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Comparison of exercise electrocardiography and magnetocardiography for detection of coronary artery disease using ST-segment fluctuation score

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Abstract.

BACKGROUND: Exercise electrocardiography (ECG) is frequently used as a diagnostic measure in patients with suspected coronary artery disease (CAD). However, it has low sensitivity for the detection of CAD. Magnetocardiography (MCG) has been proposed as an alternative tool to accurately diagnose CAD.

OBJECTIVE: To date, a direct comparison of MCG to ECG has not been performed. This study sought to compare them for predicting the presence of significantly obstructive CAD.

METHODS: The patients with chest pain or other symptoms suggestive of CAD were enrolled in the analysis. All the patients underwent a clinical evaluation, exercise ECG, a MCG exercise test, and coronary angiography (CA). CAD was defined as stenosis $\geq$70% stenosis in at least one major coronary artery on quantitative analysis of CA.

RESULTS: We prospectively enrolled 202 consecutive patients who suggested CAD. The prevalence of CAD on CA was 39.1%. Sensitivity and accuracy for CAD diagnosis was higher for MCG compared with exercise ECG (sensitivities 68.4% and 40.5%, $p < 0.001$, specificities 95.1% and 91.1%, $p = 0.267$, and accuracies 84.7% and 71.3%, $p < 0.001$, respectively). There was no incremental diagnostic value of combined MCG and ECG to detect coronary artery disease ($p = 0.357$).

CONCLUSIONS: For the patients with intermediate to high risk of CAD, MCG exercise test provides better diagnostic accuracy for the detection of relevant obstruction of the epicardial coronaries when directly compared to exercise ECG.

Keywords: Electrocardiography, magnetocardiography, diagnostic performance

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1. Introduction

Despite efforts to improve early diagnoses and preventive therapies, the prevalence of coronary artery disease (CAD) in the general population remains high and is the leading cause of death for both men and women. The detection of myocardial ischemia in patients with presumed CAD is still a challenge in routine cardiological diagnostics. The latest ACC-AHA guidelines on exercise testing, diagnosis and management of stable ischemic heart disease recommend exercise stress electrocardiography (ECG) as the initial diagnostic test in patients at intermediate pretest risk who are able to exercise and have an interpretable resting electrocardiogram [1]. Despite these recommendations, less than half of patients are evaluated non-invasively before percutaneous coronary intervention (PCI) because of low accuracy for the diagnosis of CAD [2, 3].

Magnetocardiography (MCG) is a non-invasive, non-contact, 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 ECG and MCG provide information about the same electrical activities of the heart and thus, MCG can be viewed as the magnetic equivalent of an ECG. However, the magnetic signal is much less influenced by the variations of conductance in body tissues than electric currents. Various clinical studies have already shown superior sensitivity of MCG than ECG for ischemic myocardium at rest, as well as under stress [7–11]. 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]. The aim of the present study was to directly compare exercise ECG (ST-segment deviation alone) with a new analysis method of MCG stress testing (ST-segment fluctuation score) for the detection of CAD with the use of invasive coronary angiography (CA) as the gold standard.

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 (no. 89/15_ z). The written informed consent was obtained from all subjects. The patients who were admitted to the hospital with an indication for CA due to chest pain or suspected CAD were enrolled in the study. They were older than 18 years and suited for stress testing with MCG. For the purposes of this analysis, we characterized significant coronary stenosis as $\geq$70% luminal obstruction. Although less severe stenoses might be associated with risk for cardiovascular events, we elected to use a widely accepted standard for defining angiographic significance. Exclusion criteria were acute coronary syndromes, 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 were performed in a standardized schedule within 24 hours. All MCG data were recorded before CA.

