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Advances in the Study of Magnetocardiography in Cardiovascular Diseases

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Abstract: Cardiovascular diseases (CVDs) are one of the leading reasons for death and disability in patients worldwide. Their accurate diagnosis and assessment remain a considerable challenge in clinical settings. Magnetocardiography is a non-invasive, non-radioactive, and non-contact functional test. This examination has made significant progress in diagnosing and treating CVDs recently. However, most healthcare professionals are not aware of this new examination tool. In this review, we will summarize the development history and working principle of magnetocardiography, highlight its use in diagnosing, evaluating, and monitoring CVD treatment effects, and discuss the prospects for its application in clinical settings.

Keywords: Magnetocardiography; Cardiovascular disease; Coronary heart disease; Acute coronary syndrome; Arrhythmia; Coronary microcirculatory dysfunction; Restenosis after percutaneous coronary intervention; Myocarditis

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1. Introduction

Cardiovascular diseases (CVDs) are the leading reasons for death globally and in China; they account for 40% of the mortality rate of the Chinese population [1,2]. Approximately 330 million Chinese people suffer from CVD. The burden of CVD will continue to increase because China faces the dual pressures of an aging population and a continuous increase in the prevalence of metabolic risk factors. Therefore, the accurate diagnosis and active treatment of CVDs have become particularly important [3]. Magnetocardiography (MCG) has emerged as a non-invasive, non-radioactive, non-contact, and convenient CVD detection method. It can overcome the limitations of traditional examination methods owing to its high signal fidelity. This tool holds considerable significance for diagnosing, evaluating, and monitoring the treatment effects of CVDs. Therefore, MCG may become an essential tool for diagnosing, evaluating, and monitoring the treatment effects of CVDs in the future.

2. Principles and development history of MCG

The heart generates an electric current in the body, generating a magnetic field. The Earth's magnetic field is approximately 30,000,000 picotesla (pT), whereas the cardiac magnetic field is very small, with peaks of less than one-millionth of the strength of the Earth's magnetic field, i.e., approximately 50–100 pT. The Earth's magnetic field is strong but cannot completely mask the cardiac magnetic field because of its static properties. Small temporal variations in the Earth's magnetic field produce geomagnetic noise that can interfere with the heart's magnetic field. Furthermore, the strength of the cardiac magnetic field is considerably weaker than the magnetic field of magnetic resonance imaging. Nevertheless, the strength of the cardiac magnetic field, although small, can still be detected. MCG is used to detect the heart's magnetic field. A conventional MCG comprises superconducting quantum interference devices (SQUID) and its electronics system, a gradiometer, a non-magnetic moving bed, an electromagnetic shielding room, and a data acquisition and processing system. The SQUID is an extremely sensitive magnetometer used to detect weak cardiac magnetic fields, and the gradiometer helps SQUID distinguish cardiac magnetic fields from other magnetic fields. This enhances the detectability of cardiac magnetic field signals. In 1963, Gerhard Baule and Richard McFee measured the magnetic fields generated by the human body for the first time. They recorded the cardiac magnetic field, or MCG, at a site in Syracuse, New York. After Baule's and McFee's pioneering research, David Cohen also began investigating the cardiac magnetic field. In 1967, Cohen experimented in a magnetically shielded room, using a single coil to perform MCG. Around the 1970s, the SQUID magnetometer was invented to detect abnormally weak signals. Then, Cohen began working with James Zimmerman, one of the inventors of the SQUID, to measure biomagnetic fields for the first time using the SQUID in a magnetically shielded room. The SQUID had to be kept at ultra-cold temperatures to maintain its superconducting properties; therefore, it was placed in an insulated Dewar flask filled with liquid helium. Compared with wire-wound pickup coils, the SQUID has a smaller detector and higher sensitivity but without cryogenic technology [4]. In the following decades, the SQUID magnetometer has become a state-of-the-art instrument for measuring biomagnetic fields.

