Non-invasive Resting Magnetocardiographic Imaging for the Rapid Detection of Ischaemia

a report by
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Ischaemic heart disease is the leading single cause of death in the US and elsewhere, and a major health problem worldwide.[1] The direct cost of hospitalisations for ischaemic heart disease in the US alone is enormous and amounts to more than US$15 billion. Consequently, it is very important to facilitate more definitive ischaemia evaluation while avoiding unnecessary hospital admissions of non-cardiac chest pain patients, as well as avoiding discharge of patients with myocardial infarction (MI). 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. The often extensive work-up may involve stress provocation, injection of medication, contrast, or nuclear tracer, radiation, and/or cardiac catheterisation, all of which carry risks. Stress testing is contraindicated in subjects with possible or definite acute coronary syndrome and both nuclear and echocardiographic stress testing are time-consuming to perform. Furthermore, for nuclear imaging the results are typically not available for at least four hours.

Magnetocardiography (MCG) utilises superconducting quantum interference devices (SQUIDs) for the detection and subsequent display of realtime maps of the weak magnetic fields (picoTesla range) generated by the heart's electrical currents. The magnetic field map picture, which is created from the measurements of the magnetic field, reflects the electrophysiologic state of the heart. When there is an abnormality in cardiac depolarisation or repolarisation, such as can occur in impaired coronary artery blood flow and ischaemia, this is reflected in an abnormality in the magnetic field map.[2] Until recently, the use of MCG required a magnetically shielded room to obtain images with an acceptable signal-to-noise ratio. With advances in hardware and software the MCG imaging device now operates without the need for expensive shielded rooms allowing the technology to transition from

1. *Gibbons R J, Abrams J, Chatterjee K et al., "ACC/AHA 2002 guideline update for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for the Management of Patients with Chronic Stable Angina) 2002".*
2. *Stroink G, Moshage W, Achenbach S, "Cardiomagnetism", in: Andrä W, Nowak H, eds.* Magnetism in Medicine. *Berlin: Wiley-VCH Verlag (1998): pp. 136–189.*
3. *Chen J, Thompson P D, Nolan V, Clarke J, Bakharev A, "The normal magnetocardiogram at rest and post-exercise in healthy volunteers in an unshielded clinical environment",* Biomag2002, *Proceedings of 13th International Conference on Biomagnetism, p. 533.*
4. *Sternickel K, Tralshawala N, Bakharev A et al., "Unshielded measurements of cardiac electrical activity using magnetocardiography", 4th International Conference on Bioelectromagnetism.*
5. *Brazdeikis A, Taylor A A, Mahmarian J J, Xue Y, Chu C W, "Comparison of magnetocardiograms acquired in unshielded clinical environment at rest, during and after exercise and in conjunction with myocardial perfusion imaging",* Biomag2002, *Proceedings of 13th International Conference on Biomagnetism. pp. 530–532.*
6. *Fenici R, Brisinda D, Nenonen J, Mäkijärvi M, Fenici P, "Study of ventricular repolarization in patients with myocardial ischemia, using unshielded multichannel magnetocardiography",* Biomag2002, *Proceedings of 13th International Conference on Biomagnetism, pp. 537–539.*
7. *Sternickel K, "Breathing artifact removal from MCG time series",* Biomag2000, *Proceedings of 12th International Conference on Biomagnetism, p. 1050.*
8. *Steinberg B A, Roguin A, Watkins S P 3rd, Hill P, Fernando D, Resar J R, "Magnetocardiogram recordings in a nonshielded environment – reproducibility and ischemia detection",* Ann Noninvasive Electrocardiol *(2005);10: pp. 152–160.*

