



Digital Analytic Cardiography (DACG), a New Method for Quantitative Trophism Assessment of the Myocardium

Alekseyev Michael^{1*}, Alekseyev Aleksandr², Dowzhikov Andrew³ and Labin Sergei⁴

¹Associate Professor, St. Petersburg Academic University, Russia

²Associate Professor, Pavlov's State Medical University of Saint-Petersburg, Russia

³Associate Professor, Pavlov Institute of Physiology Russian Academy of Sciences, Russia

⁴Programmer, Pavlov's State Medical University of Saint-Petersburg, Russia

*Corresponding author: Alekseyev, 197755, Saint-Petersburg, Mejevayastreet, 42, Russia, Tel: +78124348576; E-mail: Alex-skorost@mail.ru

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Abstract

Background: At present, none of the available ischemic heart disease (IHD) diagnostic methods can reveal the disease with 100% certainty.

Methods and Results: DACG, a new method of ECG signal processing, has been utilized to calculate the criteria. We observed 5 groups of patients: 2 control without IHD; one group with IHD, 8 of whom were observed before and after using nitrates; and 2 patients with syndrome X. There were authentic augmentations of all worked-out criteria (G, L, S) in the ischemia zone of the myocardium in relation to the non-ischemic zones (from 2 to 7). In the control, all criteria oscillate from 0 to 1.5. The value of the G criterion has a strict correlation with the functional classification of IHD. We observed a strong correlation between the clinical effect by nitrates and our criteria. The absence of a clinical effect by nitrates correlated with no dynamics in all criteria. The combination of the absence of criteria and clinical effect by nitrates with elevated L criteria led to acute myocardial infarction in a few hours. We developed non-locality in the ischemic process in patients with syndrome X with significant augmentation of the G and L criteria in all zones of the myocardium.

Conclusions: The proposed DACG method allows for authentically diagnosing IHD and its functional class impartially, as well as localizing the ischemic process and qualifying its depth quantitatively.

Keywords: ECG criteria; Electrocardiography, Infarct and infarction; Acute Coronary syndrome; Nitroglycerin; Trophism of myocardium; Quantitative criteria

Introduction

Ischemic Heart Disease (IHD) causes more deaths and disability and brings greater economic losses than any other illness in the

developed world. The most common causes of myocardial ischemia is atherosclerotic disease of an epicardial coronary artery, micro vascular dysfunction, and vasospasm sufficient to cause a regional reduction in myocardial blood flow and inadequate perfusion of the myocardium supplied by the involved coronary artery. All the diagnostic methods of ischemic heart disease can be divided into primary and secondary groups. The primary methods include anamnesis (symptoms, data of previous infarctions), biochemical tests, and electrocardiogram. Stress imaging, exercise electrocardiogram, echocardiography, invasive coronary angiography (the "gold standard" in depicting epicardial coronary artery disease (CAD), coronary computed tomography angiography (CTA), and magnetic resonance imaging (MRI) angiography compose the secondary methods group, because they need preliminary information for their use in every concrete clinical case.

There are many patients with or without risk factors of heart disease, but they have no symptoms of IHD in the anamnesis. According to data from the Framingham Heart Study (FHS) of the National Heart, Lung and Blood Institute (NHLBI), 5 - 50% of men and 64% of women who died suddenly of CHD or who were presented to the hospital with ACS had no previous symptoms of this disease [1,2]. Based on data from the Atherosclerosis Risk In Communities (ARIC) study of the NHLBI, this year, approximately 620,000 Americans will have a new coronary attack (defined as first hospitalized myocardial infarction (MI) or coronary heart disease (CHD) death), and 295,000 will have recurrent attack. It is estimated that 150,000 additional silent MIs occur each year. This assumes that 21% of 720,000 first and recurrent MIs are silent [3,4]. The NHLBI's FHS found that AMI rates diagnosed by electrocardiographic criteria declined ~50% [7]. The percentage of ACS or MI cases with ST-segment elevation varies from 29% to 47% in different registries/databases [5,6]. Categorizing the types of angina pectoris is clinically useful and is one of the cornerstones of estimating pre-test probability for the presence of epicardial CAD. Reliance on ischemia testing or the depiction of the coronary anatomy is often unavoidable. The difficulties associated with distinguishing between function and anatomical CAD may explain why even in the early days of coronary angiography, when the indications for this procedure were possibly more strictly handled than today, normal or near-normal coronary angiograms were found in close to 40% of patients, a percentage similar to that found today. Various studies have determined that approximately 10 to 30% of patients undergoing cardiac catheterizations to evaluate angina-like chest pain have normal coronary angiograms [8,9].

