Incremental diagnostic value of combined quantitative and qualitative parameters of magnetocardiography to detect coronary artery disease

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A B S T R A C T

Background/objectives: Magnetocardiography (MCG) has been proposed as a non-invasive and functional technique with high accuracy for diagnosis of myocardial ischemia. This study sought to investigate the incremental diagnostic value of combined quantitative and qualitative parameters of MCG to detect coronary artery disease (CAD).

Methods: Ninety six patients with suspected CAD who underwent coronary angiography were enrolled in the analysis to test the diagnostic accuracy of 2 MCG parameters (a quantitative parameter of the percent change of ST-segment fluctuation score and a qualitative parameter of non-dipole phenomenon).

Results: The best cut-off value for the percent change of ST-segment fluctuation score was −51.0%. The accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were 78.1, 73.9, 82.0, 79.1, and 77.4, in the percent change of ST-segment fluctuation score and 86.5, 84.8, 88.0, 86.7, and 86.3 in non-dipole phenomenon. The area under the curve of receiver-operating characteristics was 0.79 for the percent change of ST-segment fluctuation score and 0.86 for non-dipole phenomenon (p < 0.001). However, the incorporation of non-dipole phenomenon into a model with the percent change of ST-segment fluctuation score significantly improved C-statistics, indicating the enhancement of diagnostic performance in the detection of significant CAD (0.790 to 0.930; p < 0.001). Conclusions: Qualitative assessment of non-dipole phenomenon has a better diagnostic value than the quantitative parameter of percent change of ST-segment fluctuation score in the detection of significant CAD. Furthermore, this study found that the incorporation of non-dipole phenomenon into the percent change of ST-segment fluctuation score significantly improved the diagnostic performance of CAD detection.

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1. Introduction

Ischemic heart disease (IHD) remains a major public health burden worldwide. It is estimated that one third of adults in the United States has some forms of IHD, including more than 17 million with coronary artery disease (CAD) and nearly 10 million with angina pectoris [1]. Nevertheless, the detection of myocardial ischemia in patients with presumed CAD is still a challenge in routine cardiological diagnostics. Also, as ischemic events constantly occur in CAD after revascularization, early detection of this is significant for lifelong prognosis. Although noninvasive stress testing to detect inducible ischemia has been used to diagnose CAD [2], less than half of patients are evaluated noninvasively before percutaneous coronary intervention (PCI) [3]. This is because of testing limitation caused by low diagnostic accuracy and radiation hazard in coronary CT or SPECT.

Magnetocardiography (MCG) is a noninvasive, noncontact and radiation-free multichannel mapping technique to record cardiac electromagnetic activity with high resolution (between 10−11 Tesla and 10−14 Tesla) [4–6]. Both electrocardiography (ECG) and MCG provide information about the same electrical activities of the heart and thus a magnetocardiogram can be viewed as the magnetic equivalent of an electrocardiogram. However, the magnetic signal is much less influenced by variations of conductance than electric currents in body tissues. Various clinical studies have already shown superior sensitivity of MCG over ECG for ischemic myocardium at rest as well as under

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stress [7–11]. Recently, MCG has been recognized for its outstanding ability to detect patients with CAD [12–15]. Moreover, MCG accurately detects functionally significant CAD as defined by using fractional flow reserve (FFR), and provides an assessment of ischemic status in agreement with the percent change of ST-segment fluctuation score [16]. This study sought to investigate incremental diagnostic value of combined quantitative and qualitative parameters of MCG to detect CAD.

2. Methods

2.1. Study population

The study was conducted as a prospective registry at Coburg Hospital, Coburg, Germany with the approval of the institutional review board. Written informed consent was obtained from all subjects. Patients admitted to the hospital with an indication for coronary angiography due to chest pain or suspected CAD who were older than 18 years and suited for stress testing with MCG were included. CAD criteria included at least 70% stenosis in at least one proximal epicardial coronary artery and objective evidence of myocardial ischemia (substantial changes in ST-segment depression or T-wave inversion on the resting electrocardiogram or inducible ischemia with either exercise) or at least one coronary stenosis of at least 80% and classic angina without provocative testing. Exclusion criteria were acute coronary syndromes or recent (<3 months) acute myocardial infarction, coronary artery bypass grafting, chronic total coronary occlusion, significant valvular heart disease, end stage renal failure, or refusal to enter the registry. After enrollment, simultaneous recordings of ECG and MCG at rest as well as under stress and echocardiography were performed in a standardized schedule within 24 h. All MCG data were recorded before coronary angiography.

