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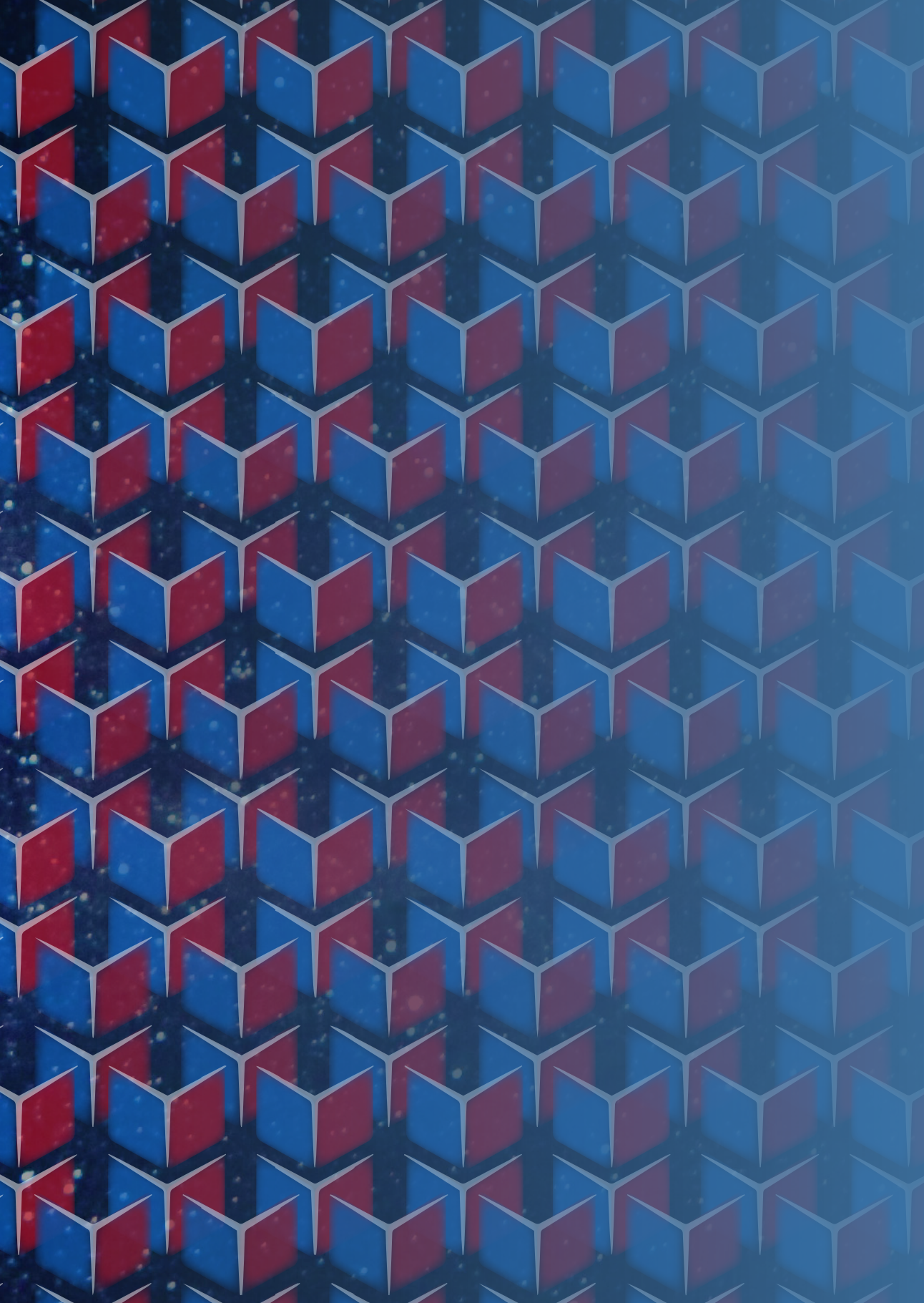

CHAPTER 8

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

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Abstract

Introduction

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

Methods

We analysed 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 favoured by the guidelines.(6)

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 also 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 analysed 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 10s ECG was selected in the baseline ECG, and a 10s 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 analysing 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.

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

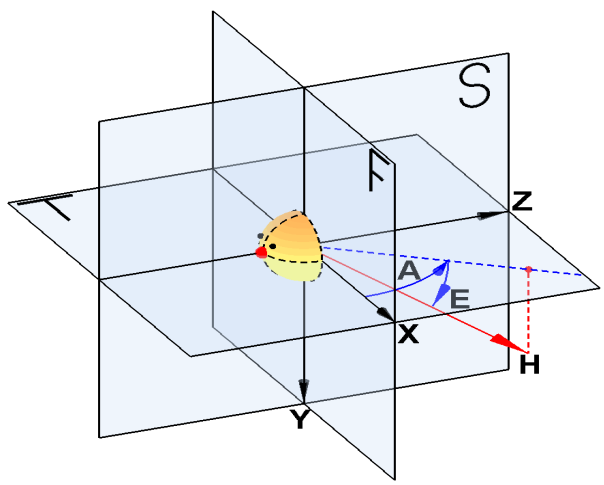

Figure 1. Graphical representation of vectorcardiographic conventions, from Man et al(16), with permission. F=frontal plane. S=sagital plane. T=transversal plane. X=vectorcardiographic x-axis, Y=vectorcardiographic y-axis, Z=vectorcardiographic z-axis. A=azimuth. E=elevation. H=heartvector. The directions of the x-, y-, and z-axes (the x-axis pointing leftwards, the y-axispointing 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)

