

MAGNETOCARDIOGRAPHY: EARLY DIAGNOSTIC OF HEART DISEASES

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ABSTRACT

Noninvasive screening technique to identify cardiac disease in its early phase is developed. Magnetic imaging of cardiac action currents is a new and an ideally suited technology for testing the level of local electric heterogeneities of myocardium. Magnetocardiography (MCG) has the potential to make a valuable contribution in basic examination and analysis of biosignals of a heart, in particular whilst all vector components are used, vast spatial coverage and excellent signal quality. Browsing the data for the sake of reliability by QT-interval can be useful for the better reproducibility of high performance MCG. MCG in therapeutic practice can be used to address the following objectives: a) determining presence and intensity of myocardial ischemia, b) assess effectiveness of antianginal therapy; c) assess the risk of paroxysm of ventricular tachycardia; d) objectivize presence of cardiac deficiency.

KEYWORDS: Magnetocardiography, Electrical Heterogeneity, ECG, Noninvasive Electrophysiology, Arrhythmia

1. CLINICAL APPLICATION OF MCG

Clinical MCG investigations have revealed applications that appear to be most attractive, and these are the localization of preexcitation sites in the WPW Syndrome and other arrhythmias along with the detection of myocardial ischemia and viability.

Since 1985, MCG studies have been focused on demonstrating the high accuracy of localization compared with other available clinical techniques. R Fenici et al. [1] demonstrated clearly the superior ability of MCG to localize a current source compared with BSPM. All these years numerous theoretical and experimental research have been conducted on the quantitative estimates of the sensitivity and specificity MCG-method applied to various cardiac failures. The result of the recent studies, which can provide certain framework for the current-structure relation in the ventricular wall and can be interpreted through MCG-data, can be stated with 4 general observations.

1. The remarkable and established fact is that electrophysiological properties of the ventricular myocardium are extremely heterogeneous and dispersion of repolarization may be an important factor that determines the manifestation of the heterogeneous ion channel function and expression. A variation in action potential duration (APD) creates the dispersion of repolarization and the baseline level of APD differences exists even in a normal myocardium [2]. Electrical differences which are the result of the difference in the recovery rates of the transient outward current are most notable between the epicardium, midmyocardium and endocardium.

Repolarization begins when the net current over the AP plateau becomes outward and several studies have indicated that a large gradient in density and rate-dependent properties of the transient outward current exist in different layers of the ventricular wall [2, 3]. This current has been suggested to contribute significantly to regional electrophysiological heterogeneity and to cause electrical gradients across the ventricular wall [4]. It has been proved that electrophysiological changes of ischemia induced regional shortening of APD to a significantly greater extent than that produced by cycle length changes [5, 6].

2. In the recent years, major advances were made in understanding that the myocardium cannot be considered electrically as a continuous medium. In contrast to the previous long-standing belief it has become accepted that the myocardium is structured to discontinuous activation and recovery. Structure affects not only the shape of the local action potential, but also the underlying ion membrane currents. There are numerous previous studies available in the literature that suggested the effect of myocardial fibers geometry on the current flow patterns, epicardial and torso potentials [7, 8]. The ventricular wall consists of discrete muscle layers that follow a curving radial path from subendocardium to the subepicardium. The adjacent layers are electrically insulated and make contact only via direct muscle branches. The anisotropic arrangement of the cardiac muscle can be described with band-line structure wrapping left and right ventricles. In pathologic cases this basic structure may be disturbed [9]. Experimental results and mathematical simulations show that important anatomical factors of the ventricular walls that affect propagation and recovery are: the elongated shape of myocardial fibers; the epi-endocardial rotation

of fiber direction; the epi-endocardial obliqueness of the fibers [10]. A key feature of this arrangement is that transmural rotation of fibers and the laminar architecture of the ventricular wall can affect electro-potential and magnetic data.

3. The modeling study by Kazutaxa Gima and Xoran Rudy [11] establish a direct and specific relationship between cellular ionic processes, the APD, and the morphology of electrocardiographic wave forms. The results show that transmural slow-delayed rectifier potassium current heterogeneity is the major determinant of T-wave morphology and the spatial gradient of the transmembrane potential during repolarization is determined by two factors: sequences of activation and local APD.

