Magnetocardiography in Coronary Artery Disease with a New System in an Unshielded Setting

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Summary

Background: The noninvasive detection of coronary artery disease (CAD) remains a clinical challenge. Magnetocardiography is a completely noninvasive method that permits the registration of cardiac electrical activity at multiple sites in a plane above the chest cage without the need for electrodes. In contrast to the electrocardiogram (ECG) which suffers from boundary effects and a variety of potential artifacts (electrode placement, etc.) the MCG is unaffected by such impediments as the magnetic field is unaltered by surrounding tissues.

Hypothesis: Magnetocardiography with a newly developed single-channel system in an unshielded setting should be a better qualitative diagnostic tool than the standard ECG for the detection and assessment of CAD.

Methods: In all, 52 patients with angiographically documented CAD and unimpaired ventricular function as well as 55 controls were included in this study. A standard 12-lead ECG was obtained in all subjects. The MCG recordings were taken from 36 positions under resting conditions. From these, current density vector maps were generated during the ST-T interval. Each map was then classified using a classification system with a scale from 0 (normal) to 4 (grossly abnormal).

Results: While the ECG was normal in all subjects, the MCG in the controls was classified as category 0, 1, or 2. However, in patients with abnormal coronary angiograms, mainly maps in categories 3 and 4 were seen ($p < 0.05$).

Conclusion: A single-channel magnetometer in an unshielded setting reveals significant differences between normals and patients with CAD with normal ECG on the basis of current density reconstruction during the ST segment when measured under resting conditions. This method might be suitable for the noninvasive detection of CAD.

Key words: coronary artery disease, electrocardiography, magnetocardiography, single-channel magnetometer, unshielded setting, current density reconstruction

Introduction

Coronary angiography remains the standard of reference for the identification of hemodynamically significant coronary artery disease (CAD), but should be restricted to symptomatic patients because of its invasive character, risk, and cost.

The noninvasive diagnosis of cardiac ischemia related to CAD remains a clinical challenge. The 12-lead electrocardiogram (ECG) at rest is frequently normal in such patients, and the predictive value of other methods such as exercise ECG, stress echocardiography, or nuclear imaging is often limited. Also, its performance may be associated with a certain risk.^{1–6}

Recent developments include new imaging techniques such as scintigraphy, positron emission tomography, electron-beam computed tomography, magnetic resonance imaging, or spiral computed tomography. Despite good values for sensitivity, specificity remains unsatisfactory and the methods require external or internal radiation.^{7–9}

The value of the 12-lead ECG can be augmented by the measurement of electrical activity at more registration sites. On the basis of body surface potential mapping (BSPM), anomalous repolarization patterns have been demonstrated in patients with ischemic heart disease at rest that were not appar-

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ent in the 12-lead ECG.^{10–13} However, this method itself is also limited because of the time-consuming procedure of lead placement and registration. Analogous to BSPM, magnetocardiography (MCG) can register cardiac activity at multiple sites over the heart,^{14, 15} while the signal can be processed and analyzed in a fashion similar to the computerized ECG (Fig. 1). In addition, the increase in the number of recording sites from the MCG augments the information on the cardiac de- and repolarization processes. Furthermore, the method itself is completely noninvasive in that even skin contact is unnecessary. Previous small-scale studies have shown that patients with CAD and normal ECG at rest could be identified on the basis of MCG.^{16, 17} However, the acceptance of this method in clinical practice remained limited mainly because of the high costs of the installation of the system inside a magnetically shielded setting. With the development of a new device not requiring shielding, a new option was created to determine whether measurement of the magnetic field of the heart was superior to the assessment of the surface potentials on the chest cage which currently remains the routine.

Thus, the essential aim of the present study was to examine the value of magnetocardiography in the diagnosis of CAD at rest using a single-channel magnetometer in an unshielded setting.

FIG. 1 (A) 6 3 6 rectangular grid used for magnetocardiography (MCG) registration, the covered precordial area is 20 3 20 cm. The sensor was positioned initially above the jugulum at position 3. (B) Example of one subject's averaged MCG signals in all 36 positions.

