



Review

Clinical utility of magnetocardiography in cardiology for the detection of myocardial ischemia



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Introduction

Ischemic heart disease (IHD) is a leading cause of premature mortality and accounted for almost 9 million deaths globally in 2017 [1]. The detection of myocardial ischemia, which is usually a result of coronary artery disease (CAD), is challenging due to its heterogeneous presentation and the difficulties of differentiating non-IHD without extensive investigation [2,3]. Therefore, there is a need for novel approaches to improve current diagnostic pathways for patients with suspected CAD.

Diagnosing acute coronary syndromes (ACS) is particularly challenging. Patients present with heterogeneous symptoms and usually have a normal physical examination [3]. The 12-lead electrocardiogram (ECG) is normal at presentation in more than one-third of patients with acute myocardial infarction (MI) [3]. Even with the use of high-sensitivity (hs) cardiac troponin assays, many patients with ACS also

have normal biomarker concentrations at presentation [3]. Diagnosis of ACS in patients with acute chest pain (including those with symptoms unlikely to be cardiac related) can be delayed by 3 h (hs cardiac troponin) to 6 h (contemporary cardiac troponin) after admission for serial biomarker testing and subsequent cardiac imaging [3]. Moreover, diagnosis of ACS has become more complex due to the evolving definition of MI, which now encompasses a spectrum of conditions associated with evidence of myocardial ischemia and an elevated cardiac troponin level [4]. While the introduction of hs cardiac troponin assays has improved identification of patients with ACS, on-site testing facilities are required, and some patients with ACS events may be missed depending on the diagnostic thresholds applied in rule-out pathways [5].

Similarly, patients with clinical suspicion of stable CAD may require extensive testing to confirm a diagnosis or exclude other conditions. These tests include an ECG exercise test and stress imaging, and/or invasive or computed tomography coronary angiography (CTCA) [2]. Invasive coronary angiography is also required to determine the need for myocardial revascularization in patients with stable CAD [2]. These tests take time and add to the patient and economic burden.

Magnetocardiography (MCG) is a non-invasive and emission-free technology which can detect and measure the weak magnetic fields generated by the electrical activity of the heart [6,7]. Time-variant MCG waveforms are similar to ECG signals (Fig. 1A and B). However, cardiac magnetic fields are not attenuated or distorted by differences in the conductivity of body tissues or fluids [8,9]. MCG is also more sensitive than an ECG to tangential currents and circular vortex currents in the heart, which occur, for example, with ischemia [8,10]. MCG can, therefore, detect weak electrophysiologic events not detected by ECG. Myocardial ischemia causes deviations in depolarization and repolarization. While ST-segment elevation MI (STEMI) can be detected by an ECG, smaller electrophysiologic changes resulting in abnormal currents can be detected using MCG [8,9], especially those occurring in the early phase of ischemia, when ECG and cardiac enzyme patterns may be non-diagnostic.

Over the last 30 years, there has been extensive research on the use of multichannel magnetometers in cardiology and other fields [9]. These

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devices enable simultaneous recording at multiple sites across the patient's chest in order to generate a bidimensional magnetic field map (MFM; Fig. 1C) of the heart, which can be used to detect transient physiologic and/or abnormal (Fig. 1C) fluctuations in the heart's magnetic field [9]. Studies have investigated the clinical application of MCG for detection of cardiac arrhythmias and assessment of arrhythmogenic risk; three-dimensional imaging of arrhythmogenic substrates before interventional electrophysiology (catheter ablation) and during invasive electrophysiology studies; detection of myocardial ischemia at rest (Fig. 1C) and post-exercise; and in fetal cardiac imaging [8,9,11]. These studies have employed a variety of MCG devices, including cryogenic superconducting quantum interference devices (SQUIDs), which have been mainly operated in a magnetically shielded room (to eliminate background environmental noise, e.g. from nearby instrumentation), but can also be reliable in unshielded environments when a second (or higher order) gradiometer configuration of the pick-up coils and/or real-time electronic noise subtraction are used [8]. The latter approach obviates the need for heavy electromagnetic shielding (EMS) and may favor the clinical use of MCG in the hospital and even in interventional settings [8,12].

More recently, different kinds of novel, non-cryogenic MCG devices have been developed, including laser-pumped optical magnetometers and novel miniaturized induction coils. These devices can be operated at room temperature with or without EMS, and may be portable (novel miniaturized induction coils), enabling the use of the device at the patient's bedside [13]. In addition, a variety of quantitative approaches and computer algorithms have been developed for the interpretation of different magnetic field patterns [12,14,15].

Despite the commercial availability of several MCG devices, clinical use has been limited by operational practicalities and uncertainties regarding the role of MCG in existing diagnostic pathways. Current approaches to the diagnosis of IHD are expensive and often invasive [2,3], and non-invasive technologies, such as MCG, might have the potential to improve the diagnostic pathway.

This article presents a review of published evidence on the use of MCG to diagnose or rule out myocardial ischemia, and discusses the implications of these findings for the potential future utility of MCG in clinical practice.