4. In physiological terms, at the cell level, the mechanic phenomena (change in the length and contraction intensity of muscles) could modify the electrical processes occurring at the membrane of cardiomyocytes through the direct impact onto the stretch-activated channels (SAC), that is ion channels, activated by stretching or, in different words, mechano-sensitive ion channels. SAC are activated by stretching, which means that the more cell membrane is being stretched, there is more chance for them to open. Cardiac mechano-sensitivity and its effect on electrical function undoubtedly form a very complex system. Mechanisms and pathways whereby mechanical events, changes in tension and force, and spatial displacement alter the hearts electrical properties are now recognized as an important dimension for development of new approaches in therapeutic cardiac control. Mechano-electric coupling or feedback (MEF) has only recently began to be explored as a topic of medical interest. We now suspect MEF to play a role in both electrical and mechanical pathological remodeling. Arrhythmogenesis by MEF is likely to go undetected in many patients, because no tool exist to identify and measure these effects. The body surface electrocardiogram, for example, is notoriously inept at detecting slow, local depolarization. MCG may be a more useful approach.

Based on this latest knowledge we can assume that the heterogeneity of an action potential is caused by an intramural heterogeneity of a current flow and for each time instant a result of the “inverse problem solution” can display a resulting current density vectors, whose quantity and direction correspond a quite particular allocation of outward current densities at a certain level (depth) and reflect the architecture of the fiber through which the current propagates. However, in fact, the map of the imaged current density is only a xy-projected picture on the frontal plane of the human heart, whereas in reality the flow of the local circuit currents is three-dimensional in various depth,

with relevance to cardiac anatomy and physiology. The discontinuities in tissue architecture affect the amount and direction of the local outward current flow. Dispersion of repolarization and, accordingly, outward currents, are dynamically modified by the restitution properties of individual myocytes and cell layers, heart rate and the direction of condition. Different pathological conditions can affect this electrical heterogeneity. Several studies reported that the density of the transient outward current may be subject to alterations during ischemia [12], in cardiac hypertrophy or failure [13], after myocardial infarction [14]. That is why our focus should be on the ionic mechanisms that contribute to the intramural nonuniformity of cellular repolarization at certain depth of myocardium and on intramural current heterogeneity as a basis for identifying patients at risk and for assessing the effects of intervention (eg, drug treatment) on the degree of heterogeneity. In the electrophysiologic view, a frequent change of the direction of the current densities vector may be interpreted as a high degree of heterogeneity inside a certain tissue region. A local shortening of the current flow duration in the area of abnormal perfusion can be an independent marker of early localized myocardial ischemia. MCG has been around for over 40 years but only recently the significant progress in instrumentation has increased the interest in the use of MCG in clinical cardiology. It is necessary to note that significant progress in the electronic MCG signal imaging technology, both in terms of hardware and software, as well as mathematical and physical modeling over the past 10 years have made for the turning point. The major problem was that a MCG-device should be operative in unshielded clinical rooms. Developments of new algorithms and hardware for the electronic balance and adaptive filtration have improved noise suppression techniques and increased the noise immunity of MCG-devices. The new methods of the data analysis and effective technical solutions were applied during numerous clinical examinations.

2. WHY DO SCIENTISTS CONTINUE TO DEVELOP MCG FOR DIAGNOSING CARDIAC DISORDERS WHEN SO MANY ALTERNATIVE TOOLS ARE AVAILABLE?

There exist several ways to answer this question, but the essence is the following. It is known that the current density and magnetic field are related by the law of Biot and Savart. That means, that the information about the current density source distribution should be present in a measured magnetic field. Using SQUID technology for measuring the magnetic field of the heart we gain a unique opportunity to identify

changes in the current density that constitute the basis of the myocardium electric activity. The first motivation for scientists is to visualize the distribution pattern of the current sources and to clarify how well these representations reflect the reality. The second motivation is to answer the question: "Whether or not MCG-study can add something new to the diagnostic information gained from the standard clinical tests?" And, then, which of the methods can be chosen as the reference?

Body Surface Potential Maps (BSPM) appear the most likely candidate for the comparison because most authors agree that "full" BSPM will provide identical information. However, BSPM reconstruction is highly sensitive to geometrical errors, potential measurement errors and computer algorithms used. In many cases epicardial potential solution as the result of BSPM study "have been unsatisfactory" [15]. It is especially essential with regard to the repolarization analysis. Although the coronary angiogram has obvious limitations, in the diagnosis of CAD it remains the clinical "gold standard" in the case of the sufficient luminal occlusion. Exercise ECG test has high sensitivity only in patients with three-vessel disease and its diagnostic performance is under the influence of baseline ECG abnormalities and is generally less than imaging procedures. Stress echocardiography has high sensitivity and specificity in patients with chronic ischemic dysfunction. SPECT imaging is used for the detection of myocardial viability as the ability of the myocardium to retain thallium-201. PET imaging is an accepted method for the detection of preserved metabolic activity in myocardial regions with reduced blood flow. The listed above diagnostic performances of many currently available techniques show that they cannot reflect the data that MCG is capable of recoding.

