between the occurrence of a STE-ECG, QRS-duration prolongation and QTc-interval shortening, might be explained by elevation of the J point due to larger overlap between depolarization and repolarization vectors, as proposed earlier.[14] In contrast, myocardial ischemia can cause alterations in both QRS duration (peri-ischemic conduction slowing)[37] and QTc interval, troubling such an assessment.[38]

ERP: Although both the pathophysiologic mechanism[39] as well as the definition[25] of the pattern called "early repolarization" are debated, ERP is known to hamper ST-elevation interpretation.[40] As recommended by the 2015 consensus paper,[25] we defined ERP as notching or slurring with or without accompanying ST elevation. Clearly, including isolated ST elevation as an ERP criterion would render statistical analysis with the occurrence of STE-ECGs futile. Interpreting ERP ECGs of patients with symptoms suggestive of STEMI remains challenging because notches and slurs can also result from ischemia.[41] Importantly, the occurrence of inferior ERP does not associate with STE-ECGs in this study, inhibiting the possibility to use inferior ERPs to exclude ACS.

Clinical implications and applications

Our study identifies multiple factors associated with the occurrence of a non-ischemic or pre-existing STE-ECG. The results of our logistic regression can modify the likelihood of an actual STEMI diagnosis by demonstrating the odds for a specific patient of having a STE-ECG in non-ischemic conditions. Automated ECG analysis systems have the opportunity to use additional checks to acknowledge ethnicity, high QRS voltages and/or ERP *etc.*, which could aid reporting. However, caution is advised since considerable overlap exists between ethnicities, sexes and age groups. Additionally, morphological features of non-ischemic and ischemic STE-ECGs can be similar.[33,34]

Although a specificity of the order of 97.5% is acceptable, our findings suggest value of ethnicity-specific modification of the current international STEMI thresholds (based predominantly on values from apparently healthy individuals from Western-European descent). Since we found a very high (20-30%) non-ischemic STE-ECG prevalence in apparently healthy male subjects originating from Ghana (Western Africa), and even higher

(>45%) when they prevail certain ECG characteristics, electrocardiographic myocardial infarction diagnostics are rather complicated. An additional approach may be comparing the acute ECG to an earlier-made non-acute ECG of the same patient, revealing whether the ST-elevation is pre-existent.[23,24] While biomarkers and echocardiography can assist inhospital ACS triage (although time consuming), the ECG is currently the only prehospital tool for ACS evaluation. Furthermore, the extremely low STE-ECG prevalence found predominantly in females and particularly in certain ethnic subgroups, could result in an undesirable high yield of false-negative STEMI diagnoses. Since their baseline value is low they have to develop a significant amount of ST-elevation to exceed the thresholds. Possibly, lowering thresholds in certain female subgroups (particularly ethnicity-dependent) could improve sensitivity.

Strengths and limitations

Our study demonstrates differences in the ethnicity-dependent prevalence of ECGs exceeding STEMI thresholds in electively-recorded ECGs in apparently healthy subjects. The scale of this study and the representation of six distinct ethnicities originating from South America, Western Africa, Northern Africa, Western Europe, Middle East and South Asia is, to our knowledge, not matched by earlier studies. Moreover, although ST amplitudes in different ethnicities were studied before,[12,14] a quantification of the problem of the exceeding of STEMI thresholds in these specific ethnicities and also the correlation with other ECG variables, has, to our knowledge, not been evaluated earlier. Additionally, this study was performed with high precision with respect to ECG assessment and subject evaluations.

Due to the inclusion of a relatively young population (Figure S1), the prevalence of STE-ECGs in subjects > 70 years was not investigated. Although, this study represents ethnicities from different areas in the world, many ethnicities remain to be investigated. Since Chinese do not form a substantial proportion of the Amsterdam population HELIUS, no Chinese subjects were included. In previous studies, Chinese were found to have even higher J point amplitudes than subjects from Sub-Saharan African descent,[6,11-13] although that difference was not significant in our "culprit" lead V4.[12] Despite our substantial efforts to exclude subjects with possible or current cardiovascular disease, possible subclinical disease may exist among our apparently healthy population. Our study also does not include ACS cases, therefore sensitivity of current STEMI thresholds remains unknown in these ethnicities. Routine registration of ethnic background, which is currently not allowed due to ethical issues, would facilitate the establishment of acute chest pain databases for multi-ethnic research. Moreover, this data is only relevant for health care professionals who work in an area with appreciable non Western-European patient populations. Finally, in accordance with the guidelines we used ST-amplitude criteria in isolation, but the ST morphology and other ECG features are also reviewed in clinical practice.

CONCLUSION

Although accurate identification of STEMI patients impacts prognosis, current STEMI thresholds are not ethnicity specific. We found a highly variable prevalence of ST-elevation ECGs exceeding STEMI thresholds in apparently healthy individuals across ethnicities, sexes and age groups. Putatively, when presenting with symptoms or signs possibly caused by acute myocardial ischemia, straightforward application of current international ST-elevation thresholds could result in diagnostic error, particularly in young males from Sub-Saharan African descent. Due to the high interindividual variability in pre-existing J-point amplitudes, current guidelines should be used with caution in subjects of certain age, sex and ethnicity and with specific ECG characteristics.

Acknowledgments: We are most grateful to the participants of the HELIUS study and the management team, research nurses, interviewers, research assistants and other staff who have taken part in gathering the data for this study and to prof. R.J. de Winter (Amsterdam UMC) for inspirational discussions.

Disclosures: None of the authors of this manuscript reported any disclosures.

REFERENCES

1. O'Gara PT, Kushner FG, Ascheim DD, *et al.* 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. Circulation. 2013;127:529-55.
2. Ibanez B, James S, Agewall S, *et al.* 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2017;39:119–177.
3. Eriksen UH, Molgaard H, Ingerslev J, *et al.* Fatal haemostatic complications due to thrombolytic therapy in patients falsely diagnosed as acute myocardial infarction. Eur Heart J. 1992;13:840-3.
4. Nahum LH, Mauro A, Levine H, *et al.* Potential field during the ST segment. J Appl Physiol. 1953;5:693-7.
5. Dellborg M, Herlitz J, Emanuelsson H, *et al.* ECG changes during myocardial ischemia. Differences between men and women. J Electrocardiol. 1994;27 Suppl:42-5.
6. Macfarlane PW. Age, sex, and the ST amplitude in health and disease. J Electrocardiol. 2001;34 Suppl:235-41.
7. Rijnbeek PR, van Herpen G, Bots ML, *et al.* Normal values of the electrocardiogram for ages 16-90 years. J Electrocardiol. 2014;47:914-21.
8. Hiss RG, Lamb LE and Allen MF. Electrocardiographic findings in 67,375 asymptomatic subjects. X. Normal values. Am J Cardiol. 1960;6:200-31.
9. Macfarlane PW, Browne D, Devine B, *et al.* Modification of ACC/ESC criteria for acute myocardial infarction. J Electrocardiol. 2004;37 Suppl:98-103.
10. Thygesen K, Alpert JS, Jaffe AS, *et al.* Fourth Universal Definition of Myocardial Infarction (2018). Circulation. 2018;138:e618-e651.
11. Wu J, Kors JA, Rijnbeek PR, *et al.* Normal limits of the electrocardiogram in Chinese subjects. Int J Cardiol. 2003;87:37-51.
12. Reddy VK, Gapstur SM, Prineas R, *et al.* Ethnic differences in ST height in the multiethnic study of atherosclerosis. Ann Noninvasive Electrocardiol. 2008;13:341-51.
13. Macfarlane PW, Katibi IA, Hamde ST, *et al.* Racial differences in the ECG--selected aspects. J Electrocardiol. 2014;47:809-14.
14. Rautaharju PM, Zhang ZM, Haisty WK, Jr., *et al.* Race- and sex-associated differences in rate-adjusted QT, QTpeak, ST elevation and other regional measures of repolarization: the Atherosclerosis Risk in Communities (ARIC) Study. J Electrocardiol. 2014;47:342-50.
15. McCabe JM, Armstrong EJ, Kulkarni A, *et al.* Prevalence and factors associated with false-positive ST-segment elevation myocardial infarction diagnoses at primary percutaneous coronary intervention-capable centers: a report from the Activate-SF registry. Arch Intern Med. 2012;172:864-71.
16. Shamim S, McCrary J, Wayne L, *et al.* Electrocardiograhic findings resulting in inappropriate cardiac catheterization laboratory activation for ST-segment elevation myocardial infarction. Cardiovasc Diagn Ther. 2014;4:215-23.
17. Cooper CJ, El-Shiekh RA, Cohen DJ, *et al.* Effect of transradial access on quality of life and cost of cardiac catheterization: A randomized comparison. Am Heart J. 1999;138:430-6.
18. Whitehead N, Williams T, Brienesse S, *et al.* Contemporary Trends in Stroke complicating Cardiac Catheterization. Intern Med J. 2019.
19. Iyengar SS and Godbole GS. Thrombolysis in the era of intervention. J Assoc Physicians India. 2011;59 Suppl:26-30.
20. Stronks K, Snijder MB, Peters RJ, *et al.* Unravelling the impact of ethnicity on health in Europe: the HELIUS study. BMC Public Health. 2013;13:402.
21. Snijder MB, Galenkamp H, Prins M, *et al.* Cohort profile: the Healthy Life in an Urban Setting (HELIUS) study in Amsterdam, The Netherlands. BMJ Open. 2017;7:e017873.
22. van Bemmel JH, Kors JA and van Herpen G. Methodology of the modular ECG analysis system MEANS. Methods Inf Med. 1990;29:346-53.
23. ter Haar CC, Maan AC, Schalij MJ, *et al.* Directionality and proportionality of the ST and ventricular gradient difference vectors during acute ischemia. J Electrocardiol. 2014;47:500-4.
24. ter Haar CC, Man SC, Maan AC, *et al.* Subtraction electrocardiography: Detection of ischemia-induced ST displacement without the need to identify the J point. J Electrocardiol. 2016;49:316-22.
25. Macfarlane PW, Antzelevitch C, Haissaguerre M, *et al.* The Early Repolarization Pattern: A Consensus Paper. J Am Coll Cardiol. 2015;66:470-7.
26. Clark EN, Katibi I and Macfarlane PW. Automatic detection of end QRS notching or slurring. J Electrocardiol. 2014;47:151-4.
27. Mancia G, Fagard R, Narkiewicz K, *et al.* 2013 ESH/ESC Practice Guidelines for the Management of Arterial Hypertension. Blood Press. 2014;23:3-16.

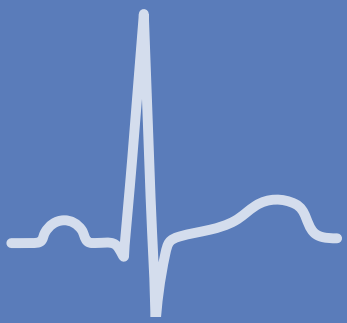
28. Bacharova L, Chen H, Estes EH, *et al.* Determinants of discrepancies in detection and comparison of the prognostic significance of left ventricular hypertrophy by electrocardiogram and cardiac magnetic resonance imaging. Am J Cardiol. 2015;115:515-22.
29. Kors JA, van Herpen G, Wu J, *et al.* Validation of a new computer program for Minnesota coding. J Electrocardiol. 1996;29 Suppl:83-8.
30. Rautaharju PM, Surawicz B, Gettes LS, *et al.* AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval. Circulation. 2009;119:e241-50.
31. Viskin S. The QT interval: too long, too short or just right. Heart Rhythm. 2009;6:711-5.
32. Man S, Rahmattulla C, Maan AC, *et al.* Acute coronary syndrome with a totally occluded culprit artery: relation of the ST injury vector with ST-elevation and non-ST elevation ECGs. J Electrocardiol. 2014;47:183-90.
33. Brady WJ, Perron AD and Chan T. Electrocardiographic ST-segment elevation: correct identification of acute myocardial infarction (AMI) and non-AMI syndromes by emergency physicians. Acad Emerg Med. 2001;8:349-60.
34. Bosson N, Sanko S, Stickney RE, *et al.* Causes of prehospital misinterpretations of ST elevation myocardial infarction. Prehosp Emerg Care. 2017;21:283-290.
35. Devereux RB and Reichek N. Repolarization abnormalities of left ventricular hypertrophy. Clinical, echocardiographic and hemodynamic correlates. J Electrocardiol. 1982;15:47-53.
36. Birnbaum Y and Alam M. LVH and the diagnosis of STEMI - how should we apply the current guidelines? J Electrocardiol. 2014;47:655-60.
37. Wagner NB, Sevilla DC, Krucoff MW, *et al.* Transient alterations of the QRS complex and ST segment during percutaneous transluminal balloon angioplasty of the left anterior descending coronary artery. Am J Cardiol. 1988;62:1038-42.
38. Surawicz B, Orr CM, Hermiller JB, *et al.* QRS changes during percutaneous transluminal coronary angioplasty and their possible mechanisms. J Am Coll Cardiol. 1997;30:452-8.
39. Postema PG and Wilde AA. Do J waves constitute a syndrome? J Electrocardiol. 2013;46:461-5.
40. Birnbaum Y. The burden of nonischemic ST-segment elevation. J Electrocardiol. 2007;40:6-9.
41. Demidova MM, Martin-Yebra A, van der Pals J, *et al.* Transient and rapid QRS-widening associated with a J-wave pattern predicts impending ventricular fibrillation in experimental myocardial infarction. Heart Rhythm. 2014;11:1195-201.

7

PART III.
Subtraction electrocardiography to detect myocardial ischemia

Chapter

8



Performance of ST and ventricular gradient difference vectors in electrocardiographic detection of acute myocardial ischemia

Roderick W. Treskes
C. Cato ter Haar
Sumche Man
Marjolein C. de Jongh
Arie C. Maan
Ron Wolterbeek
Martin J. Schalij
Galen S. Wagner
Cees A. Swenne

adapted from:
Journal of Electrocardiology
2015 Jul-Aug;48:498-504

ABSTRACT

Background

Serial analysis could improve ECG diagnosis of myocardial ischemia caused by acute coronary occlusion.

Methods

We analyzed ECG pairs of 84 cases and 398 controls. In case-patients, who underwent elective percutaneous coronary intervention, ischemic ECGs during balloon occlusion were compared with preceding non-ischemic ECGs. In control-patients, two elective non-ischemic ECGs were compared. In each ECG the ST vector at the J point and the ventricular gradient (VG) vector was computed, after which difference vectors ΔST and ΔVG were computed within patients. Finally, receiver operating characteristic analysis was done.

Results

Areas under the curve were 0.906 ($P < 0.001$; CI 0.862–0.949; SE 0.022) for ΔST and 0.880 ($P < 0.001$; CI 0.833–0.926; SE 0.024) for ΔVG. Sensitivity and specificity of conventional ST-elevation myocardial infarction (STEMI) criteria were 70.2% and 89.1%, respectively. At matched serial analysis specificity and STEMI specificity, serial analysis sensitivity was 78.6% for ΔST and 71.4% for ΔVG (not significantly different from STEMI sensitivity). At matched serial analysis sensitivity and STEMI sensitivity, serial analysis specificity was 96.5% for ΔST and 89.3% for ΔVG; ΔST and STEMI specificities differed significantly ($P < 0.001$).

Conclusion

Detection of acute myocardial ischemia by serial ECG analysis of ST and VG vectors has equal or even superior performance than the STEMI criteria. This concept should be further evaluated in triage ECGs of patients suspected from having acute myocardial ischemia.

INTRODUCTION

Myocardial infarction (MI) is typically caused by acute coronary occlusion (ACO), and its clinical outcome is primarily dependent upon the time elapsed between diagnosis and reperfusion therapy.[1] Best practice requires that the patient receives a standard 12-lead electrocardiogram (ECG) by emergency personnel, because "ST segment deviation" that meets guideline specified "STEMI criteria" is currently accepted for ACO diagnosis.[2] Although STEMI literally means "ST elevation", the deviation of the ST segment from the TP-segment baseline is a quantitative spatial difference, and therefore it may appear as either "elevation" or "depression" in individual ECG leads.[3] The criteria for the ST segment depression termed "STEMI equivalent" have been included in recent guidelines for diagnosis of ACO.[2]

The diagnosis of ACO should have high sensitivity, because a false negative diagnosis causes delayed access to acute reperfusion therapy, and consequently a potentially increased size of the infarcted area.[1] Also, this diagnosis should have high specificity, because of the high cost of activation of the acute coronary intervention laboratory.[4] However, clinical application of the STEMI criteria for optimal triage of an individual patient to acute reperfusion therapy is currently challenged by both their limited sensitivity and specificity. The ST segment deviation of ACO may be insufficient to reach the STEMI criteria threshold, especially in women,[5] whereas many other acute and chronic conditions can also cause these changes.[4] Also, pre-existing non-zero ST amplitudes are confounders for STEMI classification. Serial ECG analysis by comparison of the acute ECG with the individual's previous non-ischemic ECG could potentially facilitate a higher accuracy for the diagnosis of ACO, and is favored by the guidelines,[6] however, without describing a comparison procedure.

Serial analysis aims to detect changes instead of momentary values. This is a potential solution for ECGs of patients who have ST deviations in their baseline ECG. In the situation of acute ischemia due to ACO, the momentary ST deviations are then the result of the acute ischemic changes plus the pre-existing ST deviations. Differential analysis by serial comparison of the acute ECG and a previous ECG without acute ischemia that serves as a reference could help to reveal the ischemic component of the ST deviation. Because of that, the detection thresholds for the changes can be lower than the detection thresholds for momentary values.