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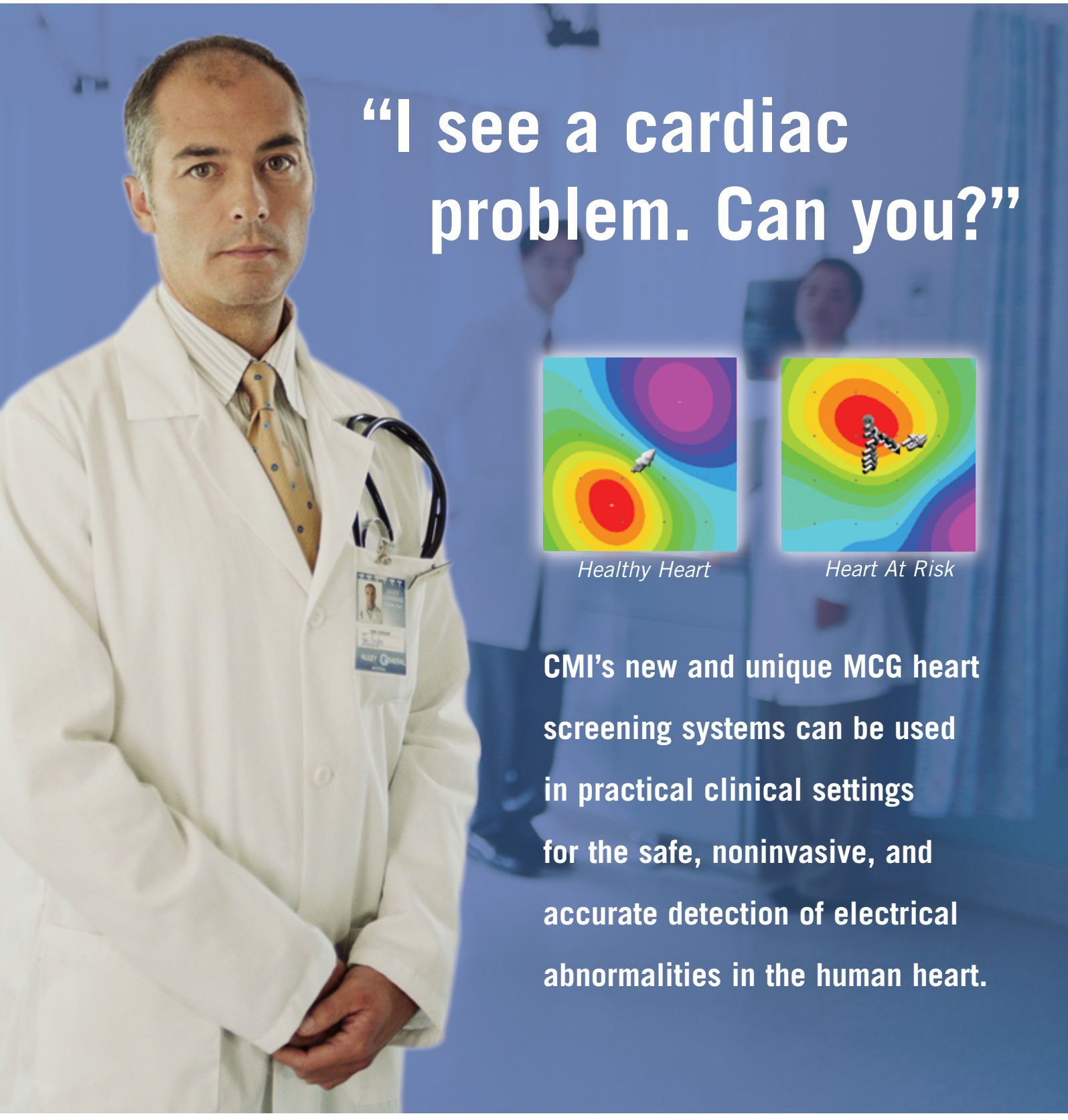

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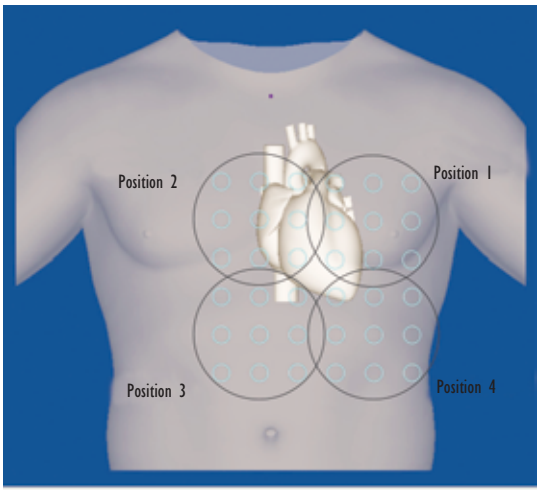
Figure 1: Positions of the 36 SQUID Channels Above the Patient's Torso



use solely in a research environment to being applied in a clinical care setting. The safety and feasibility of the acquisition of data without shielded rooms has been studied previously.[3–8] In July 2004, the US Food and Drug Administration (FDA) approved the CardioMag Imaging MCG as a safe device used for the non-invasive detection and recording of the magnetic fields arising from the heart's electrical currents.