Search methodology

Articles indexed in PubMed and Embase between 1963 and November 2018 were identified using the following Medical Subject Headings (MeSH) terms for Interventions and Populations separated by the Boolean operator "OR": Interventions ("magnetocardiography"; "magnetic fields"; "magnetometer"; and "superconducting quantum interference device") AND Populations ("ischemic heart disease"; "coronary artery disease"; "acute coronary syndrome"; and "myocardial infarction"; "angina pectoris"). Additional searches were conducted using the text terms "magnetocardiography"; "magnetocardiogram"; and "magnetocardiograph" AND the MeSH terms for Populations in order to identify relevant publications for which the Intervention terms had not been linked to the MeSH terms on indexing. Abstracts available online for the American Heart Association, the American College of Cardiology, and the European Society of Cardiology annual meetings (2013–2018) were also searched using these terms. Filters for studies published in English language and conducted in humans were applied.

Selection criteria

Titles and abstracts of articles identified in the search were screened independently by two reviewers. Studies were included if they reported data on the use of MCG to discriminate patients with stable CAD or ACS. Additional papers of relevance already known to the authors or identified in bibliographies of papers from the literature search were also eligible for inclusion. Studies were excluded if they were published as

conference proceedings in abstract books only or if full-text copies of the articles were unavailable. Case studies, reviews, and meta-analyses were also excluded. All articles meeting the eligibility criteria underwent full-text review.

Review of evidence on the use of MCG for diagnosis of ACS or stable CAD

A total of 82 publications of relevance was identified through literature searches (Supporting Fig. 1). The characteristics of the studies reviewed are presented in Supporting Table 1 [e1–e82]. A total of 59 studies investigated the use of MCG for diagnosis/rule out of stable CAD and 23 studies investigated the use of MCG for detection/rule out of ACS. These studies have employed a variety of methods for the qualitative and quantitative analysis of the magnetic field during the cardiac cycle (described in Table 1 and Supporting Tables 2–4). In the majority of studies, quantitative analysis has been based on changes in the magnetic field during ventricular repolarization, typically during the end of the ST segment (prior to the T wave) and/or the T wave. Early studies described various MCG parameters which could discriminate patients with myocardial ischemia (Table 1). These include the magnetic field angle extrema and dynamics, and the distance and ratio dynamics of the minimum and maximum poles measured during the ascending T wave from $T_{\max/3}$ (one-third of peak intensity) to T_{\max} (peak intensity) [e31,e36,e37,e39,e73], and various ST segment and T wave parameters measured during/after exercise [e2,e31]. As the magnetic field and signal-to-noise (S/N) ratio at rest is generally higher for the T wave, many subsequent studies have used variations of parameters measured during the T wave which were described originally by Park et al. [e73]. Other MCG parameters measured during the QT and QRS intervals [e9, e14,e16,e21,e22,e26,e78] and machine-learning approaches for MCG signal interpretation [e37,e58,e59] have also been reported.