There is a direction independent from the clinical practice that deserves special attention connected with the development of the new methods of revealing cardiotoxic medications. In correspondence to the regulatory documents of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) there was set forward an imperative need to test non-anti-arrhythmic medications in order to reveal their potential in extending QT interval and even to affect the length of QT(QTc) interval. To meet these requirements there is a need to conduct a large series of QT/QTc measurements in animals and people at the pre-clinical and clinical stages of drug development and launch. The safety of the future consumers of new medications and the economic impact that are of concern to pharmaceutical companies set forward the issues of precision and repeatability of the results obtained for QT(QTc) interval measurements. Up to

present 12-electrode ECG was considered the only possible means of such measurements. Although many would agree that in-precision in the positioning of the electrodes, the alterations of the contact resistance between the electrode and the skin and a whole series of other limitations related to the shape of T wave could significantly impact the results of such measurements. On the other hand, the preliminary results of applying MCG to perform similar tests on animals and people with the use of pharmacological stress-test showed impressive results. It is evident that if we want to use MCG "only when nothing else will suffice", our focus should be on the various disorders of the heart where changes of ion current densities are the dominant factor. There exist strong evidence that the electrophysiological behavior of the heart may be altered in ischaemia which causes abnormal mapping patterns during the repolarization phase. MCG-map abnormalities were detected in all patients with severe coronary lesion. Furthermore, during several patient examinations [16] significant changes were not observed in standard 12-lead ECG. And it is remarkable that the magnetic map changes in ventricular repolarization can be observed as early as in the results of healthy subject measurements during physical exercise or pharmacological stress [17, 18, 19]. In the study by Brocumeier [17] the dramatic influence of increased heart rate on repolarization magnetic mapping patterns was found for healthy volunteers. In contrast to MCG, significant stress-induced differences were not observed in ECG and BSPM - recordings. Many researchers agree on that "abnormal" mapping patterns are "the special properties of MCG such as the ability to detect so-called vortex currents (loop currents, injury currents)". Helmholtz theorem, which decomposes a vector field into the flow and vortex parts [20] was the theoretical basis for interpretation of the magnetic map changes. Discussion that the information about myocardial electrical phenomena can be present in the biomagnetic field and absent in the electrical field have been well known since very first MCG measurements. Opportunity to display the "electrically silent" magnetic sources was demonstrated in theoretical study [21] with the example of the tissue that has a "spiral-like" or "helix-like" conductivity.

3. ADVANTAGES OF MAGNETOCARDIOGRAPHY VS. ELECARDIOGRAPHY

ECG and MCG are both the methods of non-invasive diagnostics of electrophysiological processes inside the heart that is conducted by registering the signal coming from the body surface and have many similarities. Electrocardiographic signals have

similar morphology in both types of registry. The waves of atrial activation, ventricular depolarization and ventricular repolarization are termed P, QRS and T, correspondingly, in both of the examination methods. Still, MCG has a number of fundamental and methodological differences from the ECG related to a series of signal-generating variables between the heart and the sensors at the body surface. First of all, the fundamental difference between the two methods of registering biological signals is that the connection between the electric potential and the current is conditioned by specific electric resistance of membranes and muscles that could depend upon time, direction, the measuring point and the voltage value. Important information about the current flow is lost in the electric potential. Potential theory states that the voltage between two points is independent of the path traveled between two points. At the same time, in case of magnetic mapping, the proportion factor between the magnetic field and the current is determined by fundamental physical constants.

The methodological differences can be put as follows:

1. Magnetic measurements are not only non-invasive but also non-contact. Thus, there is eliminated any appearance of artifacts related to unreliability and/or fluctuating of electrode contacts with the skin. MCG is more sensible towards intra- and extracellular activation currents, whereas chest leads of ECG (or BSPM) register the difference of potentials generated by secondary (wollume) currents directly beneath the skin inside the patient's body. The difference between these two types of registration can also be illustrated by facts such as registry of coronary activity of a fetus at certain pregnancy phases, when non-conductive layers of tissue intervene in ECG measurements of the fetus. Hence, MCG examination of fetuses became a rather promising area of MCG application. The non-contact measurements appear even more advantageous if applied for measuring coronary activity in animal models. Research, development and testing of medication and gene therapy require multiple phenotype examinations of animal models. ECG registrations, for example, in rodents, is possible only if the animals are anesthetized, otherwise they get over excited and the ECG would contain intolerable signal artifacts. Another pitfall is that cardiac rhythms of an anesthetized animal are not natural. Although alternative telemetry methods are applied frequently, they are rather time- and effort- consuming. It was demonstrated that MCG of an animal in its conscious and natural condition corresponds the most to normal physiological conditions.

