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Research Article

The role of Cardiogoniometry in detecting patients with acute coronary syndrome

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ABSTRACT

Background: Cardiogoniometry (CGM) is a novel electrocardiac method utilizing computer-assisted three-dimensional information on cardiac potentials.

Objectives: To study the efficacy of CGM in diagnosing non-ST elevation acute coronary syndrome (NSTE-ACS) and comparing its sensitivity, specificity and accuracy against high sensitive troponin test and a 12-lead ECG performed on admission.

Methods: A cohort of 100 patients (mean age 57 years, 37 % female) who presented with acute chest pain without ST-segment elevation and were scheduled for coronary angiography within 72 h of admission. Pre-angiographic screening by CGM, high sensitive troponin test and 12-lead ECG were compared with the final diagnosis of NSTE-ACS or relevant significant coronary stenosis(≥70 % stenosis).

Results: NSTE-ACS was finally confirmed in 87 cases, whereas the remaining 13 cases without proof of NSTE-ACS served as a control group. Diagnostic sensitivity of CGM for NSTE-ACS was found to be 74 % and its specificity was estimated to be 61 % with an overall accuracy of approximately 66%.The sensitivity of CGM to detect NSTE-ACS or relevant stenosiswas higher than the other diagnostic tools used in this study, even in patients with normal high sensitive troponin and normal ECG.

Conclusion: CGM can detect NSTE-ACS at first medical contact. CGM in conjunction with 12-lead ECG and high sensitive troponin may offer a very good tool for early and accurate diagnosis of NSTE-ACS.

Key words: myocardial ischemia, acute coronary syndrome, cardiogoniometry.

Introduction

Acute coronary syndrome (ACS) includes a range of various presentations including unstable angina and myocardial infarction which are further subdivided into infarctions with and without ST-segment elevation. In most cases, the pathology underlying ACS results from rupture or erosion of a thin fibrous cap of a lipid-rich atheromatous plaque, leading to thrombus formation.[1] Patients with unstable angina suffer from ischaemic symptoms, although their biomarkers do not show any evidence of myocardial necrosis.[2] Patients with clinical symptoms and elevated cardiac biomarkers may present with ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI). Current guidelines recommend early reperfusion therapy for STEMI and an early invasive strategy for NSTEMI.[3-5] A simple, reliable and rapid diagnostic tool is crucial for proper management of patients with ACS.[2,6]

Although a STEMI can be rapidly diagnosed using ECG in the majority of cases, NSTEMI and unstable angina, categorized as NSTE-ACS, may not show diagnostically significant changes on the ECG or elevations of cardiac markers at first medical contact.[7] This dilemma results in a significant consumption of time and healthcare resources. Moreover, traditional 12-lead surface electrocardiography, performed at rest, is considered a non-invasive andwidely available, but insensitive method for diagnosing ischaemic heart disease asautomated interpretation of the ECG isnot always reliable and the diagnosis depends largely on the expertise of the reader[8]

So, it can be claimed that until now, no screening method had been established for wide clinical application that could detect patients with ACS, especially those without symptoms, by a non-invasive, exercise-free, easily applied tool with automated interpretation – and moreover could be considered a screening method with feasible implementation in primary care settings. Therefore, there is still an unmet need for a practical, cost-effective and accurate diagnostic tool capable of detecting patients with NSTE-ACS or even relevant stenoses at first medical contact. Admitting that a chest pain unit can improve long-term outcome by prompt diagnosis and treatment of patients with an ACS, this is even more required.[9]

Cardiogoniometry (CGM) is a novel electrodiagnostic tool using computer-assisted three-dimensional information on cardiac potentials. It was introduced by Sanz et al. and has been adjusted for detection of coronary artery disease (CAD) in recent years by Schüpbach and Hübner.[9-11] In a prospective cohort of 332 subjects undergoing coronary angiography, the diagnostic accuracy of CGM was 71 % for detecting >50 % stenoses of the coronary arteries and thereby significantly better than that of a 12-lead ECG ($p < 0.003$).[10] Birkemeyer et al. prospectively evaluated the accuracy of CGM versus cardiac

magnetic resonance imaging (MRI) in 40 patients. CGM reached a high accuracy of 83%, a sensitivity of 70 % and a specificity of 95%.[12]

In summary, there are CGM studies of approximately 2,000 patients in various settings versus different reference standards available. In a review based on meta-analyses, the sensitivity of CGM has been described to be around 73 % and the specificity around 84 %, respectively, to detect CAD, myocardial ischaemia or structural myocardial damages.[13] Therefore, this study was conducted to investigate the potential of ECG, troponin and CGM to detect patients with NSTE-ACS after hospital admission.