Stable coronary artery disease

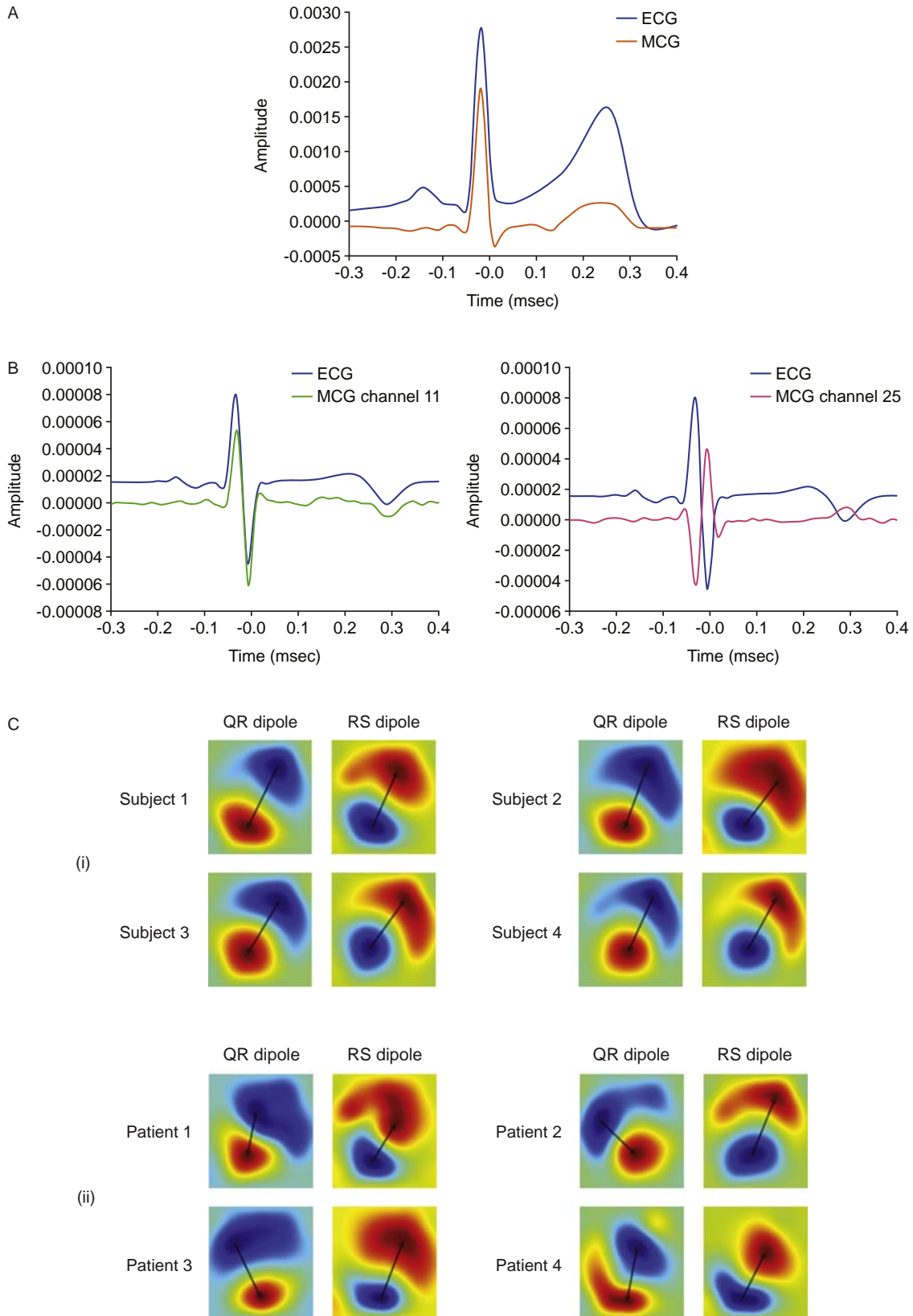
A number of studies have demonstrated that MCG (conducted in a shielded or unshielded environment, at rest or under conditions of exercise or pharmacologic stress) can differentiate patients with angiographically documented stable CAD with or without prior MI from healthy subjects [e2–e9,e11–e13,e15–e17,e19–e23,e25,e30–e32,e34–e38,e41,e43–e48,e50,e51,e53–e59] or from patients with chest pain without evidence of CAD on angiography or other diagnostic tests [e1, e14,e18,e26–e29,e39,e42,e44,e49]. Diagnostic performance data from these studies (where reported) are summarized in Supporting Table 2 and suggest a level of diagnostic accuracy which may be acceptable for use in clinical practice. Caution is needed in interpreting these results, however, as many of these studies were small and enrolled highly selected patient cohorts with or without disease, which may not be representative of unselected populations seen in clinical practice. While a few studies have included separate training and validation sets for internal validation of MCG discriminants [e29,e58], external validation among large and undifferentiated populations is lacking.

MCG under conditions of stress

Early studies on MCG in patients with CAD demonstrated the ability to detect changes in various MCG parameters during exercise- or drug-induced stress [e1–e4,e6,e7,e18,e31,e52]. One of the earliest studies, conducted in a shielded environment, included seven patients with CAD with $\geq 75\%$ stenosis in at least one vessel, and showed that 36-channel MCG could detect changes in the spatial distribution of QT dispersion at rest that were not evident on 12-lead ECG at rest or under stress [e1]. In another study, statistically significant changes in the orientation of the maximum spatial gradient of the magnetic field during the ST segment (on cessation of exercise) and T wave (post exercise) were reported in patients with CAD without prior transmural MI ($n = 27$) compared with

healthy controls [e2]. Subsequent analysis suggested that the ST segment MCG parameters were more sensitive to exercise-induced ischemia in patients without prior MI ($n = 27$), while the T wave MCG parameters were the most sensitive to change in patients with previous MI ($n = 17$) [e6]. An analytical approach based on the epicardial current distribution at the timepoint of

maximal amplitude of the QRS complex (QRS_{max}) was used for 42 patients with CAD who were assessed with MCG after a dobutamine-stress test [e18]. MCG demonstrated sensitivity >90% for the detection of CAD, regardless of location of stenosis or number of vessels involved [e18]. In a study of shielded, 64-channel MCG that included patients with angina pectoris, current-ratio



map patterns (calculated from the current vectors of the MCG signal measured during the QRS wave) have been used to locate areas of cardiac ischemia [e4]. Since these early studies, multichannel devices for use in an unshielded laboratory have been investigated. One of the first studies demonstrated that an unshielded MCG device can be used to detect exercise-induced ischemia in patients with CAD ($n = 6$) without interference from background magnetic fields [e31]. Abnormalities of the orientation of the magnetic field gradient during the ST segment, consistent with those reported by Hänninen et al. [e2], were identified in all six patients in this study, five of whom did not show evidence of stress-induced ischemia on an ECG [e31].