A previous study has shown that serial ECG analysis can potentially improve the sensitivity of acute ischemia detection.[7] This study included 84 clinically stable patients undergoing elective PCI with an ECG recorded hours before elective PCI (baseline ECG), and an ECG recorded during balloon inflation (occlusion ECG). Vectorcardiographic ST vectors were calculated in the baseline and occlusion ECGs and then used to determine the ST difference vector. Depending on the threshold value for the difference vector magnitude, the sensitivity of differential ischemia detection outperformed consideration of the ST segment deviation during balloon occlusion alone with the conventional threshold of 100 μV. Also, serial analysis of the ventricular gradient (the spatial integrals of the heart vector over the QT interval) yielded better sensitivity than STEMI criteria.[7]

However, in the previous study, only patients with an ACO were studied. All patients were therefore true positives. Detection thresholds were suggested on the basis of earlier studies,[8] which concluded that ST vector differences of 50 μV could possibly be used when serial analysis was available. However, detection thresholds are always a compromise between sensitivity and specificity. Because a control group was lacking in the previous study, this compromise could not be determined.[7] It is therefore the purpose of this study to find the compromise between sensitivity and specificity of serial ECG vector analysis for acute myocardial ischemia detection, and to determine the concurrent ST and VG difference vector thresholds. The current study also serves as a pilot study for later real-world investigations in triage ECGs of patients suspected from ACO.

METHODS

Study group, controls

To determine specificity, a group of patients was selected who had no myocardial ischemia during their ECG recordings, thereby serving as controls. The ECGs of these patients were retrospectively selected from the Leiden University Medical Center ECG database, founded in 1986 and now comprising more than 800,000 standard 10-second 12-lead resting ECGs. Only elective ECGs made in the outpatient clinic were selected; ECGs made in the emergency department or during hospital admission were not included. Further requirements were an acceptable technical quality of the ECG and presence of regular sinus rhythm. ECGs with arrhythmias or with paced beats were excluded.

A computer algorithm searched the database for patients who had two suitable ECGs that were made 1–2 years apart in time. To ascertain clinical stability, such ECG pairs were only selected 1) if there was no other ECG made within a 1-year period immediately preceding the first ECG of the pair, 2) if there was no ECG made within the time interval formed by the selected ECG pair, and 3) if there was no mentioning in the patient file of any clinical event in the year before the first ECG of the selected pair or within the time interval formed by the selected ECG pair.

All selected ECGs were analyzed by the Leiden ECG Analysis and Decomposition Software (LEADS),[9] described in more detail in the ECG analysis section below. Main cardiologic diagnoses were noted and were divided in categories that are listed in Table 1 in the Results section. A total of 398 control patients were included.

Study group, cases

To determine sensitivity, the results from a previous study by Ter Haar *et al.*[7] were used. Details about this study population and the inclusion and exclusion criteria have been previously described.[7,10] Briefly, the database consists of patients who underwent elective PCI with long balloon inflation times and therefore had a completely occluded coronary artery during several minutes (cases). This database is called the STAFF database and was created from 1995 till 1996, before stenting became available.[11] Each patient had two long ECGs made. One ECG was made prior to PCI when the patient was in stable condition ("baseline ECG"). The other ECG was made during balloon inflation ("occlusion-ECG") when the patient had a completely occluded culprit artery. For each patient, a stable,

representative 10-s ECG was selected in the baseline ECG, and a 10-s ECG was selected after 3 minutes of balloon occlusion. A pair of control and occlusion ECGs could be obtained in 84 patients in the STAFF database.

ECG analysis

General: All analyzed ECGs were interpreted by the Glasgow ECG Analysis Program,[12] and categorized into abnormal or normal with respect to P wave, AV conduction, frontal QRS axis, QRS duration, QT interval, QRS amplitude, ST segment and T wave.

Serial comparison of the ST segment and ventricular gradient vectors: The ECGs of the 398 patients in control population and of the 84 patients in the cases population were analyzed by the Leiden ECG Analysis and Decomposition Software (LEADS) program. This MATLAB program takes the following steps in analyzing ECGs:

1. A 3-lead vectorcardiogram (VCG) is synthesized out of a 12-lead electrocardiogram (ECG) using the Kors matrix.[13]
2. Ectopic beats or beats of bad technical quality are automatically and/or manually rejected.
3. An averaged beat is computed.
4. The QRS onset, J-point and T-wave offset are automatically determined. The QRS onset is automatically determined by the first detectable deflection of the heart vector from the PQ-segment baseline. The J point is automatically localized at the instant where the heart vector between the QRS complex and the T wave reaches its minimum value. The offset of the T wave is localized in the vector magnitude signal as the time instant where the tangent to the point with the steepest slope of the descending limb of the T wave intersects the baseline.
5. The automatically determined QRST onset, J point and T wave offset time instants were then manually verified by two observers (RWT and CAS) and when necessary corrected (*e.g.*, in case of notches and slurs at the J point, or in case of a low-amplitude or odd-shaped T wave. Nearly always, small corrections were made in the J point localization, as we adopted the Minnesota procedure[14] for this study. LEADS facilitates a very accurate manual adjustment of the J point by offering the analyst a cross-hair cursor adjustment procedure in an enlarged view of the superimposed 12 ECG leads.
6. LEADS computes magnitude, azimuth and elevation of ST vectors in the average beat. Furthermore, it computes the QRST integral vector, which equals, by definition, the ventricular gradient vector (VG). The computation of the VG out of a vectorcardiogram is illustrated in Figures 1 and 2.

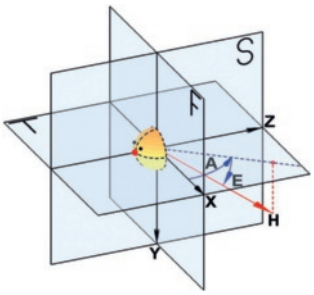


FIGURE 1. Graphical representation of vectorcardiographic conventions, from Man *et al.*,[16] with permission. F = frontal plane; S = sagittal plane; T = transversal plane; X = vectorcardiographic x-axis; Y = vectorcardiographic y-axis; Z = vectorcardiographic z-axis; A = azimuth; E = elevation; H = heart vector. The directions of the x-, y-, and z-axes (the x-axis pointing leftwards, the y-axis pointing downward and the z-axis pointing backward) are according to the AHA standard.[1] An arbitrary heart vector, H (drawn in red) is chosen as an example. The angle between the x-axis and the projection of the heart vector in the transversal plane (blue dotted line) is the azimuth. The angle between the blue dotted line and the heart vector is the elevation.[16]

After ST and VG had been determined in both the first and the second ECGs of each ECG pair, the ST and VG difference vectors, ΔST and ΔVG, were calculated.

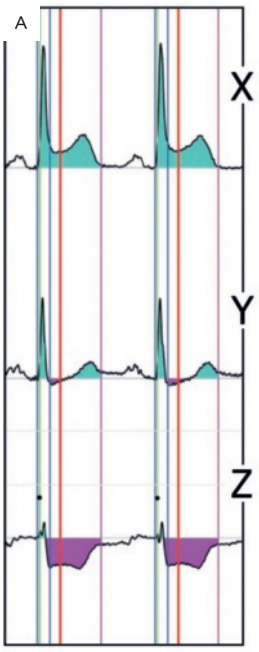
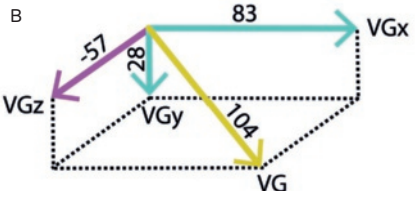


FIGURE 2. Illustration of the computation of the ventricular gradient, from Ter Haar *et al.*,[7] with permission.
X = x-axis of the vectorcardiogram
Y = y-axis
Z = z-axis.
Panel A depicts a vectorcardiogram, synthesized from a 12-lead 10-s ECG during balloon inflation, in which the patient had a completely occluded culprit artery. This vectorcardiogram consists of three leads: X, Y and Z. The time markers indicate onset QRS, the J points, J point + 60 ms and end of the T wave. In these leads, the areas under the curve from onset QRS to the end of the T wave are measured. Positive amplitudes in the area contribute positively to the area and negative amplitudes contribute negatively to the area. In this example, the net areas under the curve in lead X and lead Y are positive and the net area under the curve in lead Z is negative. These areas constitute the x-, y- and z-components of the VG vector, as shown in Panel B. Vector components VGx and VGy point in the same direction as the corresponding lead axes of the vectorcardiogram, because of the positive net areas under the curve. Vector component VGz points in the opposite direction of the corresponding lead axis of the vectorcardiogram, because of the negative net area under the curve. Vectorial summation of the three vector components VGx, VGy and VGz yields the resultant VG vector.[7]



STEMI criteria: STEMI criteria were applied to the second ECGs of the 398 controls, and to the 84 cases in the STAFF database. An ECG was classified as STEMI when two contiguous leads showed ST elevation of ≥ 0.1 mV, except for leads V2 and V3, which had to show elevation of ≥ 0.2 mV to be classified as STEMI, or when lead V2 and V3 showed ST depression of ≥ 0.05 mV (STEMI equivalent).[2]

STEMI sensitivity was computed as the fraction of the occlusion ECGs that met the STEMI criteria. STEMI specificity was computed as 1 minus the fraction of non-ischemic ECGs that met the STEMI criteria.

ROC analysis

The ΔST and ΔVG values measured in the total study population consisting of 398 controls and 84 cases were used to construct two receiver operating characteristics (ROCs) for the detection of ischemic changes between the two ECGs of each patient. To construct the ΔST ROC, ECGs were classified as ischemic when ΔST was larger than the threshold that was varied along the ROC. To construct the ΔVG ROC, ECGs were classified as ischemic when ΔVG was larger than the threshold that was varied along the ROC. After the ROCs were constructed, ROC analysis was done by computing the area under the curve (AUC) and by computing the statistical significance of the difference between the AUC and 0.5 (random performance).

Comparison of the ΔST and ΔVG ROCs and the STEMI classification performance

Finally we compared the performance of the ischemia classification by either ΔST or ΔVG with the STEMI analysis. To compare the ΔST and ΔVG sensitivities with the STEMI sensitivity, we computed the sensitivities in the ΔST and ΔVG ROCs at the STEMI specificity. To compare the ΔST and ΔVG specificities with the STEMI specificity, we computed the specificities in the ΔST and ΔVG ROCs at the STEMI sensitivity.

Statistical analysis

We used SPSS (IMB Corp. Released 2014. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) to perform a Receiver Operating Analysis. "Acute Ischemia" was set as state variable, while ΔST and ΔVG were set as "test variable". MedCalc (MedCalc Software, Ostend, Belgium) was used to test if the two ROC curves were statistically different. Finally, SPSS was used to calculate if the sensitivity and specificity of the STEMI criteria and the ΔST differed significantly, using a McNemar's test.

RESULTS

A number of 398 clinically stable patients were studied as controls. The average age of these patients was 57 years, with a 16.6 standard deviation; 64% was male. Mean BMI was 26.4 kg·m2, which means that a slightly overweight population was studied (Table 1).

	N	%
N	398	
Age (years)	57 ± 16.6	
Sex (male/female)	254/144	64/36
BMI (kg·m^2)	26	32

TABLE 1. Patient characteristics of the controls.

All controls had at least one clinical diagnosis. Systemic hypertension was most prevalent, affecting 28.4% of the population. Second and third most prevalent were valvular heart disease and arrhythmias, present in 26.9% and 26.4% of the population respectively. The prevalences of all noted diagnoses are shown in Table 2.

Diagnosis	*N*	%
Systemic hypertension	113	28.4
Valvular heart disease	107	26.9
Arrhythmia	105	26.4
Myocardial infarction	81	20.4
Conduction disorders	65	16.3
Stable angina	64	16.1
Non-ischemic cardiomyopathy	63	15.8
M. Marfan	56	14.1
Diabetes mellitus	54	13.6
Non-cardiac diagnoses	24	6.0
Heart failure	11	2.8
Pulmonary hypertension	7	1.8

TABLE 2. Prevalence of diagnoses in the controls. The sum of the diagnoses exceeds the number of patients in the controls, because more than one diagnosis can apply to a single patient. *N* = number of patients.

According to the Glasgow ECG interpretation program, 445/796 (55.9%) of the ECGs were classified as abnormal or borderline abnormal; 20.4% of all ECGs were classified as having an abnormal ST segment. An overview of ECG abnormalties is given in Table 3.

Category of ECG abnormality	*N*	%
Sinus tachycardia or sinus bradycardia	239	30.0
Abnormal P wave	66	8.3
Abnormal AV conduction	107	13.4
Abnormal frontal QRS axis	157	19.7
Prolonged QRS duration	168	21.1
High QRS amplitude	47	5.9
Abnormal ST segment	162	20.4
Abnormal T wave	223	28.0
Long QT	19	2.4
Abnormal or borderline abnormal ECG	445	55.9

TABLE 3. Major categories of ECG abnormalities in the 796 ECGs of the 398 controls, according to the Glasgow ECG interpretation program.
N = number of patients.

A number of 84 patients were studied as cases. The average age of all cases was 60 years, with an 11-year standard deviation; 64% of all patients were male.

The area under the curve (AUC) of the ΔST ROC was 0.906 (P < 0.001; CI 0.862–0.949; SE 0.022). The AUC for the ΔVG ROC was 0.880 (P < 0.001; CI 0.833–0.926; SE 0.024). The ROC curves were shown not to be statistically significant (ΔAUC 0.0263, 95% CI − 0.0114 to 0.0640, P = 0.1712). The ROCs are both shown in Figure 3.

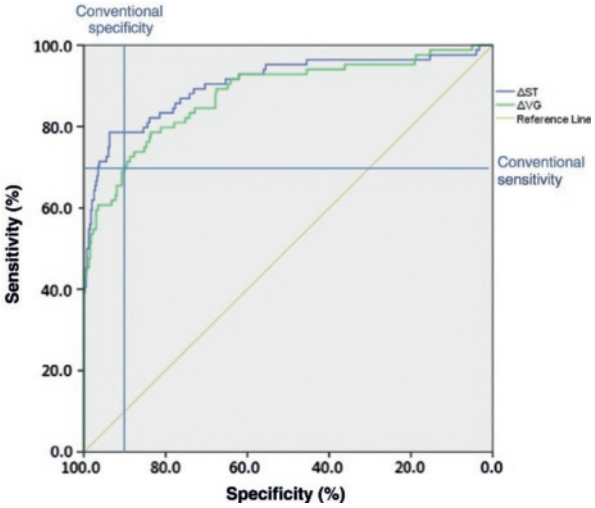


FIGURE 3. ROCs derived from ΔST (blue) and from ΔVG (green). The horizontal and vertical lines indicate the sensitivity and the specificity of the STEMI criteria, respectively. Sensitivity and specificity of the conventional ST-elevation myocardial infarction (STEMI) criteria were 70.2% and 89.1%, respectively.

When matching serial analysis specificity with STEMI specificity, serial analysis sensitivity was 78.6% for ΔST and 71.4% for ΔVG, the ΔST and STEMI sensitivities did not differ significantly (P = 0.143, McNemar's test). At matched specificity, the ischemia detection thresholds of ΔST and of ΔVG were 57.5 μV and 25.8 mV·ms, respectively.

When matching serial analysis sensitivity with STEMI sensitivity, serial analysis specificity was 96.5% for ΔST and 89.3% for ΔVG, the ΔST and STEMI specificities differed significantly ($P < 0.001$, McNemar's test). At matched STEMI sensitivity, the ischemia detection thresholds of ΔST and of ΔVG were 77.7 μV and 26.1 mV·ms, respectively.

The results are given in Tables 4 and 5. A scatterplot of ΔST and corresponding ΔVG of all patients (both cases and controls) is given in Figure 4.

	Sensitivity (%)	Threshold, derived from ROC
STEMI criteria	70.2	
ΔST	78.6	57.5 μV
ΔVG	71.4	25.8 mV·ms

TABLE 4. Comparison of the sensitivity of the STEMI criteria and of ΔST and ΔVG ischemia detection when specificity of ΔST and ΔVG ischemia detection is matched with STEMI specificity (89.1%). The corresponding ΔST and ΔVG thresholds are in the third column. There were no statistically significant differences between ΔST and ΔVG sensitivity and STEMI sensitivity.

	Specificity (%)	Threshold, derived from ROC
STEMI criteria	89.1	
ΔST	96.5*	77.7 μV
ΔVG	89.3	26.1 mV·ms

TABLE 5. Specificity of the STEMI criteria and specificity of ΔST and ΔVG ischemia detection when sensitivity of ΔST and ΔVG ischemia detection is matched with STEMI sensitivity (70.2%). The corresponding ΔST and ΔVG thresholds are in the third column.
*ΔST specificity differed significantly from STEMI specificity ($P < 0.001$).

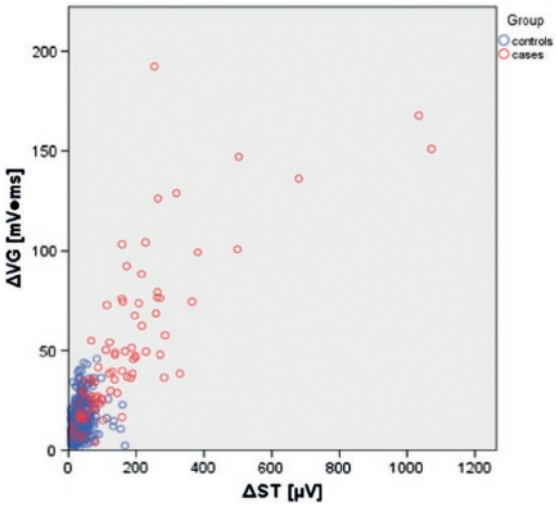


FIGURE 4. Scatterplot of the ΔST and corresponding ΔVG values of both cases (red) and controls (blue).