Materials and methods

Study design and patients

This is a prospective observational study conducted at Wadi El Nile hospital to compare the specificity, sensitivity and accuracy of high-sensitive troponin test, 12-lead ECG and CGM for detecting NSTE-ACS on admission. Final confirmation of the diagnosis was based on all clinical data and coronary angiography findings.

In this study, patients admitted with acute chest pain and/or dyspnea were eligible for inclusion if they received an ECG and troponin test on admission and were scheduled for coronary angiography within 72 h. Exclusion criteria included ST-segment elevation myocardial infarction (STEMI), cardiogenic shock, presence of frequent cardiac ectopic beats (>50%), pacemaker, tachycardia >120 beats/min, bundle branch block and/or atrial fibrillation. All patients had to provide informed consent before inclusion. One hundred patients were finally eligible for analysis.

The following parameters were available for all patients enrolled in the study: patient history, cardiovascular risk profile, symptoms at admission, 12 lead ECG, two-dimensional and M-Mode echocardiography, troponin, CK, CK-MB and creatinine. Serial recordings of ECG and serial biomarker results were made available whenever needed. Two independent, blinded investigators evaluated the clinical diagnosis of the patients based on the data collected in addition to coronary angiography images that were analyzed using quantitative coronary assessment. A stenosis of at least 70 % in diameter of a major coronary artery was considered as significant.

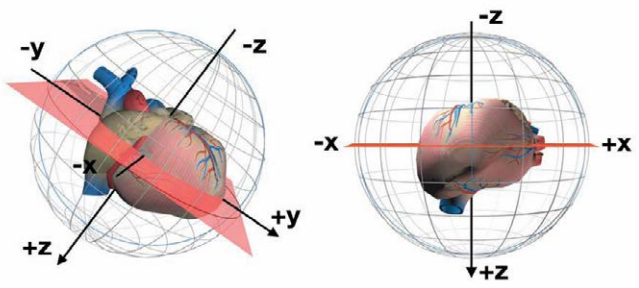

Figure 1: The projections x, y, and z are oriented relative to the heart. The OSP (red in the drawing) is the main plane, defined by the projections x and y. A globe is defined around the heart, with its centre at the origin of the orthogonal system, ie, at the point where the three rectangular axes x, y, and z cross. The spatial orientation of any vector measured can be defined with its projection onto the globe positioned around the heart [11].

Based on this validation of the patient's clinical course, including coronary angiography, patients were divided into two clinically distinct groups blinded by the results of CGM: The first group, NSTE-ACS, subcategorized into NSTEMI and unstable angina. NSTEMI was defined as patients presenting with acute chest pain without persistent ST-segment elevation according to the definition provided by Thygesen et al., but with elevation of myocardial markers such as troponin or CK-MB showing a typical rising and falling pattern. Unstable angina was defined according to Cannon and Braunwald in patients with negative biomarkers.[14,15] The second group included all patients with either cardiac symptoms, but no ACS, or non-cardiac symptoms.

The results of the immediate CGM, first ECG at rest and first high sensitive troponin test taken at the moment of admission to the hospital were compared with the final diagnosis established by the review board. When clinically indicated, serial sets of troponin tests were performed and included in the comparison. Then, we evaluated the true positive and false negative results obtained in the detection of NSTE-ACS and the true negative and false positive results used to detect patients of the control group, respectively. Finally, comparative analysis was performed as regard to significant coronary stenoses revealed by coronary angiography.