2.2. Exercise electrocardiography

All patients underwent symptom-limited cycle ergometer testing with continuous 12-lead ECG monitoring. A 25-Watt incremental protocol in every 2 minutes was used and a 12-lead ECG hard copy was recorded before exercise, at the end of each exercise stage, at peak exercise and during recovery. The test was discontinued for limiting symptoms (angina, dyspnea, fatigue), abnormalities in rhythm or blood pressure, marked ST-segment deviation (>0.2 mV in the presence of typical angina), or attainment of age predicted maximal heart rate (calculated as 220–age) [17]. All exercise ECG recordings were interpreted by consensus of two experienced readers. The ECG criterion for a positive test was greater than or equal to 1 mm of horizontal or downsloping ST-segment deviation (depression or elevation) in any lead except aVR for at least 60 to 80 milliseconds after the end of the QRS complex, either during or after exercise. Patients with left-bundle branch block on resting ECG, which interferes with interpretation of the exercise test, were considered non-diagnostic and were not included in the final analysis [17].

2.3. Exercise magnetocardiography

The MCG recordings were performed using a 64-channel gradiometer system in a magnetically shielded room (MSR) (CS-MAG II, BMP GmbH, Hamburg, Germany) [18]. The MCG system utilizes double relaxation oscillation superconducting quantum interference device (DROSQUID) sensors [19, 20]. The average noise spectral density of the entire system in the MSR room is 10 $\mathrm{fT}/\sqrt{\mathrm{Hz}}$ at 1 Hz and 5 $\mathrm{fT}/\sqrt{\mathrm{Hz}}$ over 100 Hz. Tangential components of the cardiomagnetic fields were measured, which were effective in obtaining the overall heart information with a relatively small area of the sensor array [21]. However, in order to apply the well-known magnetic field map variables, the tri-polar field map patterns were changed into ordinary dipolar field maps using minimum norm estimation [22]. The signal processing software provided automatic digital filtering, averaging, synthetic gradiometer formation and baseline correction of the acquired recordings.

The MCG signals were digitally recorded at rest for 100 seconds 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 [23]. 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 [23].

2.5. Statistical analysis

All statistical analyses were performed using SPSS 21.0 (SPSS Inc, Chicago, Illinois). Continuous variables are expressed as mean ± standard deviation and categorical variables are expressed as counts and %. Diagnostic measures including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were calculated. The McNemar's test was used to compare sensitivities and specificities of exercise MCG and exercise ECG. The receiver operating characteristic

Table 1
Baseline characteristics

	CAD (n = 79)	No CAD (n = 123)	p value
Men	50 (63.3)	79 (64.2)	0.892
Age (years)	66.6 ± 11.0	63.3 ± 10.1	0.034
Hypertension	62 (79.5)	95 (77.2)	0.707
Diabetes mellitus	33 (42.3)	40 (32.5)	0.160
Hyperlipidemia	37 (47.4)	59 (48.0)	0.941
Previous CAD	18 (23.1)	10 (8.1)	0.003
Ejection fraction (%)	54.0 ± 9.0	58.5 ± 7.1	<0.001
Multivessel disease	20 (25.3)	0	<0.001
Positive exercise ECG	32 (40.5)	11 (8.9)	<0.001
ST-segment fluctuation score	−35.9 ± 20.0	−56.3±12.5	<0.001

Values are n (%) or mean ± SD.
CAD = coronary artery disease; ECG = electrocardiography.

(ROC) curve analyses were performed to compare the diagnostic performance of the exercise MCG and exercise ECG. For all analyses, $p < 0.05$ was considered to be statistically significant.

3. Results

3.1. Study patients

A total of 202 patients (129 men and 73 women; the mean age of 64.6 years) were recruited for the study. Seventy seven patients (38.1%) had typical angina, 100 patients (49.5%) had atypical angina, and 25 patients (12.4%) were asymptomatic. Clinical characteristics of the patients are presented in Table 1.

3.2. Exercise ECG

The prevalence of CAD on CA was 79 patients (39.1%). Among them, 32 patients (40.5%) had positive exercise ECG. The diagnostic performance of exercise ECG was evaluated and the sensitivity, specificity, and accuracy were 40.5%, 91.1%, and 71.3%, respectively, for the detection of CAD $\geq$70% (Table 2). ROC analysis showed an area under the curve (AUC) of 0.658 (95% CI: 0.577 to 0.738, $p < 0.0001$) (Fig. 1).