Methods

Subjects

The study initially included 110 subjects: 55 patients with stable angina and CAD documented by coronary angiography without prior myocardial infarction, and 55 healthy subjects. The patients were selected consecutively from all patients admitted to the hospital over a period of 6 months with the indication for coronary angiography due to chest pain. Subjects with narrowing of the coronary arteries $\geq 50\%$ in one or more vessels and no prior myocardial infarction or wall motion disturbances at rest were assigned to the CAD group. The control group consisted of healthy subjects with no history of any cardiovascular disease, normal ECG at rest and stress, as well as a normal echocardiogram at rest. Patients excluded from the study were those with atrial fibrillation or atrial flutter, bundle-branch block, pacemaker therapy, left ventricular hypertrophy as assessed by echocardiography, valvular heart disease, renal insufficiency with need for dialysis, or other catabolic disease. A further exclusion criterion was a poor quality of the MCG signal that did not allow to determine the events (J point, T offset) of the cardiac cycle. This occurred in 2.7% of the patients initially assigned to this study.

Baseline characteristics of all subjects are given in Table I; all patients gave their written informed consent.

Data Acquisition

Magnetocardiography was performed using a single-channel SQUID-magnetometer (SQUID AG, Essen, Germany, developed in 1999 and put in clinical service in 2000) in an unshielded setting (Fig. 2). Single MCG recordings were taken from a total of 36 positions within a 20 3 20 cm rectangular grid with a 4 cm pitch over the precordial area. The sensor was positioned as close to the thorax as possible, directly over the heart, initially at the jugulum (position 3 in Fig. 1). The examination table with the patient resting in the same position was then moved in a systematic fashion to each of the 36 predetermined positions under the SQUID detector. Data were record-

TABLE I Patient characteristics

	N n = 55	CAD n = 55
Male	39	32
Age (years)	60 $\pm$ 11	66 $\pm$ 11
Coronary status		
1-Vessel		19
2-Vessel		17
3-Vessel		19
Beta-blocker therapy		24

Abbreviations: CAD = patients with coronary artery disease, N = healthy subjects.

FIG. 2 One-channel magnetocardiograph in unshielded setting. Squid AG, Essen.

ed at each registration point for 30 s with simultaneous registration of lead II of the surface ECG and stored on hard disk for further evaluation. Coronary angiography and left-heart catheterization were acquired in multiple projections using the Judkins technique according to standard clinical practice (Siemens Cathcor, Erlangen, Germany) in close time relationship (within 24 h) to the MCG recording.

Data Analysis

From the coronary angiograms, two experienced observers assessed the degree of stenosis visually in the major branches. Only those patients with narrowing of the coronary arteries $\geq 50\%$ in one or more vessels were included in this study. No quantitative assessment of individual lesions was made.

For MCG, all beats were averaged at each position over a period of 30 s excluding premature beats. For further analysis, the current density vectors (CDV) were reconstructed from the stored data.^{18–20} The calculation of these maps is based on an “inverse problem solution” implemented in the software package MAGwin. This solution refers to the mathematical reconstruction of electrical, respectively magnetic sources in the heart.²¹ The CDV maps thus reflect the three-dimensional image of the cardiac de- and repolarization process on 100 positions, whereby every map is recalculated from data of all 36 points of registration. From all volunteers and patients, CDV maps were generated every 10 ms within the ST-T interval starting with the J point. For timing purposes, lead II of the surface ECG served as reference channel (Fig. 3). In the CDV maps, the length and color of each current density vector is proportional to the current density value at each point; the direction of the vector reflects the direction of the electrical, respectively magnetic cardiac activity.

FIG. 3 Example of reconstruction of several current density vector maps in the course of the ST interval with the magnetocardiography signal above, the corresponding magnetic fields in the middle, and the current density vector maps below.

FIG. 4 Two examples of the classification system. (A) "Ideal" map: the main current vectors are located in the center or left part of the map and directed within a 10° to 80° sector; the pattern is dipolar and the vortices are equal (Category 0). (B) The main current vectors are located in the upper part of the map and directed within a 220° to 110° sector; there is no dipolar pattern (Category 4).

Each CDV map in the course of the ST-T interval was analyzed visually by two independent observers who were blinded to the clinical status of the 107 individuals. A classification system with a scale from 0 to 4 was employed. The classification is mainly based on the dipolar or nondipolar structure of the map and the direction of the main current density vectors. The symmetry or asymmetry of the vortices served for further

specification. In case of homogeneous conductivity, the volume currents constitute two vortices that are symmetrical and equal in strength. The resulting map has an "ideal" dipolar structure (Figs. 4 and 5).

Each CDV map within the ST-T interval of all patients and healthy volunteers was classified in this manner. For both groups, the percentage of each class of map distribution was

FIG. 5 Flow chart of the classification system including one example of the corresponding current density vector map.