Cardiogoniometry

The trigonometric principles of CGM have been previously described in detail in several publications. Briefly, four electrodes define two perpendicular planes. Vectorial addition of the potentials measured between three electrodes in each plane generates a vector that corresponds to the projection of the heart vector into this plane. Using the vector projections in the two orthogonal planes, the heart vector can be reconstructed for every millisecond. The vector orientation denotes the direction and the vector length indicates the intensity of the electrical field generated by the heart.[9-13]

Three mutually orthogonal projections X, Y and Z are calculated in a trigonometrical manner. This Cartesian coordinate system (XYZ) is roughly orientated according to the anatomy of the heart and its orientation in the chest. This enables the visualization of spatial depolarization-repolarization and yields an instant cardiac interpretation of the recorded vectorial information (Figure 1).[9]

In CGM, deviations from the classical stimulus conduction pattern are mainly indicated as changes in the direction of maximum vectors. Hence, the spatial orientation of these vectors and their angles relative to each other are essentially sensitive in the detection of myocardial ischemia.[10] A total number of approximately 350 parameters can be obtained from the CGM featured automated data and divided into various classes. As CAD may alter the surface potential of the global cardiac activity in different ways, depending on the affected area of the myocardium, a combination of independent penalizing variables has been established to extract rhythm specific sets and is used in the standard CGM method since 2008.[11]

Hübner et al. stated that the specific parameters and the systematically computerized algorithm in the standard CGMare beneficial for detection of CAD categories. Although not every parameter is useful for every CAD category, the overall parameter set inside the standard CGM algorithm is independent of coronary stenosis localization and distribution or ischemia pattern. All parameters of a set must be in their reference range to give a score of zero (normal CGM). Each parameter outside of its presumed reference range counts for a negative score point. Any negative score point reflects a pathological (positive) CGM. In summary, CGM collects the temporal spatial information and their beat-to-beat variation and analyzes them to several relevant and measurable parameters that can be used as reference. On the contrary, traditional ECG only detects the cardiac electricity at 12 lead points over one heart cycle.[10-12]

In simple words, Cardiogoniometry is a new method to test heart function. It comprises a simple computerized vectorcardiography with a system of leads derived for the construction of three orthogonal projections. With the aid of these three-dimensional projections the cardiogoniometer, a microprocessor system, measures and computes the maximal vectors of depolarization (QRS) and repolarization (T). It also corrects the orientation of these two spatial vectors by projection on two planes (frontal and oblique sagittal) and determines the solid angle phi between them. Every third heart beat these five parameters and the preceding beat interval are captured and printed out. In such a way, a set of measurements is produced in which only minor disturbances of the signals of cardiac de- and repolarization occur. In patients with coronary insufficiency an abnormal position of the T vector can be detected long before a pathological pattern appears in the standard ECG.

The CGM measurements were obtained by positioning five leads on the supine patient and using commercially available hard and software (Cardiologic Explorer system, enverdis, Jena, Germany- model: E12K3U). During the recording, the patient was asked to perform shallow breathing to minimize thoracic excursions.

If all the parameters recorded on a patient are within normal range, a score of zero is given, i.e., the CGM is negative. If any parameter is out of range, the score is below zero, thus denoting a pathological or "positive" CGM. The instant, automatically produced finding was registered as the CGM diagnosis. Although the term "score" is used, the CGM yields a distinct result of "positive" or "negative" CGM. The numerical value of the score below zero does not indicate the severity or extent of ischemia.

Troponin and ECG

Highly sensitive troponin T was used. A value within the reference limit of the test kit was considered to be negative, while a value above the upper limit of the normal reference was regarded as positive. With respect to serial troponin results, a test was considered positive if at least one of the measurements was positive. Conversely, a serial troponin testing had to be regarded negative if every single test at different time points was negative. An ECG with persistent or transient ST-segment, new horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads and/or T inversion ≥0.1 mV in two contiguous leads with prominent R-wave or R/S ratio >1 was regarded as indicative of acute myocardial ischaemia and therefore considered positive; all other cases were registered as negative.[14]

Statistical analysis

Data are presented as absolute numbers, percentage or medians as appropriate. Categorical values and the predictive values were compared by Chi-square test or Fisher's exact test in smaller sample sizes. Continuous variables were compared using the two-tailed Wilcoxon rank sum test. The McNemar test was performed to compare sensitivities, specificities and the diagnostic accuracy of CGM, ECG, and Troponin. p values <0.05 were considered significant. All statistical analyses were performed using SAS statistical analysis software 9.1.

Results

The baseline characteristics, demographic data, past history and clinical presentation of the patients enrolled in this study are listed in table 1.