DISCUSSION

The results of our study showed that serial analysis of ST vectors yielded a significantly higher specificity than the STEMI criteria, while there was no significant difference in sensitivity between serial analysis of ST vectors and STEMI criteria, in spite of the fact that the difference in sensitivity, 8.4% (serial: 78.6%; STEMI: 70.2%) was larger than the difference in specificity, 7.4% (serial: 96.5%; STEMI: 89.1%). Obviously, this was caused by the difference between the control group and case group sizes (398 and 84 patients, respectively). A larger group of case patients would likely have yielded a significantly better sensitivity as well. We feel that potential diagnostic improvements in both sensitivity and specificity in the order of magnitude of 8% are clinically relevant, and that further research should follow in order to demonstrate that such improvements can be attained in the "real world" (here: the setting of patients with acute chest pain suspected of having acute coronary syndrome). Admittedly, our current study groups are insufficiently representative.

The practical use of this type of difference analysis requires not only an additional, previous, ECG, but also computerized analysis. Although the difference in ST, ΔST, seems intuitive, it cannot be eyeballed from the 12-lead ECG because of the complexity of the computation of the heart vector. The ventricular gradient is even more complicated as this involves integration (area under the QRST curve). Technical artifacts can hamper this computerized analysis. However, if about 30% to 40% of the beats are of good technical quality, the computer program can make an adequate calculation of the ΔST and ΔVG vectors by only including these good quality beats.

The ventricular gradient did not really perform better than the STEMI criteria, but we should realize that the ventricular gradient is independent of conduction,[15] and that it is expected to work equally well in patients who have either pre-existent or acute conduction disturbances. In that case, the STEMI criteria cannot be applied, and also the ΔST vector cannot be computed, because the J point is lacking. In those situations the ventricular gradient could be an alternative. Due to the composition of the current study group we have not been able to test this hypothesis, but the data generated by our study prompt for a study in patients with conduction disturbances to assess the potential of the ventricular gradient for ischemia detection.

Several limitations of our study need to be mentioned. One limitation of serial ECG analysis is that it requires a previously made, non-acute resting ECG. Patients that are admitted to the hospital with symptoms of myocardial infarction but without a reference ECG cannot be triaged using this method. However, patients with myocardial infarction often do have a history of stable angina, for which they are followed up by their physician at least once a year including a reference ECG. Many patients will therefore have a previously made non-ischemic resting ECG. In addition, due to increasing technical possibilities it is likely that patients will in the nearby future be able to collect a resting ECG by themselves, which can be collected in a digital patient file, thereby providing a reference ECG for serial ECG analysis. Secondly, all patients in the non-ischemic population were clinically stable. Patients with other acute causes of ST elevation and chest pain (*e.g.*, pericarditis and myocarditis) were

not included in the study. Such conditions could lead to false positive detection of acute ischemia, although it must be realized that ST elevation in many ECG leads gives a relatively small ST vector, due to the cancellation effect. Thirdly, all patients in the ischemic population had a completely occluded artery due to balloon inflation. However, balloon inflation is a too static simulation of ACO, that is caused by a thrombus or a vasospasm. Thrombi can resolve partly or completely, while vasospasms can be temporarily. Therefore, in the prehospital phase, it depends on what time exactly the acute ECG is taken whether it will detect acute ischemia. Because of these limitations, the sensitivity and the specificity shown in the ROC might be too optimistic. Further research in the prehospital phase to corroborate the diagnostic performance of ΔST and ΔVG to detect myocardial ischemia is therefore needed, in which special attention is paid to confounders of ST elevation, for example early repolarization pattern, pericarditis and left ventricular hypertrophy.

Summarizing, we studied differential ECG analysis in ECG pairs of cases and controls, and all second ECGs of the case patients were made under conditions of acute coronary occlusion. These data facilitated a comparison of conventional STEMI ischemia diagnosis and acute myocardial ischemia diagnosis by serial comparison. We found that serial comparison had similar performance to (for ΔVG) or better (for ΔST) performance than STEMI ischemia diagnosis. These results suggest that serial ECG analysis for acute myocardial ischemia detection is feasible, but this should be confirmed in realistic patient cohorts in the setting of spontaneous acute coronary occlusion. Our study was done with the perspective to be able to deal with situations in which STEMI analysis is hampered, either by nonzero baseline ST deviations, or by absence of a J point, which completely disables ST analysis for ischemia detection. In that case, differential ECG analysis using the ventricular gradient would be a potential solution. These specific patient groups should explicitly be dealt with in future research. Our study was done as an initial feasibility study for serial ECG analysis for acute myocardial ischemia detection, and its positive outcome favors further exploration of this concept.

CONCLUSION

ROC analysis of the performance of both ΔST and ΔVG and comparison with the performance of conventional STEMI ischemia diagnosis suggests that serial ECG analysis of ST and VG vectors to detect acute myocardial ischemia is feasible and has either equal performance to or even superior performance than the conventional method. This concept should be further evaluated in triage ECGs of patients suspected from having acute myocardial ischemia. Specifically, serial ECG analysis for ischemia detection should be studied in patients with conditions that hamper conventional STEMI diagnosis (patients with pre-existing nonzero ST deviations, and patients in whom during ischemia no J point can be determined).

Conflict of interest: None declared.

Financial support: None declared.

REFERENCES

1. Armstrong PW, Wagner G, Goodman SG, *et al.* ST segment resolution in ASSENT 3: insights into the role of three different treatment strategies for acute myocardial infarction. Eur Heart J. 2003;24:1515-22.
2. Wagner GS, Macfarlane P, Wellens H, *et al.* AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part VI: acute ischemia/infarction. Circulation. 2009;119:e262-70.
3. Martin TN, Groenning BA, Murray HM, *et al.* ST-segment deviation analysis of the admission 12-lead electrocardiogram as an aid to early diagnosis of acute myocardial infarction with a cardiac magnetic resonance imaging gold standard. J Am Coll Cardiol. 2007;50:1021-8.
4. Jayroe JB, Spodick DH, Nikus K, *et al.* Differentiating ST elevation myocardial infarction and nonischemic causes of ST elevation by analyzing the presenting electrocardiogram. Am J Cardiol. 2009;103:301-6.
5. Maynard C, Selker HP, Beshansky JR, *et al.* The exclusion of women from clinical trials of thrombolytic therapy: implications for developing the thrombolytic predictive instrument database. Med Decis Making. 1995;15:38-43.
6. Steg P, James S, Atar D, *et al.* ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012;33:2569-619.
7. ter Haar CC, Maan AC, Warren SG, *et al.* Difference vectors to describe dynamics of the ST segment and the ventricular gradient in acute ischemia. J Electrocardiol. 2013;46:302-11.
8. Jensen SM, Johansson G, Osterman G, *et al.* On-line computerized vectorcardiography monitoring of myocardial ischemia during coronary angioplasty: comparison with 12-lead electrocardiography. Coron Artery Dis. 1994;5:507-14.
9. Draisma HHM, Swenne CA, van de Vooren H, *et al.* LEADS: An Interactive Research Oriented ECG/VCG Analysis System. Computers in Cardiology. 2005:515-518.
10. ter Haar CC, Maan AC, Schalij MJ, *et al.* Directionality and proportionality of the ST and ventricular gradient difference vectors during acute ischemia. J Electrocardiol. 2014;47:500-4.
11. Warren SG and Wagner GS. The STAFF studies of the first 5 minutes of percutaneous coronary angioplasty balloon occlusion in man. J Electrocardiol. 2014;47:402-7.
12. Macfarlane PW, Devine B, Latif S, *et al.* Methodology of ECG interpretation in the Glasgow program. Methods Inf Med. 1990;29:354-61.
13. Kors JA, van Herpen G, Sittig AC, *et al.* Reconstruction of the Frank vectorcardiogram from standard electrocardiographic leads: diagnostic comparison of different methods. Eur Heart J. 1990;11:1083-92.
14. Prineas R, Crow R and Zhang Z. The Minnesota code manual of electrocardiograhic findings. 2nd ed: Springer; 2010.
15. Burger HC. A theoretical elucidation of the notion ventricular gradient. Am Heart J. 1957;53:240-6.
16. Man S, Rahmattulla C, Maan AC, *et al.* Acute coronary syndrome with a totally occluded culprit artery: relation of the ST injury vector with ST-elevation and non-ST elevation ECGs. J Electrocardiol. 2014;47:183-90.

Chapter

9

An initial exploration of subtraction electrocardiography to detect myocardial ischemia in the prehospital setting

C. Cato ter Haar
Ron J.G. Peters
Jan Bosch
Agnese Sbrollini
Sophia Gripenstedt
Rob Adams
Eduard Bleijenberg
Charles J.H.J. Kirchhof
Reza Alizadeh Dehnavi
Laura Burattini
Robbert J. de Winter
Peter W. Macfarlane
Pieter G. Postema
Sumche Man
Roderick W.C. Scherptong
Martin J. Schalij
Arie C. Maan
Cees A. Swenne

Submitted

ABSTRACT

Background

In the prehospital triage of patients presenting with symptoms suggestive of acute myocardial ischemia, reliable myocardial ischemia detection in the electrocardiogram (ECG) is pivotal. Due to large interindividual variability and overlap between ischemic and non-ischemic ECG patterns, incorporation of a previous elective (reference) ECG may improve accuracy. The aim of the current study was to explore the potential value of serial ECG analysis using subtraction electrocardiography.

Methods

SUBTRACT is a multicenter retrospective observational study, including patients who were prehospitally evaluated for acute myocardial ischemia. For each patient an elective previously-recorded reference ECG was subtracted from the ambulance ECG. Patients were classified as myocardial ischemia cases or controls, based on the in-hospital diagnosis. The diagnostic performance of subtraction electrocardiography was tested using logistic regression of 28 variables describing the differences between the reference and ambulance ECGs. The Uni-G ECG Analysis Program was used for state-of-the-art single ECG interpretation of the ambulance ECG.

Results

In 1,229 patients, the mean area-under-the-curve of subtraction electrocardiography was 0.80 (95%CI: 0.77-0.82). The performance of our new method was comparable to single ECG analysis using the Uni-G algorithm: sensitivities were 66% vs 67% (*P*-value > 0.05), respectively; specificities were 80% vs 81% (*P*-value > 0.05), respectively.

Conclusions

In our initial exploration, the diagnostic performance of subtraction electrocardiography for the detection of acute myocardial ischemia proved equal to that of state-of-the-art automated single ECG analysis by the Uni-G algorithm. Possibly, refinement of both algorithms, or even integration of the two, could surpass current electrocardiographic myocardial ischemia detection.

INTRODUCTION

Accurate prehospital triage of patients presenting with symptoms suggestive of acute myocardial ischemia is crucial. Any diagnosis involving myocardial ischemia necessitates rapid transport to a hospital for treatment of the underlying cause in order to salvage as much myocardium as possible.[1,2] In contrast, inaccurate triage could result in flooding of emergency/cardiology departments, performing unnecessary urgent catheterization and/or and administering potentially hazardous thrombolytics. Prehospital clinical decision making requires reliable myocardial ischemia detection. Although biomarkers, *e.g.*, troponins, are widely used to assess myocardial ischemia, biomarkers are not always reliable in this early stage of ischemia and take time to process. In contrast, the electrocardiogram (ECG) is easily acquirable and directly interpretable and is therefore considered the key objective prehospital diagnostic tool for myocardial ischemia detection.

Usually, and according to the guidelines,[1,2] the ECG is evaluated for signs of ST elevation or depression measured at the J point. Although J-amplitude deviations often accompany myocardial ischemia, ischemia-induced myocardial action potential changes create injury currents during all phases of the cardiac cycle[3] leading to ECG changes throughout the QRST complex.[4-6] J-point restricted electrocardiographic criteria could therefore gravely affect diagnostic accuracy, even in patients with completely acutely occluded coronary arteries.[7-9]

Unfortunately, signs of ischemia in the QRS complex and in the T wave cannot readily be detected due to the wide ranges of normal values which can overlap with ischemic changes.[10,11] Additionally, non-acute pathology, *e.g.*, left ventricular aneurysm, can severely alter the ECG. Indeed, considerable overlap of even J-point amplitudes exists between ischemic and non-ischemic ECGs.[12] Consequently, ischemia detection in the entire QRST complex, including the J point, without knowing the pre-existing ECG of the patient can be incorrect. A serial approach, *i.e.*, comparing the current ECG to a previously-acquired ECG, corrects for interindividual variability thus revealing the actual intra-individual ischemic changes, and is, indeed, recommended by the guidelines.[1,2]

In the context of serial ECG analysis, we earlier proposed subtraction electrocardiography,[13,14] analysis of the differences between an acute and a previously-made non-acute ECG from the same patient. This method uses several ECG features, ECG difference descriptors, *e.g.*, the ST and ventricular gradient (VG) difference vectors. These variables have shown promising results for ischemia detection.[13-15] In this study, we hypothesize that subtraction electrocardiography can serve as an alternative for, or can have additional value to conventional analysis of the acute ECG alone. Our present study explores the diagnostic value of subtraction electrocardiography for the detection of myocardial ischemia in the prehospital setting.

METHODS

Study design

The current research is part of the SUBTRACT study, a multicenter retrospective observational study with the objective of exploring subtraction electrocardiography for the detection of myocardial ischemia in the prehospital phase. This study was conducted in two emergency medical services (EMS) regions in which four hospitals participated. The study protocol has been approved by the medical ethical committees (METCs) of the academic hospitals, the AMC and the LUMC, and by the boards of directors of the other centers.

Study population and collected data

The study population consists of patients at least 18 years old, who were urgently attended by one of the participating EMSs, and in whom an ambulance ECG was recorded for ruling-in or ruling-out myocardial ischemia. Further inclusion criteria were: transport to one of the participating hospitals, and availability of an elective previously-recorded non-acute ECG in one of the ECG databases of the participating hospitals, to serve as a reference ECG. For each patient, a data set was collected consisting of all ECGs recorded during the ambulance visit/ride, the most recent usable (see Exclusion criteria) reference ECG, symptoms at EMS presentation, and clinical data from the admission (diagnoses, laboratory values, imaging results).

Exclusion criteria

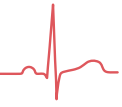
ECGs with poor signal quality, without a regular supraventricular rhythm or with atrial flutter, and also ambulance ECGs that could not be processed (*e.g.*, in case of suspected lead interchange) by the University of Glasgow (Uni-G) ECG Analysis Program,[16] were not analyzed. Patients were excluded in case of insufficient information, *e.g.*, due to death before a reliable diagnosis could be established. Patients with a major cardiac event, *e.g.*, open-heart surgery or myocardial infarction, between the recording dates of the ambulance and reference ECGs were excluded. Finally, if a patient had multiple ambulance visits by the EMS during the study period, only data regarding the most recent visit were included.

Clinical diagnosis

From the medical records (admission and discharge letter), we extracted the clinical diagnosis, which was based on the entire assessment of the patient by the attending physician. We defined the clinical diagnosis as the diagnosis explaining the symptoms at presentation to the EMS. This diagnosis is often the same as the initial diagnosis at admission, but can be altered because of additional diagnostics performed after the initial assessment.

Discrimination of myocardial-ischemia cases and controls

To retrospectively assess the presence or absence of myocardial ischemia at the time of recording of the ambulance ECG, we defined and applied a myocardial ischemia classification algorithm. The myocardial ischemia classification algorithm aims to retrospectively assess the likelihood of the presence of myocardial ischemia at the



time of recording of the ambulance ECG, without using the ambulance ECG itself. The algorithm is based on interpretation of the clinical in-hospital data, with the purpose of retrospectively constructing the prehospital scenario. For instance, when clinically necrosis has convincingly been demonstrated, we estimate a high likelihood of the presence of myocardial ischemia during the immediately preceding prehospital episode. In contrast, if cardiac decompensation is diagnosed accompanied by slightly elevated troponin levels, the presence of myocardial ischemia during the immediately preceding prehospital episode, is less likely, although probable. For this purpose, the algorithm uses a 5-point scale, ranging from likely ischemic, probably ischemic, uncertain, probably non-ischemic to likely non-ischemic. The algorithm does not make use of the properties of the ambulance ECG itself, but is based on data from the subsequent hospital admission: on the clinical diagnosis, and additionally, insofar as available and relevant, on troponin samples and on cardiac imaging data. Of note, this ischemia classification algorithm does not distinguish between the supposed mechanism of ischemia.[17] In addition, the algorithm does not estimate the amount of ischemia, only its presence or absence in the ambulance ECG. Because our study is a retrospective observational multicenter study, troponin samples were obtained and interpreted according to the local protocols of the participating hospitals. Since troponin levels are affected by renal function,[18] we applied a linear correction.[19] The myocardial ischemia classification algorithm, which is a systematic description including examples, is provided below.