2.2. MCG recording

The MCG recordings were performed using a 64-channel gradiometer system in a magnetically shielded room (MSR) (CS-MAG II, BMP GmbH, Hamburg, Germany) [17]. The MCG system utilizes double relaxation oscillation superconducting quantum interference device (DRORSQUID) sensors [18,19]. The average noise spectral density of the entire system in the MSR room is 10 fT/√Hz at 1 Hz and 5 fT/√Hz over 100 Hz. Tangential components of the cardiomagnetic fields were measured, which was effective in obtaining the overall heart information with a relatively small area of the sensor array [20]. However, in order to apply the well-known magnetic field map parameters, the tri-polar field map patterns were changed into ordinary dipolar field maps using minimum norm estimation [21]. The signal processing software provided automatic digital filtering, averaging, synthetic gradiometer formation and baseline correction of the acquired recordings.

2.3. MCG data acquisition

The MCG signals were digitally recorded at rest for 100 s at a sampling rate of 500 Hz, with the patient in the supine position and the SQUID’s 2-D arrayed sensors positioned close to, but not in contact with the left chest wall. Stress recordings were acquired by bicycle exercise test. An independent investigator performed quality evaluation and analysis of ECG and MCG.

2.4. ST-segment fluctuation score

For the calculation of the ST-segment fluctuation score, the structures of high-frequency components of magnetic signals from the heart during the plateau phase of the action potential were analyzed as previously described for the QRS fragmentation score [22]. In brief, after averaging and broadband filtering with a binomial bandpass filter (37 Hz–90 Hz), the fluctuation of the ST-segment (between end of QRS and beginning of T-wave) is quantified by calculating the sum of the absolute values of the differences in neighboring extrema (spans). In addition, the absolute values of the first and the last remaining extrema are added to this sum. Thus the ST-segment fluctuation score is calculated as the multiplication of the determined sum by the number of extrema. This single quantity reflects the fluctuation covering the number of peaks and their heights within the ST-segment of the bandpass-filtered signal-averaged magnetocardiogram [22].

2.5. Dipole and non-dipole phenomenon

Assessment of non-dipole phenomenon was performed in the interval between T-wave begin (Tbeg) and T-wave maximum (Tmax) at the peak of T-wave at stress in every patient. A dipole phenomenon was defined as a magnetic field containing two poles. If the number of poles was either one or >2, it was defined as a non-dipole phenomenon. Fig. 1 presents the representative case of normal repolarization showing a dipole pattern under both resting and stress conditions. Fig. 2 shows abnormal repolarization with a non-dipole phenomenon under a stress condition.

MCG was interpreted independently without clinical information. For the inter-observer agreement of ischemic analysis by MCG (for ST-segment fluctuation score as well as non-dipole phenomenon analysis), kappa statistic was used. The percent change of ST-segment fluctuation score [(stress – rest) × 100 / rest] between rest and stress was evaluated to find the cut-off value of ischemia.

![Representative case with no evidence of coronary artery disease. The sum of MCG tracing is shown under resting and stress conditions (A and D), and the ST-segment fluctuation score is −49.1%. The magnetic field map (B and E) and the current vector density map (C and F) show two poles under both resting and stress conditions.](image-url)
2.6. Statistical analysis

Data analysis was performed using SPSS version 19.0 (SPSS Inc., Chicago, Illinois). Diagnostic measures including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated. The analysis of receiver-operating characteristic (ROC) curve was performed to examine the discriminatory power of the percent change of ST-segment fluctuation score and non-dipole phenomenon for the detection of significant CAD. The differences in C-statistics (with 95% confidence interval [CI]) after the addition of the non-dipole phenomenon to the percent change of ST-segment fluctuation score model were obtained. The interobserver and intraobserver variability of ischemia analysis of MCG were calculated using the kappa coefficient. For all analyses, \( p < 0.05 \) was considered to be statistically significant.