Values are mean ± SD or n (%).

In the total cohort of 100 patients, NSTE-ACS was confirmed in 87 patients, the remaining 13 patients were diagnosed to have cardiac disease other than ACS or to have chest pain of extra-cardiac origin after the final analysis and establishment of the diagnosis by the study review board.

The diagnostic yield of the different diagnostic methods used in identifying NSTE-ACS versus control and in detecting relevant coronary stenoses (≥70 % diameter) is shown in Table 2. It was demonstrated on the study population that CGM was the most sensitive and consistent method for detecting and classifying a NSTE-ACS at first medical contact with the patients. CGM showed a total sensitivity of 74% and a specificity of 51% in detecting NSTE-ACS, whilst, its overall accuracy was found to be 64%.

In patients presented with acute chest pain, 56% had a

Table 1: Baseline characteristics of the study population.

Demographic information	
Age, yrs	57±6
Female, %	37%
BMI, kg/m^2	26±3
Relevant medical history	
Arterial hypertension	66%
Diabetes mellitus	23%
Smoking	41%
Hyperlipidemia	26%
Family history of CAD	8%
Previous MI	2%
Previous PCI	4%
Previous CABG	0%
Previous Stroke	1%
Peripheral vascular disease	2%
Clinical presentation	
Chest discomfort	88%
Dyspnea	8%
Others (e.g. sweating, left arm pain,…)	4%

Table 2: Comparison between the different diagnostic tools used.

	First ECG*	First troponin	Serial troponin**	First CGM
Sensitivity	28%	34%	52%	74%
Specificity	77%	89%	87%	61%
PPV	67%	90%	91%	69%
NPV	26%	35%	43%	56%
Accuracy(correct classification rate)	42%	47%	58%	66%

* ST elevation or ST segment depression, T inversion or ventricular arrhythmia or LBBB or RBBB = "Test positive"
** 1st, 2nd or 3rd troponin test abnormal = "Test positive"
PPV, Positive predictive value; NPV, Negative predictive value

without any evidence of acute ischemic episode, while the remaining 20% were diagnosed to have non-cardiac conditions.

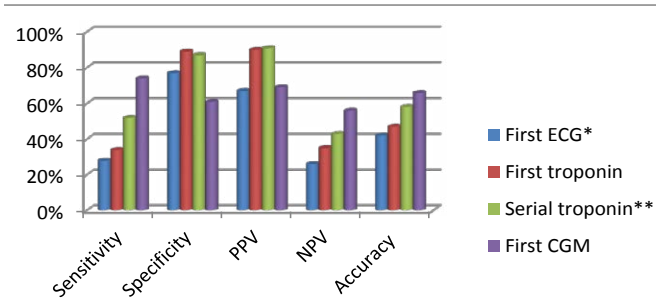

Figure 2:Diagrammatic representation of the diagnostic yield of the different diagnostic methods.