- Classification "Likely ischemic": clinical diagnoses where either necrosis is inherent to the diagnosis, *e.g.*, STEMI or NSTEMI (*i.e.*, myocardial infarction), or if the diagnosis could involve myocardial ischemia, *e.g.*, pulmonary embolism, in combination with supporting evidence for myocardial necrosis (elevated troponin levels and/or positive cardiac imaging).[20]
- Classification "Probably ischemic": clinical diagnoses that could involve myocardial ischemia, in combination with troponin levels or imaging results that are slightly, but not clearly, pointing in the direction of myocardial necrosis, *e.g.*, cardiac decompensation with moderately elevated troponin levels.[21]
- Classification "Uncertain": assigned in case of insufficient diagnostics, or if the actual occurrence of ischemia during the recording of the ambulance ECG remains unknown due to presumed fluctuations in myocardial perfusion, *e.g.*, with the diagnosis of unstable angina pectoris.[22]
- Classification "Probably non-ischemic": clinical diagnoses that could be associated with myocardial ischemia, but neither troponin levels nor cardiac imaging results were available to definitely exclude myocardial ischemia, *e.g.*, severe pneumothorax,[23] with a single non-representative low troponin level; in this case myocardial ischemia cannot be excluded, and hence the resulting classification is "probably non-ischemic".
- Classification "Likely non-ischemic": clinical diagnoses which are not associated with myocardial ischemia, *e.g.*, hyperventilation syndrome,[24] or possibly associated with myocardial ischemia but for which there is no support by the troponin levels and/or imaging, *e.g.*, cardiac decompensation with negative representative troponin levels.[21]

In case of multiple diagnoses in one patient, the diagnosis with the highest probability of causing myocardial ischemia was used for our ischemia classification algorithm.

For the current study, we combined the patients with classifications "Likely ischemic" or "Probably ischemic" as cases and the patients with classifications "Likely non-ischemic" or "Probably non-ischemic" as controls. Hence, patients with the classification "Uncertain" were excluded since it was impossible to decide about the presence or absence of myocardial ischemia at the moment of the ambulance ECG recording.

ECG processing

ECGs (10 seconds, 12 leads) were obtained as raw (unfiltered) data. Ambulance ECGs (recorded with the LIFEPAK 12, Physio-Control, now part of Stryker) were extracted from the EMS databases. Reference ECGs were acquired from the ECG databases of the participating hospitals, recorded by different electrocardiographs (GE, Schiller, Mortara, Siemens/Dräger). Before further processing, ambulance ECGs (recorded with Mason-Likar electrode positions) were converted to standard 12-lead ECGs with the Leiden matrix.[25]

ECG analysis

LEADS program

All ECGs were analyzed by the LEADS program.[26] This software synthesizes a vectorcardiogram of the averaged dominant QRST complex after automated and manually reviewed/edited deselection of noisy or abnormal beats, *e.g.*, extrasystoles. Subsequently, the automatically determined default onset-QRS, J-point and end-T settings were reviewed and manually corrected if necessary.

Computation of ECG difference descriptors

The differences between the ambulance and reference ECGs of each patient were expressed as 28 difference descriptors (see Table 1), each of which was obtained by subtracting LEADS reference ECG output variables from LEADS ambulance ECG output variables.[15] Within patients, when multiple ambulance ECGs were recorded, the ECG with the largest VG difference vector was selected for analysis, motivated by the notion that differences in the VG reflect changes throughout the QRST-complex.

State-of-the art traditional ECG analysis: Uni-G algorithm

The ambulance and reference ECGs were analyzed by the Uni-G ECG Analysis Program.[16] First, this was performed to obtain a general description of the ECGs in terms of diagnostic categories needed for application of the exclusion criteria. Second, in the reference ECGs, we used the Uni-G program to assess pre-existing ECG pathology. Finally, for the ambulance ECGs, we used the Uni-G algorithm for comparison with our new methods, *i.e.*, this program served as a standardized and objective equivalent of a cardiologists' expert panel for electrocardiographic myocardial ischemia detection based solely on the acute ECG. The Uni-G algorithm gives a wide range of myocardial ischemia diagnostic statements concerning ischemia probability. For the current study, all statements including ischemia were considered a positive score for ischemia.

Category	#	Symbol	Unit	Description
QRS	1	ΔQRSdur	ms	QRS-duration difference, signed
	2	|ΔQRSdur|	ms	QRS-duration difference, absolute value
	3	Δ|$\overline{\text{QRSmax}}$|	μV	Maximal QRS-vector magnitude difference, signed
	4	|Δ|$\overline{\text{QRSmax}}$||	μV	Maximal QRS-vector magnitude difference, absolute value
	5	Δ|$\overline{\text{QRSintegral}}$|	mV·ms	QRS-integral vector magnitude difference, signed
	6	|Δ|$\overline{\text{QRSintegral}}$||	mV·ms	QRS-integral vector magnitude difference, absolute value
	7	ΔQRScmplx		QRS-complexity difference, signed
	8	|ΔQRScmplx|		QRS-complexity difference, absolute value
J	9	|$\overline{\Delta \text{J}}$|	μV	J difference-vector magnitude
	10	∑|ΔJi|; 8 leads	μV	Summed absolute values of relative J-shifts, 8 leads
	11	∑|ΔJi|; 12 leads	μV	Summed absolute values of relative J-shifts, 12 leads
T	12	Δ|$\overline{\text{Tmax}}$|	μV	Maximal T-vector magnitude difference, signed
	13	|Δ|$\overline{\text{Tmax}}$||	μV	Maximal T-vector magnitude difference, absolute value
	14	Δ|$\overline{\text{Tintegral}}$|	mV·ms	T-integral vector magnitude difference, signed
	15	|Δ|$\overline{\text{Tintegral}}$||	mV·ms	T-integral vector magnitude difference, absolute value
	16	ΔTcmplx		T-wave complexity difference, signed
	17	|ΔTcmplx|		T-wave complexity difference, absolute value
	18	ΔTsym		T-wave symmetry difference, signed
	19	|ΔTsym|		T-wave symmetry difference, absolute value
	20	Δ# leads with positive T-waves		Difference in the number of leads with positive T-waves
	21	# leads with a T-wave polarity Δ		Number of leads with a T-wave polarity change
General	22	ΔQTinterval	ms	QT-duration difference, signed
	23	|ΔQTinterval|	ms	QT-duration difference, absolute value
	24	|$\overline{\Delta \text{VG}}$|	mV·ms	Ventricular gradient difference-vector magnitude
	25	ΔSA	°	QRS-T spatial-angle difference, signed
	26	|ΔSA|	°	QRS-T spatial-angle difference, absolute value
	27	ΔHR	bpm	Heart-rate difference, signed
	28	|ΔHR|	bpm	Heart-rate difference, absolute value
Age & Sex	29	Sex	M/F	
	30	Age	years	

TABLE 1. Subtraction electrocardiography: list of ECG difference descriptors.
Variables used as input for LR model.
Abbreviations: M = male. F = female.

Statistical analysis

Descriptive statistics, univariate analysis

All statistical computations were performed in Matlab (Matworks, version R2018a). As descriptive statistics, the medians of the difference descriptors were computed for both myocardial ischemia cases and controls, and statistically compared by the Wilcoxon rank-sum text. *P*-values < 0.05 were considered statistically significant. We constructed, for each variable, receiver operator characteristics (ROCs) for the univariate discrimination of cases and controls including the computation of corresponding areas-under-the-curve (AUCs) with 95% confidence intervals (95% CIs).

Building an overall logistic regression model

An initial logistic regression (LR) model was built using all data. This overall model was chosen from 59 LR models that were constructed with the case/control classification based on the ischemia classification algorithm as dependent variable, and the 28 ECG difference descriptors plus age and sex as independent variables (total of 30 independent variables). The first of these 59 LR models was constructed by using solely the independent variable with the largest univariate AUC. The 2nd to 29th LR models were constructed by adding the remaining independent variables one-by-one to the set of variables that had already been entered in the model; each time, the newly added variable was chosen because it yielded, together with the variables already entered, the largest AUC. The 30th LR model contained all independent variables. The 31st to 59th models were constructed by removing the independent variables from the model one-by-one; each time, the variable that was removed was chosen because the remaining variables yielded the largest AUC. From the 59 thus constructed LR models, the model that had produced the largest AUC was chosen as the final overall model.

Sensitivity analysis of the overall logistic regression model

The overall LR model, constructed with the complete data set, was subjected to sensitivity analysis. This analysis consisted of the comparison of the AUC of the overall model with the AUCs of the LR models constructed after removal of a specific groups of variables (all QRS-related, J-related, T-wave related, or general variables, see Table 1). The drop in AUC upon removal of each of the variable groups characterizes the relative importance of this variable group in the overall LR model.

Learning and testing performance evaluation

Using the same procedure that was used to construct the overall model, 100 LR models were built during a learning and testing evaluation procedure. Each time, the LR model was built on the basis of a random selection of 70% of the total data and then tested on the remaining 30% of the total data. Finally, ROCs and AUCs of each of the 100 randomly selected test data sets were calculated as well as the mean ROC and AUC of these 100 realizations.

Comparison of the logistic regression model and the Uni-G algorithm

To statistically compare the diagnostic performance of the Uni-G algorithm and the LR model, we computed, for each of the 100 randomly selected test data sets, confusion matrices of the Uni-G algorithm. The sensitivity-specificity score of the LR model was found by computing the intersection of the line that connected the Uni-G median performance point and the top-left corner of the ROC plot box and the mean LR model ROC. Finally, we computed the median and the 5th and 95th percentiles of the sensitivity and specificity values of the Uni-G algorithm and of the LR model and compared these using the paired Wilcoxon test.

RESULTS

Study group characteristics

Patient characteristics

A total of 3,261 patients were included in the SUBTRACT study. After application of the exclusion criteria (Figure 1) 1,425 patients remained. The exclusions were mainly due to unusable ambulance ECGs (*n* = 1,419). The study group's demographic and anthropomorphic data and the medical history are listed in Table 2 and 3, respectively. There were slightly more males than females in the study group (52% vs. 48%). The median age was 69 years. About two third of the study group had a cardiac medical history, while almost 10% had no relevant medical history. In 79% of these EMS presentations, chest pain was one of the symptoms while 21% of the patients had only other symptoms, *e.g.*, acute upper abdominal pain that was also recognized as a symptom suggestive of acute myocardial ischemia. Table 4 lists the clinical diagnoses and the corresponding ischemia classification as assessed by the ischemia classification algorithm. The ischemia status of 196 patients was classified as "Uncertain", leaving 1,229 patients for the current statistical analysis.

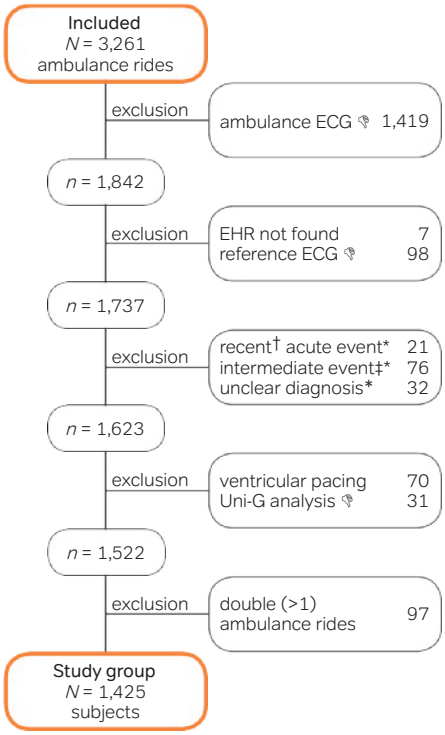


FIGURE 1. Exclusion flowchart.
Flowchart illustrating the exclusion steps leading from the patients who satisfied the inclusion criteria (1. urgent transport by the emergency medical services to one of the participating hospitals in the regions Hollands Midden and Amsterdam; 2. and at least one ECG recording was made during the ambulance ride; 3 to include or exclude myocardial ischemia) to the composition of the patient group studied in the here described research project. Symbols: = not usable, † = < 7 days before acute event, ‡ = major cardiac event between the recording of the reference ECG and the ambulance ECG, *=categories may overlap.
Abbreviations: EHR = electronic health record

				Study group		
				N = 1,425		
Sex (*n*)	male/female	(%/%)		736/689	51.6/48.4	
Age (years)	median	(min-max)	[Q1-Q3]	69	(18-97)	[58-79]
Height (cm)	median	(min-max)	[Q1-Q3]	171	(141-198)	[164-178]
Weight (kg)	median	(min-max)	[Q1-Q3]	79	(42-170)	[69-90]
BMI (kg/m^2)	median	(min-max)	[Q1-Q3]	26.9	(16.6-49.1)	[24.3-30.4]

TABLE 2. Characteristics and medical history of the study group.
Data concerning demographic and anthropomorphic characteristics of the study group.
Abbreviations: *N*/*n* = number of patients, BMI = body mass index, Q1 = first interquartile, Q3 = third interquartile.

N (%)			
Cardiac disease*		961	(67.4)
	myocardial infarction	420	(43.7)
	CAD without myocardial infarction	278	(28.9)
	other cardiac disease	263	(27.4)
TIA/iCVA*		179	(12.6)
Non-coronary or cerebrovascular arterial disease*		158	(11.1)
DVT/Pulmonary embolism*		75	(5.3)
Hypertension*		850	(59.7)
Pulmonary disease*		282	(19.8)
Diabetes mellitus type 2*		354	(24.8)
Chronic kidney disease*		140	(9.8)
Significant disease, any of above		1,291	(90.6)
No significant disease		134	(9.4)

TABLE 3. Medical history of the study group.
Data concerning medical history of the study group. The medical history comprises the patients' health issues and events which are relevant to this study prior to the time of inclusion in the SUBTRACT study (i.e., visit by the EMS). Symbols: *=Categories may overlap.
Abbreviations: *N* = number of patients, CAD = coronary artery disease, TIA = transient ischemic attack, CVA = cerebrovascular accident, DVT = deep venous thrombosis.

Reference ECG characteristics

The elective previously-recorded reference ECGs had a median "age" (time difference between the ambulance ECG and the reference ECG) of 12 months (minimum: 0, Q1: 4, Q3: 34, maximum 332 months). According to the Uni-G algorithm 32% of these ECGs were normal, 33% borderline abnormal and 35% abnormal.

n (%) patients with one or more diagnoses in group	totals	likely ischemic	probably ischemic	uncertain	probably not ischemic	likely not ischemic
Cardiac	465(32.6)	152(91.6)	24(85.7)	127(64.8)	16(76.2)	146(14.4)
Primary myocardial ischemia	273(19.2)	134(80.7)	9(32.1)	90(45.9)	2(9.5)	38(3.7)
STEMI	68(4.8)	67(40.4)	1(3.6)	0(0.0)	0(0.0)	0(0.0)
NSTEMI	76(5.3)	67(40.4)	8(28.6)	1(0.5)	0(0.0)	0(0.0)
UAP	87(6.1)	0(0.0)	0(0.0)	87(44.4)	0(0.0)	0(0.0)
Stable angina	42(2.9)	0(0.0)	0(0.0)	2(1)	2(9.5)	38(3.7)
Arrhythmia/conduct. dist.	111(7.8)	10(6)	3(10.7)	15(7.7)	1(4.8)	82(8.1)
Cardiac decompensation	74(5.2)	16(9.6)	12(42.9)	25(12.8)	15(71.4)	6(0.6)
Valvular disease	22(1.5)	3(1.8)	2(7.1)	11(5.6)	0(0.0)	6(0.6)
Inflammatory	17(1.2)	0(0.0)	0(0.0)	1(0.5)	0(0.0)	16(1.6)
Resuscitation	12(0.8)	9(5.4)	0(0.0)	3(1.5)	0(0.0)	0(0.0)
Hypotension/hypertension	117(8.2)	4(2.4)	5(17.9)	41(20.9)	1(4.8)	66(6.5)
Non-coronary vessel disease	36(2.5)	6(3.6)	1(3.6)	8(4.1)	0(0.0)	21(2.1)
Pulmonary (excl. PE)	108(7.6)	6(3.6)	3(10.7)	13(6.6)	1(4.8)	85(8.4)
Gastrointestinal	161(11.3)	0(0.0)	2(7.1)	3(1.5)	4(19)	152(15)
Neurology (excl. CVA)	11(0.8)	0(0.0)	0(0.0)	0(0.0)	1(4.8)	10(1)
General infectious disease	32(2.2)	3(1.8)	3(10.7)	13(6.6)	0(0.0)	13(1.3)
ENT/endocrine/urogenital/gyn.	22(1.5)	0(0.0)	2(7.1)	2(1)	1(4.8)	17(1.7)
Dermal/costo/tendo/myogenic	139(9.8)	0(0.0)	0(0.0)	4(2)	0(0.0)	135(13.3)
Psychiatry	61(4.3)	0(0.0)	0(0.0)	3(1.5)	0(0.0)	58(5.7)
No acute pathology nos*	368(25.8)	0(0.0)	0(0.0)	5(2.6)	1(4.8)	362(35.7)
Laboratory abnormalities	23(1.6)	3(1.8)	1(3.6)	11(5.6)	1(4.8)	7(0.7)
Other	22(1.5)	0(0.0)	0(0.0)	4(2)	0(0.0)	18(1.8)
Total *N* patients	1,425 (100)	166 (100)	28 (100)	196 (100)	21 (100)	1,014 (100)

TABLE 4. Clinical diagnoses and ischemia classes.
For the total study group and stratified by ischemia class, numbers of patients with one (or more) clinical diagnosis in a group with corresponding percentages. The percentages between parentheses relate to the total number of patients in the study group or ischemia class. Of the likely ischemic patients, 81%/19% had a diagnosis involving primary/secondary myocardial ischemia, as opposed to 32%/68% of the probably ischemic patients. Hence, secondary ischemia was more often causing a probable ischemic classification rather than a likely ischemic classification. Symbols: * = no acute pathology, this refers to diagnoses in which no explicit diagnosis is stated, but in which all relevant acute diagnoses have been excluded by the physician. † = laboratory abnormalities not including troponin levels.
Abbreviations: STEMI = ST-elevation myocardial infarction, NSTEMI = non ST-elevation myocardial infarction, UAP = unstable angina pectoris, conduct. dist. = conduction disturbances, excl. = exclusive of, PE = pulmonary embolism, CVA = cerebral vascular accident, ENT = ear-nose-throat, gyn. = gynaecology, nos = not otherwise specified.