Image Acquisition and Data Processing

Image Acquisition

For MCG imaging, all magnetic, electronic and larger metallic objects such as watches, bracelets, bras with metal inserts, zippers, earrings, removable dentures, etc., are removed, and the patient is placed on the moving bed. For triggering purposes three ECG electrodes are attached to the patient (lead I configuration). The patient's position on the MCG bed is adjusted using a built-in laser pointer, which is directed towards the suprasternal notch. The sensor head is then lowered to just above the patient's chest. Data are recorded sequentially at four pre-defined bed positions for 90 seconds at each position for a total imaging time of six minutes. The interspacing of the sensors is 4cm in a 3x3 grid configuration. By performing four sequential measurements an area of 20x20cm over the chest is covered (see *Figure 1*). After data acquisition, raw, unfiltered MCG data are stored. Following data processing the software calculates one averaged cardiac cycle for each of the 36 positions.

Data Processing

First, the raw MCG data traces are processed manually to assure proper positioning and to delete any major magnetic influences. Next, a proprietary automated MCG analysis programme is used to further process and interpret the acquired MCG data. The manual processing and automated software analysis typically takes less than five minutes. The method, effective magnetic dipole vector (EMDV) analysis, is based on an automated analysis of ventricular repolarisation.[9] The electrical activity during repolarisation 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 repolarisation). The detection of repolarisation 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: pre-peak T-wave mean frontal angle, trajectory, and angle deviation; post-peak T-wave mean frontal angle, trajectory, and angle deviation; and difference in mean frontal angle between pre- and post-peak T-wave. If any of the seven parameters lie in the abnormal range, then the patient's repolarisation pattern is consistent with ischaemia.

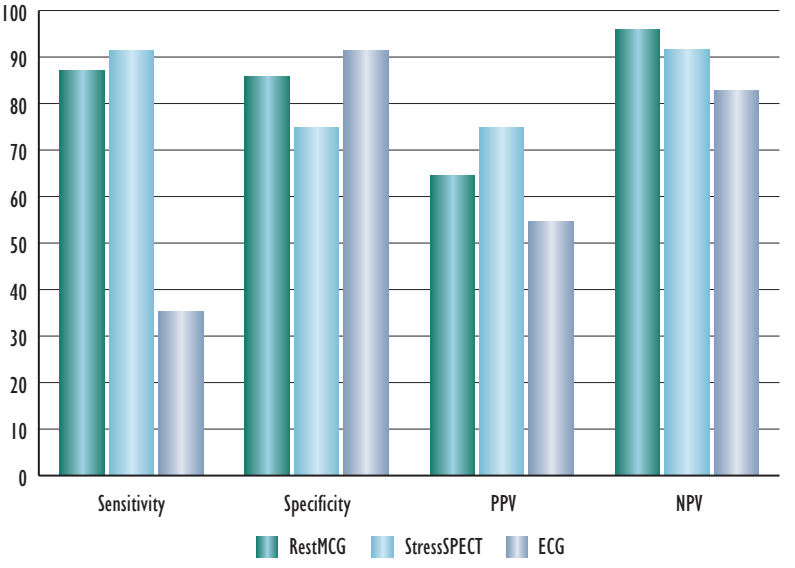
Resting MCG in Chest Pain Syndrome

The first reported data on 136 patients (57.6% men, mean age 59.5 years) presenting with chest pain and enrolled from the emergency department observation unit, coronary care unit, and telemetry unit at three participating institutions demonstrated that an abnormal MCG scan was strongly associated with ischaemia ($p<0.0001$).[10] Stepwise logistic regression analysis, including the standard cardiovascular risk factors (age, hypertension, diabetes, smoking, hypercholesterolaemia and prior MI), ECG (positive or negative), and the MCG effective magnetic dipole vector score, demonstrated that the MCG score had the strongest relationship with an ischaemic outcome ($p<0.0001$), followed by hypertension ($p=0.005$) and history of prior MI ($p=0.026$). The clinician's discharge diagnoses were used as determinants of whether the patients had suffered ischaemic events.