MCG conducted at rest

Many studies have subsequently investigated resting magnetic field patterns in patients with CAD with the objective of developing a practical test that can be deployed in a number of clinical settings and is more acceptable to patients. These studies have assessed a variety of MCG parameters and have attempted to improve diagnostic accuracy and reduce background noise through the use of different analytical approaches and algorithms.

One of the earliest studies conducted at rest included 101 patients with stable CAD without previous MI who underwent multichannel MCG in a shielded room [e15]. There were significant differences in multiple MCG parameters (ST slope, ST shift, T peak amplitude, ST-T integer, and the MFM orientation) between patients with CAD and healthy subjects ($n = 59$) [e15]. A linear discriminant analysis (LDA) based on three of these MCG parameters (ST slopes at A4 and A6, and change in the MFM orientation) provided specificity and sensitivity of 83% and 84% (area under the curve [AUC] for the receiver operating curve [ROC] 91.2%), respectively, for discrimination of a selected cohort of patients with CAD without MI. The rate of CAD classification of 84% was not significantly affected by the number of vessels involved nor stenosis severity [e15]. Another LDA approach, based on four MCG indices measured during repolarization in an unshielded setting (moment of maximal ventricular repolarization, number of maps with abnormal current direction, indicator of heterogeneity in the current density, and indicator of variability of the current density) had specificity of 67–70% and sensitivity of 58–67% for discrimination of patients with CAD ($n = 42$) from healthy volunteers without evidence of CAD ($n = 44$) [e34]. Gapelyuk et al. [e22] have also reported the use of a combined diagnostic algorithm based on the magnetic field distribution (Kullback–Leibler entropy) for the repolarization period and the residual field strength parameter for the depolarization period to improve the classification of CAD (specificity and sensitivity 88%; AUC of ROC 94%) [e22]. Other quantitative methods which have been used to discriminate CAD include: binary classification methods based on cut-off values for MCG indices [e14,e16,e24,e25,e27,e38,e39,e43,e49,e56]; integrated indices based on MCG parameter values [e19,e29,e44,e57]; number of abnormal MCG parameters [e31]; spatial distribution analysis of the QT interval [e9]; and automated machine learning algorithms [e37,e41,e45,e55,e58,e59]. A recent study combining quantitative (change in the ST-segment fluctuation score) and qualitative (non-dipole phenomenon) parameters demonstrated enhanced diagnostic performance of shielded MCG in differentiation of patients with stable

Table 1

Examples of quantitative MCG parameters developed to determine myocardial ischemia associated with CAD.

Quantitative MCG parameters measured at rest during the T wave from $T_{\max/3}$ to T_{\max} [e73]
Direction of the main vector from the plus to minus pole between -20° and $+110^\circ$
Change in the angle of the main vector $\geq 45^\circ$ in a time interval of 30 msec between $T_{\max/3}$ and T_{\max}
Change in the distance separating the plus and minus poles ≥ 20 mm in a time interval of 30 msec between $T_{\max/3}$ and T_{\max}
Change in the ratio of the pole strengths ≥ 0.3 in a time interval of 30 msec between $T_{\max/3}$ and T_{\max}
Quantitative MCG parameters measured during exercise-induced ischemia during the ST segment and/or the T wave [e2,e6]
Magnetic field map angle α for the ST segment ($ST\alpha$) and the T wave apex ($T\alpha$) ^a
Amplitude of the MCG signal at 60 msec after the J point of the ST segment and at the T wave apex ST slope
Integral of the signal from the J point to the end of the T wave (ST-T integral)

MCG = magnetocardiography; CAD = coronary artery disease; $T_{\max/3}$ = one-third of peak intensity; T_{\max} = peak intensity.

^a α represents the angle between the direction of the largest gradient and the patient's right-left line.

angina from asymptomatic patients without CAD [e28]. Incorporation of the non-dipole phenomenon increased the AUC of the ROC curve from 0.79 (change in ST segment fluctuation score alone) to 0.93 [e28].

The sensitivity and specificity of MCG have been shown to be higher in some specific patient subgroups. For example, van Leeuwen et al. [e14] reported that sensitivity, as well as deviations in the MFM during the QRS complex and T wave, were greater in patients with previous MI compared with those patients with CAD without prior MI (sensitivity 85% and 68%, respectively).

The use of MCG to evaluate myocardial viability has been investigated in 11 patients with CAD with prior MI [e10]. The MCG parameters for maximum amplitude of the R and T waves, and minimum amplitude of the T wave were able to discriminate patients according to the extent of the myocardial scar.