3. Results

3.1. Study patients

A total of 96 patients (75 men and 21 women, the mean age of 65 years) were recruited for the study. Clinical characteristics of patients are presented in Table 1. Thirty four patients (38.5%) had typical angina, 37 patients (38.5%) had atypical angina, and 25 patients (26.0%) were asymptomatic.

3.2. ST-segment fluctuation score

The percent change of ST-segment fluctuation score on MCG from rest to stress was \(-47.5 \pm 22.5\%\). Patients with CAD revealed a mean fluctuation score of \(-36.3 \pm 25.0\%\), while patients without CAD revealed a mean fluctuation score of \(-57.8 \pm 13.4\%\). ROC analysis showed an area under the curve of 0.790 (95% CI: 0.695 to 0.867; \( p < 0.0001 \)) (Fig. 3). The best cut-off value of the percent change of ST-segment fluctuation score was \(-51.0\%\) with sensitivity of 73.9%, specificity of 82.0%, PPV of 79.1%, and NPV of 77.4% (Table 2). The agreement between 2 observers for the ST-segment fluctuation score showed a kappa of 0.92 (\( p < 0.001 \)), indicating good agreement.

3.3. Dipole and non-dipole phenomenon

A non-dipole phenomenon was observed at the interval between \( T_{beg} \) and \( T_{max} \) in 45 patients (46.9%). Patients with CAD revealed a non-dipole phenomenon of 84.8%, while patients without CAD revealed 62.8%.

![Figure 2](image_url). Representative case of coronary artery disease. The sum of MCG tracing is shown under resting and stress conditions (A and D), and the ST-segment fluctuation score is 87.6%. The magnetic field map under a resting condition shows dipole (B) but non-dipole under a stress condition (E). The current vector density map shows the same finding as the magnetic field map (C and F).

### Table 1

Patient demographic characteristics and MCG parameters.

<table>
<thead>
<tr>
<th>Variables</th>
<th>(n = 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n (%)</td>
<td>75 (78.1)</td>
</tr>
<tr>
<td>Age, years</td>
<td>65.0 ± 10.8</td>
</tr>
<tr>
<td>Range</td>
<td>34–82</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.3 ± 4.9</td>
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<tr>
<td>Cardiovascular risk factors</td>
<td></td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>23 (24.0)</td>
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<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>58 (60.4)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>72 (75.0)</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>14 (14.6)</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>8 (8.3)</td>
</tr>
<tr>
<td>Previous PCI, n (%)</td>
<td>17 (17.7)</td>
</tr>
<tr>
<td>MCG indication, n (%)</td>
<td></td>
</tr>
<tr>
<td>Typical angina</td>
<td>34 (35.4)</td>
</tr>
<tr>
<td>Atypical angina</td>
<td>37 (38.5)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>25 (26.0)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>135.0 ± 23.7</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>76.7 ± 13.2</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>58.5 ± 8.6</td>
</tr>
<tr>
<td>% change of ST-segment fluctuation score</td>
<td>−47.5 ± 22.5%</td>
</tr>
<tr>
<td>Non-dipole phenomenon</td>
<td>45 (46.9)</td>
</tr>
</tbody>
</table>

Values are n (%) or mean ± SD. MI, myocardial infarction; PCI, percutaneous coronary intervention.
a dipole phenomenon of 88.0%. ROC analysis showed an area under the curve of 0.864 (95% CI: 0.779 to 0.925; \( p < 0.0001 \)) (Fig. 3). The non-dipole phenomenon had sensitivity of 84.8%, specificity of 88.0%, PPV of 86.7%, and NPV of 86.3% (Table 2). The agreement between 2 observers for the identification of non-dipole phenomenon showed a kappa of 0.92 (\( p < 0.001 \)), indicating good agreement.

3.4. Incremental diagnostic value of combined 2 parameters

Adding the non-dipole phenomenon to the percent change of ST-segment fluctuation score enhanced diagnostic performance for the detection of significant CAD. ROC analysis showed an area under the curve of 0.930 (95% CI: 0.860 to 0.972; \( p < 0.001 \)) (Fig. 3).