3.3. Exercise MCG: ST-segment fluctuation score

The mean percent change of ST-segment fluctuation score on MCG from rest to stress was −48.3 ± 18.7%. Patients with CAD revealed a mean fluctuation score of −35.9 ± 20.0%, while patients without CAD revealed a mean fluctuation score of −56.3 ± 12.5%. ROC analysis showed an AUC of 0.839 (95% CI: 0.776 to 0.902, $p < 0.0001$). The best cut-off value of the percent change of ST-segment fluctuation score was −40.0% with sensitivity of 68.4%, specificity of 95.1%, PPV of 90.0%, and NPV of 82.4%. A representative case of ST-segment fluctuation score with the corresponding exercise ECG and CA is shown in Fig. 2.

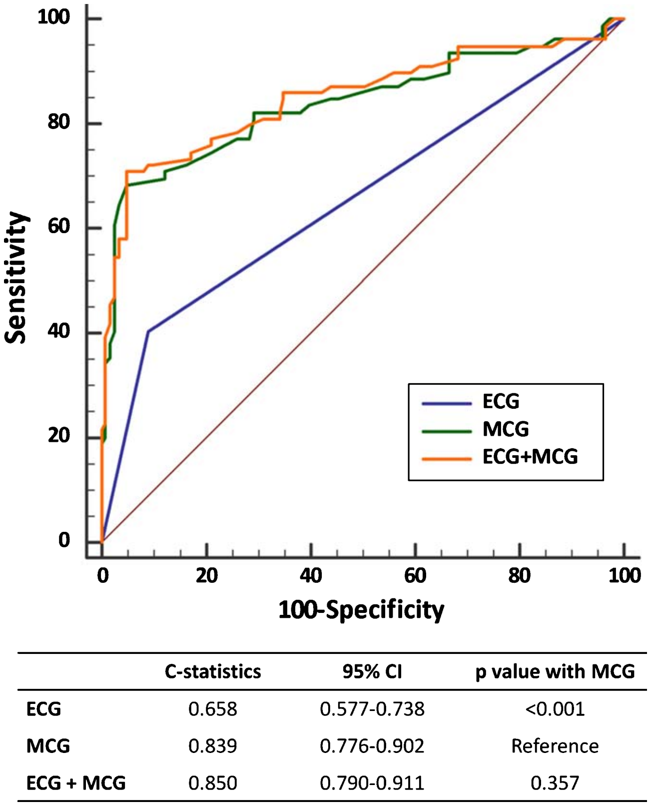
Table 2

Diagnostic performances of the exercise ECG and the percent change of ST–segment fluctuation score (MCG) for the detection of coronary artery disease

	ECG	MCG	ECG + MCG
Accuracy	71.3(65.0−77.5)	84.7(79.7−89.6)	85.6(80.8−90.5)
Sensitivity	40.5(29.7−51.3)	68.4(58.1−78.6)	70.9(60.9−80.9)
Specificity	91.1(86.0−96.1)	95.1(91.3−98.9)	95.1(91.3−98.9)
Positive predictive value	74.4(61.4−87.5)	90.0(82.4−97.6)	90.3(83.0−97.7)
Negative predictive value	70.4(63.3−77.5)	82.4(76.1−88.7)	83.6(77.4−89.7)

Values are % (95% CI).

CI = confidence interval; ECG = electrocardiography; MCG = magnetocardiography.