Comparative studies of MCG

The diagnostic performance of MCG has been compared directly with other tests in several studies (Supporting Table 4). Park et al. reported higher sensitivity for MCG compared with 12-lead ECG for detection of CAD using a standard dobutamine stress protocol [e18]. Two studies reported the performance of MCG in diagnosis of CAD, compared with the resting ECG: Steinberg et al. demonstrated higher sensitivity for MCG with lower specificity, and lower positive predictive value (PPV) with higher negative predictive value (NPV) than three-lead ECG [e39]. Fenici and Brisinda reported higher sensitivity with comparable specificity for MCG relative to one-lead ECG, and similar PPV and NPV, for diagnosis of stable angina [e41]. One study has reported higher specificity and comparable sensitivity, PPV and NPV for MCG relative to single photon emission computed tomography (SPECT) in the discrimination of patients with stable or unstable angina [e40]. Since these studies used analogous MCG recording systems, the differences in outcomes could be due to distinct

Fig. 1. MCG and ECG integral signal (A) and signal derivative (B), and magnetic field maps for non-ischemic subjects and patients with CAD (C). (A) Single-channel MCG* (one of 15 channels recorded) and the lead 2 ECG from the same patient. This figure shows good alignment of the QRS and T features. (B) The “raw” MCG* traces from the sensors (sites 11 and 25), compared with the derivative ECG recording from the same subject, showing QRS-T complexes occurring in the same positions. The ECG is the same in both images and is the derivative of lead 2. All comparisons are made using the derivative (slope) of the signals and the peaks show the maximum recorded slope. (C) Magnetic field maps* representing the QRS complex from (i) subjects without ischemia, showing a bipolar field map throughout the cardiac cycle, and (ii) patients with ACS, showing a distorted, fragmented, or multipolar field map which is characteristic of ischemia. Dipoles from healthy subjects (i) are generally aligned in the same direction and have only two dominant poles (positive and negative); maps from subjects with ischemia (ii) are more complex with a wider distribution of angles and distances between poles, and the presence of more than two peaks. These magnetic field maps arise from the derivative of the signals and the signals are sampled at the point of the maximum absolute value of rate of change from the Q to R peaks and the R to S peaks (QR and RS, respectively). *MCG recording obtained in a study using a mobile 15-sensor induction coil prototype device developed at the University of Leeds [e78]. MCG = magnetocardiogram; ECG = electrocardiogram; CAD = coronary artery disease; ACS = acute coronary syndrome. (Figures provided by Ben Varcoe and Shima Ghasemi-Roudsari [University of Leeds, Leeds, United Kingdom])

patient selection and analytic methods, or reflect a lack of statistical power.

Acute coronary syndromes

In studies of patients with acute chest pain and suspected ACS, analysis of the MFM measured at rest or post-exercise in shielded or unshielded environments has revealed qualitative and quantitative differences which enable differentiation of patients with ACS from healthy controls [e34,e60,e61,e63,e64,e66,e68,e70,e72,e78,e80] and from patients (with or without chest pain) without objective evidence of ACS or CAD in diagnostic tests [e63,e64,e67–e69,e73–e76,e78]. Available data on the diagnostic performance of MCG as a rule-in/rule-out test for ACS are presented in Supporting Table 3.

Differentiation of acute MI and unstable angina from controls using MCG was also possible for patients with a diagnosis confirmed by other imaging methods (e.g., coronary angiography), but for whom 12-lead ECG and/or biomarker tests were non-diagnostic. For example, a retrospective study reported the use of shielded, 64-channel MCG at rest in patients with suspected ACS without ST-segment elevation [e68]. Classification as CAD, based on the distribution of five MCG parameters measured during the ST interval or during the R wave, was reported for 84% of the cohort of 237 patients with angiographic documentation of CAD, including 91 patients with MI and 128 with unstable angina. Among the subgroup of 102 patients with significant CAD without biomarker or ECG findings, sensitivity of MCG for detection of CAD was 73.5% [e68]. An earlier study using shielded, 64-channel MCG [e64] demonstrated the ability of 15 MCG parameters to differentiate patients with a diagnosis of non-STEMI (NSTEMI) ($n = 83$) from age-matched subjects presenting with chest pain without clinical evidence of CAD, with the field map angle of the T wave peak producing the highest diagnostic accuracy with 86% sensitivity and 75% specificity [e64]. Recently, Ghasemi-Roudsari et al. investigated the use of a portable, 15-channel, prototype magnetometer (based on a novel induction coil configuration) to discriminate patients with IHD, including 15 patients with NSTEMI requiring admission for chest pain, from healthy subjects and patients with chest pain without evidence of ischemia on magnetic resonance imaging or stress echocardiography [e78]. Three MCG parameters measured during depolarization showed a significant difference between patients with IHD and the control group of age-matched healthy subjects and patients with non-ischemia-related chest pain: QR_peak, RS_peak, and RS_MMR, while other parameters were also significantly different in patients versus young, healthy subjects (QR_MMR, QR_angle, QR_interval, QR_pd, RS_angle, and RS_pd) [e78]. Logistic regression analysis yielded 95.4% sensitivity for ruling out ischemia, with a high level of confidence for avoiding false negatives (NPV for ruling out the control group without cardiac ischemia was 97.7%) [e78].