FIG. 6 Presentation of the percentage of each current density vector map distribution for both groups using box plots and whisker plots; the median value is marked for each category. CAD = coronary artery disease, N = healthy subjects.

calculated and displayed as “box & whisker” plots (Fig. 6; Table II). Then, for each class of maps, the number of patients and healthy subjects with at least one map of the respective category was calculated (Table III).

Statistical Analysis

In both normals and patients with CAD, the portion of each class of map distribution was calculated and compared between the groups on the basis of the Mann-Whitney-U test. Furthermore, for each class of map distribution, the portion of normals and patients with CAD, respectively, with at least one of the applicable map categories was calculated and compared using Fisher’s exact test. A *p* value of <0.05 was considered statistically significant.

Results

On the basis of coronary angiography, 19 patients had single-vessel disease, 17 double-vessel disease, and another 19 patients had triple-vessel disease.

The 12-lead surface ECG was normal in all subjects. Blood pressure was $\leq 140/90$ mmHg in all subjects at the time of MCG registration.

After the MCG registration of the patients with CAD, three (5.4%) had to be excluded because of poor signal quality. The

remaining 52 patients, together with all 55 healthy subjects, were included for comparison.

On average per patient, 21.7 ± 2.2 CDV maps were generated. Comparing the patterns of the CDV map distribution between healthy subjects and patients with CAD, differences could be visualized on the basis of “box & whisker” plots to quantify the percentage of each class of map distribution for both groups (Fig. 6). In normals, the majority of maps was classified as category 0, 1, or, rarely, 2 when compared with patients with CAD in whom occasionally category 2 but mainly categories 3 and 4 were found. To quantify the differences between both groups, we compared the percentage of each single class of map distribution on the basis of the Mann-Whitney-U test. The differences were statistically significant for all classes (Table II).

These results could be further confirmed by analyzing in each category the number of patients and healthy subjects with at least one CDV map of the class concerned. In normals, CDV maps of the categories 0, 1, and 2 were found more frequently when compared with patients with CAD ($p < 0.001$ for category 0; $p < 0.0001$ for categories 1 and 2), whereas CDV maps classified as category 4 were more often found in pa-

TABLE II Comparison of the percental portion of each class of map distribution; *p* values are given for the difference between normals and the patient group ($p < 0.05$ in bold)

Class	<i>p</i> Value for comparison CAD—N
0	0.001
1	0.0001
2	0.002
3	0.018
4	0.0001

Abbreviations as in Table I.

TABLE III Comparison of the number of patients and healthy subjects with at least one current density vector map distribution of the particular category; *p* values are given for the difference between normals and patient group ($p < 0.05$ in bold)

	Number of CDV maps		<i>p</i> Value
	N n = 55	CAD n = 52	
Category 0	11	0	0.001
Category 1	43	9	0.0001
Category 2	54	38	0.0001
Category 3	39	38	0.833
Category 4	24	39	0.002

Abbreviation: CDV = current density vector. Other abbreviations as in Table I.

tients with CAD ($p < 0.002$). For category 3, the difference between both groups was not found to be significant (Table III).

Discussion

The present study analyzed cardiac repolarization in healthy subjects and in patients with CAD without myocardial infarction under resting conditions with a single-channel MCG system outside a shielded room. As in none of the patients and controls the 12-lead ECG revealed typical changes in repolarization, suggesting the diagnosis of myocardial ischemia, it is striking that the MCG showed obvious differences between both groups on the basis of maps reconstructing the current density distribution. Healthy subjects displayed the area of main current density vectors in the center or left part of most maps during the ST-T interval directed left downward within a 10° to 80° sector. Most maps within the ST-T interval were classified as class 0, 1, or 2. In patients with CAD we could see two obvious differences: first, there was a change in the direction of the main current vector with a deviation more to the right or left upward; the second difference refers to the nondipolar structure of these maps. Most maps within the ST-T interval were classified as categories 3 or 4 in patients with CAD. The percentage of each class of map within the ST-T interval was statistically significant between patients with CAD and healthy subjects for all classes. In each subject we also identified the map classes in which at least one map was present. This was used as a measure for the presence and, conversely, the absence of certain map types in individual patients. None of the patients with CAD demonstrated CDV maps of class 0. The difference between both groups was statistically significant for all classes except class 3 (Table III).