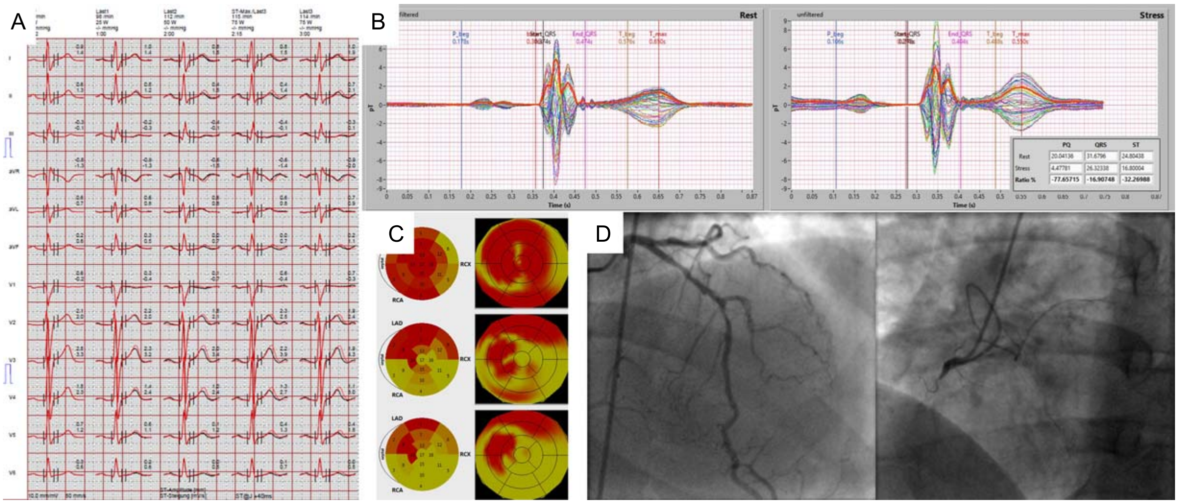


	C-statistics	95% CI	p value with MCG
ECG	0.658	0.577-0.738	<0.001
MCG	0.839	0.776-0.902	Reference
ECG + MCG	0.850	0.790-0.911	0.357

Fig. 1. **Receiver operating characteristic curves.** Receiver operator characteristic curve analyses comparing MCG and ECG for the detection CAD in all patients. The diagnostic accuracy of exercise MCG was significantly greater than the exercise ECG ($p < 0.001$). There was no incremental diagnostic value of combined MCG and ECG to detect coronary artery disease ($p = 0.357$) compared with MCG alone.

3.4. Comparison between exercise ECG and MCG

The diagnostic performance of MCG and exercise ECG is shown in Table 2. MCG exercise testing showed significantly higher sensitivity (68.4% vs 40.5%, $p < 0.001$) but showed similar specificity (95.1% vs. 91.1%, $p = 0.267$) than exercise ECG. The accuracy of MCG was higher compared to exercise ECG (84.7% vs. 71.3%, $p < 0.001$). Overall, MCG and exercise ECG were concordant in 157



	PQ	QRS	ST
Rest	20.04138	31.6796	24.80438
Stress	4.47781	26.32338	16.80004
Ratio %	-77.65715	-16.90748	-32.26988

Fig. 2. **Representative case of ECG, MCG and CA.** (A) negative exercise ECG (B) positive ST-fluctuation score (−32%) (C) epicardial current vectors at rest, stress and subtraction (D) normal left coronary arteries but totally occluded right coronary artery.

(77.7%) patients and discordant in 45 (22.3%) patients. Among the patients with discordant results, 14 had positive exercise ECG with negative MCG. In 9 (64.3%) of those patients, no obstructive CADs were found on CA. Conversely, 31 patients had negative exercise ECG with positive MCG. In 27 (87.1%) of those patients, significant CAD was found on CA.

Adding the exercise ECG to the percent change of ST-segment fluctuation score (MCG) did not enhance the diagnostic performance for the detection of significant CAD. MCG showed significant benefit over ECG (AUC: 0.839 vs. 0.658, $p < 0.001$), but combining ECG and MCG did not improve the performance compared with MCG alone (AUC: 0.850 vs. 0.839, $p = 0.357$).

4. Discussion

The major finding of the present study was that exercise MCG has a higher accuracy for the detection of CAD when directly compared with exercise ECG in patients who are capable of maximal exercise and have an interpretable resting ECG. The sensitivity of 68.4% and specificity of 95.1% with MCG was obtained in symptomatic patients with intermediate to high risk of CAD. Post-test referral bias was minimized in that all patients underwent the reference test (coronary angiography) independent of the results of both exercise ECG and MCG.