Statistical analysis of the complete dataset – overall model

Descriptive statistics, univariate classification performance

Medians of the cases differed significantly from the controls in all variables except for the absolute value of the QRS-duration difference, signed maximal QRS-vector magnitude difference, signed T-wave complexity, signed T-wave symmetry difference and the signed QRS-T spatial-angle difference. Univariate ROC analyses of the 28 ECG difference descriptors, as well as the variables age and sex for the discrimination of cases from controls all yielded AUCs that were significantly larger than 0.5 except for the absolute value of the QRS-duration difference. The largest AUC was the sum of the absolute values of relative J shifts in all 12 leads: 0.83 (95% CI: 0.82-0.84).

Diagnostic performance of the overall model and Uni-G algorithm

After addition and removal of variables to establish the overall LR model with the largest AUC, the best AUC was 0.86 (95% CI: 0.85-0.87), consisting of 21 variables. Removal of groups of difference descriptors (QRS, J, T, General) led only to a significant drop in AUC in case of removal of all J-point related variables: AUC 0.74 (95% CI: 0.72-0.75). The Uni-G algorithm yielded a sensitivity of 67% and a specificity of 81% for detecting myocardial ischemia.

Misclassifications of the logistic regression overall model

We investigated the clinical characteristics and the ECG characteristics of the most serious misclassifications of the logistic regression overall model (cases for which the model generated a low probability score, and controls for which the model generated a high probability score). Of the 2.5% lowest probability scores within the cases, 80% of patients had NSTEMI diagnoses due to coronary artery spasm or a transient thrombus. This is presumably due to fluctuations in the degree of coronary artery occlusion and thus its electrocardiographical reflection. The 2.5% highest probability scores within the controls had diverse diagnoses. The most frequent diagnoses in this group were pneumonia (23%) and pericarditis (8%); no other diagnosis frequently occurred. While further attempting to explain these high probability scores within the controls, we noticed prevalent tachycardia-induced ST-deviations and possible deviating electrode placement in combination with pre-existing ST-deviations, causing spurious differences.

Learning and testing

Logistic regression

The 100 learning sets had a mean AUC of 0.88 (95% CI: 0.85-0.88), and the 100 test sets had a mean AUC of 0.80 (95% CI: 0.77-0.82), see Figure 2.

Uni-G ECG algorithm

Figure 2 also presents the diagnostic performance of the Uni-G algorithm in the 100 learning and test sets. Because the learning sets were randomly drawn from the data, this effectively resulted in a random composition of the test sets as well. Hence, as expected, the performance of the Uni-G algorithm appeared to be similar in the learning and test sets. Mean Uni-G sensitivity and specificity were 67% and 81%, respectively.

Comparison of the logistic regression model and the Uni-G algorithm

A meaningful comparison of the diagnostic performance of the LR model and the Uni-G algorithm can be made by comparing the test results of the LR models with the Uni-G results on the same test data. The Uni-G algorithm had a sensitivity of 67% (5th-95th percentiles: 59%-74%) and a specificity of 81% (5th-95th percentiles: 78%-84%). The LR model had a sensitivity of 66% (5th-95th percentiles: 60%-74%) and a specificity of 80% (5th-95th percentiles: 76%-85%). There was no statistically significant difference (*P*-values > 0.10) between the diagnostic performances as expressed in sensitivity and specificity of the two algorithms. Panel B of Figure 2 shows that the mean performance of the Uni-G algorithm is almost exactly on the mean of the ROC curves.

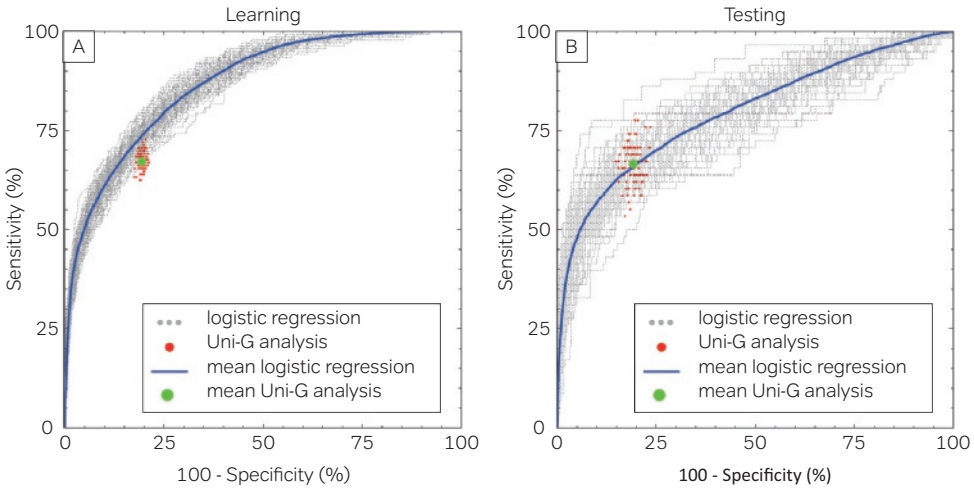


FIGURE 2. Receiver-operating-characteristics of learning and testing.
ROCs of the 100 learning and testing realizations. From the plot can be appreciated that the differences with the Uni-G algorithm in the test sets were not significant.

DISCUSSION

Subtraction electrocardiography for detecting myocardial ischemia

In this first exploratory study of subtraction electrocardiography, we found this technique – here, using logistic regression – to be equivalent to an existing automated and validated ECG analysis algorithm based on the acute ECG alone. Prehospital myocardial ischemia detection, in which the ECG is a key diagnostic, can be challenging. Subtraction electrocardiography has considerable, and when further developed possibly even increased diagnostic value, by taking pre-existing ECG abnormalities into account. In parallel to single ECG analysis, in which J-point amplitudes contain the most important diagnostic information, we found that amplitude differences at the J point were the most informative. However, removal of the J-point related variables yielded an AUC that was still valuable for ischemia detection. Hence, broadening of the diagnostic scope beyond the J point appears useful.

Challenges in subtraction electrocardiography

One of the expected pitfalls of subtraction electrocardiography was the difference in electrode placement between the ambulance and reference ECG. In multiple cases, clear differences in precordial P-wave and QRS-complex orientation could be observed between the ambulance and reference ECG, suggesting that also J-point and T-wave differences may be electrode-position related. Moreover, we presume that differences in heart rate and post-tachycardia T-wave changes influence J-point amplitude, hence negatively affecting our results. This could possibly be addressed by a deep-learning approach.[15] It is conceivable that lapsed time between the ambulance and reference ECG influences diagnostic accuracy.[27] However, the "age" of the reference ECG was, with the exception of a few extremes, rather low (median 12 months). Possibly, day-to-day variation and irreproducible electrode positions have more influence. An approach to at least deal with ECG changes caused by the progression of disease could be to use only recent (*e.g.*, <5 years old) reference ECGs.

Further development of electrocardiographic myocardial ischemia detection

While subtraction ECG analysis/electrocardiography is solely based on differences, its performance in our study appeared to equal conventional single ECG analysis. This demonstrates that intra-individual ECG differences contain valuable information. This information is, however, in daily practice not yet intensively used. Our current method, LR, assumes a linear interaction of variables, and cannot, for instance, eliminate the use of a variable when another exceeds a certain threshold. The latter, non-linear interaction would be, for instance, helpful when in case of severe tachycardia global ST-depressions (resulting in a high sum of J-point deviations, but a small ST-vector magnitude due to cancellation) would be eliminated from the analysis. Presumably, an alternative method, *e.g.* neural networks,[15] could further improve subtraction electrocardiography's performance. Lastly, adding alternative variables, *e.g.*, the direction of the ST vector instead of merely including the magnitude, could further improve the algorithm especially in case ECG changes in the QRS complex and T wave also manifest in this specific spatial direction. Additionally,

the interpretational logic of the Uni-G algorithm could possibly also be improved using the data collected in the current study. Moreover, integration of the further refined subtraction electrocardiography and the Uni-G algorithm might possibly further enhance the diagnostic performance of current electrocardiographic acute myocardial ischemia detection.

Clinical implications and applications

Guidelines[1,2] recommend a comparison of the acute ECG which is under suspicion of myocardial ischemia to an older non-ischemic ECG. Our study is consistent with this approach. In the future, after construction of a secure ECG cloud containing reference ECGs, prehospital subtraction electrocardiography could be automatically performed in the prehospital ECG electrocardiograph.[28] The paramedic can use the results of subtraction electrocardiography, in addition to, or instead of, visual ECG interpretation, in conjunction with the medical history and physical examinations. Moreover, an attending cardiologist can be consulted.

Study's strengths and limitations

This study is, to our knowledge, the first to systematically explore the concept of prehospital serial ECG analysis by subtracting an elective previously-recorded ECG of the same patient from the ambulance ECG, while using detailed clinical information of each patient. Despite our extensive efforts to discriminate myocardial-ischemia cases from controls by the ischemia classification algorithm, the (retrospective) objective assessment of myocardial ischemia remains a challenge. Additionally, we chose not to discriminate types of the pathophysiological mechanism of myocardial ischemia since, in our opinion, the first prehospital priority is to detect myocardial ischemia in general.

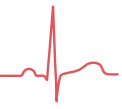
For this analysis we only included patients with an available reference ECG, rendering this study non-representative for the total EMS population since not all EMS patients have an earlier ECG available. However, a reference ECG could be found in about half of the patients with an ambulance ECG, rendering it a feasible method.

By only including patients who were transported to one of our participating hospitals, we also introduced inclusion bias. We assume this bias to be small, since most myocardial ischemia cases initially left at home, are eventually, when symptoms increase, brought to a hospital by the EMS, and would then have been included in our study.

CONCLUSIONS

Subtraction electrocardiography, which exclusively uses intra-individual differences between ECGs, is a promising new method to detect myocardial ischemia. Currently, diagnostic performance of this crude first exploration of subtraction electrocardiography proved equal to current sophisticated single ECG analysis. Possibly, refinement of both the subtraction electrocardiography algorithm as well as the Uni-G algorithm, or even integration of the two, could surpass current electrocardiographic acute myocardial ischemia detection.

Acknowledgments: We are most grateful to the participating EMSs (Regionale Ambulance Voorziening Hollands Midden, Leiden; Ambulance Amsterdam), the participating hospitals (Amsterdam University Medical Centers, University of Amsterdam, in Amsterdam; Alrijne Hospitals in Leiden and Leiderdorp; Groene Hart Hospital, Gouda; Leiden University Medical Center), and their staff for enabling us to collect the relevant data. Our thanks also go out to Physio-Control, now part of Stryker, for providing us with software to extract the ambulance ECGs from the EMS databases.

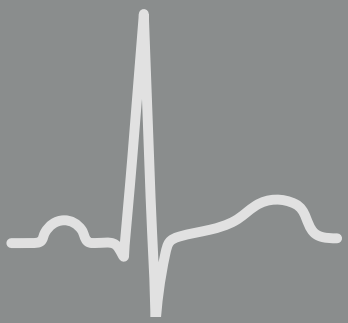


REFERENCES

1. Ibanez B, James S, Agewall S, *et al.* 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2017;39:119–177.
2. O'Gara PT, Kushner FG, Ascheim DD, *et al.* 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. Circulation. 2013;127:e362-425.
3. Downar E, Janse MJ and Durrer D. The effect of acute coronary artery occlusion on subepicardial transmembrane potentials in the intact porcine heart. Circulation. 1977;56:217-24.
4. Wagner NB, Sevilla DC, Krucoff MW, *et al.* Transient alterations of the QRS complex and ST segment during percutaneous transluminal balloon angioplasty of the left anterior descending coronary artery. Am J Cardiol. 1988;62:1038-42.
5. Surawicz B, Orr CM, Hermiller JB, *et al.* QRS changes during percutaneous transluminal coronary angioplasty and their possible mechanisms. J Am Coll Cardiol. 1997;30:452-8.
6. ter Haar CC, Maan AC, Warren SG, *et al.* Difference vectors to describe dynamics of the ST segment and the ventricular gradient in acute ischemia. J Electrocardiol. 2013;46:302-11.
7. Man S, Rahmattulla C, Maan AC, *et al.* Acute coronary syndrome with a totally occluded culprit artery: relation of the ST injury vector with ST-elevation and non-ST elevation ECGs. J Electrocardiol. 2014;47:183-90.
8. ter Haar CC, Maan AC, Schalij MJ, *et al.* Improved electrocardiographic detection of hyperacute ischemia by difference vector analysis. Comput in Cardiol. 2013:9-12.
9. Koyama Y, Hansen PS, Hanratty CG, *et al.* Prevalence of coronary occlusion and outcome of an immediate invasive strategy in suspected acute myocardial infarction with and without ST-segment elevation. Am J Cardiol. 2002;90:579-84.
10. Rijnbeek PR, van Herpen G, Bots ML, *et al.* Normal values of the electrocardiogram for ages 16-90 years. J Electrocardiol. 2014;47:914-21.
11. Macfarlane PW, Katibi IA, Hamde ST, *et al.* Racial differences in the ECG--selected aspects. J Electrocardiol. 2014;47:809-14.
12. Deshpande A and Birnbaum Y. ST-segment elevation: Distinguishing ST elevation myocardial infarction from ST elevation secondary to nonischemic etiologies. World J Cardiol. 2014;6:1067-79.
13. ter Haar CC, Man SC, Maan AC, *et al.* Subtraction electrocardiography: Detection of ischemia-induced ST displacement without the need to identify the J point. J Electrocardiol. 2016;49:316-22.
14. Treskes RW, ter Haar CC, Man S, *et al.* Performance of ST and ventricular gradient difference vectors in electrocardiographic detection of acute myocardial ischemia. J Electrocardiol. 2015;48:498-504.
15. Sbrollini A, de Jongh MC, ter Haar CC, *et al.* Serial electrocardiography to detect newly emerging or aggravating cardiac pathology: a deep-learning approach. Biomed Eng Online. 2019;18:15.
16. Macfarlane PW, Devine B and E. C. The University of Glasgow (Uni-G) ECG Analysis Program. Computers in Cardiology. 2005.
17. Thygesen K, Alpert JS, Jaffe AS, *et al.* Fourth Universal Definition of Myocardial Infarction (2018). Circulation. 2018;138:e618-e651.
18. Gunsolus I, Sandoval Y, Smith SW, *et al.* Renal Dysfunction Influences the Diagnostic and Prognostic Performance of High-Sensitivity Cardiac Troponin I. J Am Soc Nephrol. 2018;29:636-643.
19. Friden V, Starnberg K, Muslimovic A, *et al.* Clearance of cardiac troponin T with and without kidney function. Clin Biochem. 2017;50:468-474.
20. Douketis JD, Crowther MA, Stanton EB, *et al.* Elevated cardiac troponin levels in patients with submassive pulmonary embolism. Arch Intern Med. 2002;162:79-81.
21. Januzzi JL, Jr., Filippatos G, Nieminen M, *et al.* Troponin elevation in patients with heart failure: on behalf of the third Universal Definition of Myocardial Infarction Global Task Force: Heart Failure Section. Eur Heart J. 2012;33:2265-71.
22. Sheridan PJ and Crossman DC. Critical review of unstable angina and non-ST elevation myocardial infarction. Postgrad Med J. 2002;78:717-26.
23. Janssens U, Koch KC, Graf J, *et al.* Severe transmyocardial ischemia in a patient with tension pneumothorax. Crit Care Med. 2000;28:1638-41.
24. Wheatley CE. Hyperventilation syndrome: a frequent cause of chest pain. Chest. 1975;68:195-9.
25. Man SC, Maan AC, Kim E, *et al.* Reconstruction of standard 12-lead electrocardiograms from 12-lead electrocardiograms recorded with the Mason-Likar electrode configuration. J Electrocardiol. 2008;41:211-9.
26. Draisma HHM, Swenne CA, van de Vooren H, *et al.* LEADS: An Interactive Research Oriented ECG/VCG Analysis System. Computers in Cardiology. 2005:515-518.
27. de Jongh MC, ter Haar CC, Man S, *et al.* Intra-individual ECG changes over 25 years: How long can elective ECGs be used as reference for acute ischemia detection? J Electrocardiol. 2015;48:490-7.
28. Macfarlane PW and Pahlm O. Bedside serial comparison of electrocardiograms. J Electrocardiol. 1988;21 Suppl:S159-62.

Chapter

10



Summary

SUMMARY

As outlined in the introduction to this thesis, prehospital triage of patients presenting with symptoms suggestive of myocardial ischemia is complicated. On the one hand, ischemia can cause rapid decay of myocardium requiring swift treatment and hospital transport.[1-5] On the other hand, patients falsely suspected of myocardial ischemia could incorrectly receive prehospital administration of thrombolysis, could incorrectly undergo invasive diagnostics, and/or cause flooding of emergency departments. This opposes unacceptable risks to these patients and gives rise to high costs,[6-8] and both should be limited.