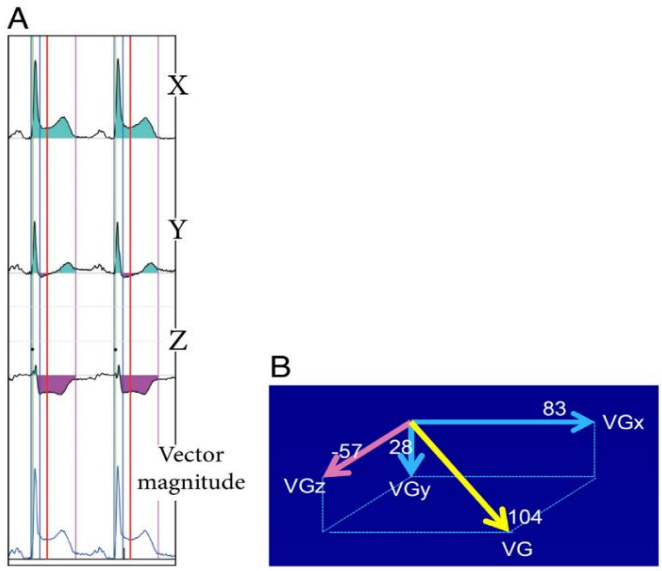

Figure 2. Illustration of the computation of the ventricular gradient, from Ter Haar et al., with permission(7). X=x-axis of the vectorcardiogram. Y=y-axis. Z=z-axis. Panel A depicts a vectorcardiogram, synthesized from a 12-lead 10-seconds ECG during balloon inflation, in which the patient had a completely occluded culprit artery. This vectorcardiogram consists of a x-axis, a y-axis and a z-axis. The time markers indicate onset QRS, the J points, J point + 60 milliseconds and end of the T wave. In this vectorcardiogram, the area under the curve from onset QRS to the end of the T wave is measured. Positive amplitudes in the area contribute positive to the area and negative amplitudes contribute negatively to the area. In this figure, 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. Panel B shows the x-, y- and z-components of the VG vector. 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 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 $kg \cdot m^2$, which means that a slightly overweight population was studied (Table 1).

Table 1. Patient characteristics of the controls

	N	%
N	398	
Age (years)	57±16.6	
Sex (male/female)	254/144	64/36
BMI ($kg \cdot m^{-2}$)	26.4±4.1	

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.

Table 2. Prevalence of main 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

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

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 abnormalities is given in Table 3.

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

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

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

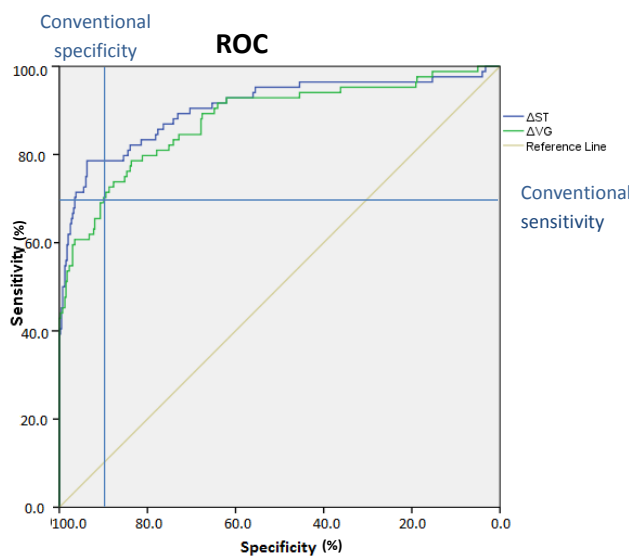

Figure 3. ROCs derived from DST (blue) and from DVG (green). The horizontal and vertical lines indicate the sensitivity and the specificity of the STEMI criteria, respectively.

Sensitivity and specificity of the conventional ST-elevation myocardial infarction (STEMI) criteria was 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, by a 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.

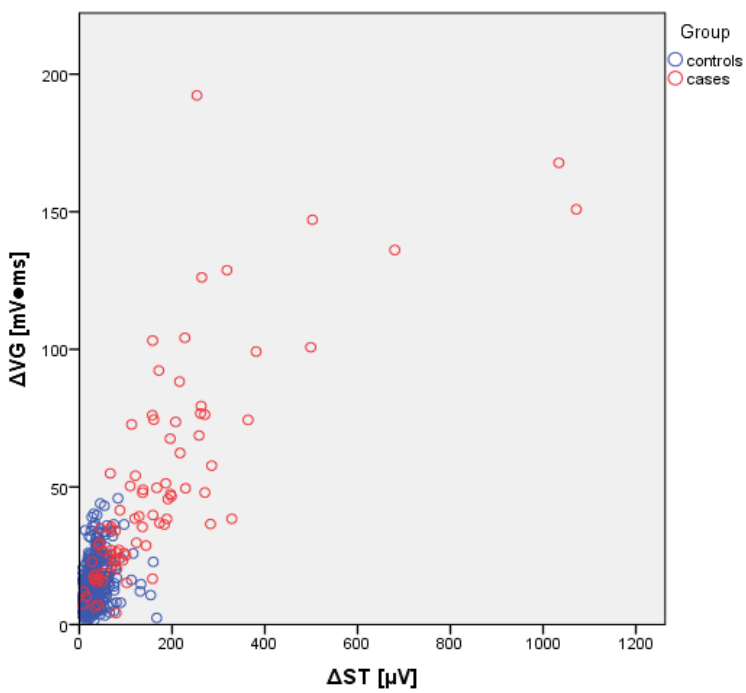

Figure 4. Scatterplot of the ΔST and corresponding ΔVG of both cases (red) and controls (blue).

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

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

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

*ΔST specificity differed significantly from STEMI specificity (*P*<.001).

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 artefacts 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, 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 (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 favours 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 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).

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