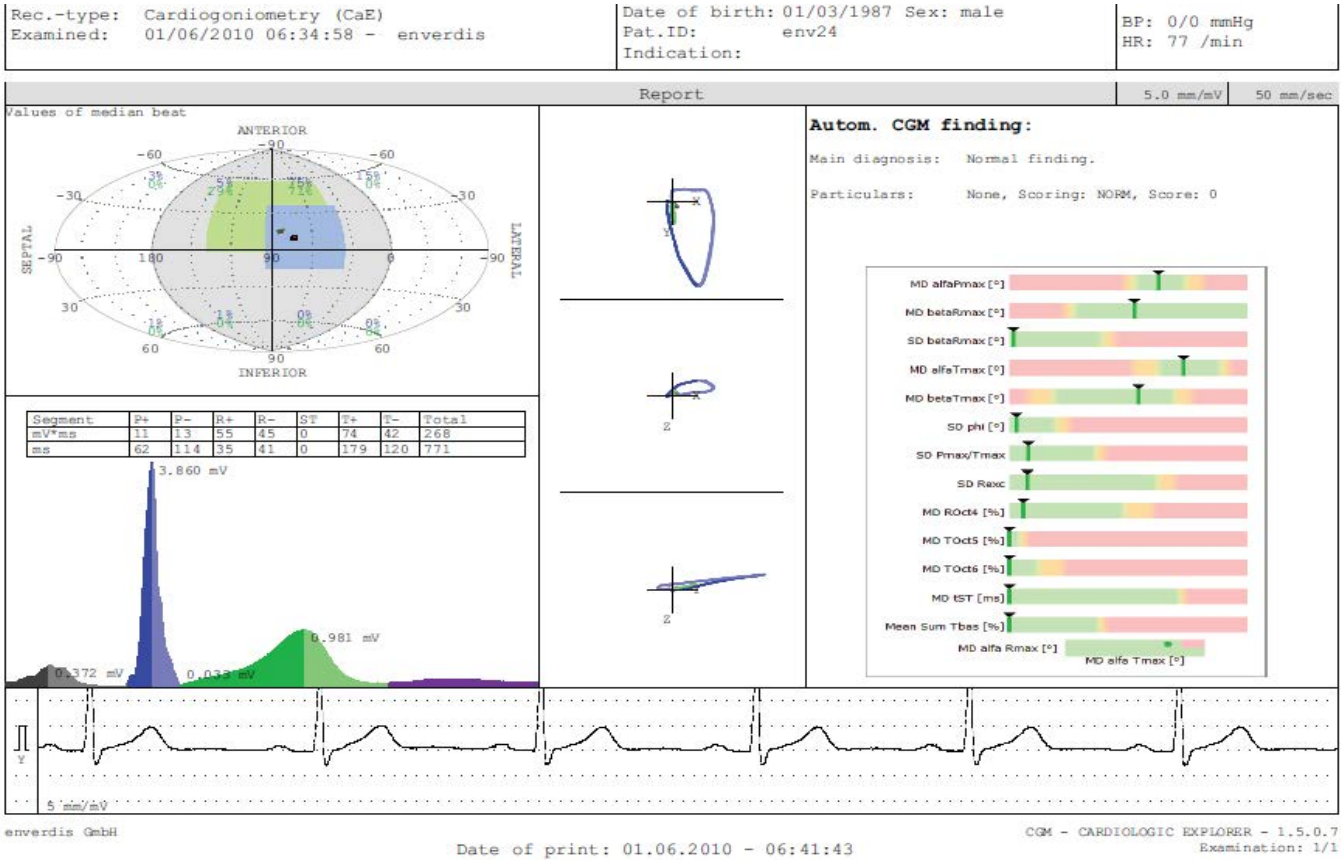

Figure 3: Example of normal CGM result.

negative ECG and a negative troponin. In this subgroup, CGM revealed a sensitivity of 68 % and accuracy of 66 % in detecting NSTE-ACS and a sensitivity of 72 % and accuracy of 65 % in detecting patients with significant coronary stenoses in the coronary angiogram (figure 2).

Patients who were later confirmed to have NSTE-ACS had a longer duration of symptoms prior to hospital admission than the control group; however, this was not significant. Conversely, the time from presentation to coronary angiography (door-to-needle time) was significantly shorter in NSTE-ACS patients. The clinical presentation and haemodynamics of patients with NSTE-ACS were similar to those of the control group, although associated dyspnea was found to be more frequent in the NSTE-ACS group. In addition, 80% of the control groups were found to have chronic stable myocardial ischemia

Discussion

Acute coronary syndrome still comprises a major health problem in both industrialized and developing countries. Owing to its deleterious impact on the public health, resulting in profound morbidity and mortality, a considerable amount of resources is directed towards its early detection and prompt management. Unfortunately, until now, no procedure has been established for clinical application, which is non-invasive, stress-free, easy to apply and automatically interprets the results, especially at first medical contact in the primary care units.

Admittedly, the accuracy of resting 12-lead ECG for diagnosing unstable angina or non-ST-segment elevation infarctions tends to be substantially low. One study on this