The thus pivotal accurate detection of myocardial ischemia is frequently challenging since patients often present with non-specific complaints[9] and objective diagnostics, *e.g.*, high-sensitivity troponin, are not reliable in the prehospital setting.[10,11] Measurement of cardiac troponin takes time, and necrosis can only be detected after a significant period of ischemia.[11] Currently, the ECG is the most important, quick, easy, objective and non-invasive tool for prehospital myocardial ischemia detection[2,3,12] Although much knowledge about the electrocardiographic manifestations of myocardial ischemia has been accumulated and sophisticated diagnostic algorithms have been developed, there remains considerable room for improvement of electrocardiographic myocardial ischemia detection.

Improvement of myocardial ischemia detection could potentially partly be achieved by a new approach dealing with the large interindividual variability in non-ischemic ECGs of healthy individuals[13,14] and in patients with cardiovascular diseases.[15,16] This large interindividual variability makes it difficult to define generally valid criteria and detect ischemic ECG changes in an acute ambulance ECG without comparing it with a previously made non-acute ECG of the same individual.[17,18] An approach to serial ECG analysis for myocardial ischemia detection is, for instance, the use of the ST and the ventricular gradient difference vectors, after a 3D vectorcardiogram has been computed from the scalar 12-lead ECG.[19,20] An additional advantage of the VG is that this vector reflects all myocardial-ischemia-induced electrocardiographic changes, while current ECG diagnostics are mainly focused on the J point. In this thesis, based on the concept of serial ECG analysis, new approaches to electrocardiographic evaluation of acute myocardial ischemia are presented that aim to correct for interindividual ECG variability.

PART I. ECG changes during hyperacute myocardial ischemia

In Part I of this thesis we investigated difference vectorcardiography in the STAFF III database,[21] in which during elective Dotter procedures hyperacute myocardial ischemia by balloon occlusion was induced in 84 patients with stable angina, while an ECG was continuously recorded. We studied the use of an ST difference vector (ΔST), which has not been investigated extensively before,[22,23] and we revived the ventricular gradient (VG)[24] for the purpose of myocardial ischemia diagnosis, in the form of the ventricular gradient difference vector (ΔVG). Both difference vectors, ΔST and ΔVG, were computed by subtraction of the vectors in the preprocedural (non-ischemic) ECG from the vectors in the ischemic ECG.

In **Chapter 2**, we describe that ΔST and ΔVG behave similarly during hyperacute myocardial ischemia: three minutes after balloon inflation, we found a small planar angle (14.9° ± 14.0°) between the ΔST and ΔVG vectors and a high correlation (r = 0.85, $P < 0.01$) with respect to magnitude. This suggests the ΔVG to be an alternative method for ischemia detection. This may be particularly helpful, when the J point (and thus the beginning of the ST segment) is hardly recognizable, and hence the ΔST vector cannot be computed. In contrast, computation of the ΔVG is in this situation still possible, since it is solely based on the timing of onset QRS and end of the T wave.

We further investigated the relation between these two difference vectors during the full progress of balloon-occlusion induced myocardial ischemia in **Chapter 3**. In the course of myocardial ischemia, the difference vectors had a comparable behavior in both directionality of the spatial orientation and proportionality of the magnitude, proven, respectively, by a small (12.0°) stable angle between the two vectors and a significant ($P < 0.01$) "broken-stick" linear regression (segmented linear regression with two segments).

The sensitivity of ΔST and ΔVG for the detection of myocardial ischemia was tested in **Chapter 4** by applying variable thresholds. While ST-elevation myocardial infarction (STEMI) criteria could only detect 55% of all occluded coronary arteries, ΔST and ΔVG, and especially the combination of these two difference vectors, yielded increased sensitivity.

In **Chapter 5**, we describe a highly significant correlation (r = 0.93, $P < 0.01$) between the difference heart vector, ΔH, at 160 ms after onset QRS and 40 ms after the J point. Therefore, onset QRS could act as an objective ΔST-independent and thus J-point independent synchronization point for the comparison of two ECGs.

PART II. Non-ischemic ECG changes and variants

In Part II individuals without myocardial ischemia were investigated to assess changes in ECG values and ECG variants under non-ischemic conditions. **Chapter 6**, investigates, in 88 cardiology outpatient-clinic patients, the influence of the passing of time on ΔST and ΔVG over a 25-year period. Linear regression with time as the independent variable yielded rather large intercepts (ΔST_{J+0ms}: 0.051 mV, ΔST_{J+60ms}: 0.037 mV, ΔVG: 21 mV·ms) as initial estimates of reproducibility. Furthermore, time significantly *(P* < 0.05) increased the difference vector values (for ΔST_{J+0ms}, ΔST_{J+60ms} and ΔVG, 0.0007 mV, 0.001 mV and 0.7 mV·ms per year, respectively), illustrating that the validity of a previously recorded non-ischemic ECG decreases with time. It should perhaps carry an "expiration date", *e.g.*, 5 years, when it is used as a reference ECG to be compared with an acute ECG.

Pre-existing ECG abnormalities, but also normal variations in ECGs between individuals can considerably trouble ECG interpretation.[25] Since normal variations can be ethnicity dependent,[26-29] in **Chapter 7**, we assessed the prevalence of ECGs exceeding STEMI thresholds in 10,783 apparently healthy individuals in the multi-ethnic HELIUS population.[30,31] We found a strikingly high percentage of "STEMI" ECGs in young (<40 years) male subgroups of Sub-Saharan African descent (up to 27.5% in individuals of Ghanaian ethnicity). In contrast, other ethnicity-, sex-, and age-based subgroups showed no STEMI pattern at all, suggesting low sensitivity for a STEMI diagnosis. This urges STEMI thresholds not only to be based on age and sex,[17] but also to be ethnicity dependent. Moreover, various ECG variables were found to be significantly (*P* < 0.001) associated with STEMI labelling: QRS duration (positive association), QTc interval (negative association), the presence of high QRS voltages (positive association) and the presence an antero-lateral early repolarization pattern (positive association), resulting in a subgroup with a "STEMI" ECG prevalence of more than 45%. We also found that in 89% of STEMI patterns lead V4 exceeded the STEMI thresholds.

PART III. Subtraction electrocardiography to detect myocardial ischemia

While in Part I of this thesis cases, and in Part II controls were separately investigated, Part III provides case-control mixes of patients in which subtraction electrocardiography for the purpose of myocardial ischemia detection was tested.

By combining 84 STAFF III database[21] patients with a database consisting of 398 patients with non-ischemic ECG changes (two outpatient clinic ECGs of the same patient, recorded 1-2 years apart), in **Chapter 8**, we constructed a database consisting of both cases and controls. ΔST and ΔVG vectors had receiver-operator-characteristics (ROC) analysis areas-under-the-curve for myocardial ischemia detection, of 0.91 and 0.88, respectively, establishing the diagnostic value of this form of serial ECG analysis, subtraction electrocardiography, for myocardial ischemia detection.

Finally, we tested this concept in the prehospital setting in **Chapter 9** by studying 1,425 patients presenting to the emergency medical services with acute complaints suggestive of myocardial ischemia. ECG difference descriptors were calculated by subtracting ECG variables (often based on the vectorcardiogram) from a previously made non-ischemic ECG from the same variables from the ambulance ECG. Using logistic regression with these difference descriptors as independent variables yielded for this initial exploration of subtraction electrocardiography for the detection of myocardial ischemia already an impressive diagnostic performance (since it is, in contrast to Chapter 8, performed in the real-life practice impacting diagnostic performance) with an area-under-the curve of 0.80. The diagnostic performance (sensitivity 67% and specificity 81%) of state-of-the-art conventional single ECG analysis (University of Glasgow ECG analysis software) applied to the ambulance ECG,[32] did not significantly differ ($P > 0.05$). Hence, our analysis, notably solely based on ECG differences, suggests subtraction electrocardiography to be an alternative method for myocardial ischemia detection, which could potentially be superior to single ECG analysis when further developed.

REFERENCES

1. Thygesen K, Alpert JS, Jaffe AS, *et al.* Fourth Universal Definition of Myocardial Infarction (2018). Circulation. 2018;138:e618-e651.
2. Ibanez B, James S, Agewall S, *et al.* 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2017;39:119–177.
3. O'Gara PT, Kushner FG, Ascheim DD, *et al.* 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. Circulation. 2013;127:e362-425.
4. Bacharova L, Mateasik A, Carnicky J, *et al.* The Dipolar ElectroCARdioTOpographic (DECARTO)-like method for graphic presentation of location and extent of area at risk estimated from ST-segment deviations in patients with acute myocardial infarction. J Electrocardiol. 2009;42:172-80.
5. Wilson JM. When relativity has no relevance. Tex Heart Inst J. 2010;37:159-60.
6. Whitehead N, Williams T, Brienesse S, *et al.* Contemporary Trends in Stroke complicating Cardiac Catheterization. Intern Med J. 2019.
7. Iyengar SS and Godbole GS. Thrombolysis in the era of intervention. J Assoc Physicians India. 2011;59 Suppl:26-30.
8. Cooper CJ, El-Shiekh RA, Cohen DJ, *et al.* Effect of transradial access on quality of life and cost of cardiac catheterization: A randomized comparison. Am Heart J. 1999;138:430-6.
9. Brieger D, Eagle KA, Goodman SG, *et al.* Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group: insights from the Global Registry of Acute Coronary Events. Chest. 2004;126:461-9.
10. Alghamdi A and Body R. BET 1: Prehospital cardiac troponin testing to 'rule out' acute coronary syndromes using point of care assays. Emerg Med J. 2018;35:572-574.
11. van der Laarse A, Cobbaert CM, Gorgels AP, *et al.* Will future troponin measurement overrule the ECG as the primary diagnostic tool in patients with acute coronary syndrome? J Electrocardiol. 2013;46:312-7.
12. Ting HH, Krumholz HM, Bradley EH, *et al.* Implementation and integration of prehospital ECGs into systems of care for acute coronary syndrome: a scientific statement from the American Heart Association Interdisciplinary Council on Quality of Care and Outcomes Research, Emergency Cardiovascular Care Committee, Council on Cardiovascular Nursing, and Council on Clinical Cardiology. Circulation. 2008;118:1066-79.
13. Birnbaum Y. The burden of nonischemic ST-segment elevation. J Electrocardiol. 2007;40:6-9.
14. Zarafshar S, Wong M, Singh N, *et al.* Resting ST amplitude: prognosis and normal values in an ambulatory clinical population. Ann Noninvasive Electrocardiol. 2013;18:519-29.
15. Brady WJ, Perron AD, Ullman EA, *et al.* Electrocardiographic ST segment elevation: a comparison of AMI and non-AMI ECG syndromes. Am J Emerg Med. 2002;20:609-12.
16. McCabe JM, Armstrong EJ, Kulkarni A, *et al.* Prevalence and factors associated with false-positive ST-segment elevation myocardial infarction diagnoses at primary percutaneous coronary intervention-capable centers: a report from the Activate-SF registry. Arch Intern Med. 2012;172:864-71.
17. Macfarlane PW, Browne D, Devine B, *et al.* Modification of ACC/ESC criteria for acute myocardial infarction. J Electrocardiol. 2004;37 Suppl:98-103.
18. Man S, Rahmattulla C, Maan AC, *et al.* Acute coronary syndrome with a totally occluded culprit artery: relation of the ST injury vector with ST-elevation and non-ST elevation ECGs. J Electrocardiol. 2014;47:183-90.
19. Kors JA, van Herpen G, Sittig AC, *et al.* Reconstruction of the Frank vectorcardiogram from standard electrocardiographic leads: diagnostic comparison of different methods. Eur Heart J. 1990;11:1083-92.
20. Man SC, Maan AC, Kim E, *et al.* Reconstruction of standard 12-lead electrocardiograms from 12-lead electrocardiograms recorded with the Mason-Likar electrode configuration. J Electrocardiol. 2008;41:211-9.
21. Warren SG and Wagner GS. The STAFF studies of the first 5 minutes of percutaneous coronary angioplasty balloon occlusion in man. J Electrocardiol. 2014;47:402-7.
22. Lundin P, Eriksson SV, Erhardt L, *et al.* Continuous vectorcardiography in patients with chest pain indicative of acute ischemic heart disease. Cardiology. 1992;81:145-56.
23. Naslund U, Haggmark S, Johansson G, *et al.* Quantification of myocardium at risk and detection of reperfusion by dynamic vectorcardiographic ST segment monitoring in a pig occlusion-reperfusion model. Cardiovasc Res. 1993;27:2170-8.
24. Draisma HH, Schalij MJ, van der Wall EE, *et al.* Elucidation of the spatial ventricular gradient and its link with dispersion of repolarization. Heart Rhythm. 2006;3:1092-9.
25. Deshpande A and Birnbaum Y. ST-segment elevation: Distinguishing ST elevation myocardial infarction from ST elevation secondary to nonischemic etiologies. World J Cardiol. 2014;6:1067-79.
26. Rijnbeek PR, van Herpen G, Bots ML, *et al.* Normal values of the electrocardiogram for ages 16-90 years. J Electrocardiol. 2014;47:914-21.

27. Hiss RG, Averill KH and Lamb LE. Electrocardiographic findings in 67,375 asymptomatic subjects. VIII. Nonspecific T wave changes. Am J Cardiol. 1960;6:178-89.
28. Lorimer AR, Macfarlane PW, Provan G, *et al.* Blood pressure and catecholamine responses to 'stress' in normotensive and hypertensive subjects. Cardiovasc Res. 1971;5:169-73.
29. Macfarlane PW, Katibi IA, Hamde ST, *et al.* Racial differences in the ECG--selected aspects. J Electrocardiol. 2014;47:809-14.
30. Stronks K, Snijder MB, Peters RJ, *et al.* Unravelling the impact of ethnicity on health in Europe: the HELIUS study. BMC Public Health. 2013;13:402.
31. Snijder MB, Galenkamp H, Prins M, *et al.* Cohort profile: the Healthy Life in an Urban Setting (HELIUS) study in Amsterdam, The Netherlands. BMJ Open. 2017;7:e017873.
32. Macfarlane PW, Devine B and E. C. The University of Glasgow (Uni-G) ECG Analysis Program. Computers in Cardiology. 2005.

Chapter

11

Samenvatting

SAMENVATTING

Besluitvorming rondom patiënten die zich buiten het ziekenhuis presenteren met symptomen van verminderde doorbloeding van de hartspier (myocardiale ischemie), zoals pijn op de borst, is lastig. Enerzijds kunnen snelle behandeling en vervoer naar een ziekenhuis cruciaal zijn daar het bedreigde deel van de hartspier bij verminderde doorbloeding snel kan afsterven.[1-5] Anderzijds kan onterechte verdenking van myocardiale ischemie leiden tot het nemen van onnodige risico's[6,7] middels de toediening van sterke bloedverdunners (trombolyse) dan wel tot het verrichten van onnodig dure en ook risicovolle invasieve diagnostiek (catheterisatie).[8] Iedereen naar het ziekenhuis vervoeren om daar het bloedonderzoek af te wachten of om bijvoorbeeld een echo te maken is niet haalbaar aangezien dit de spoedeisende hulp zou overbelasten en zodoende de (acute) zorg voor anderen zou bemoeilijk of onmogelijk zou maken. Correcte detectie van de aanwezigheid van verminderde hartspierdoorbloeding is dus erg belangrijk.

Het herkennen van myocardiale ischemie kan echter moeilijk zijn omdat patiënten vaak aspecifieke klachten hebben[9] en veel objectieve testen buiten het ziekenhuis niet te gebruiken zijn.[10,11] Een belangrijke test is bijvoorbeeld het meten van cardiaal troponine, dat vrij komt in het bloed als hartspiercellen beschadigen. Omdat patiënten zich veelal melden voordat de doorbloedingsstoornis tot celdood heeft geleid is deze bepaling lang niet altijd betrouwbaar.[11] Bovendien is de bepaling tijdrovend en vergt deze speciale apparatuur.

Daarom is het electrocardiogram (ECG) momenteel de belangrijkste, snelle, gemakkelijke, objectieve en vrijwel risicoloze (niet-invasieve) meting voor het detecteren van myocardiale ischemie.[2,3,12] Omdat een ECG de elektrische activiteit van het hart weergeeft en de elektrische stromen in het hart door een verminderde doorbloeding anders gaan lopen, is myocardiale ischemie vaak goed van het ECG af te lezen. Hoewel hierover in de loop der jaren veel kennis is vergaard, en er verfijnde diagnostische algoritmes ontwikkeld zijn, blijft er toch nog aanzienlijke ruimte over voor verbetering.

