

Non-Invasive Resting Magnetocardiographic Imaging for the Rapid Detection of Ischemia in Subjects Presenting with Chest Pain

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Key Words

Magnetocardiography · Ischemia · Unstable angina

Abstract

Background: Early diagnosis of ischemia is complicated by the poor sensitivity of standard tests and contraindication for stress testing in unstable angina patients. Magnetocardiography (MCG) imaging can be used for the rapid, non-invasive detection of ischemia at rest. **Methods:** We studied 125 patients with presumed ischemic chest pain. All were chest pain free at the time of scanning. A 6-minute resting MCG scan (CardioMag Imaging, Inc., New York, 9-channel system) was performed. Following the MCG scan, automated software data analysis was performed, and quantitative scores were automatically calculated for each subject. The presence of ischemia was determined after testing with serial troponins, stress testing, and/or coronary angiography. **Results:** The mean age was 59.4 ± 13.6 years. Most patients (86.4%) had non-ischemic 12-lead ECG and normal troponin (86.2%). Fifty-five patients (44.0%) were determined to be ischemic. The MCG sensitivity, specificity, positive and negative predictive value was 76.4, 74.3, 70.0 and 80.0%, respec-

tively, for the detection of ischemia ($p < 0.0001$). **Conclusions:** MCG is a new rapid, non-invasive imaging tool able to detect repolarization abnormalities at rest consistent with ischemia in patients presenting with chest pain syndrome and normal or non-specific 12-lead ECG and normal troponin.

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Introduction

Ischemic heart disease is the leading single cause of death in the United States and a major health problem worldwide [1]. The direct cost of hospitalizations for ischemic heart disease in the US alone is enormous and amounts to >15 billion USD. Consequently, it is very important to facilitate more definitive ischemia evaluation, while avoiding unnecessary hospital admissions of non-cardiac chest pain patients as well as avoiding discharge of patients with myocardial infarction. For this purpose many centers have established chest pain units in the emergency department. The initial evaluation involves a 12-lead electrocardiogram (ECG) and cardiac markers

such as troponins, both of which are very insensitive but highly specific. Therefore, the majority of chest pain patients will have a normal or non-specific ECG and a normal initial troponin and will often require further testing and evaluation to achieve an accurate diagnosis. Currently this often involves admission to the hospital and/or some form of stress testing, either with or without imaging. However, these tests are contraindicated in subjects with possible or definite acute coronary syndrome. Furthermore, both nuclear and echocardiographic stress testing are time consuming to perform, and for nuclear imaging the results are typically not available for at least 4 h.

Magnetocardiography (MCG) is a new modality, which utilizes superconducting quantum interference devices for the detection of the weak magnetic fields (picoTesla range) generated by the heart's electrical currents. The magnetic field map picture, which is created by the measurements of the magnetic field, reflects the electrophysiologic state of the heart. When there is an abnormality in cardiac depolarization or repolarization, such as in ischemia, this is reflected in an abnormality in the magnetic field map [2]. The MCG has been used predominantly in Europe since the 1970s [2]. Most studies were done to localize arrhythmias in conditions with ventricular pre-excitation, Wolf-Parkinson-White and accessory pathways, and more recently atrial fibrillation [3–11]. The sensitivity and capability of the MCG for the detection of ischemia has been evaluated in only a few small clinical studies [12–14]. However, all these studies were performed on early generation MCG machines, which required a magnetically shielded room to obtain images with an acceptable signal-to-noise ratio. In addition, none of those studies utilized an automated software program or standardized method for the analysis of the acquired data. Recently, CardioMag Imaging, Inc. has developed an MCG imaging device which operates without the need for expensive shielded rooms. This MCG device is capable of non-invasive recording of magnetic fields arising from the electrical activity of the heart with very high spatial and temporal resolution (utilizing a bandwidth from 0 to 1,000 Hz), and has been specifically developed for the general purpose (without shielded room) of non-contact, non-invasive diagnosis of repolarization abnormalities indicative of ischemia. Several studies have confirmed the safety and feasibility of the acquisition of data without shielded rooms [15–20]. The departure of MCG from the shielded environment allows it to transition from use solely in a research environment to being applied in a clinical care setting.