3. Advantages of MCG in CVDs

MCG has been around for 60 years. However, it has not been routinely used in clinical settings because of the high cost associated with the equipment and maintenance. Current clinical studies have revealed that compared with traditional non-invasive electrocardiography (ECG), MCG is more effective in diagnosing coronary artery disease (CAD) [5]. While ECG indirectly measures the electrical activity of the heart via electrodes placed on the skin, MCG is a non-contact method of recording the magnetic field generated by the electrophysiological activity inside the heart using a highly sensitive magnetic sensor placed outside the body. Unlike the heart's electrical signals, the magnetic permeability of the human body is constant, and the recording of the cardiac magnetic field by the MCG is not significantly affected by the differing conductivity and resistance of various body tissues between the heart and the surface sensor. This makes MCG more reliable than ECG for detecting biological phenomena. Furthermore, MCG has a better gain value owing to its higher sensitivity to tangential and eddy currents than ECG. In addition, MCG has a higher sensitivity in detecting improvements in cardiovascular function in patients with CVD, it can detect changes in cardiac function at an earlier stage compared with ECG [6]. Single photon emission computed tomography poses a potential radiation risk, whereas MCG does not pose a potential radiation risk and demonstrates high accuracy in diagnosing myocardial injury [7]. In a study comparing exercise ECG and MCG scores for detecting ST-segment fluctuations in CAD, researchers reported that exercise MCG was significantly

more accurate than exercise ECG for diagnosing coronary artery obstruction in patients with intermediate-to-high-risk CAD [8]. Overall, these findings suggest the considerable application advantage of MCG for diagnosing CVDs.

4. Advances in the study of MCG for CVDs

4.1. Progress of MCG research in coronary heart disease

Ischemic heart disease is one of the leading reasons for death worldwide. Inadequate blood supply to the heart causes myocardial ischemia, resulting in abnormal repolarization and excitation wave conduction in the myocardial tissue; this ultimately results in arrhythmias and even sudden death. The current diagnosis of myocardial ischemia via 12-lead ECG has shortcomings because, in some cases, particularly non-ST-segment elevation myocardial infarction (NSTEMI), ECG may not demonstrate typical ST-segment changes. As a non-invasive, non-contact technique, MCG can be used for the early identification of myocardial ischemia. This helps in the risk stratification of myocardial ischemia. Erick A Perez Alday et al. used 12- and 36-lead ECGs and 36-lead MCG and investigated the signaling differences between regions in cardiac ischemia. They noted that both MCGs and ECGs exhibited region-dependent changes in cardiac ischemia. The differences between 36-lead ECG and MCG were more significant compared with 12-lead ECG (sensitivities of 34%, 37%, and 26%, respectively); however, MCG exhibited a stronger correlation to the response of cardiac ischemic region, providing an alternative method for diagnosing this condition [9]. In clinical settings, accurately identifying patients with acute coronary syndrome (ACS) is often challenging, particularly when ECG does not exhibit typical ST-segment elevation. In a retrospective study, Kwon *et al.* selected 364 patients with suspected ACS without ST-segment elevation. They noted that the sensitivity of MCG was 84.0% of patients with CAD, compared with that of 44.7% for ECG. In patients with no significant abnormalities detected on ECG or biomarker tests, MCG exhibited a sensitivity of 73.5% and a specificity of 82.3% [10]. Therefore, MCG is more conducive to the early diagnosis of patients with acute chest pain compared with ECG. Furthermore, MCG exhibits a better diagnostic rate for patients with acute chest pain who do not have significant abnormalities on ECG.

Lim *et al.* used 64-channel MCG to assess 20 patients with NSTEMI, 15 young individuals, and 13 age-matched healthy participants. They noted significant differences in all MCG parameters between the 28 healthy subjects and 20 patients with NSTEMI [11]. None of the healthy subjects had more than four abnormal MCG parameters. In contrast, 19 patients with NSTEMI had more than four abnormal MCG parameters. Furthermore, significant differences were noted in the pairwise temporal activation maps and T-wave peaks in MCG parameters between healthy subjects and patients with NSTEMI. Collectively, these results suggest that MCG is sensitive to changes in myocardial repolarization after myocardial infarction (MI) and that MCG is a valuable tool for identifying patients with severe ischemia.

Peter *et al.* performed MCG at rest on 144 participants. Among the 144 participants, 50 were healthy, 43 had CAD without MI, 36 had MI, and 15 had spontaneous ventricular tachycardia (VT) [12]. The percentage of patients with CAD without MI and patients with MI and QT interval magnetogram localization deviating from normal values was 67% and 85%, respectively. The number of trajectory diagrams deviating from normal values increased with disease severity. The distribution of QT interval duration was subsequently quantified using the smoothing index, exhibiting significant differences between healthy participants and patients without MI and between patients with MI with and without VT. This demonstrates that malignant arrhythmias owing to CAD can be assessed by analyzing MCG signals.