2. It is known that the distribution of the wave fronts of the myocardium excitation and restoration moves from the endocardium to epicardium and backwards and normally is ensured by the prevalence

of radial action currents. In a general case, the temporal and amplitude correlation between the radial and tangential components of the currents is determined by current-structure interaction inside the myocardium. Registering ECG potential signals gives the possibility to analyze the dynamic changes of predominantly the radial current components. By registering Z component of the heart magnetic field, in fact, the signals registered are related to the current that is tangent-directed relative to the measuring plane. It is evident, that abnormal alteration of the tangent component of the current demonstrates functional and/or pathological changes in the current-structure balance even in cases when the radial current components remain intact.

3. Another advantage along with the no contact procedure is the immobility and hence repeatability of the detector configuration. The regularity and repeatability of the positions of the measuring points of the grid overplays any of the electrode systems.

4. MCG takes account of the space components of the heart magnetic field that are measured as vector values, whereas in case of ECG the heart electric field is defined as scalar value. The new feature vs. the standard ECG is the transition from the registering of one-dimensional curves in time to MCG mapping (tracing of 2D dynamic maps of the magnetic field) that enables to visualize the electro-physiological substrate. The most topical MCG application is the 3D imaging of electro-physiological processes in case of arrhythmias that occur as the result of re-entry mechanism. According to the authors' proper observations and also those of certain other researchers, the patients affected with paroxysmal or persistent types of atrium tremor can show circular distribution of the current density vector even during the inter-paroxysm period. It is also noteworthy, that abnormal currents are registered in the period corresponding to the P wave at the surface ECG, which proves the atrial origin of the former.

4. ASSESSMENT OF THE LEVEL OF PROARRHYTHMIC HETEROGENEITY OF THE MYOCARDIUM

Sudden cardiac death is the most severe and immediate case of IHD that is most often connected to the ventricular tachyarrhythmias both of the ischemic and non-ischemic origin, that is why identification of the high risk patients' groups is of high importance. Similar to the standard 12-channel ECG, magnetocardiography allows to see the prolongation of QT interval, heterogeneity of de- and repolarization, calculate the variability of the cardiac rhythm. At the same time, MCG is more sensitive to the arrhythmogenic tangent currents and

identifies the electrically hidden eddy currents. It is known from certain sources that the autopsy of post-infarction patients affected by ventricular tachycardia often shows the areas of narrowed fibrosis-affected subendocardium that can be the source and the generator of such currents. The electric properties of the ventricular myocardium are extremely heterogeneous and the dispersion of repolarization can be an important factor that precondition the heterogeneous phenomena in the function of the ionic channels. The electrophysiological mechanism for the development of significant electric heterogeneity of repolarization in heart disease is not well understood. The changes in the action potential duration (APD) precondition the dispersion of repolarization, hence the initial level of APD differences exists even in the healthy myocardium. Electrical differences that are the result of the differences in the speed of renewal of the transitory outgoing ion fluxes that are most visible in-between the epicardium, the medium section of the myocardium (M-cells) and the endocardium. Results from a number of research demonstrated that high gradients of density and frequency-dependent properties of the transitory source current exist inside different layers of ventricle wall. It is known, that the principle singularity of an M-cell is its capacity to prolong the action potential compared to epi- and endocardial layers for the period of rhythm deceleration. According to data from different research, accumulation of M-type cells characterized by the most prolonged action potential is observed in the side wall along the distance from the subepicardium stratum up to the medium myocardium layer, inside the anterior wall in the subendocardium stratum up to the medium layer of myocardium, and along the whole area of left ventricle outflow tract. M-cells are also present inside the deep layers of papillary muscles, trabecules and the interventricular septum. The tissue sections obtained from M-areas showed the increased AP duration by 100msec compared to the sections of epicardium and endocardium for the 2000msec cycle or more. Although in case of normal electrophysiological properties, in the intact cardiac muscle the local differences in the AP duration are not registered by electro-potential methods due to the electrotonic connection between the cells and their layers. As the result of the difference in duration of the 3rd and 3rd phases of repolarization in the three types of cells, on the two sides from M-cells there develop electrically opposite gradients that are mostly responsible for forming the T wave. At the beginning of the T wave the epicardium is being repolarized and at its end – the M-cells. The final section of the epicardium repolarization coincides with the peak of the T wave, and repolarization of M-cells coincides with the end of T wave. This means that the action