Syndrome X takes a special place among modern cardiology problems. Patients with normal coronary arteries in angiography are known to have typical angina pectoris and myocardial infarction [8-14]. Typical ischemic chest pain associated with cardiac enzyme elevations but without identifiable lesions in coronary angiography occurs more frequently in clinical practice than often realized. A majority of these patients (70%) are peri- or postmenopausal women [15-22] and younger than usual age for atherosclerotic CAD (sportsmen). It has been observed that more than 50% of angiograms done on women show no significant CAD [23]. Several investigators have demonstrated that despite normal coronary vessels, electrocardiographic evidence of myocardial ischemia exists in affected patients as well as in their metabolism [25-30].

Although the origin of the syndrome is still debated, studies suggest that coronary microvascular dysfunction plays a crucial role in its genesis [29]. Management of CSX represents a major challenge to both the patient and the physician, and understanding the mechanism underlying the condition is of vital importance for patient management. These findings may explain why corresponding groups of patients do not receive the adequate medicine control that they need.

That is why the current study is devoted to the development of quantitative criteria to allow for reliable IHD diagnostics.

Material and Methods

A few series of digital ECG registration were made with a 12-channel electrocardiograph (Diamant-Holter) on certain groups of patients within this study framework. The ECG signal records were processed by the original program, which estimates temporal and amplitude parameters which reflects the process of myocardium depolarization and repolarization. The patient groups consisted of 25 young healthy people of age 18 ± 2.2 , 10 patients of age 42 ± 6 without clinical presentations of IHD (according to ECG (Echocardiogram) data), and 32 patients of age 68 ± 10 suffering from proven IHD of different functional classes. For the last group, the IHD diagnosis was confirmed by clinical implications in 32 cases, by anamnesis of angina pectoris with a good positive effect of nitrates in 29 cases, by myocardial infarction data in anamnesis in 16 cases, by common ECG diagnostic ST changes in 25 cases, by coronary angiography in 17 cases, by treadmill test in 5 cases, by stress echocardiography in 3 cases, and by positron emission tomography in 2 cases.

During clinical work with these 32 patients, 8 episodes of typical angina pectoris were observed. The pain episodes were treated in 7 cases with 0.4 mg of nitroglycerin sublingually, resulting in complete relief of symptoms in 5 cases and partial relief in 2 cases, while in one special case, the treatment involved use of a long-lasting nitrate drug (isosorbidedinitrate, 5.0 mg/h intravenous). In this last case, the treatment had no effect, and an AMI episode eventually occurred in a few hours. Also, we observed and recorded 2 patients with syndrome X (81 and 59 years old) with everyday episodes of chest pain and a good effect of nitrates, with transient myocardial ischemia and prolongation of repolarization (QT lengthening) without evidence of coronary atherosclerosis or vasospasm on coronary angiograms.

Results

For obtaining an intuitive idea of the trophism of the myocardium, we used a method involving the regularity of the criteria distribution among pectoral ECG leads (V1-V6) in every case. The ischemic process in the heart is almost always localized in clinical practice. Anecdotally, the total ischemic process (AMI) was observed in only 3 cases in 40 years of clinical experience, and all 3 cases were diagnosed in autopsy.

For clarity, the values of the criteria were reduced to unity. The regularity of the criteria distribution among pectoral leads (V1-V6) for the first control group (18 ± 2.1 years old) is presented on the Supplementary Figure 1. All 3 criteria (G, L, S) have different values. The oscillations of the mean corresponding to the G criteria among the pectoral ECG leads vary from 4.7 to 6.8, those corresponding to L criteria vary from 2 to 3.1, and those of the S criteria vary from 1.04 to 1.12. The magnitude of these oscillations is not significantly different among pectoral leads ($p > 0.05$).

The regularity of the criteria distribution among pectoral leads (V1-V6) is presented for the second control group (53 ± 8 years old) in Supplementary Figure 2. All 3 criteria also have different values in this case. The oscillations of the mean corresponding to the G criteria among pectoral ECG leads vary from 4.6 to 6.85, those of the L criteria vary from 2.12 to 3.25, and those of S criteria vary from 1 to 1.14. Like in the first control group, the magnitude of these oscillations is not significantly different among pectoral leads ($p > 0.05$).