Objectives

Pilot data were collected to: (1) Evaluate the diagnostic utility and accuracy of the magnetic field map imaging for the detection of repolarization abnormalities at rest consistent with ischemia in patients presenting to the hospital with suspected ischemic chest pain, and (2) provide additional data to optimize the automated data analysis prior to commencing a larger prospective trial.

Methods

Subject Population

Patients presenting with chest pain were enrolled from the emergency department observation unit, the coronary care unit, and the telemetry unit at the three participating institutions, utilizing an identical protocol for enrollment and MCG imaging. Informed consent was obtained from each subject in accordance with the institutional review boards.

Inclusion Criteria

Patients presenting with acute chest pain, who underwent testing with at least two tests to work up the presence of ischemia (cardiac enzymes, stress testing and/or coronary angiography) and where the discharge diagnosis clearly could be linked to the index presentation, were included.

Exclusion Criteria

Included hemodynamic instability, ST-elevation myocardial infarction, tachycardia with heart rates exceeding 150 bpm just prior to the MCG testing, third degree atrio-ventricular block, atrial flutter, left bundle branch block, pacemakers or internal cardiac defibrillators, inability of the patient to lie in a supine position for the MCG examination, enrollment refusal, or age < 18 years.

Procedures

All subjects had a 12-lead ECG just prior to the MCG imaging. The MCG images were obtained on a CardioMag Imaging, Inc., Schenectady, New York 9-channel MCG Model 2409 in unshielded locations within the clinical departments. In 77 patients, the MCG was performed in the emergency room within 24 h of presentation, before any stress test and/or cardiac catheterization, but after the first troponin was obtained. Eight-teen patients were studied within 24 h after direct admission to the CCU, after cardiac enzymes were drawn, but before cardiac catheterization. All other patients (n = 30) were studied after admission to the telemetry unit while undergoing a rule out myocardial infarction protocol. All tests were performed during the index hospitalization and the MCG was typically performed within 24 h of the other tests. All patients were treated and stabilized by their primary physicians according to the clinical presentation and all patients were chest pain free at the time of the MCG scan. For the MCG imaging, all magnetic, electronic and larger metallic objects (watch, bracelets, bra with metal inserts, zippers, earrings, removable dentures, etc.) were removed. Three ECG electrodes were placed for single-lead measurement as a reference signal for MCG signal averaging. The patient's position on the MCG bed was noted and the sensor head was lowered to just above the patient's chest (fig. 1). The MCG was recorded sequen-

tially at four pre-defined bed positions for 90 s at each position for a total imaging time of 6 min. At each position the MCG is recorded in an 80 × 80 mm area simultaneously by nine sensors arranged in a 3 × 3 square grid and separated from each other by 40 mm. At the end of four sequential recordings, raw, unfiltered MCG data are stored. After a 2-min data processing, one thousand data points of magnetic field strength represent one cardiac cycle at each of the 36 points (36 leads) forming a 200 mm square 6 × 6 grid in a horizontal plane close to the torso. The vertical position of this plane is defined by the elevation of the sensor head, which is set by the operator.

The presence of traditional cardiovascular risk factors was recorded: Hypertension (BP >140/90 mm Hg or on antihypertensive medication), diabetes mellitus (fasting glucose >126 mg/dl or on diabetes medication), past or present smoking history, hypercholesterolemia (National Cholesterol Education Program guidelines [21], or on lipid reduction therapy), family history of early coronary artery disease, and history of previous myocardial infarction.