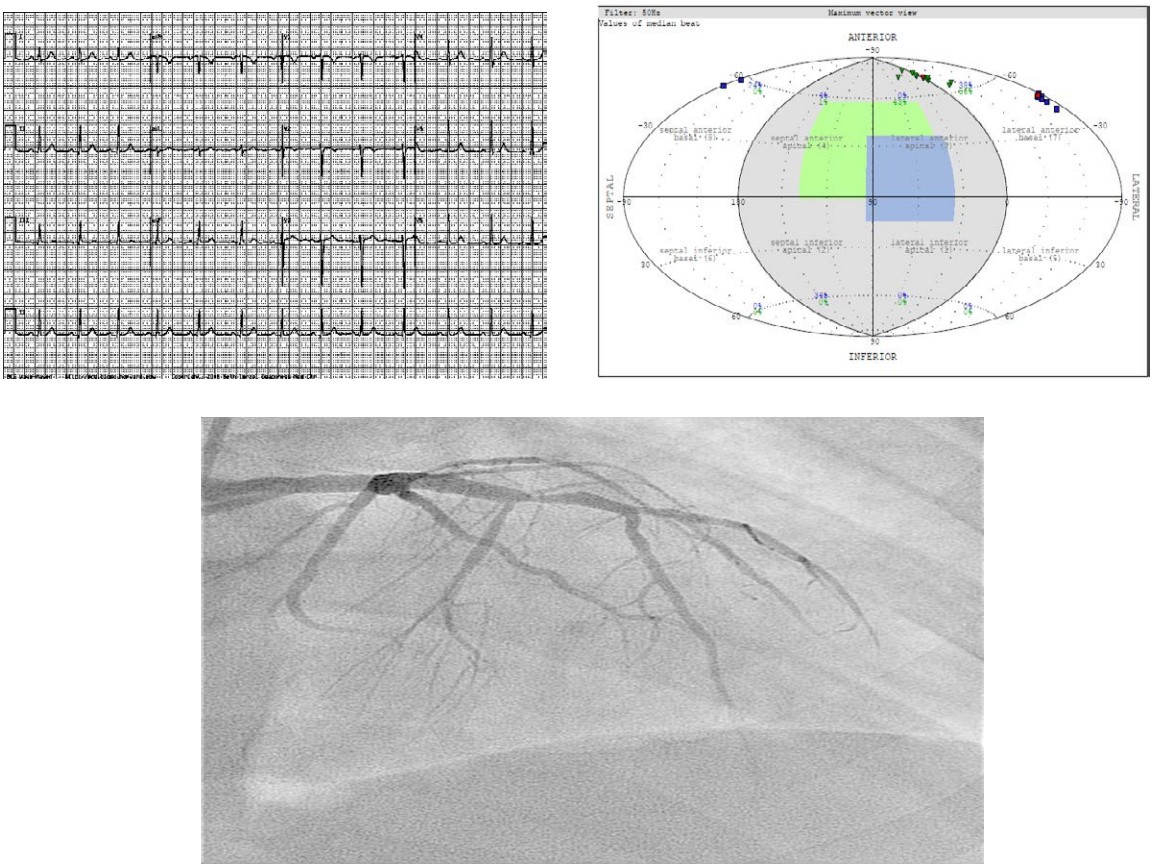

Figure 4: In this case, while ECG was normal (a) and First set of troponin was negative, CGM indicated anterior ischemia which was later confirmed by coronary angiography and the patient was proved to have ACS.

subject reported a sensitivity for detecting NSTE-ACS of not more than30%.[13] On the other hand, the troponin test can bring ultimate certainty in diagnosing non-STEMI; yet, the enzymes relevant to this test are not released until 4-6 hours after the infarction and are therefore not detectable until after this delay. So, there is a 4-6-hour window of uncertainty as to whether a non-STEMI has already taken place. Moreover, by definition, patients with unstable angina cannot be diagnosed by troponin. Particularly in the case of incipient infarction, the earliest possible detection and therapy of acute ischemic conditions is of profound prognostic importance.[16]

Cardiogoniometry (CGM) can close this gap. It is an automated procedure for the diagnosis of acute myocardial ischemia which can be performed on a resting patient within a few minutes. Since our knowledge of the transient or persisting mechanical abnormalities in acute or chronic myocardial ischemia like stunning or hibernating myocardium is limited to the cellular level, it is well conceivable that we can detect more electrical phenomena at rest related to acute myocardial ischemia with the use of a more sensitive electrocardiographic probe. This might overcome the paradigm that electrocardiographic methods necessarily need to be combined with stress to detect ischemia.

We hypothesized that CGM can detect changes in the electric cardiac phenomena, even at rest, in patients suffering from acute myocardial ischemia. The rationale for this is based on three fundamental criteria:

1) CGM provides three-dimensional information about the voltage and spatial orientation of the summation vector of the surface potential, which cannot be obtained by the conventional ECG.