Of particular importance is the group of 32 patients with different IHD localizations and functional class at the moment of recording. For better illustration of the results in this group, we show the concrete patients with different localization of ischemic changes of the myocardium. In Supplementary Figure 3, we show a patient with anterior lateral wall ischemia.

There are significant changes in all 3 worked-out criteria. They demonstrate authentic elevation in the ischemic zone in relation to the non-ischemic one (by times in the S criteria, 5.7 times in the L criteria, and 5 times in the G criteria). The maximum sensitivity is shown in the L criteria in lead V4. All results correlate with the changes in routine ECG and the coronary angiogram.

In Supplementary Figure 4, a patient with ischemia changes of the lateral wall of the left ventricle are presented. The results show significant changes in all criteria, as in the previous case. The S criterion is elevated by 2 times in the ischemic zones in relation to the non-ischemic areas, while the L criterion is elevated by 5 times and the G criterion by 3.7 times. Also, in this case, the maximum sensitivity shows the L criteria in lead V6 (elevation by 5 times). All results correlate with the changes in routine ECG in leads V4, V5, and V6. These two patients were registered during an episode of angina pectoris. Another 30 cases have the same differences among pectoral leads, and the significance of these depended on the functional class of IHD and the localization of the ischemic process.

All patients with IHD were divided into groups at the moment of our ECG registration according to the functional class by NYHA. The group with class II involves 11 patients, the group with class III- has 13 patients, and the group with class IV and unstable angina pectoris (UA) involves 8 patients. The results are presented in Supplementary Figure 5.

In the group with class II, the ratio of the G criteria in the ischemic zone in relation to the non-ischemic one is 1.47 ± 0.44 , that in the group with class III is 3.38 ± 0.61 , and that in the group with class IV and UA is 5.87 ± 1.28 . The differences among means ($p = 0.0068$ among III and IV classes, $p < 0.001$ among classes II and III, II and IV).

The results of nitrates administration take a special place in our study. 8 patients using nitrates for the reduction of angina pectoris were included in the group. In 7 cases, 0.4 mg of nitroglycerin spray was used, and 5.0 mg/h of intravenous isosorbidedinitrate was used in only 1 case (Patient G). The recording was made before using the nitroglycerin and from 8 to 10 minutes after. In the case with patient G, the recording was made before using the isosorbidedinitrate and 1 hour after.

Supplementary Table 1 presents the results of criteria value before and after administration of nitrates. The values were also calculated as the ratio of the peak mean of the criteria in the ischemic zone to the minimal mean in the non-ischemic zone of the myocardium. As shown in the table, the ratio of the G criteria decreased in all cases corresponding to the normalization of trophism in the ischemic zone.

The variability ranges from 11% to 42%. The dynamics of the L criteria was multidirectional from 67% in the direction towards the normalization of trophism to 175% in the negative direction. In 3 cases, there were no changes of the ratio of the L criteria. For the S criteria, the ratio changes in the positive direction from 28% to 75% in only 3 cases, and 5 patients had no changes.

The reaction of patient P is given as an example for illustration in Supplementary Figure 6, who was treated with 0.4 mg of nitroglycerin with a positive clinical effect. In this diagram, the value of G criteria in lead V4 decreased from 20 to 6 towards the mean of non-ischemic zones of the myocardium (leads V1-V3). The value of G criteria in V5 also decreased from 13 to 11, but in V6, the value increased from 6 to 10. The mean of L criteria in lead V4 also decreased from 17 to 6 and approximated the value in other leads. In contrast, the S criteria increased its mean in leads V1, V2, and V5 and had no reaction in leads V3, V4, and V6. The absence of dynamics of the S criteria in the ischemic zone and reverse dynamics in the non-ischemic zones of the myocardium are notable. The administration of nitrates balances the trophism of the myocardium in the majority of patients presented. This fact developed in arresting the episode of angina pectoris. The reverse dynamic of L criteria was only observed in 2 cases (patients S* and A*), which indicates no significant positive clinical effect by using nitrates.