4.2. Progress of MCG in restenosis after percutaneous coronary intervention

The non-invasive testing of patients with restenosis after percutaneous coronary intervention (PCI) remains a clinical challenge. Most patients with recurrent chest pain after PCI still require coronary angiography or coronary computed tomography angiography (CTA). Furthermore, the 12-lead ECG results are often typical for patients with post-PCI restenosis. However, other non-invasive methods, such as stress ECG, radionuclide imaging, and echocardiography, are not as sensitive as coronary angiography in detecting restenosis [13]. To avoid X-ray exposure and possible serious side effects, repeat angiography should be performed only if re-intervention is warranted. Coronary CTA, although a commonly used tool for post-procedural review at present, still exerts radiological and contrast-related side effects. The advent of MCG will be a practical addition to the traditional non-invasive modalities of routine examination. Hailer *et al.* evaluated the potential value of MCG in the outcome of post-PCI patients. They included 111 participants, including 54 patients with stable or unstable angina, all of whom were treated with PCI [14]. The control group comprised 57 healthy participants. Fifty patients with CAD and 57 healthy participants were subjected to 12-lead ECG and 4-channel MCG recordings, and current density vector (CDV) maps were compared and categorized at pre-PCI, 24 h post-procedure, and 1 month post-procedure, with CDV maps categorized from category 0 (normal) to category 4 (severely abnormal). Compared with pre-PCI patients with CAD, most normal individuals had CDV maps classified as category 0, 1, or 2. At 24 h after PCI, more CDV maps of patients with CAD were classified as category 2, and only a few CDV maps of patients with CAD were classified as category 4. One month after PCI, the MCG results of patients with CAD improved further, with more CDV maps classified as categories 1 and 2. In contrast, fewer CDV maps were classified as category 4. ECG did not demonstrate significant changes in patients undergoing PCI. Hailer *et al.* have reported that MCG can monitor significant changes in CDV maps of patients with CAD during successful PCI by using MCG to reconstruct CDV maps during repolarization. Therefore, this method may be suitable for the follow-up of patients after PCI. Overall, these findings demonstrate that MCG is of great value in the post-PCI process. In the future, MCG may become an effective non-invasive tool for post-PCI patients during consultation and follow-up.

4.3. Advances in MCG in coronary microcirculatory dysfunction

Coronary microcirculation dysfunction (CMD) is also an important pathophysiological mechanism of ischemic heart disease. It is closely associated with adverse cardiovascular events, with patients with CMD experiencing a four-fold increase in mortality and a five-fold increase in major adverse cardiovascular events (MACE) compared with patients without CMD [15]. In 2020, the European Society of Cardiology proposed more concise and practical diagnostic criteria for CMD in a consensus document on non-obstructive CAD [16]. The classification of CMD was further refined into five types by the 2020 Chinese multidisciplinary expert consensus on the diagnosis and treatment of microvascular disease: primary CMD without myocardial disease or obstructive epicardial CAD, CMD with myocardial disease but without obstructive epicardial CAD, CMD with obstructive epicardial CAD, medically induced CMD, and post-transplantation CMD. At present, a shortage of time-saving, sensitive, accurate, and economical non-invasive adjuncts exists. Recent studies have revealed that MCG may be useful as an adjunctive diagnostic tool for CMD [17]. At present, the application of MCG in CMD diagnosis remains in the exploratory stage, with further confirmation via more and larger sample size studies. Presumably, with technological advances and the popularity of clinical applications, MCG will play an essential role in CMD diagnosis.

4.4. Advances in MCG in cardiac arrhythmias

4.4.1. Progress of MCG in fetal arrhythmias

The dangers of arrhythmia are enormous. Patients with arrhythmia who are not timely and effectively diagnosed and treated may suffer serious consequences such as fainting or even sudden death. In particular, hereditary arrhythmias (fetal arrhythmias) are complex and harmful to diagnose. Although echocardiography has long been a routinely used technique for diagnosing fetal arrhythmias, the advent of MCG will help further improve the accuracy of diagnosis and risk assessment of fetal arrhythmias. At present, echocardiography cannot assess the electrophysiological activity of the fetal heart, and the clinical use of MCG may accelerate research progress on the electrophysiological activity of the fetal heart. Wacker-Gussmann *et al.* reviewed 215 pregnancies admitted to the Biomagnetism Laboratory at the University of Wisconsin-Madison over the past decade due to fetal arrhythmia or the presence of arrhythmia [6]. They compared the diagnosis and treatment plan at the referral time with the fMCG diagnosis, focusing on 144 cases in three categories: tachycardia, bradycardia/atrioventricular block, and familial long QT syndrome. Based on the effect of the MCG diagnosis, 81 of the 144 patients experienced a significant change in diagnostic outcomes, and 35 experienced a significant change in the treatment plan. Similar to ambulatory ECG, MCG can monitor and record continuous heartbeats, which can help capture transient arrhythmias. Overall, the clinical use of MCG may enhance the prenatal and postnatal care of the fetus in hospitals.