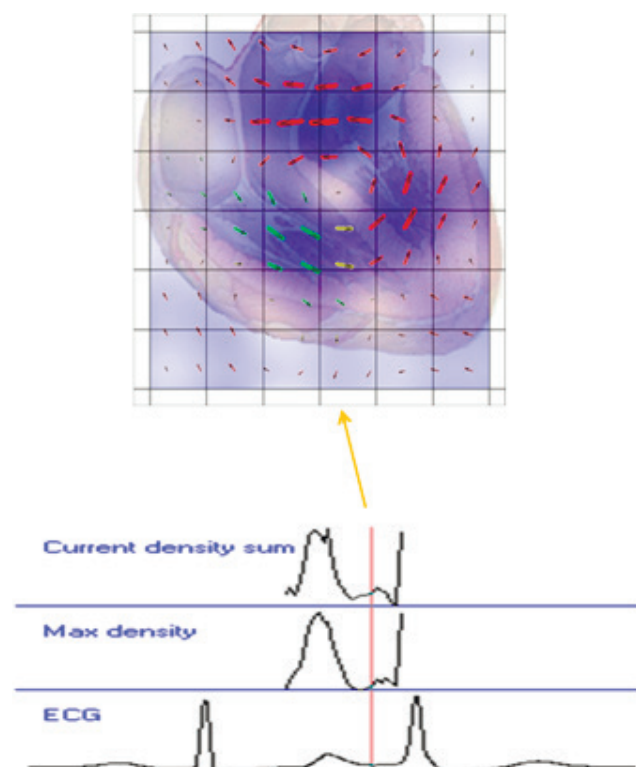
potential duration of M-cells terminates QT interval. At the same time, APD of the epicardium determines the QT wave interval. Hence, the interval Tapex-Tend can be used for the analysis of the transmural electrical heterogeneity of the repolarization inside the medium layer of the myocardium. C.Yan GX and C.Antzelevitch insist that it is the interval Tapex-Tend that reflects the transmural dispersion of refractoriness that can be related to the 2nd phase of re-entry [22]. The heterogeneity of the repolarization should be measured in diseased myocardial segments under physiological conditions by means of non-invasive imaging of cardiac electrogenesis with magnetic field mapping. Under these recording conditions the transmural heterogeneity of the repolarization in patients with ventricular extrasystolia (VE) would be greater than in similar patients without VE and would be associated with ventricular mechanical remodeling. MCG mapping creates the opportunity to identify myocardium segments affected by abnormally increased heterogeneity, which serves as an independent marker of high arrhythmogenic predisposition and of the increased risk of arrhythmia, specifically in case of ventricular tachycardia and ventricular fibrillation.

At the Tapex-Tend interval the following MCG parameters are being assessed: the direction angle of the current density, the angle shift of the maximum current density, deviation of the vector of maximum current density (VMCD), measured at every 10msec of repolarization. In the results, values for direction of the largest CDV, its deviation ($16.4^\circ \pm 1.2$ vs. $5.06^\circ \pm 0.9$; $p < 0.0001$) and shift (8.78 ± 0.67 vs. 4.71 ± 1.2 sm; $p < 0.01$) during the T wave-end interval differed significantly between the groups of patients with VE and without VE. So, transmural repolarization heterogeneity was greater ($p < 0.01$) in patients with VE than in those without VE. The patients with VE had significantly ($p < 0.05$) reduced left ventricular systole-diastolic velocities (Sm 8.73 ± 0.64 vs. 11.06 ± 0.56 sm/s; $p < 0.01$, Em 10.6 ± 0.81 vs. 13.7 ± 0.84 sm/s; $p < 0.05$, Am 8.73 ± 0.64 vs. 11.07 ± 0.56 sm/s; $p < 0.05$), thickened interventricular septum (1.12 ± 0.028 vs. 1.02 ± 0.04 sm; $p < 0.05$) and also increased intra- (0.03 ± 0.004 vs. 0.016 ± 0.003 s; $p < 0.05$) and interventricular (0.037 ± 0.005 vs. 0.022 ± 0.003 s; $p < 0.05$) delay [49]. Increase in the values of the angle direction, deviation, and, especially, shift of VMCD at Tapex-Tend interval in patients affected by ventricular extrasystole are conditioned by the non-homogeneous distribution of ion fluxes under the conditions of defeated electrotonic connection between the cells and the layers. Obviously, the discontinuity in the myocardium tissue architecture affects the reflection of the density and direction of the local source currents. Dispersion of repolarization and, correspondingly, of