Data Interpretation

The ECG's were interpreted by the research teams at the three institutions and categorized into ischemic or non-ischemic according to standard criteria as follows: Ischemic: Definite: ≥ 1 mm horizontal/downsloping ST depressions in ≥ 2 contiguous leads; Probable: <1 mm ST depressions in ≥ 2 contiguous leads and/or T wave inversions in ≥ 2 contiguous leads; Possible: Left ventricular hypertrophy with strain, and non-ischemic; Normal ECG; left ventricular hypertrophy without strain; ST-T changes in <2 contiguous leads; Q waves without ST-T changes. ST-elevation myocardial infarctions were excluded, but ST-depression (non-Q) myocardial infarctions were included. First, the raw MCG data traces were pre-processed manually by each research team to assure proper positioning and to delete any major magnetic influences. Next, a proprietary automated MCG analysis program (CardioMag Imaging Inc.) was used to further process and interpret the acquired MCG data. The pre-processing and automated software analysis typically takes less than 5 min. The method, effective magnetic dipole vector (EMDV) analysis, is based on an automated analysis of the ventricular repolarization [22]. From the averaged data the software compares all T-waves simultaneously and calculates the difference between the most positive and most negative magnetic signal at each time point during cardiac repolarization. The maximum calculated difference represents the peak of repolarization magnetic field activity, and the window for ischemia analysis is centered around this peak. The electrical activity during repolarization gives rise to effective magnetic vectors, the dynamic motion of which describes the displacement of the electrical source. The software calculates 40 magnetic vectors at equally spaced time intervals around the peak of the T-wave (pre- and post-peak repolarization). The detection of repolarization abnormalities is directly related to the direction and dynamic motion of the magnetic vector around the peak of the T-wave. The magnitude and strength of motion of the vector can be described by seven pre-defined parameters (table 1). If any of the seven parameters lie in the abnormal range, then the patient is assigned a score of one and determined to be ischemic. The reference values for detection of repolarization abnormalities according to the seven criteria were established based on analysis of 197 ischemic and non-ischemic patients who had undergone cardiac work up at other institutions prior to commencing

Table 1. Effective magnetic dipole vector (EMDV) analysis parameters

Parameter	Unit	Abnormal value range
<i>Pre-peak repolarization</i>		
EMDV angle (frontal plane)	Degrees	≥ -15 or ≤ -110
EMDV trajectory	Centimeters	≥ 7.5
EMDV angular deviation	Radians	≥ 1.0
<i>Post-peak repolarization</i>		
EMDV angle (frontal plane)	Degrees	≥ -22 or ≤ -100
EMDV trajectory	Centimeters	≥ 5.0
EMDV angular deviation	Radians	≥ 0.7
Pre- to post-orientation change in EMDV angle	Degrees	≥ -12 or ≤ -35

this study. The data of these 197 patients were entered and analyzed using the automated software analysis program located at CardioMag Imaging, Inc., and based on these results normal reference values were selected.

We recorded the results of cardiac troponin (performed in all but two patients), stress tests (treadmill exercise test, stress echo or stress sestamibi scans performed in 101 patients) and coronary angiography (in 59 patients). All patients had at least two tests performed and all tests were ordered for clinical indication by their treating physicians, who were unaware of the MCG data. A 50% left main stenosis, and 70% stenosis of either the left anterior descending artery and its branches, left circumflex artery and its branches, and/or right coronary artery and branches were considered significant obstructive coronary artery disease.

Gold Standard

We used the clinicians' discharge diagnosis as the determinant whether the patient had suffered an ischemic event. This conclusion was derived after testing with serial troponin, stress testing and/or coronary angiography. The standard 12-lead ECG was not used as the reference standard, but was used for direct comparison with the MCG results. The decision to perform stress testing or coronary angiography was based on clinical grounds alone. All tests were performed during the index hospitalization.