Notably, with patient G** (Supplementary Figure 7), we observed ischemic changes mostly in leads V3, V4, V5, and V6 (by more than 4.25 times that in the non-ischemic zone of the myocardium in the G criteria and more than 7.5 times in lead V5 in the L criteria). After using the nitrates, there was no significant dynamics in G, L, and S criteria. The maximum ischemic changes retained by G criteria and especially L criteria in leads V4, V5, and V6 is 4 to 4.5 times in relation to the non-ischemic myocardium. Acute myocardial infarction was diagnosed in the lateral wall of the left ventricle with elevation of its biomarkers. 2 facts come to our attention. According to the routine electrocardiographic data and the data of coronary angiography, the ischemic changes were expected in the anterior wall. AMI was developed in the lateral wall of the left ventricle, which was indicated in the G criteria and especially the L criteria in V4, V5 and V6.

The result of processing the data of 2 cases with syndrome X is also notable. The results of one case are presented in Supplementary Figure 8. As shown in these diagrams, there is significant elevation of the G criteria in all leads, which attains a level of 19. This elevation of the G criteria is comparable with evident ischemia, but there is no locality of the pathologic process. The ratio of the maximum value in V4 in relation to the minimum values of V1 and V6 ranges from 1.9 to 2.1. The same changes are in the L criteria, and the mean oscillates between 5 and 7, which also indicates ischemia without precise locality of the process.

Discussion

The proposed DACG method of ECG registration and analysis allows for the assignment of criteria which give a quantitative estimation of trophism systems of the myocardium. The most labile is the G criterion. Significant elevation of the G criteria in ischemic zones (by 7 times in relation to the non-ischemic zones) along with strong correlation between G criteria and functional class by NYHA give confidence in the diagnostics of ischemic heart disease. Even in difficult clinical cases with atypical chest pain, the diagnosis of IHD with low functional class was proven by stress testing and elevation by

2 times of the G and L criteria in appropriate leads (corresponding to zones of the myocardium).

The L criterion is no less important, though less labile, and it is elevated by 7 times in the ischemic zone before the development of AMI within a few hours. This method allows us to prove the diagnosis in all patients we observed with ischemic heart disease. The parallel diffuse elevation of both G and L criteria in all leads without clear localization of the pathologic process has been observed in only patients with cardiac syndrome X. Angina-like chest pain without flow-limiting stenosis in coronary angiography and the data of our study allow for another mechanism of IHD to be revealed, which is independent of the condition of the coronary arteries.

The combination of an absence of dynamic criteria and clinical effect by nitrates with increasing elevation of the criteria, especially the L criteria, speaks in a favor of a fundamentally new and much more drastic process in the ischemic zone, which precedes the development of AMI. It can be concluded that the criteria are very sensitive (especially the G criteria), and the dynamics of their changes during management of nitrates has been demonstrated. These findings can be used in usual clinical practice and further research.

Clearly opposite dynamics of the criteria exactly in the ischemic zone after the administration of nitrates allows us to assume the participation of adenosine receptors (A1, A2) in the genesis of ischemic zone [35]. This assumption was made based on data of the adenosine effect in adenosine A1, A2 receptors, the features of its metabolism in the ischemic myocardium, and data of altered cardiac sensation in patients with chest pain [35-43]. Significant elevation of the G and L criteria in patients with syndrome X and response to the administration of adenosine according to experimental data of enhanced pain perception [31-33] also allow us to prove the participation of adenosine receptors in both the genesis of the ischemia zone and in the genesis of cardiac syndrome X [39].

Besides the localization of the ischemic process, its depth has decisive importance. To categorize the evidence of ischemia, classifications are used in clinical practice, which divide patients into functional classes according to their tolerance and amount of physical activity. However, factors like individual tolerance, trained status of patient, the value of individual pain threshold (including the asymptomatic ischemia with and without diabetes mellitus) and emotional status are not taken into account. That is why in Supplementary Figure 5, a clear correlation between the functional classes of patients and G criteria was demonstrated, which can be used to impartially estimate the ischemic status of the heart.

Conclusions

The developed method DACG allows for authentically diagnosing IHD and its functional class impartially, as well as localizing the ischemic process and qualifying its depth quantitatively. Highest sensitivity can be used for the adjustment of individual therapies in each clinical case on-line with the prognosis of its efficacy. The diagnostic criteria of syndrome X and their combination preceding acute myocardial infarction have been detected. Another mechanism of IHD which is independent of the condition of coronary arteries has been indicated.

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