the source currents are dynamically modified by both the renewal properties of individual cardiomyocytes and cell layers and the frequency of cardiac contractions and the grading of the process. The substantiation of the above approaches is based on the notion that electrophysiological alternation of cells and their membranes is associated with remodeling after an ischemic attack or after a myocardium infarction and is active in the process of arrhythmogenesis and the development of 'electromechanical irresponsibility' in the areas of myocardial dysfunction. It is known that electrical remodeling antecedes the structural and geometrical changes in myocardium and this makes MCG more sensitive compared to other non-invasive methods in reflecting pathology processes that take place. The increased transmural heterogeneity of the repolarization, which can be tested by the newest non-invasive imaging technique, magnetocardiography, may lead to ventricular arrhythmia associated with slight (below the pathology margin) ventricular mechanical remodeling. To estimate the efficacy and the individual selection of anti-arrhythmic therapy, up till now the clinics apply electrophysiological examinations on a wide scale. Yet, results received from applying the method described herein show 30-70 per cent discrepancy vs. the clinical effect of long-term anti-arrhythmic therapy. Dynamic MCG examinations could help receive additional factors indicating the readiness of myocardium towards electrical destabilization and the risk of arrhythmia. Patients affected with ventricular dysfunctions show abnormalities in repolarization characterized by circular direction and revealed, correspondingly, at the interval of T wave. Identifying of the transmural dispersion of repolarization characterized by the abnormal current direction or the presence of additional currents at the interval Tapex-Tend gives the marker of increased risk in developing ventricular tachyarrhythmia. The conducted examinations also proved that MCG data correlate with the ECG data of high resolution. It was determined that patients with late potentials of ventricles or late potentials of atria show abnormalities at MCG expressed as increased heterogeneity of de- and repolarization. In this connection rather conspicuous are the results of examinations conducted on patients affected with frequent ventricular extrasystole as the result of delayed after depolarization (DADs). Human ventricular cell studies have shown that the $\text{Na}^+/\text{Ca}^{2+}$ exchange current ($I_{\text{Na}/\text{Ca}}$) contribute to the transient sink current (I_{ti}). I_{ti} is responsible for the proarrhythmic delayed after-depolarizations (DADs). Although DADs are generally accepted to be Ca^{2+} -dependent, the relationship between sarcoplasmic reticulum Ca^{2+} release and DAD amplitude has not been measured, partly because the underlying Ca^{2+} -

activated currents are hard to control. The overall objective of our study demonstrated the efficacy of MCG in the diagnosis of the Ca^{2+} overload in an area of the heart in patients showing DADs. Three MCG-based indices, namely direction of the largest CDV, total current density and maximum value of the current density vectors during T wave-Tend and electric diastole showed a significant difference between DADs patients and the control group. Although Ta-Te interval was shortened in patients presenting with DADs they had additional current density peak during electric diastole interval (fig.1.)

Figure 1. The patients presenting with DADs had additional current density peak during electric diastole interval



5. DIAGNOSIS OF MYOCARDIAL ISCHEMIA AND ASSESSMENT OF ITS INTENSITY

Studies of the diagnostic properties of MCG to identify ischemia and myocardial disorders started as early as in 70-s of last century. D. Cohen et al. [24] in 1975 carried out experiments on dogs in order to study ST segment after the occlusion of the coronary artery, and in 1983 they studied ST segment while the test was conducted with a physical load. It was noted that with the myocardial ischemia isoline and ST segment are moving in opposite direction. With GMI the shift of an isoline approximately equaled to that of ST. With exertional stenocardia shift of ST segment makes about 70% of that of an isoline. With subendocrinal ischemia the depression of ST segment

is seen, whereas with transmural myocardial ischemia ST segment is elevated. If left bundle branch block occurs the differences are not possible to assess. If pains occur behind a thorax with complete bundle branch block on ECG it is important to make an early diagnosis of acute coronary syndrome. Since then numerous research were carried out and various approaches developed, including morphology analysis of magnetic field maps, analysis of MC-curves, inverse problem solutions and analysis of current distributions with a number of indicators identified. For instance, in the last decade such indicators were proposed as ST-T integral and shifts in ST angle to assess the presence of myocardial ischemia and a pool where hemodynamically significant stenosis of a coronary artery can be identified.

J. Park et al. [25] proved better sensitivity and specificity of the MCG as against studies of I-troponin in patients before coronarography, which evidently is connected with earlier changes in repolarization. E.g. specificity and sensitivity of MCG made 93.5% and 86.9% accordingly, whereas those with studies of I-troponin made 37.5% and 56.8%. Density of transitory currents of action can change along with ischemia after distinct myocardial infarction, with myocardium hypertrophy etc. Local change of the duration of currents of action in the area of pathological perfusion can be an independent marker of developing myocardial ischemia. MCG studies are essential of intramural inhomogeneity of excitation and restoration of myocardium so as to diagnose, predict the course of disease and assess how effective is the treatment.