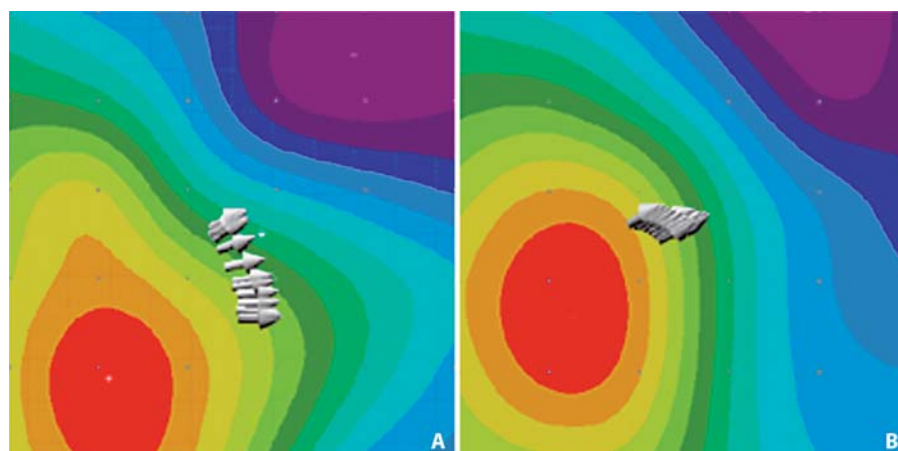
Statistics

Group differences in categorical variables were assessed by Fisher's exact test. Group differences in continuous variables were assessed by Student's t test. Stepwise logistic regression was used to determine variables associated with the presence of ischemia; candidate predictor variables included standard cardiac risk factors, ECG (positive or negative) and MCG (positive or negative). Logistic regression (specifically the log likelihood statistic -2 log L) was used to evaluate the incremental improvement of MCG over ECG in the prediction of ischemia. A p value of <0.05 was considered significant. All statistical tests were performed using the software package SAS version 9.1 (SAS Institute, Cary, N.C., USA).

Fig. 1. The 9-channel CardioMag Imaging, Inc. Magnetocardiograph installed at Cedars-Sinai Medical Center (model photo). * Sensor tower containing the cryostat with nine SQUIDs embedded in liquid helium; ** Gantry tower containing the cryostat and SQUID electronics; *** Sliding couch. SQUID = Super Conducting Quantum Interference Devices



Fig. 2. A Magnetic field map imaging of 61-year-old man with atypical chest pain and non-Q wave myocardial infarction (troponin I 2.2). Left ventricular ejection fraction was 57%. Coronary angiography demonstrated 90% left anterior descending artery and 90% obtuse marginal lesions. The quantitative EMDV score obtained 2 days after peak of troponin and the day before cardiac catheterization was positive (Increased dynamic motion of the effective dipole vector). **B** 45-year-old woman with hypertension, hypercholesterolemia, and diabetes presented with typical chest pain. Troponins were negative. A stress echocardiogram was markedly positive. Cardiac catheterization revealed no coronary artery disease and a left ventricular ejection fraction of 45–50%. The magnetocardiographic effective dipole vector score obtained 1½ h after the stress test was negative (stable, minimal dynamic motion of the effective dipole vector). Both images show the magnetic dipole at the peak of the T-wave. Arrows demonstrate the magnetic dipole vector trajectory during ventricular repolarization.



Results

Patient Demographics

The study group was comprised of 125 patients (57.6% men), average age 59.5 years \pm 13.6 years (range: 32–86 years). All patients were stabilized and chest pain free at the time of scanning. The prevalence of cardiovascular risk factors is shown in table 2. The presence of cardiovascular risk factors was, as expected, higher in the ischemic group (table 2).

Clinical Data

Of the 125 patients, 86.4% had a non-ischemic 12-lead ECG. Serial troponins were normal in 86.2%. Almost half (47.2%) underwent cardiac catheterization, of which 62.7% were found to have obstructive coronary artery disease. Fifty-one patients (40.8%) had nuclear imaging (positive in 51.0%). Using the clinical gold standard, 44.0% (n = 55) were determined to have chest pain caused by ischemia.

MCG Results

The automated quantitative EMDV method was highly statistically significant between the ischemic and the

Table 2. Prevalence of cardiovascular risk factors

	All (n = 125)	Ischemic (n = 55)	Non-ischemic (n = 70)	p value
Age, mean ± STD ^a , years	59.5 ± 13.6	65.0 ± 12.3	55.1 ± 13.2	<0.0001
Men, %	57.6	67.3	50.0	0.068
Hypertension, %	57.3	77.8	41.4	0.0001
Diabetes, %	16.1	22.2	11.4	0.143
Smoking, %	49.6	56.6	44.3	0.205
Hypercholesterolemia, %	56.6	63.6	50.8	0.199
Family history, %	29.7	39.5	23.8	0.118
Prior MI ^b , %	20.2	33.3	10.0	0.002

^a Standard deviation.