Exercise ECG is considered as the initial test of choice in patients with suspected CAD [24], which is based on a large number of studies demonstrating its utility for the detection of CAD. In a meta-analysis including 19 exercise ECG studies with 3721 women, the mean sensitivity was 61%, and mean specificity was 70%. However, a wide range of sensitivities (27%-91%) and specificities (46-86%) was observed in the individual studies, which is largely attributed to differences in prevalence of CAD (ranging from 18% to 75%), different influence by post-test referral bias, and different thresholds for interpreting a test as positive [2].

Exercise MCG is a relatively new noninvasive method that 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, 25]. Electrophysiological alteration is the first consequence of myocardial hypoxia occurring in less than a minute after the reduction of blood flow unmet metabolic demand. The changes of the magnetic field under hypoxia are due to the reduction of the transmembrane action potential of cardiomyocytes [26–28], which can be demonstrated by MCG [29]. In our previous study, we showed that the change of ST-segment fluctuation score accurately predicts the presence of hemodynamically significant CAD when compared to FFR [16]. 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 [30]. We found that ST segment fluctuation decreases with stress. However, there is a smaller decrease in patients with CAD with a cutoff value of -40.0% (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 [12]. Possibly, the ST-segment is the most sensitive phase to detect the ischemia-induced electromagnetic deviation [29]. 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 present study is to investigate comparative effectiveness between exercise ECG and MCG by directly comparing results of both diagnostic measures in the same populations. Consistent with earlier findings, the change of ST-segment fluctuation score was an independent predictor of CAD. Furthermore, MCG exercise test (the change of ST-segment fluctuation score) provides better diagnostic accuracy for the detection of relevant obstruction of the epicardial coronaries when directly compared to exercise ECG. However, there was no incremental diagnostic value of the stress ECG for the prediction of significant CAD.

Limitations of the present study are that not all potential sources of pretest referral bias were removed because patients were selected from those already scheduled for invasive angiography. In addition, invasive CA is not necessarily the ideal gold-standard for comparison as functional significance of coronary obstruction and luminal diameter stenosis are moderately correlated. Furthermore, it is important to keep in mind that the algorithm used for MCG analysis is intended to detect significant obstruction of the epicardial coronaries compared to invasive CA (e.g. $\geq 70\%$ stenosis). Thus, magnetic field defects that were regarded as artifacts according to the algorithm used in the present analysis may in fact represent microvascular dysfunction. Since microvascular dysfunction is hardly detectable by conventional invasive CA these patients were regarded as "healthy" by CA, and correctly identified as such by MCG explaining the high specificity, despite the possible presence of microvascular dysfunction responsible for the clinical complaints of these patients. Therefore, additional data with regard to the role of microvascular dysfunction is needed to fully understand the diagnostic performance of MCG in patients with chest pain or other signs and symptoms suggestive of CAD. The present study did also not include a comprehensive cost-comparison. A lower cost of the exercise ECG test, however, does not necessarily translate into lower overall cost of patient care, because the sum of the cost of additional downstream testing and interventions may be higher when the initial exercise ECG is less accurate than MCG test. Cost analysis poses several challenges. The cost of a false positive ECG results is readily quantifiable by the cost of unnecessary cardiac catheterization. However, the cost of a false negative test is more difficult to quantify as it involves not only cost associated with morbidity (hospitalization, procedures) but also cost related to mortality, which is much more difficult to quantify.

In conclusion, the present study demonstrates that in patients with intermediate to high risk of CAD who are able to exercise and have interpretable resting ECG, MCG exercise testing provides better diagnostic performance for the detection of relevant obstruction of the epicardial coronaries. Further investigations are required to evaluate both accuracy and cost to justify MCG stress testing as the initial test in this population.

Conflict of interest

The authors declare that they have no conflict of interest.

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