K. Tolstrup et al. [26] were comparing MCG characteristics and positive and negative predictive value (PPV and NPV) of the results of stress single photon tomography (SPECT), MCG and ECG in 75 patients before coronarography. Symptoms, pain in thorax, level of I-troponin were examined in each patient. The account was taken of age, sex, presence of hypercholesterinemia, hypertension, diabetes, myocardial infarction, and coronary ventriculography (CVG) in the anamnesis. Results of examinations along with the indicated characteristics demonstrated high specificity and sensitivity, PPV and NPV of the method were 85.7%, 87.1%, 64.3% and 95.7% accordingly. Changes in depolarization and repolarization processes caused by metabolic dysfunctions in viable myocardium are not always registered by surface ECG. In patients with IHD, acute myocardial infarction the load testing is informative and has proved prognostic value, although it is connected with certain limitations and contraindications. Therefore, MCG as a non-invasive technique, application of which does not require loading and which furnishes information on electrophysiological processes in

myocardium sensitive to ischemia, is an important and promising area in present cardiology. It is known that ischemia changes electrophysiological properties of myocardium and, in particular, results in regional differences of APD to a larger extent than tachycardia. To identify ischemia with MCG examinations the current density vectors of ST segment are mapped. Repolarization interval is conditionally divided in two subintervals (ST-Tapex and Tapex-Tend) in each of which three characteristics are considered (direction angle of vector of maximum current density, direction deviation of maximum current density vector). ST-Tapex interval is the most specific and sensitive to identify ischemia and evaluate forecast of the disease progress — 60 ms from point J to the peak of T wave which characterizes regional electric heterogeneity of myocardium in the “ischemia window”. Clinical examinations showed that in patients with proved IHD spatial and time changes in current density vectors in the said interval differ from those in healthy individuals and progress depending on the graveness of the disease. Thus, total deviation of current density vector by ST-Tapex makes in average 2,5° in healthy individuals. In patients with acute myocardial infarctions and positive stress-test it increases up to 10° and more. Let us analyze Δ -RTapex, the new MCG parameter which we proposed for the first time. It is calculated as a difference between direction angles of CDV of the peak of T-wave and R-wave. α -Tapex corresponds to the basic direction of electric activity of a heart during repolarization and α -R during depolarization. Presence of residual ischemia in patients (pts) with acute myocardial infarction (AMI) may result from failed or incomplete revascularization or it may be associated with inadequate tissue perfusion and no-reflow phenomena [27-29]. Hence, value of detection of viable myocardium susceptible to ischemia early after AMI could not be overestimated. It is important for reconsidering treatment plan for more aggressive medical management or referral of AMI pts to cardiac catheterization [28]. De- and repolarization abnormalities associated with reversible metabolic differences in viable myocardium are not always detectable by means of resting ECG. Stress testing have established prognostic value and may help to reveal ischemic differences which are likely to be associated with abnormal myocardial perfusion [30-32]. Despite convenience and accessibility of this methodology there are certain limitations and contraindications, especially early after AMI [31]. Therefore we focused on development of risk-free non-invasive method which would be able to provide information on electrophysiological properties of myocardium susceptible to ischemia. It was reported in numerous studies that MCG is safe and useful for assessment of pts with coronary artery disease and

may locate myocardial damage after MI but data on assessment of pts with acute ST-segment elevation MI (STEMI) in terms of detection of electrophysiological differences in viable underperfused myocardium is still lacking. Of MCG parameters directions of main vector of current density distributions (VCDD) on T-apex (α -Tapex) and differences in directions of VCDD on R and Tapex (Δ -RTapex) were analyzed. Presence of signs of ischemic differences in AMI pts were assessed using treadmill testing on 7-10 day after AMI. EchoCG, MCG-mapping and exercise ECG were performed within 24-hours period. Additionally signal-averaged high resolution ECG was performed on in pts with AMI and positive stress test and in AMI pts without ischemic changes on stress test. Dispersion of descending part of T-wave was measured and corrected for heart rate using Basset's formula (cTa-Te). Parameters were compared using ANOVA with post-hoc tests after assessment for normality of distributions and equality of variances. Statistical analyses were performed using SPSS 10.0. Our study revealed that abnormalities in electrophysiological properties of myocardium were most pronounced in STEMI pts with positive stress ECG. Δ -RTapex was highest in the patients with AMI and positive stress test (90.8 ± 10.7 degrees) compared to other patients: 51.6 ± 12.4 degrees in AMI pts without ischemic changes on stress test, 43.0 ± 4.5 in CAD pts without MI history and 30.0 ± 16.4 degrees in healthy (fig.2). We have assumed that AMI patients who developed ischemic changes in stress ECG were most likely to have viable underperfused myocardium. Hence, we evaluated sensitivity and specificity of MCG parameters using stress-ECG data as a standard. It was detected that parameter Δ -RTapex >650 had 70% sensitivity and 82% specificity for detection of electrophysiological changes in viable myocardium susceptible to ischemia. ROC-curve was informative of area under the curve of 0.82 (95% CI 0.69 to 0.95) indicative of a good diagnostic accuracy of Δ -RTapex (fig.2).