9. *Alexander A, Bakharev, "Ischemia identification, quantification and partial localization in MCG2001",* PCT Application Based on US Prov. Appl. No.: 60/228,640.
10. *Tolstrup K, Madsen B E,Ruiz J A et al., "Non-invasive resting magnetocardiographic imaging for the rapid detection of ischemia in subjects presenting with chest pain.* Cardiology *(2006), in press.*

The effective magnetic dipole vector method had a sensitivity of 76.4%, specificity of 74.3%, positive predictive value of 70.0%, and negative predictive value of 80.0% for the MCG detection of repolarisation abnormalities at rest. The overall accuracy was 75.2%. In comparison, the 12-lead ECG had an overall accuracy of 61.6%, but with very poor sensitivity and negative predictive value (21.8% and 60.2%, respectively). 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 MI, coronary artery bypass graft (CABG) surgery or percutaneous intervention (the de-novo group). We found that there was a significant incremental value to MCG imaging over ECG for the prediction of ischaemia (odds ratio (OR) 8.6; 95% confidence interval (CI) 3.1–20.3; p<0.0001), while there was no added value of the ECG over the MCG.

Figure 2: Diagnostic Value of Resting Magnetocardiographic (MCG) Imaging, Stress Single Photon Emission Tomography (SPECT) Imaging, and 12-lead Electrocardiography (ECG) for the Detection of Ischaemia



Learning from the above-mentioned pilot trial, improvements were made, especially in data acquisition, while still using the automated software programme effective magnetic dipole vector scores. In 75 acute chest pain patients (mean age 58.2 years, 70.7% men) and 61 healthy volunteers (mean age 42.2 years, 49.2% men), an abnormal MCG scan was highly statistically associated with ischaemia as assessed by evaluation of symptoms, troponin I, stress single photon emission tomography (SPECT), and/or coronary angiography (OR 14.5; CI 4.2–49.3; p<0.0001).[11] In addition, age, hypercholesterolaemia, prior MI, prior CABG, and history of percutaneous coronary intervention were associated with ischaemia (p=0.01, p=0.01, p<0.0001, p=0.0004, and p=0.01, respectively). However, stepwise logistic regression analysis with age, hypertension, diabetes, hypercholesterolaemia, prior MI, prior CABG, prior percutaneous coronary intervention, and the ECG (ischaemic or non-ischaemic) and MCG scores, as candidate factors, demonstrated that the MCG score had the strongest relationship with an ischaemic outcome (OR 13.3; p<0.0001), followed by a history of prior MI (OR 7.9; p=0.001). Other candidate variables were non-significant.

An abnormal resting MCG repolarisation pattern according to the seven pre-defined criteria had a sensitivity of 87.1%, specificity of 85.7%, positive predictive value of 64.3%, and negative predictive value of 95.7% for the detection of acute ischaemic chest pain syndrome (see *Figure 2*). In comparison, the diagnostic value of the stress SPECT imaging was 91.3%, 75%, 75% and 91.3% for sensitivity, specificity, positive and negative predictive value, respectively (see *Figure 2*). Also shown in *Figure 2* is the diagnostic value of the 12-lead ECG. In the group of patients who underwent coronary angiography the MCG sensitivity, specificity, positive and negative predictive values were 90.3%, 68.6%, 71.8% and 88.9%, respectively, for diagnosis of obstructive coronary artery disease (CAD).

We found that there was a significant incremental value to the MCG imaging over the ECG for the prediction of ischaemia (OR 40.5; CI 12.4–132.3; p<0.0001), while there was no added value of the ECG over the MCG.

A small study presented the MCG results in a group of chest pain patients who had undergone both stress SPECT and coronary angiography.[12] Approximately half of the subjects (n=17) had the tests carried out for evaluation of chronic ischaemic heart disease and stable class 1–2 angina, while the other half (n=19) had their evaluations carried out

11. *Tolstrup K, Rashti S, Cheung B et al., "Resting magnetocardiography detects ischemia with high accuracy in patients with acute coronary syndrome",* J Am Coll Cardiol *(2006);47: p. 182A.*
12. *Tolstrup K, Brisinda D, Meloni A M et al., "Comparison of resting magnetocardiography with stress single photon emission computed tomography in patients with stable and unstable angina",* J Am Coll Cardiol *(2006);47: p. 176A.*
13. *Chen Y, Liu X, Qi X et al., "Resting magnetocardiographic imaging can accurately detect obstructive coronary artery disease in patients with chronic ischemia",* J Am Coll Cardiol *(2005);45 Suppl A.*

Table 1: Diagnostic Value of the Magnetocardiography (MCG), Troponin I, and Echocardiography (Echo) in 62 Patients with Bundle Branch Block