2) CGM produces measured quantitative computer analysis of this three dimensional information; the rating does not require a qualitative evaluation by an expert.

3) CGM allows spatial analysis of beat-to-beat variability.

Clinical trials validating CGM have been published including a total number of approximately 2,000 patients with different patterns of myocardial ischemia and in comparison to various reference methods (e.g. coronary angiography, cardiac-MRI, SPECT). The average sensitivity and specificity of the CGM for the detection of acute myocardial ischemia was estimated to be around 73% and 84% respectively. Further controlled studies determine the significance of CGM as a diagnostic method for suspected coronary heart disease as well as an acute coronary syndrome without ST-elevation.

CGM differs from conventional seven-lead Frank vectorcardiography in two main aspects. First, CGM is recorded with five leads (4 electrodes and 1 ground) without intercalated resistor networks (uncorrected technique). The geometrical electrode placement in an orthogonal system avoids the distortions associated with the traditional vectorcardiography. In CGM, the electrode position and the trigonometrical constructions result in a mathematically correct orthogonality of XYZ projections. Second, CGM projection planes are not

aligned with the body planes but rotated to approximately match the anatomical orientation of the heart similar to the short axis scan of an MRI.[12]

The findings of our pilot study suggest that CGM is significantly superior to 12-lead resting ECG and first set of high sensitive troponin test at first medical contact for detecting patients with acute myocardial ischemia. On the other hand, by definition of NSTEMI, defined by elevation of myocardial markers, false positive troponin due to other causes is very rare. Logically, the positive predictive value of troponin was found to be high, which only means if there is a positive troponin, the diagnosis of NSTE-ACS is very likely. Notably, the negative predictive value of CGM exceeded that of troponin, so itsability to detect a true "healthy" subject is considerable.

Hence, CGM produced a high sensitivity and accuracy for the early detection of NSTE-ACS in the overall cohort. Furthermore, CGM results were obtained immediately at the time of admission and their sensitivity did not show any time dependency. CGM should neither challenge the role and clinical importance of cardiac biomarkers like troponin, nor does it provide any information on outcome so far, but with its sensitivity for NSTE-ACS it can be used as a complementary diagnostic tool in the first assessment of patients with suspected ACS, particularly in case of early presentation after chest pain, as the first ECG and troponin at admission seemed to have a poor sensitivity of 28 and 34 %, respectively.

Clearly, this does not necessarily mean that all positive CGM should be followed by an immediate coronary angiography but could at least alert the physicians' attention especially in the case of a normal ECG and normal troponin at admission. Overall, performance of CGM was at least superior to conventional 12-lead ECG. Although, a significantly higher sensitivity is contrasted by a significantly lower specificity of CGM compared to ECG, but CGM shows higher positive and negative predictive values and a better accuracy than ECG.

Due to the simplicity, cost-efficiency of an automatic analysis as well as a diagnosis without physical or medical stress, this method is primarily suitable for general practitioners. Consequently, in patients with non-specific chest pain, unspecific ECG and initially negative troponin test, a positive CGM substantiates the suspicion of a present acute coronary syndrome. If all three methods of examination are negative, a non-ischemic cause is the possible reason for chest pain.

The major limitations of this study are the relatively small overall sample size and the fact that the majority of patients in the control group had stable coronary artery disease (80%) without ACS, which is thought to be the reason for the relatively low specificity estimated for CGM (being able to detect all patterns of myocardial ischemia both acute and chronic).Besides, we investigated a highly selected cohort of patients with chest pain who underwent an early invasive treatment strategy. We therefore might have a higher pre-test probability for NSTE-ACS patients resulting in a larger number of patients in the final NSTE-ACS group and fewer patients in the control group.

Conclusion

Cardiogoniometry is a novel, easy-to-use electro-diagnostic method that can help detect patients with acute coronary syndrome at first medical contact. CGM demonstrated high diagnostic sensitivity and accuracy in detecting patients with NSTE-ACS or relevant coronary stenoses. Owing to its considerable high sensitivity and accuracy in cases where both troponin and ECG are negative, it may provide an added benefit as a diagnostic tool in the early detection of ACS.

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