^b Myocardial infarction.

Table 3. Effective magnetic dipole vector (EMDV) scores by magnetocardiography

	All (n = 125)	Ischemic (n = 55)	Non-ischemic (n = 70)	p value
EMDV analysis	0.47 ± 0.50	0.75 ± 0.44	0.26 ± 0.44	9.5 × 10 ⁻⁹

non-ischemic group with a p value of <0.0001 (table 3). Stepwise logistic regression analysis including the standard cardiovascular risk factors (age, hypertension, diabetes, smoking, hypercholesterolemia, and prior myocardial infarction), ECG (positive or negative), and the MCG EMDV score demonstrated that the MCG score had the strongest relationship with an ischemic outcome (p < 0.0001), followed by hypertension (p = 0.005), and history of prior myocardial infarction (p = 0.026). A positive MCG imaging was demonstrated in 60 (48.0%) of the patients. This group was older, had higher prevalence of hypertension, and hypercholesterolemia than the group with a negative MCG imaging scan. Also, they were more likely to have a previous history of myocardial infarction and coronary artery graft bypass surgery. The presence of an abnormal MCG scan was highly predictive of ischemia (p < 0.0001). Figures 2A and B show an instantaneous picture of the magnetic dipole field map in an ischemic versus a non-ischemic patient.

Diagnostic Value of the MCG

The EMDV method had a sensitivity of 76.4%, specificity of 74.3%, positive predictive value of 70.0%, and a negative predictive value of 80.0% for the MCG detection

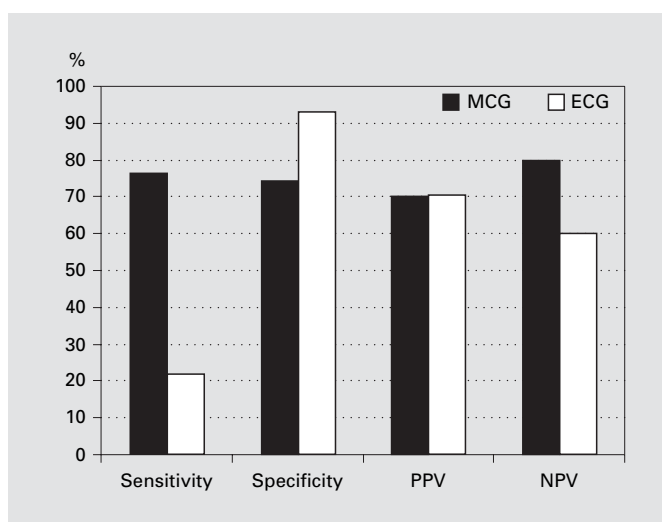


Fig. 3. Diagnostic value of the resting magnetocardiographic imaging in 125 patients compared with the diagnostic accuracy of the 12-lead ECG. ECG = 12-lead electrocardiography; MCG = magnetocardiography; NPV = negative predictive value; PPV = positive predictive value.

of repolarization abnormalities at rest. The overall accuracy was 75.2% (fig. 3). The 12-lead ECG had an overall accuracy of 61.6%, but with very poor sensitivity and negative predictive value (fig. 3). The negative predictive value of the MCG increased to 86.7 and 86.5%, respectively, when evaluating the subgroup of patients with negative ECG and troponin, and the group of patients without a history of prior myocardial infarction, CABG, or percutaneous intervention, the de-novo group. We found that there was a significant incremental value to the MCG imaging over the ECG for the prediction of ischemia (OR

8.6; CI 3.1–20.3, $p < 0.0001$), while there was no added value of the ECG over the MCG.