MCG-derived, three-dimensional current density mapping has been investigated for the detection of STEMI [e72] and ischemic damage in ACS [e82]; however, the sensitivity and specificity in the latter small sample of patients were both <60%, and therefore further studies in ACS are required. In another study of 124 patients with recent acute MI, non-dipole patterns at T peak were associated with an increased risk of major adverse cardiovascular events (MACE; $n = 31$), including revascularization, re-infarction or death, during a 6-year follow-up [e71]. A prospective study of 402 patients presenting with acute chest pain without ST-segment elevation demonstrated that abnormalities on the MFM between the beginning and maximum of the T wave at admission, predicted an increased 3-year mortality risk (relative risk for MCG 4.58 vs 1.69 for diagnostic ECG vs 2.58 for elevated troponin) [e76]. Studies suggest that MCG can also discriminate patients with ACS and bundle branch block (BBB), which can complicate the diagnosis of ACS by ECG [e77]; reduced left ventricular ejection fraction [e21]; and previous MI [e62]. Further studies with larger numbers of patients are

required, however, to investigate the potential of MCG in these conditions.

Comparative studies of MCG

A direct comparison of MCG (with visual or automated analysis; [e74]) with other diagnostic tests (ECG, cardiac troponin I, and echocardiography) (Supporting Table 4) demonstrated that MCG had higher sensitivity, comparable specificity, comparable PPV, and higher NPV for discrimination of patients with CAD and acute chest pain from patients with chest pain and normal diagnostic tests [e74].

Implications for the clinical utility of MCG in the detection of ischemia

Formal review of the literature has identified a large number of studies conducted during the last 30 years to evaluate the use of a variety of MCG parameters to improve detection of stable CAD and ACS (Supporting Tables 1–3). Many of these studies have used MCG to differentiate patients with ischemia associated with CAD from subjects without objective evidence of ischemia or documented CAD. These studies have included a spectrum of clinical presentations of CAD diagnosed by functional tests or coronary angiography, including patients with stable CAD with different degrees of stenosis affecting single or multiple coronary arteries in various locations of the heart; patients with stable CAD with or without prior MI; patients with stable or unstable angina; patients with acute MI, including both STEMI and NSTEMI; and patients with CAD with concomitant heart failure or cardiac arrhythmias (Supporting Tables 1–3). Identification of ischemia was also possible using MCG in patients who had no abnormalities on ECG or cardiac biomarker testing. Preliminary evidence on the diagnostic performance (Supporting Tables 2–4) suggests acceptable levels of sensitivity and specificity for detecting IHD in selected cohorts with stable CAD or ACS using devices operated in shielded or unshielded environments. In some studies where the diagnostic accuracy of MCG was compared directly with that of other diagnostic tests (Supporting Table 4), MCG has shown higher sensitivity than ECG, echocardiography, and conventional cardiac troponin assays in detecting stable CAD and ACS, suggesting that MCG may be a valuable test on initial presentation.

Collectively, these data highlight a potential role for MCG as a non-invasive tool for routine assessment of patients with suspected obstructive CAD, including ACS. However, further research is needed to determine which MCG parameters are of greatest value and to confirm diagnostic performance in unselected cohorts. Research is also needed to define how MCG could be implemented in the clinic and whether it adds incremental value to existing diagnostic pathways. Such research might help to define MCG criteria to rule out patients without ischemia or CAD earlier in the diagnostic pathway, thereby avoiding the need for extensive testing and imaging, and reducing use of hospital resources.

Assessment of patients with suspected ACS is one area of emergency medicine which could potentially benefit from the use of MCG. Chest pain is one of the commonest causes of visits to the emergency department (ED) [16], yet 60–90% of patients with chest pain are not found to have an acute cardiac cause for their pain [17–20]. Diagnosis of ACS in patients presenting with acute undifferentiated chest pain currently requires a resting 12-lead ECG, multiple measurements of cardiac troponin levels over 3–12 h, and clinical judgment [3]. Incorporation of MCG into the diagnostic pathway could help to reduce the time to diagnosis and the costs of serial troponin testing. An additional problem in emergency medicine is the potential for missed diagnosis of patients with NSTEMI or unstable angina who may then experience adverse coronary outcomes after discharge [21–23]. MCG has the potential to reduce the likelihood of a missed diagnosis, thereby improving clinical outcomes. The benefits of earlier identification of patients with non-cardiac versus cardiac-related pain have been demonstrated through the introduction of accelerated risk algorithms incorporating hs cardiac

troponin assays which have led to significant improvements in time to discharge, cardiac outcomes, and hospital resource use [24–30]. Further evaluation in prospective observational studies of unselected cohorts of patients presenting to the ED with acute chest pain will indicate whether MCG could be used ahead of hs cardiac troponin to accelerate patient assessment.