Een nieuwe benadering die rekening houdt met de grote verschillen in ECG's tussen personen (interindividuele variabiliteit) zou uitkomst kunnen bieden. Het ECG verschilt namelijk niet alleen tussen gezonde personen en patiënten met een cardiovasculaire voorgeschiedenis, maar binnen deze groepen is het ECG per persoon ook steeds anders.[13-16] Deze interindividuele variabiliteit maakt het moeilijk algemeen geldende criteria op te stellen om te bepalen welke afwijkingen in acute ambulance ECG's echt door een verminderde doorbloeding van de hartspier komen, dan wel eenvoudigweg bij de persoon passen. Door het ambulance ECG te vergelijken met een eerder gemaakt niet-acuut ECG van diezelfde persoon kan bepaald worden of het ECG veranderd is en eventuele afwijkingen dus nieuw zijn.[17,18] Een aanpak voor een dusdanige ECG-vergelijkingsanalyse (seriële ECG analyse) voor het herkennen van myocardiale ischemie is het gebruik van de ST- en de ventriculaire gradiënt (VG) verschilvector. Deze vectoren worden berekend door eerst een 3D-ECG (het vectorcardiogram, VCG) te berekenen uit het 12-afleidingen ECG.[19,20] Een bijkomend voordeel van de VG is dat deze gevoelig is voor alle ECG-veranderingen die door myocardiale ischemie veroorzaakt worden, terwijl de huidige ECG-diagnostiek voornamelijk op één punt gericht is (ST-elevatie/ST-depressie). In dit proefschrift worden, gebaseerd op het concept van seriële ECG analyse, nieuwe benaderingen onderzocht om te corrigeren voor interindividuele ECG variabiliteit, waarmee de evaluatie van acute myocardiale ischemie in het ECG verbeterd kan worden.

DEEL I. ECG-veranderingen tijdens hyperacute myocardiale ischemie

In deel I van dit proefschrift hebben we verschilvectorcardiografie onderzocht in de STAFF III database.[21] Uit deze database hebben we de gegevens van 84 patiënten gebruikt die enkel bij inspanning pijn op de borst ervaren (stabiele angina pectoris). Deze patiënten ondergingen ter behandeling een dotterprocedure. In dit onderzoek werd de dotterballon extra lang (een aantal minuten) in de coronairarterie opgeblazen gelaten om te evalueren of dat betere resultaten zou geven. Hiermee werd echter, terwijl de procedure tot doel heeft de ischemie bij inspanning te verminderen, nu juist als bijeffect een korte periode myocardiale ischemie gecreëerd. Tijdens deze procedure werd continu een ECG gemaakt, dat de eerste elektrische uitingen registreerde van deze door de ballon veroorzaakte complete onderbreking van de hartspierdoorbloedding. We bestudeerden de ST-verschilvector (ΔST), die eerder nog niet uitgebreid onderzocht was,[22,23] en bliezen ook de ventriculaire gradiënt (VG)[24] nieuw leven in om myocardiale ischemie te detecteren als ventriculaire gradiënt verschilvector (ΔVG). Beide verschilvectoren, ΔST en ΔVG, werden uitgerekend door de vectoren in het ECG voorafgaand aan de procedure (waarbij er dus nog geen ischemie was) af te trekken van dezelfde vectoren in het ischemische ECG dat tijdens de behandeling gemaakt werd.

In **Hoofdstuk 2** beschrijven we dat de ΔST- en ΔVG-verschilvectoren zich gedurende de afsluiting van een coronairarterie op overeenkomstige wijze gedragen: drie minuten na het opblazen van de ballon vonden we namelijk slechts een kleine ruimtehoek tussen de ΔST- en ΔVG-vectoren (14,9° ± 14,0°) en een hoge correlatie tussen de groottes van de twee vectoren (r = 0,85, $P < 0,01$). Dit wekt de suggestie dat de ΔVG een alternatieve methode voor ischemiedetectie is. Deze methode kan vooral nuttig zijn als het J-punt, dus het begin van het ST-segment, moeilijk of niet te herkennen is, waardoor de ΔST-vector niet meer berekend kan worden. De berekening van de ΔVG-vector kan dan nog wel plaatsvinden omdat deze berekend wordt uit het interval lopende van aanvang van het QRS-complex tot het einde van de T-golf, en dus onafhankelijk is van de timing van het J-punt.

De relatie tussen deze twee verschilvectoren in het volledige proces van door ballonafsluiting geïnduceerde myocardiale ischemie hebben we verder onderzocht in **Hoofdstuk 3**. Hierbij bleken de verschilvectoren zich gedurende het beloop van myocardiale ischemie gelijkwaardig te gedragen wat betreft zowel richting als grootte. Dit valt af te lezen aan respectievelijk een kleine (12.0°) stabiele hoek tussen de vectoren en in de grootte een significante ($P < 0,01$) "broken-stick" lineaire regressie (gesegmenteerde lineaire regressie bestaande uit twee segmenten).

Door het toepassen van verschillende drempels werd in **Hoofdstuk 4** de sensitiviteit van de ΔST en ΔVG vectoren voor het detecteren van myocardiale ischemie getest. Terwijl ST-elevatie myocardinfarct (STEMI) criteria slechts 55% van alle afgesloten vaten kon herkennen, verhoogde het gebruik van de ΔST en ΔVG, en vooral de combinatie van de twee verschilvectoren, de sensitiviteit.

In **Hoofdstuk 5** vonden we een sterke correlatie (r = 0,93, $P < 0,01$) tussen de verschilhartvector, ΔH, op 160 ms na het begin van het QRS-complex en op 40 ms na het J-punt. Hieruit valt te concluderen dat het begin van het QRS-complex eventueel als objectief ΔST-onafhankelijk en dus J-punt-onafhankelijk synchronisatiepunt gebruikt zou kunnen worden voor de vergelijking van twee ECG's.

DEEL II. Niet-ischemische ECG-veranderingen en -varianten

In Deel II werden personen zonder myocardiale ischemie onderzocht om de veranderingen in ECG-variabelen en de ECG-varianten onder niet-ischemische condities te evalueren. **Hoofdstuk 6** onderzoekt de invloed van de factor tijd (gebruik makend van ECG's die gedurende een periode van 25 jaar gemaakt zijn) op de ΔST- en ΔVG-vectoren in 88 cardiologische poliklinische patiënten. Lineaire regressie met tijd als de onafhankelijke variabele resulteerde voor elke variabele in een vrij grote constante (ΔST_{J+0ms}: 0,051 mV, ΔST_{J+60ms}: 0,037 mV, ΔVG: 21 mV·ms). Deze resultaten kunnen als initiële schatting voor de reproduceerbaarheid van het ECG gezien worden. Echter, de verschilvectoren namen ook significant toe ($P < 0,05$) door de tijd (respectievelijk, voor ΔST_{J+0ms}, ΔST_{J+60ms} en ΔVG, 0,0007 mV, 0,001 mV en 0,7 mV·ms, per jaar). Deze tijdsafhankelijke toename illustreert dat als dit ECG als referentie ECG gebruikt wordt om een acuut ECG mee te vergelijken, het mogelijk een "houdbaarheidsdatum" heeft (van bijvoorbeeld 5 jaar).

Pre-existente ECG-afwijkingen, maar ook normale varianten van ECG's, kunnen de interpretatie van het ECG bemoeilijken.[25] Gezien normale varianten afhankelijk kunnen zijn van iemands etnische achtergrond,[26-29] hebben we in **Hoofdstuk 7**, de ECG's van 10.783 gezonde deelnemers van de multi-etnische HELIUS studie[30,31] onderzocht. Hierin hebben we een inschatting gemaakt hoe groot het probleem van interindividuele ECG variabiliteit voor myocardiale ischemie detectie zou kunnen zijn. Dit hebben we gedaan, door het vóórkomen (prevalentie) te berekenen van ECG's die weliswaar gemaakt zijn in gezonde personen maar toch de diagnostische drempels van een ST-elevatie hartinfarct (ST-elevation myocardial infarction, STEMI) overschrijden. We vonden een opvallend hoog percentage "STEMI" ECG's in subgroepen van jonge (< 40 jaar) gezonde mannen van Sub-Sahara Afrikaanse afkomst (tot 27,5% in deelnemers met een Ghanese etniciteit). Daarentegen lieten andere op etniciteit, geslacht en leeftijd gebaseerde subgroepen bij geen enkel individu een STEMI-patroon zien. Hieruit zou geconcludeerd kunnen worden dat de sensitiviteit voor een STEMI-diagnose in deze etnische groepen juist laag is. Hieruit volgt dat diagnostische STEMI-drempels dus niet alleen afhankelijk van leeftijd en geslacht zouden moeten zijn,[17] maar ook van etniciteit. Tevens waren meerdere ECG-variabelen significant geassocieerd ($P < 0,001$) met het al dan niet voldoen aan de STEMI-criteria: QRS-duur (positieve associatie), QTc-interval (negatieve associatie), hoge QRS-voltages (positieve associatie) en een anterolateraal "early repolarization" patroon (positieve associatie), hetgeen resulteerde in een subgroep met een "STEMI"-ECG-prevalentie van meer dan 45%. Ook vonden we dat in 89% van STEMI patronen afleiding V4 de STEMI-drempel overschreed.

DEEL III. Subtractie-electrocardiografie voor de detectie van myocardiale ischemie

Terwijl in Deel I van dit proefschrift personen zonder, en in Deel II personen met, myocardiale ischemie onderzocht werden, werd in Deel III subtractie-electrocardiografie als diagnosticum voor myocardiale ischemie onderzocht in case-control patiëntenmixen.

In **Hoofdstuk 8 c**ombineerden wij de 84 patiënten van de STAFF III database[21] met een database met 398 patiënten met ECG veranderingen die niet door acute myocardiale ischemie veroorzaakt werden (twee poliklinische ECG's van dezelfde patiënt die twee jaar na elkaar gemaakt waren). Hiermee stelden wij een database samen van ECG-paren afkomstig van patiënten mét en zónder acute myocardiale ischemie. In deze database testten wij de diagnostische waarde van subtractie-electrocardiografie (een door ons gedefinieerde nieuwe vorm van seriële ECG analyse) voor de detectie van myocardiale ischemie. Dit resulteerde in een receiver-operator-characteristics (ROC) analyse in hoge "areas-under-the-curve", van 0,91 en 0,88 respectievelijk voor ΔST en ΔVG.

In **Hoofdstuk 9** hebben we dit concept van het aftrekken van een eerder gemaakt niet-acuut ECG van het acute ECG getest in de prehospitale setting door 1.425 patiënten te onderzoeken die zich bij de ambulancedienst presenteerden met acute klachten passend bij myocardiale ischemie. Door de ECG-variabelen (vaak gebaseerd op het VCG) van een eerder gemaakt niet-ischemisch ECG van dezelfde ECG variabelen van het ambulance ECG af te trekken, berekenden we de "ECG difference descriptors". Logistische regressie met deze verschilvariabelen als onafhankelijke variabelen resulteerde in een goede diagnostische prestatie (sensitiviteit: 67%, specificiteit: 81%, "area-under-the curve": 0,80) voor deze eerste verkenning van subtractie electrocardiografie voor het detecteren van myocardiale ischemie. Conventionele ECG analyse gebaseerd op alleen het acute ECG (University of Glasgow ECG analyse software)[32] was niet significant beter ($P > 0,05$). Hieruit valt te concluderen dat subtractie electrocardiografie – welke dus uitsluitend op verschillen van het acute ECG met een eerder gemaakt niet-acuut referentie ECG gebaseerd is in plaats van op de absolute waarden in het acute ECG – zichzelf als een waardevol alternatief voor het detecteren van myocardiale ischemie bewezen heeft. Wanneer de methode verder ontwikkeld wordt, heeft deze onzes inziens potentie om zelfs beter te worden dan de huidige ECG-analyse die alleen gebaseerd is op het acute ECG.

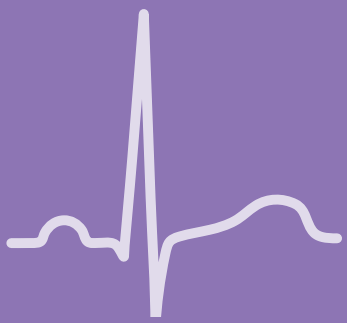
REFERENTIES

1. Thygesen K, Alpert JS, Jaffe AS, *et al.* Fourth Universal Definition of Myocardial Infarction (2018). Circulation. 2018;138:e618-e651.
2. Ibanez B, James S, Agewall S, *et al.* 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2017;39:119–177.
3. O'Gara PT, Kushner FG, Ascheim DD, *et al.* 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. Circulation. 2013;127:e362-425.
4. Bacharova L, Mateasik A, Carnicky J, *et al.* The Dipolar ElectroCARdioTOpographic (DECARTO)-like method for graphic presentation of location and extent of area at risk estimated from ST-segment deviations in patients with acute myocardial infarction. J Electrocardiol. 2009;42:172-80.
5. Wilson JM. When relativity has no relevance. Tex Heart Inst J. 2010;37:159-60.
6. Whitehead N, Williams T, Brienesse S, *et al.* Contemporary Trends in Stroke complicating Cardiac Catheterization. Intern Med J. 2019.
7. Iyengar SS and Godbole GS. Thrombolysis in the era of intervention. J Assoc Physicians India. 2011;59 Suppl:26-30.
8. Cooper CJ, El-Shiekh RA, Cohen DJ, *et al.* Effect of transradial access on quality of life and cost of cardiac catheterization: A randomized comparison. Am Heart J. 1999;138:430-6.
9. Brieger D, Eagle KA, Goodman SG, *et al.* Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group: insights from the Global Registry of Acute Coronary Events. Chest. 2004;126:461-9.
10. Alghamdi A and Body R. BET 1: Prehospital cardiac troponin testing to 'rule out' acute coronary syndromes using point of care assays. Emerg Med J. 2018;35:572-574.
11. van der Laarse A, Cobbaert CM, Gorgels AP, *et al.* Will future troponin measurement overrule the ECG as the primary diagnostic tool in patients with acute coronary syndrome? J Electrocardiol. 2013;46:312-7.
12. Ting HH, Krumholz HM, Bradley EH, *et al.* Implementation and integration of prehospital ECGs into systems of care for acute coronary syndrome: a scientific statement from the American Heart Association Interdisciplinary Council on Quality of Care and Outcomes Research, Emergency Cardiovascular Care Committee, Council on Cardiovascular Nursing, and Council on Clinical Cardiology. Circulation. 2008;118:1066-79.
13. Birnbaum Y. The burden of nonischemic ST-segment elevation. J Electrocardiol. 2007;40:6-9.
14. Zarafshar S, Wong M, Singh N, *et al.* Resting ST amplitude: prognosis and normal values in an ambulatory clinical population. Ann Noninvasive Electrocardiol. 2013;18:519-29.
15. Brady WJ, Perron AD, Ullman EA, *et al.* Electrocardiographic ST segment elevation: a comparison of AMI and non-AMI ECG syndromes. Am J Emerg Med. 2002;20:609-12.
16. McCabe JM, Armstrong EJ, Kulkarni A, *et al.* Prevalence and factors associated with false-positive ST-segment elevation myocardial infarction diagnoses at primary percutaneous coronary intervention-capable centers: a report from the Activate-SF registry. Arch Intern Med. 2012;172:864-71.
17. Macfarlane PW, Browne D, Devine B, *et al.* Modification of ACC/ESC criteria for acute myocardial infarction. J Electrocardiol. 2004;37 Suppl:98-103.
18. Man S, Rahmattulla C, Maan AC, *et al.* Acute coronary syndrome with a totally occluded culprit artery: relation of the ST injury vector with ST-elevation and non-ST elevation ECGs. J Electrocardiol. 2014;47:183-90.
19. Kors JA, van Herpen G, Sittig AC, *et al.* Reconstruction of the Frank vectorcardiogram from standard electrocardiographic leads: diagnostic comparison of different methods. Eur Heart J. 1990;11:1083-92.
20. Man SC, Maan AC, Kim E, *et al.* Reconstruction of standard 12-lead electrocardiograms from 12-lead electrocardiograms recorded with the Mason-Likar electrode configuration. J Electrocardiol. 2008;41:211-9.
21. Warren SG and Wagner GS. The STAFF studies of the first 5 minutes of percutaneous coronary angioplasty balloon occlusion in man. J Electrocardiol. 2014;47:402-7.
22. Lundin P, Eriksson SV, Erhardt L, *et al.* Continuous vectorcardiography in patients with chest pain indicative of acute ischemic heart disease. Cardiology. 1992;81:145-56.
23. Naslund U, Haggmark S, Johansson G, *et al.* Quantification of myocardium at risk and detection of reperfusion by dynamic vectorcardiographic ST segment monitoring in a pig occlusion-reperfusion model. Cardiovasc Res. 1993;27:2170-8.
24. Draisma HH, Schalij MJ, van der Wall EE, *et al.* Elucidation of the spatial ventricular gradient and its link with dispersion of repolarization. Heart Rhythm. 2006;3:1092-9.
25. Deshpande A and Birnbaum Y. ST-segment elevation: Distinguishing ST elevation myocardial infarction from ST elevation secondary to nonischemic etiologies. World J Cardiol. 2014;6:1067-79.
26. Rijnbeek PR, van Herpen G, Bots ML, *et al.* Normal values of the electrocardiogram for ages 16-90 years. J Electrocardiol. 2014;47:914-21.

27. Hiss RG, Averill KH and Lamb LE. Electrocardiographic findings in 67,375 asymptomatic subjects. VIII. Nonspecific T wave changes. Am J Cardiol. 1960;6:178-89.
28. Lorimer AR, Macfarlane PW, Provan G, *et al.* Blood pressure and catecholamine responses to 'stress' in normotensive and hypertensive subjects. Cardiovasc Res. 1971;5:169-73.
29. Macfarlane PW, Katibi IA, Hamde ST, *et al.* Racial differences in the ECG--selected aspects. J Electrocardiol. 2014;47:809-14.
30. Stronks K, Snijder MB, Peters RJ, *et al.* Unravelling the impact of ethnicity on health in Europe: the HELIUS study. BMC Public Health. 2013;13:402.
31. Snijder MB, Galenkamp H, Prins M, *et al.* Cohort profile: the Healthy Life in an Urban Setting (HELIUS) study in Amsterdam, The Netherlands. BMJ Open. 2017;7:e017873.
32. Macfarlane PW, Devine B and E. C. The University of Glasgow (Uni-G) ECG Analysis Program. Computers in Cardiology. 2005.