Discussion

This is the first prospective study on the use of magnetocardiographic imaging in the general clinical environment for the detection of ischemia. Other very small case studies have suggested that in the presence of a normal 12-lead ECG the resting MCG is capable of detecting ischemia in patients with coronary artery disease [12–14, 16–18, 23, 24]. However, most of these earlier studies used a magnetically shielded room to avoid ambient magnetic noise, and the interpretation of the field maps were subject to non-objective qualitative interpretations. This is the first report in which an automated quantitative analysis method has been used for interpretation of the MCG. Our study demonstrates the feasibility of operating without a shielded room to non-invasively and rapidly measure the magnetic field during the cardiac cycle in subjects with chest pain. The magnetic field map obtained in this way reflects the electrical currents in the heart and will be altered in conditions where the electrical currents are disturbed. We found that the spatial features of the magnetic field maps of normal subjects were similar at specific times during de- and repolarization. This is often referred to as a 'stable pattern'. For the patients who had an ischemic event during the hospitalization there were clear deviations in the magnetic field maps as compared with the normal subjects at specific times. This difference was reflected in the difference in the automated score between the group with and without repolarization abnormalities by MCG ($p < 0.0001$). This separation of scores is even more remarkable considering that all patients were chest pain free at the time of scanning and the vast majority had a normal or non-specific 12-lead ECG and a normal troponin. Furthermore, the MCG imaging was acquired at rest and the results were available immediately.

Although MCG and ECG both measure the cardiac depolarization and repolarization patterns, they have fundamental differences. MCG is most sensitive to tangential currents, whereas ECG is most sensitive to radial currents in relation to the chest surface [2, 25–27]. Cardiac abnormalities, which interfere with the normal activation and deactivation sequence, such as occurs in ischemia, increase the contribution of tangential currents. In addition, the MCG detects the vortex currents which are not evident by ECG. Finally, the MCG is less affected by conductivity variations caused by lungs, skin, and muscles and

there is no skin electrode contact problem since the device does not come in direct contact with the skin. Therefore, the MCG may be able to detect differences in depolarization and repolarization in a different manner and with a higher sensitivity than the ECG. This was clearly demonstrated in our study where the MCG had a sensitivity and accuracy of 76.4 and 75.2% as compared to the ECG's sensitivity and accuracy of 21.8 and 61.6%, respectively. We speculate that the variation in the magnetic field pattern is due to early subtle changes in cellular mechanisms or metabolism caused by alterations in coronary flow. These changes create a heterogenous repolarization pattern probably caused by local currents appearing at the border zones between normal and diseased myocardium. This implies that changes in the MCG may appear even earlier in the cascade of ischemia than wall motion abnormalities or ECG changes, and without elevations in troponin levels (subclinical or pre-ischemia).

Limitations

The patients were heterogenous in regard to their risk for coronary artery disease and the presence of cardiovascular risk factors. Although this complicates the understanding of the MCG pattern under varied conditions, this is the patient population that we see daily in the general clinical setting and whom we would want to test. It may, therefore, be a strength rather than a weakness because we have demonstrated that MCG imaging is a useful tool up front in the emergency department, in the telemetry unit as well as in the coronary intensive care setting.

Due to the inhomogeneity of the patients and the differences in test availability at different hospital sites, we used a clinical endpoint as the gold standard for the presence of ischemia. Due to the lack of a real and clear gold standard for ischemia, we feel the choice of the clinical standard comes closest to common practice.

We focused on cardiac repolarization only (T-wave) for the detection of ischemia. It appears that by limiting the data analysis to the T-wave only we may miss some of the ischemic patients. It is possible to improve the accuracy of the MCG test by evaluating other parts of the cardiac cycle. However, this has not been incorporated into the software program and we wanted to avoid any subjective classification of the scores to avoid bias.

Finally, patient positioning and anatomic variations of torso versus heart may lead to misinterpretation of the magnetic field measurement. Further work to standardize patient positioning, heart versus measuring device, is needed.

Conclusion

Magnetocardiographic imaging is a new, rapid, entirely non-invasive, no risk scanning, with the capability of detecting repolarization abnormalities at rest consistent with ischemia in patients presenting with chest pain syndrome and normal or non-specific 12-lead ECG and normal troponin. The possibility of accurate, rapid, and no risk diagnosis of ischemia could potentially greatly impact healthcare for a large group of subjects by avoiding a delay in diagnosis of ischemic patients while avoid-

ing unnecessary admissions and testing of non-ischemic subjects.

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