4. Discussion

In the present study, the incremental diagnostic value of a non-dipole phenomenon on the change of ST-segment fluctuation score was assessed in the detection of CAD. The main results obtained from this study are as follows. First, the change of ST-segment fluctuation score predicts the presence of CAD. Second, the non-dipole phenomenon has an incremental predictive value over the change of ST-segment fluctuation score. Third, the addition of the non-dipole phenomenon to the change of ST-segment fluctuation score improves the predictive power for the detection of CAD.

MCG is a non-contact and non-invasive technique to assess the electromagnetic activity of a human heart particularly for ischemic myocardium both at rest and under stress with superior sensitivity [4,6]. Transient myocardial ischemia causes well-recognizable changes in a variety of MCG parameters [7,8,12]. Electrophysiological alteration is the first consequence of myocardial hypoxia occurring in less than a minute after the reduction of blood flow or unmet metabolic demand. The changes of the magnetic field under hypoxia are due to the reduction of the transmembrane action potential of cardiomyocytes [23–25], which can be demonstrated by MCG [26].

Through this study, we would introduce two new approaches for cardiac magnetic field analysis in order to detect CAD. 1) We named a quantitative parameter as the change of ST-segment fluctuation score. It is based on a previously described signal-processing solution known as QRS fragmentation score, which can be used with MCG [22,27]. In our previous study, the change of ST-segment fluctuation score accurately predicts the presence of hemodynamically significant CAD when compared to FFR. 2) As a qualitative parameter, the non-dipole phenomenon showed better accuracy to detect CAD than the quantitative parameter, the change of ST-segment fluctuation score. MCG facilitated the detection of non-dipoles because of its superior spatial resolution and its ability to show the differences in physical properties between magnetic and electrical fields. Therefore, it is useful for detecting cardiac changes at early stages, which are currently undetectable by ECG [28]. Complex polyphasic waveforms (fractionation or fluctuation) could arise from transmembrane action potentials—membrane currents associated with a complex or multicomponent phase of depolarization of individual cells. Fluctuation might also derive from the superposition of extracellular currents from asynchronous depolarization in a number of functionally different cells with normally formed action potentials [29]. We found that ST segment fluctuation decreases with stress. However, there is a smaller decrease in patients with CAD with a cutoff value of –51.0% (sensitivity 73.8% and specificity 82.0%) compared to the baseline at rest. Hailer and colleagues found a decrease in the homogeneity of repolarization (QT dispersion) during stress by means of the smoothness index (SI) in patients with significant coronary stenosis [30]. Possibly, the ST-segment is the most sensitive phase to detect the ischemia-induced electromagnetic deviation [26]. Our findings suggest that the irregular fluctuation of the filtered ST-segment provides a means to identify conduction impairment related to the occurrence of myocardial ischemia, thereby describing the electrical activity extending beyond the late potential of QRS complex.

The onset of myocardial ischemia is followed by a progressive fall in the amplitude of the action potential [24]. Based on these experimental findings, it can be assumed that there are regional differences of myocardial current strength under stress due to flow-limiting stenosis in the corresponding vascular branch.

Consistent with earlier findings, the change of ST-segment fluctuation score was an independent predictor of CAD. Furthermore, the non-dipole phenomenon had more incremental diagnostic value than the previous parameter, the change of ST-segment fluctuation score. Notably, the sensitivity and negative predictive value of a non-dipole phenomenon were 84.8% and 88.0% as compared to 73.9% and 82.0% for the change of ST-segment fluctuation score, respectively. In summary, this study found more incremental diagnostic value of the measurement of the non-dipole phenomenon than the change of ST-segment fluctuation score for the prediction of significant CAD. Therefore, the assessment of the non-dipole phenomenon will provide valuable insight.

4.1. Study limitations

There are some limitations that should be acknowledged. Firstly, the current study has limitations inherent to its retrospective nature. Secondly, this study investigated a population with high disease
prevalence, and thus further studies are required to establish the diagnostic performance of MCG in lower-risk patients. In spite of these limitations, this is the first study to determine the diagnostic value of the non-dipole phenomenon to detect CAD.

4.2. Conclusions

This study has found that the qualitative assessment of the non-dipole phenomenon has more increased diagnostic value than the percent change of ST-segment fluctuation score in the detection of significant CAD.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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References