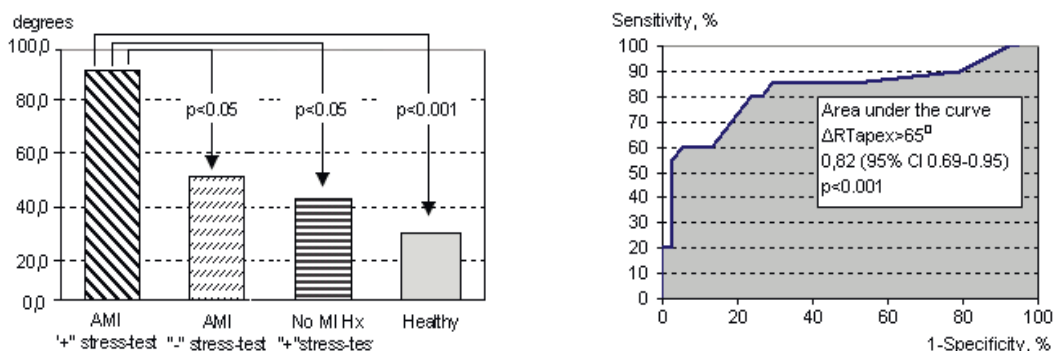
Parameter α -Tapex was significantly higher in STEMI pts parameter with positive stress-test compared

to healthy (149.0 vs. 41.8 degrees, $p < 0.05$) but did not differ significantly between the other groups. This parameter did not have sufficient diagnostic accuracy (area under the ROC-curve 0.52, $p = ns$). Parameter α -Tapex corresponds to direction of VCDD during repolarization, reflecting main orientation of electrical activity of the heart during repolarization. Δ -RTapex considers differences in directions of VCDD during de- and repolarization, thus is different from α -Tapex and may reflect concept of "ventricular gradient" [33]. It is known that de- and repolarization are synchronized, determined and provide well-coordinated contraction and relaxation of cardiac myocytes. Desynchronization of de- and repolarization may occur under conditions of ischemia, injury and inadequate perfusion of myocardium. We consider that Δ -RTapex may reflect this process. Gradual increase of this parameter in study groups depending of presence of ischemia and myocardial injury may prove this hypothesis. As our study revealed Δ -RTapex was significantly correlated with cTa-Te in the patients with AMI and positive stress test. This may be a result of increased transmural dispersion of repolarization in AMI patients with signs of ischemia and indicated that these pts are under higher risk of development of cardiac arrhythmias.

6. CONCLUSIONS

Magnetocardiography has the potential to make a valuable contribution in basic examination and analysis of biosignals of a heart, in particular whilst all vector components are used, vast spatial coverage and excellent signal quality. Browsing the data for the sake of reliability by QT-interval can be useful for the better reproducibility of high performance MCG. Improvement of the signal analysis and visualization technique will be essential for better view of the method. Magnetocardiogram of a fetus and models of animals possesses solid advantages and soon can be implemented. Depending on the results of recent clinical tests first applications can become available for the routine diagnostic examinations.

Figure 2. a- Parameter Δ -RTapex in study groups; b- ROC-curve for Δ -RTapex >650



MCG in therapeutic practice can be used to address the following objectives: a) determining presence and intensity of myocardial ischemia, including that at an early stage. It is shown that MCG at rest has high sensitivity to chronic IHD even in patients with stable or slightly changed ECG at rest; MCG examination helps to realize if there are indications for medical antianginal therapy, specify indications for coronarography; b) assess effectiveness of antianginal therapy, including period after cardiac infarction. The examination helps to determine change of dose or antianginal medicine; c) assess the risk of paroxysm of ventricular tachycardia. The examination allows to select individual regime of antiarrhythmic therapy, specify indications for invasive electrophysiological examination (EPE); d) objectivize presence of cardiac deficiency (CD). Examination helps to assess electrophysiological differences caused by CD at preclinical or early stage of the disease, helps to make unbiased and timely assessment of intoxication by cardiac glycosides. To address these objectives it is possible to employ unique qualitative and quantitative diagnostic sensitivity of which makes from 70% to 95%, specificity from 60% to 90%.

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