Chapter

12



Future perspectives

FUTURE PERSPECTIVES

The role of the ECG in prehospital triage

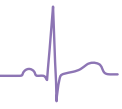
Ever since the introduction of thrombolysis, the main diagnostic focus in patients presenting with symptoms suggestive of acute myocardial ischemia has been on the identification of patients who would benefit from urgent invasive treatment (*i.e.*, PCI, or in more remote areas, thrombolysis).[1-4] Ideally, the initial diagnostic focus should move to an earlier stage of the triage, *i.e.*, the separation of patients with and without myocardial ischemia regardless of the pathophysiological mechanism. Once the presence of myocardial ischemia is established and the decision of transporting the patient to a hospital is made, the second decision should be taken whether or not the hospital should be one with percutaneous coronary intervention (PCI) facilities, and whether or not the patient should receive prehospital thrombolysis. Diagnostic criteria for the first decision, *i.e.*, the detection of myocardial ischemia, should have high sensitivity in order to prevent false negative conclusions, *i.e.*, mistakenly leaving patients at home. The second decision should be supported by criteria with high specificity to prevent false positive activations of the catheterization laboratory or hazardous false positive thrombolysis. The prehospital ECG, being an easy-to-record low-cost and non-invasive tool,[3-5] is essential for both decisions. Currently, the role of the ECG in the first decision, *i.e.*, the detection of the complete spectrum of myocardial ischemia, is underemphasized and may be improved.

Human and computer in perfect harmony

Despite the fact that computers are currently surpassing the performance of man in selected areas,[6] medicine can not exclusively be practiced by robots. The "human touch" is not only necessary for empathic purposes (*i.e.*, care), results from computer programs should also always be checked and authorized by individuals. This is important not only to prevent error, it is also essential that a professional assumes legal responsibility for the individual decision taken. In the case of ECG interpretation, a computer-assisted approach can be developed. The software would, for instance, calculate a score for the presence of myocardial ischemia, *e.g.*, from 1 until 100. The paramedic subsequently decides, based on all data including symptoms and pretest probability, whether or not to transport the patient to a hospital, or, for example, to additionally consult an attending cardiologist.

Future discoveries in the ischemic ECG

Health care and specifically cardiology is continuously developing. In this context, the ECG may be lagging behind. Despite the multitude of information the ECG possesses,[7-9] it is now sub-optimally used for myocardial ischemia detection. Most ECG patterns currently used for the detection of myocardial ischemia have been discovered by chance and by human observation.[10] It is conceivable, however, that multiple additional (difference) patterns are hidden in the ischemic ECG, waiting to be discovered by advanced methods. The further development of electrocardiographic criteria could be assisted by techniques such as machine learning.[11]



More to the ECG than the J point

Although prudent recommendations are stated in guidelines concerning T-wave patterns caused by ischemia, most diagnostic criteria for myocardial ischemia are solely based on ST-segment/J-point displacements.[12] Addition of non J-point related ECG variables for the purpose of myocardial ischemia detection could potentially improve diagnostic performance. Obviously, using the complete QRST complex to measure ischemia is complicated due to wide interindividual differences in both normal and pathological ECGs under non-ischemic conditions that decrease specificity,[13,14] but also due to limited sensitivity resulting for instance from pseudonormalization.[15] Therefore, the inclusion of non J-point related ECG variables in criteria for ischemia detection requires sophisticated algorithms or intra-individual ECG comparison to deal with this interindividual ECG variability.

Detection of changes instead of absolute values

An increase of specificity while maintaining high sensitivity, could be accomplished by solely focusing on ECG differences, and thus dynamics, between an acute and non-acute ECG of the same individual. This approach has two challenges. First, differences in, for example, QRS complexity are hard to visually observe, therefore, automated ECG analysis should aid ECG interpretation. Second, the reproducibility of electrode positioning should be improved, to minimize pseudo-differences. In order to accomplish high ECG reproducibility, training and feedback (both on-site and retrospective) in correct electrode placement should be intensified. Additionally, tools for consistent electrode placement are being introduced to the market.[16] To facilitate subtraction electrocardiography in prehospital practice a secure database "in the cloud" containing reference ECGs should be created, from which the previously made non-ischemic ECG could be instantly accessed for comparison.

Taking non-ECG related variables into account

Myocardial ischemia detection algorithms, but also manually applied criteria, may be further improved by more intensively accounting for non-ECG related variables. Patient-specific factors, such as age, could be used as continuous variables as opposed to binary variables used in the current guidelines (under or over 40 years old),[3,4,12] Moreover, the easily obtained, but often not registered, height and weight should also be considered when interpreting the ECG.[17]

In addition to the standard non-ECG related variables, age, sex, height and weight, registering the patient's ethnic background should also be considered. Especially, non-Western ethnic groups would benefit of ethnicity-specific myocardial ischemia evaluation, since current criteria originate from mainly Western-European populations. Although registration of ethnicity remains a sensitive issue in Western countries,[18] the potential benefits may surpass the disadvantages if appropriate precautions for assuring privacy and for prevention of misuse are taken. In parallel, studies could be performed in non Western-European countries to facilitate local improvement of health care.

Finally, since cardiovascular disease, *e.g.*, left ventricular hypertrophy, affects the ECG,[19] a patient's medical history should also be considered during ECG interpretation. Although currently algorithms exist that account for one or more of these variables,[20] further refinement is possible. A secure database "in the cloud" could be constructed containing, in addition to all previously made ECGs, a collection of the patient's hospital records including non-ECG related variables. Finally, other prehospital information, *e.g.*, blood pressure (and changes), could potentially further improve ECG interpretation. Additionally, other diagnostics such as point-of-care blood tests (*e.g.*, for hemoglobin to assess anemia possibly causing myocardial ischemia) could corroborate a diagnosis of myocardial ischemia.

Conclusion

This thesis demonstrates that despite its long clinical tradition, the ECG as a diagnostic tool for myocardial ischemia is still in full development. Diagnostic accuracy may increase by using the complete ECG instead of mainly focusing on J-point amplitudes, and by correction for non-ischemic interindividual ECG variability.

REFERENCES

1. (GISSI) GIpISdS-nnIM. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet. 1986;1:397-402.
2. (GISSI) GIpISdS-nnIM. Long-term effects of intravenous thrombolysis in acute myocardial infarction: final report of the GISSI study. Lancet. 1987;2:871-4.
3. Ibanez B, James S, Agewall S, *et al.* 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2017;39:119–177.
4. O'Gara PT, Kushner FG, Ascheim DD, *et al.* 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. Circulation. 2013;127:e362-425.
5. Ting HH, Krumholz HM, Bradley EH, *et al.* Implementation and integration of prehospital ECGs into systems of care for acute coronary syndrome: a scientific statement from the American Heart Association Interdisciplinary Council on Quality of Care and Outcomes Research, Emergency Cardiovascular Care Committee, Council on Cardiovascular Nursing, and Council on Clinical Cardiology. Circulation. 2008;118:1066-79.
6. Kamphuis VP, Wagner GS, Pahlm O, *et al.* Comparison of model-based and expert-rule based electrocardiographic identification of the culprit artery in patients with acute coronary syndrome. J Electrocardiol. 2015;48:483-9.
7. Kleber AG, Janse MJ, van Capelle FJ, *et al.* Mechanism and time course of S-T and T-Q segment changes during acute regional myocardial ischemia in the pig heart determined by extracellular and intracellular recordings. Circ Res. 1978;42:603-13.
8. Surawicz B. Reversible QRS changes during acute myocardial ischemia. J Electrocardiol. 1998;31:209-20.
9. Surawicz B. ST-segment, T-wave, and U-wave changes during myocardial ischemia and after myocardial infarction. Can J Cardiol. 1986;Suppl A:71A-84A.
10. de Winter RJ, Verouden NJ, Wellens HJ, *et al.* A new ECG sign of proximal LAD occlusion. N Engl J Med. 2008;359:2071-3.
11. Sbrollini A, de Jongh MC, ter Haar CC, *et al.* Serial electrocardiography to detect newly emerging or aggravating cardiac pathology: a deep-learning approach. Biomed Eng Online. 2019;18:15.
12. Thygesen K, Alpert JS, Jaffe AS, *et al.* Fourth Universal Definition of Myocardial Infarction (2018). Circulation. 2018;138:e618-e651.
13. Birnbaum Y. The burden of nonischemic ST-segment elevation. J Electrocardiol. 2007;40:6-9.
14. Rijnbeek PR, van Herpen G, Bots ML, *et al.* Normal values of the electrocardiogram for ages 16-90 years. J Electrocardiol. 2014;47:914-21.
15. Ulucan C, Yavuzgil O, Kayikcioglu M, *et al.* Pseudonormalization: clinical, electrocardiographic, echocardiographic, and angiographic characteristics. Anadolu Kardiyol Derg. 2007;7 Suppl 1:175-7.
16. PEACS. Alvale (expected 2019). 2019.
17. Pipberger HV, Goldman MJ, Littmann D, *et al.* Correlations of the orthogonal electrocardiogram and vectorcardiogram with consitutional variables in 518 normal men. Circulation. 1967;35:536-51.
18. Ploem MC. [Registration of ethnicity allowed with conditions]. Ned Tijdschr Geneeskd. 2009;153:A600.
19. Huwez FU, Pringle SD and Macfarlane PW. Variable patterns of ST-T abnormalities in patients with left ventricular hypertrophy and normal coronary arteries. Br Heart J. 1992;67:304-7.
20. Macfarlane PW, Devine B, Latif S, *et al.* Methodology of ECG interpretation in the Glasgow program. Methods Inf Med. 1990;29:354-61.

Appendices

- Contributing authors
- About the author (curriculum vitae)
- PhD portofolio
- List of publications
- Acknowledgments/dankwoord

CONTRIBUTING AUTHORS

Rob Adams
Amsterdam UMC, University of Amsterdam, Heart Center, Department of Cardiology, Amsterdam, the Netherlands

Reza Alizadeh Dehnavi
Leiden University Medical Center, Heart-Lung Center, Department of Cardiology, Leiden, the Netherlands *and* Groene Hart Hospital, Cardiology Department, Gouda, the Netherlands

Ed Bleijenberg
Ambulance Amsterdam, Amsterdam, the Netherlands

Jan Bosch
Regionale Ambulancevoorziening Hollands Midden, Department of R&D, Leiden, the Netherlands

Laura Burattini
Università Politecnica delle Marche, Department of Information Engineering, Ancona, Italy

Sophia Gripenstedt
Amsterdam UMC, University of Amsterdam, Heart Center, Department of Cardiology, Amsterdam, the Netherlands

B. Milan Horáček
Dalhousie University, Department of Electrical and Computer Engineering, Halifax, NS, Canada

Jonas S.S.G. de Jong
Onze Lieve Vrouwe Gasthuis, Heart Center, Amsterdam, The Netherlands

Marjolein C. de Jongh
Leiden University Medical Center, Heart-Lung Center, Department of Cardiology, Leiden, the Netherlands

Charles J.H.J. Kirchhof
Alrijne Hospital, Cardiology Department, Leiderdorp, the Netherlands

Jan A. Kors
Erasmus MC, University Medical Center Rotterdam, Department of Medical Informatics, Rotterdam, the Netherlands

Arie C. Maan
Leiden University Medical Center, Heart-Lung Center, Department of Cardiology, Leiden, the Netherlands

Peter W. Macfarlane
Institute of Health and Wellbeing, University of Glasgow, Glasgow, Scotland, UK

Sumche Man
Leiden University Medical Center, Heart-Lung Center, Department of Cardiology, Leiden, the Netherlands

Ron J.G. Peters
Amsterdam UMC, University of Amsterdam, Heart Center, Department of Cardiology, Amsterdam, the Netherlands

Pieter G. Postema
Amsterdam UMC, University of Amsterdam, Heart Center, Department of Cardiology, Amsterdam, the Netherlands

Michael Ringborn
Lund University, Cardiology Department, Lund, Sweden

Agnese Sbrollini
Università Politecnica delle Marche, Department of Information Engineering, Ancona, Italy

Martin J. Schalij
Leiden University Medical Center, Heart-Lung Center, Department of Cardiology, Leiden, the Netherlands

Roderick W.C. Scherptong
Leiden University Medical Center, Heart-Lung Center, Department of Cardiology, Leiden, the Netherlands

Marieke B. Snijder
Amsterdam UMC, University of Amsterdam, Department of Clinical Epidemiology, Biostatistics & Bioinformatics, *and* Department of Public Health, Public Health research institute, Amsterdam, the Netherlands

Cees A. Swenne
Leiden University Medical Center, Heart-Lung Center, Department of Cardiology, Leiden, the Netherlands

Michael W. Tanck
Amsterdam UMC, University of Amsterdam, Department of Clinical Epidemiology, Biostatistics & Bioinformatics, Amsterdam Public Health research institute, Amsterdam, the Netherlands

Roderick W. Treskes
Leiden University Medical Center, Heart-Lung Center, Department of Cardiology, Leiden, the Netherlands

Galen S. Wagner
Duke University Medical Center, Duke Clinical Research Institute, Durham, NC, USA

Stafford G. Warren
Chesapeake Cardiac Care, Annapolis, MD, USA

Robbert J. de Winter
Amsterdam UMC, University of Amsterdam, Heart Center, Department of Cardiology, Amsterdam, the Netherlands

Ron Wolterbeek
Leiden University Medical Center, Department of Medical Statistics, Leiden, the Netherlands

LIST OF PUBLICATIONS

Included in this thesis:

ter Haar CC, Peter RJG, Bosch J, Sbrollini A, Gripenstedt S, Adams R, Bleijenberg E, Kirchhoff CJHJ, Alizadeh Dehnavi R, Burattini L, de Winter RJ, Macfarlane PW, Postema PG, Man SC, Scherptong RWC, Schalij MJ, Maan AC, Swenne CA. An initial exploration of subtraction electrocardiography to detect myocardial ischemia in the prehospital setting. *submitted*

ter Haar CC, Kors JA, Peters RJG, Tanck MWT, Snijder MB, Maan AC, Swenne CA, de Jong JSSG, Macfarlane PW, Postema PG. The prevalence of ECGs fulfilling STEMI criteria in apparently healthy individuals: the role of ethnicity. *submitted*

ter Haar CC, Man S, Maan AC, Schalij MJ, Swenne CA. Subtraction electrocardiography: Detection of ischemia-induced ST displacement without the need to identify the J point. *J Electrocardiol.* 2016 May-Jun;49:316-22.

de Jongh MC, **ter Haar CC,** Man S, Treskes RW, Maan AC, Schalij MJ, Swenne CA. Intra-individual ECG changes over 25 years: how long can elective ECGs be used as reference for acute ischemia detection? *J Electrocardiol.* 2015 Jul-Aug;48(4):490-7.

Treskes RW, **ter Haar CC**, Man S, de Jongh MC, Maan AC, Schalij MJ, Wagner GS, Swenne CA. Performance of ST and ventricular gradient difference vectors in the detection of acute ischemia on the ECG. *J Electrocardiol.* 2015 Jul-Aug;48(4):498-504.

ter Haar CC, Maan AC, Schalij MJ, Swenne CA. Directionality and Proportionality of the ST and Ventricular Gradient Difference Vectors During Acute Ischemia. *J Electrocardiol.* 2014 Jul-Aug;47(4):500-4.

ter Haar CC, Maan AC, Schalij M.J., Swenne C.A. Improved Electrocardiographic Detection of Hyperacute Ischemia by Difference Vector Analysis. *Computing in Cardiology* 2013

ter Haar CC, Maan AC, Warren SG, Ringborn M, Horáček BM, Schalij MJ, Swenne CA. Difference vectors to describe dynamics of the ST segment and the ventricular gradient in acute ischemia. *J Electrocardiol.* 2013 Jul-Aug;46(4):302-11.

Not included in this thesis:

Sbrollini A, de Jongh MC, **ter Haar CC**, Treskes RW, Man S, Burattini L, Swenne CA. Serial electrocardiography to detect newly emerging or aggravating cardiac pathology: a deeplearning approach. *Biomed Eng Online.* 2019 Feb 12;18(1):15.

Man S, **ter Haar CC**, Maan AC, Schalij MJ, Swenne CA. Position of ST-deviation measurements relative to the J-point: impact for ischemia detection. *J Electrocardiol.* 2017 Jan-Feb;50(1):74-81.

de Jongh MC, **ter Haar CC**, Man S, van der Heide MFJ, Treskes RW, Maan AC, Schalij MJ, Swenne CA. Changes in the ST- and Ventricular Gradient Vectors over a Period of 25 Years. *Computing in Cardiology* 2014

Treskes RW, **ter Haar CC**, Man S, de Jongh MC, van der Heide MFJ, Maan AC, Schalij MJ, Swenne CA. Reproducibility of ST and Ventricular Gradient Vectors. *Computing in Cardiology* 2014

ter Haar CC, Maan AC, Schalij MJ, Swenne CA. ST and Ventricular Gradient Dynamics During Percutaneous Transluminal Coronary Angioplasty. *Computing in Cardiology* 2012