MCG technology has advanced considerably from the original single-channel devices operated in shielded rooms. Multichannel MCG devices have reduced the time required for scanning to a few minutes, although most of the original multichannel devices still have specific operational requirements and high running costs, mainly related to the need for external EMS or cooling with liquid helium. However, the S/N ratio of unshielded devices has also improved through use of specific hardware design, coupled with advanced computer algorithms to subtract the signal recorded from background magnetic fields (Fig. 2). The recent development of portable MCG devices [13] could potentially enable bedside assessment of patients with acute chest pain on initial presentation to the ED. Improvements in the practical aspects of MCG devices will also be a key determinant of how easily they can be implemented in clinical practice, for example footprint, ease of use, operator training requirements, and the need for a shielded operating environment.

The available studies on the use of MCG in CAD have been conducted over several decades during which MCG technology and diagnostic criteria have evolved, and this confounds interpretation and integration of the results. These limitations need to be addressed in future studies. Firstly, there is a lack of standardization across studies in terms of the number of MCG channels and recording sites used, as well as heterogeneity in the MCG parameters measured at different parts of the cardiac cycle and the methodology used for analysis. This heterogeneity across studies has largely precluded robust meta-analysis of the available data. While substantial advances have been made in MCG device technology

and the machine-learning approaches used for analysis, validation of the potential diagnostic parameters is still required in large unselected patient cohorts. The studies of MCG included in this review generally included small numbers of patients, and employed inconsistent enrollment criteria and methods for detection of myocardial ischemia and CAD. Only a small number of studies have investigated the use of MCG to rule in/rule out suspected acute ACS. Validation studies are required to establish the diagnostic accuracy of MCG parameters versus current diagnostic pathways that may include the “gold standards” coronary angiography and hs cardiac troponin in undifferentiated patient populations. Validated MCG diagnostic criteria should also be assessed in studies of well-defined cohorts, including patients with ACS, non-ACS CAD, inducible ischemia (e.g. by coronary angioplasty), and non-ischemic chest pain in order to establish the utility of MCG in these groups. Systematic study of patients with CAD and cardiac comorbidities (e.g. atrial fibrillation and BBB) is also needed, as identification of these conditions will have implications for prognosis and treatment. There are also indications in the literature that MCG may have wider clinical application in CAD than diagnosis. For example, its use in stress testing to detect functional ischemia could provide valuable prognostic information for risk stratification. Exploration of other endpoints, such as location and severity of infarction, and prediction of MACE and post-MI arrhythmia, should be incorporated into future clinical studies.

Conclusions

MCG offers a non-invasive, contactless, and emission-free imaging modality with the potential to improve the management of patients with CAD. The clinical utility of MCG has been limited in the past due to its lack of deployability, operational requirements, and high running costs. Improvements in technology have led to the development of a