These discrepancies between healthy subjects and patients with CAD at rest could be explained from a pathophysiologic point of view by the assumption of a more inhomogeneous repolarization process in patients with CAD, an explanation that would presume the presence of myocardial ischemia at rest. Indeed, the very absence of ischemia under resting conditions is generally accepted to be the explanation for a normal ECG at rest in patients with CAD. Keeping in mind that ischemia is a dynamic process with an important temporal continuum, starting with changes on molecular basis followed by some unspecific changes in the 12-lead standard ECG progressing to wall motion disturbances and angina as a last step, it could be possible that this new method is able to detect signs of ischemia in a very early phase of such a dynamic process.^{12, 22} Such a concept is suggested by the fact that a method like BSPM, which analyzes cardiac repolarization in more detail than the ECG, could also identify CAD in patients with a normal ECG at rest.^{12, 13} This superiority of BSPM over 12-lead ECG might be the result of the registration technique itself, as cardiac activity is measured at multiple points above the thorax, thus increasing the information about cardiac electrogenesis.^{23, 24}

The MCG expressed in μ Ampere is comparable with BSPM measured in mini Volts to the extent that the number of

recording sites is increased in the latter to a minimum of 120 leads.²⁵ In the discussion why MCG contributes additional information to the understanding of the heart's electrophysiology, the registration of vortex components of the magnetic field was suggested as the physical explanation.²⁶ Using this potential for the analysis of spatial aspects of cardiac activity, we could show previously that patients with CAD could be identified at rest because of their increased heterogeneity of repolarization as revealed by temporal and spatial changes of QT dispersion.¹⁶ Yet it is generally accepted that QT dispersion reflects the homogeneity or inhomogeneity of cardiac repolarization in terms of body surface potentials in mV. The current density vector map reconstruction is another approach to visualize the cardiac repolarization process in terms of μ Ampere. It should therefore not be surprising that both methods display differences between patients with CAD and normal subjects under the same resting conditions, as the additional advantage of the MCG is the fact that it does not require the tedious placement of multiple electrodes.

Reviewing the possible causes of inhomogeneity of repolarization there might be different approaches. Electrophysiologically, they may reflect differences in the duration of monophasic action potentials; morphologically, these electrophysiological changes might be due to apoptosis. Also, earlier episodes of myocardial ischemia could have led to circumscribed regions of cell necrosis resulting in impaired electrogenesis. Finally, there are multiple shifts in ionic transfer depending on the metabolic state of cardiac cells.²⁷

Although there seemed to be a relationship between the deviation of the main current vectors and the affected coronary vessel, this dependency, given the small series of observations, was not strong enough to predict the coronary status on the basis of the MCG result, especially in case of multivessel disease. Overall, a left upward shift of the main current vector could be seen in patients with stenosis of the left anterior descending artery and a right downward shift in the case of a stenosis of the right coronary artery.

However, the fact that patients with CAD, presumably with ischemia but a normal ECG at rest, might be identified on the basis of a completely noninvasive method is of great clinical interest.

Despite the encouraging results of former studies using a multichannel MCG system inside a shielded setting, the method was limited by the high costs of the system itself.^{15, 25, 28} The present data show the results of a much less expensive single-channel system not requiring a shielded room. A further confirmation of these results in a larger population would be an important step toward the aim of restricting invasive procedures such as coronary angiography to those patients in whom the diagnosis of CAD is confirmed prior to the procedure and in whom interventional therapy appears to be indicated.

Study Limitations

This study is limited for several reasons. Beside the small population size, the method is limited because of the registration technique itself. A single-channel system allows no

temporal synchrony between the registration sites. While this disadvantage can be abolished by ongoing developments of software and multichannel systems, on the other hand the temporal conformity seems to be of no great importance for the analysis of more stable processes such as cardiac repolarization under resting conditions. This would be completely different for the examination of cardiac arrhythmias or other cardiac disorders.

Moreover, further research has to be done to assess the influence of drugs such as beta-receptor antagonists on the CDV map distribution.

A main limitation of this study is the data analysis itself, as the predictive value of the method has not been evaluated. Differences between patients with CAD and normal subjects are obvious but it will require further observations to assign one single measurement as absolutely normal or pathological. As long as the score system depends to some degree on the experience of the observers, with the need for a training procedure, the implementation of an automatic process following the described criteria for each category should improve this aspect.

Further development of multichannel magnetocardiographs and improvement in the data analysis appear warranted in order to take advantage of the existing potential of this new device in the detection of cardiac ischemia in coronary artery disease patients.

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