	Bundle Branch Block			LBBB			RBBB		
	MCG n=62	Trop I n=62	Echo n=62	MCG n=32	Trop I n=32	Echo n=32	MCG n=30	Trop I n=30	Echo n=30
SPE	93.5%	37.5%	68.8%	91.7%	41.7%	66.7%	100%	25.0%	75.0%
SEN	86.9%	56.8%	34.8%	90.0%	63.2%	35.0%	84.6%	52.2%	34.6%
NPV	71.4%	33.3%	26.8%	84.6%	41.7%	38.0%	50%	7.7%	15.0%
PPV	97.6%	71.4%	76.2%	94.7%	63.2%	63.6%	100%	81.3%	90.0%

SPE = specificity, SEN = sensitivity, NPV = negative predictive value, PPV = positive predictive value, LBBB = left bundle branch block, RBBB = right bundle branch block.

as part of work-up for ischaemia after presentation with acute chest pain. The results are depicted in *Figure 2* and demonstrate that the resting MCG has high diagnostic accuracy compared with stress nuclear scan using obstructive CAD as the gold standard. Chen et al.[13] studied 77 patients with stable angina and confirmed CAD by angiography. They evaluated seven parameters obtained during a resting MCG scan and found that with three parameters positive, the specificity of the scan was 97% and the accuracy was 80% to 85%.

It is well known that the diagnosis of ischaemia in the setting of left bundle branch block (LBBB) is complicated, causing patients with LBBB and acute chest pain to all be treated as presumed acute ST elevation MI necessitating early cardiac catheterisation upon presentation. Park et al.[14] have shown that the MCG may have great utility in this setting. They utilised four parameters calculated during the cardiac repolarisation and found very high diagnostic value of the resting MCG over troponin I measurements and echocardiography (see *Table 1*).

Figures 4a and *4b* demonstrate the magnetic field map picture in a patient with ischaemia and a non-ischaemic subject.

Discussion

This is an overview of the contemporary use of MCG imaging in the general clinical environment for the detection of ischaemia. Other, earlier, very small case studies have suggested that in the presence of a normal 12-lead ECG the resting MCG is capable of detecting ischaemia in patients with CAD[4–6,15–19]. However, most of these 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. However, now, several prospective studies are demonstrating a high diagnostic accuracy of automated resting MCG imaging for the detection of ischaemic heart disease.

The possibility of accurate, rapid and risk-free diagnosis of ischaemia could potentially greatly impact healthcare for a large group of individuals by avoiding a delay in the diagnosis of ischaemic patients while avoiding unnecessary admissions and testing of non-ischaemic patients. Among the many tests offered to chest pain syndrome patients, the MCG scan may add valuable information early after the often normal first 12-lead ECG and troponin I. Since the MCG does not require stress provocation, the test can be performed while the patient is still being ruled out for MI, saving valuable time to accurate diagnosis. ■

A version of this article containing additional graphics can be found in the Reference Section on the website supporting this briefing (www.touchbriefings.com).

14. *Park J-W, Hill P M, Tolstrup K et al., "Magnetocardiography predicts coronary artery disease in bundle branch block patients with acute chest pain", Poster P3447, The Abstract Book,* Eur Heart J *(2005) Suppl.*
15. *Van Leeuwen P, Hailer B, Lange S, Donker D, Grönemeier D, "Spatial and temporal changes during the QT-interval in the magnetic field of patients with coronary artery disease",* Biomedizinische Technik *(1999);44: pp. 139–142.*
16. *Chaikovsky I, Kohler J, Hecker T et al., "Detection of coronary artery disease in patients with normal or unspecifically changed ECG on the basis of magnetocardiography",* Biomag2000, *Proceedings of 12th International Conference on Biomagnetism.*
17. *Sato M, Terada Y, Mitsui T et al., "Detection of myocardial ischemia by magnetocardiogram using 64-channel SQUID system",* Biomag2000, *Proceedings of 12th International Conference on Biomagnetism.*
18. *Chaikovsky I, Primin M, Nedayvoda I et al., "Computerized classification of patients with coronary artery disease but normal or unspecifically changed ECG and healthy volunteers",* Biomag2002, *Proceedings of 13th International Conference on Biomagnetism, pp. 534–536.*
19. *Hailer B, Van Leeuwen P, Klein A et al. "Magnetocardiographic changes in the course of coronary intervention",* Biomag2002, *Proceedings of 13th International Conference on Biomagnetism, pp. 541–543.*