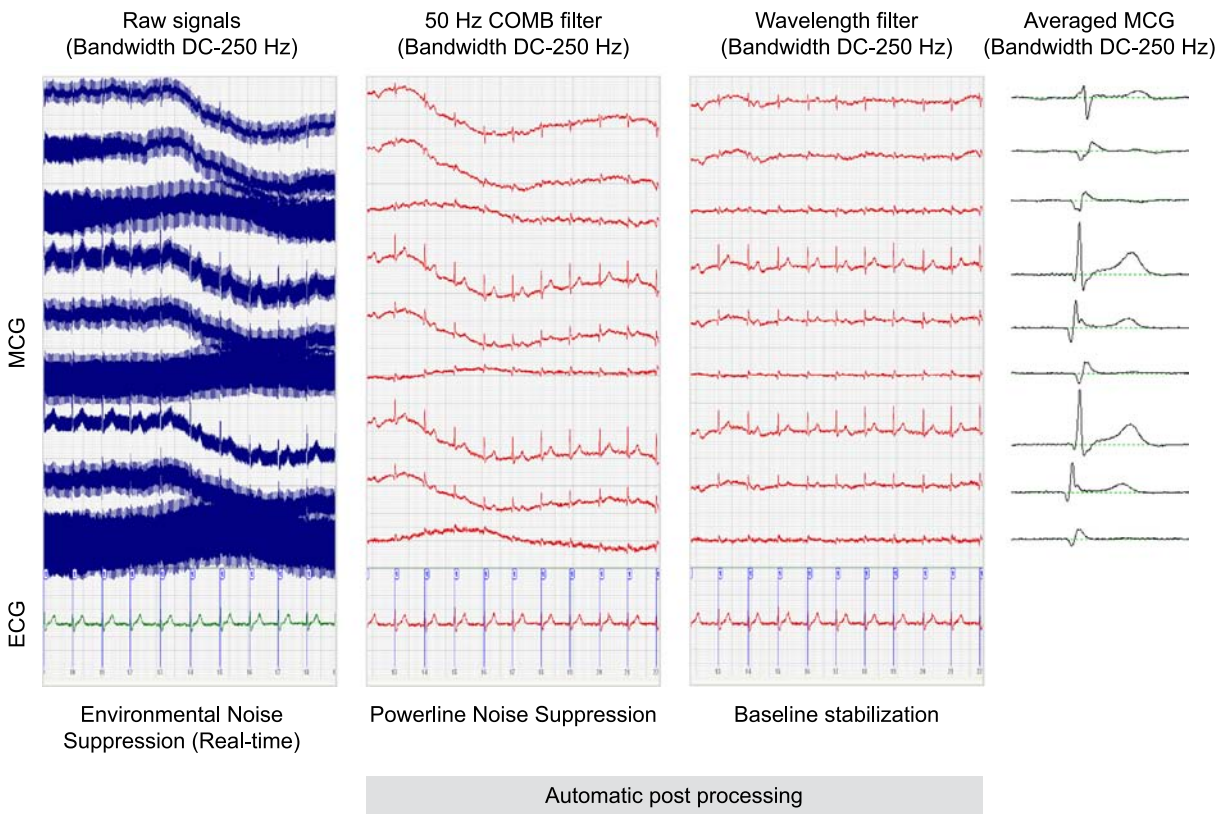


Fig. 2. Example of methods used to improve the S/N ratio of unshielded, in-hospital MCG recordings. Nine MCG channels and one (reference) ECG are shown. Real-time environmental noise suppression is provided by dedicated firmware. Digital filtering and signal averaging are automatic post-processing features. ECG = electrocardiogram; MCG = magnetocardiography; S/N = signal to noise.

(Figures provided by Donatella Brisinda and Riccardo Fenici [Catholic University of Sacred Heart, Rome, Italy])

new generation of non-cryogenic devices, which do not require the complexity and cost related to cooling with liquid helium. While the majority of older, optically pumped magnetometers still need some electromagnetic shielding, the newer devices are more easily deployed in a hospital setting and do not require specialist user training, supporting broader application. A recently developed portable multi-channel system based on induction coil sensors, which do not need external EMS, provides greater operational flexibility [13]. It is not yet possible to make firm conclusions about the relative sensitivity/specificity of MCG versus currently used diagnostic tests or whether it would replace any tests in risk algorithms. However, the available data suggest that MCG will achieve an NPV (based on the ability to rule out ischemia), which will enable physicians to discharge a significant number of patients without further testing. Standardization of MCG parameters and development of validated algorithms and thresholds for discriminating patients will be essential to ensure understanding and acceptance of MCG among cardiologists and emergency physicians. Further clinical trials are already under way to define the role for MCG in the assessment of patients with acute chest pain. Rule out of ischemia, initially in the ED, is the focus of these ongoing studies, but other future clinical uses for MCG which could be investigated further, include detection and measurement of ischemia in the ED and cardiology clinic, and potentially in other areas of medicine where ischemia or other abnormal electrophysiologic substrates develop. The renewed interest in MCG highlights a need for collaboration and consensus on the objectives of future research studies on the potential applications of MCG in cardiology.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jelectrocard.2019.07.009>.

Clinical significance

Myocardial ischemia can be detected using unshielded MCG in cohorts of patients with stable CAD and ACS, including NSTEMI. Further clinical studies of MCG in undifferentiated patient cohorts, and validation and standardization of MCG analytical techniques and parameters, are warranted. Prospective, multicenter observational studies are ongoing to investigate the utility of MCG in rule-out of ACS in the emergency setting and will help to define the utility of newer MCG devices which could be deployed in routine clinical settings to complement standard diagnostic tests.

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Declaration of Competing Interest

A. John Camm is a member of the Medical Advisory Board of Creavo Medical Technologies Ltd., and has received honoraria/speaker fees from Allergan, Alta Thera, Astellas, AstraZeneca, Acesion, Huya, Incarda, Merck, Menarini, Milestone, Sanofi, Servier, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, Portola, Boston Scientific, Abbott, Biotronik, Medtronic, Actelion, GlaxoSmithKline, Anidium, InfoBionic, Cardiac Insight, Infobionics, Johnson and Johnson, Mitsubishi, Novartis, Radius, and Takeda.

Robert Henderson is a member of the Medical Advisory Board of Creavo Medical Technologies Ltd. and was a member of NICE guideline committees on Unstable Angina/NSTEMI, STEMI, and Stable Angina.

Donatella Brisinda is a scientific advisor to Mesuron Inc., and her research center has received research grants/funding from Genetesis.

Richard Body was Chair of the Trial Steering Committee for a trial evaluating MCG sponsored by Creavo Medical Technologies Ltd., and received reimbursement for his time from Creavo Medical Technologies

Ltd. He has received honoraria/speaker fees from Roche, Singulex, Siemens, Beckman, Abbott, Ortho, ET Healthcare and Alere, and has advised Roche, Singulex, LumiraDx, and FABPulous BV. Richard Body's institution has received research grants from Roche, Singulex, Abbott Point of Care, and FABPulous BV.

Richard Charles is Chair of the Medical Advisory Board of Creavo Medical Technologies Ltd.

Ben Varcoe is an employee and shareholder of Creavo Medical Technologies Ltd.

Riccardo Fenici is a scientific advisor to Mesuron Inc. and Genetesis, and his research center has received research grants/funding from Genetesis.

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