4.4.2. Advances in MCG in atrial and ventricular arrhythmias

The weak magnetic field generated by the human heart is another manifestation of the heart's electrical activity. Theoretically, MCG can provide the non-invasive localization of the underlying electrical activity. Moshage *et al.* subjected 10 patients with spontaneous early-onset premature ventricular beats, 3 patients with ventricular tachycardia, and 4 healthy participants to MCG [18]. The location of the ectopic pacing point detected in the MCG had an error of only a few millimeters compared with the location of the ectopic pacing point determined by the electrophysiological specimen catheter. This demonstrates that the MCG can non-invasively help locate the origin of ventricular arrhythmias.

Nakai *et al.* generated three-dimensional cardiac contours and conduction pathways using a 64-channel SQUID system. They evaluated the importance of MCG in managing patients with atrial flutter (AFL) and atrial fibrillation (AFIB) [19]. The participants were 20 healthy volunteers, 3 patients with AFL, and 4 patients with AFIB. MCGs were recorded before and after the intervention to assess treatment efficacy. MCG revealed a counterclockwise rotational conduction pattern in patients with AFL and a random microreentrant conduction pattern in patients with AFIB. Sinus rhythm was restored in both patients with AFL and AFIB after the intervention. Evaluating the three-dimensional cardiac contour and conduction pathways in patients with AFIB via MCG may provide a more time-saving and effective non-invasive routine examination in managing patients with AFL and AFIB. In another study, Nakai *et al.* used MCG to perform three-dimensional spectral mapping in 16 patients with valvular heart disease who had chronic AFIB [20]. These 16 patients with valvular heart disease and chronic AFIB were subjected to surgical pulmonary vein isolation (PVI) and valve repair. One year after surgery, sinus rhythm was restored in 7 patients but persistent AFIB remained in 9. Mean three-dimensional AFIB frequency before PVI in patients with restored sinus rhythm was compared with those with persistent AFIB after PVI, with significant differences. This suggests that three-dimensional spectral mapping using MCG may be a meaningful non-invasive screening strategy for patients with AFIB undergoing interventional procedures.

At present, differences in the electrical characteristics of the left and right atria after PVI in patients with AFIB remain unclear. Using MCG, Sato *et al.* investigated the effect of PVI on biventricular magnetic field changes and its association with clinical outcomes. MCG recordings at baseline, 1 day, 8 weeks, and 24 weeks after ablation were recorded in 71 patients with paroxysmal AFIB subjected to PVI [21]. In addition, they compared the peak amplitude of left and right atrial segmental P waves before and after PVI. At 16 months after ablation, AFIB did not recur in 53 patients. The magnetic field intensity of the left artery consistently decreased for 24 weeks in patients with no recurrence and was significantly lower than that in patients with recurrence at 8 weeks. Multifactorial analysis revealed that magnetic field strengths in the left and right atria could be significantly altered after PVI in patients with AFIB. However, the magnetic field strength in the right atrium at 8 weeks was the strongest predictor of AF recurrence. Therefore, persistent elevation of magnetic field strength in the right atrium may be an important predictor of AF recurrence after ablation.

Kandori *et al.* developed a whole-cardiac bull's-eye map to demonstrate current distribution on a circular map by MCG [22]. Subsequently, MCG was recorded at rest in 16 patients with Brugada syndrome, 10 patients with complete right bundle branch block, and 12 members in the control group. They reported that the amplitude of the anterolateral right-superiorly oriented S-wave currents was higher in patients with Brugada syndrome than in patients in the control group on whole-heart bull's-eye maps. Furthermore, a small anomalous current was noted during ventricular depolarization in the patients with Brugada syndrome. This demonstrates that the whole-heart bull's-eye map can detect heart disease features.

4.5. Advances in the study of MCG in myocarditis

Viral myocarditis is an infectious inflammatory disease that is more common in patients of all ages and may have serious adverse consequences; if undetected, it can lead to sudden cardiac death [23]. Inflammatory cardiomyopathy is one of the most common reasons for sudden cardiac death in young adults. The rapid screening of patients with suspected myocarditis has become essential to prevent serious adverse outcomes of myocarditis. Recently, Pille *et al.* reported that analyzing historical MCG and MCG device data using the Kullback–Leibler entropy method can help reliably distinguish patients with clinically suspected myocarditis from healthy controls. Pille *et al.* implemented automated feature selection based on linear discriminant analysis to replace the reliance on manually determined thresholds by observers in previous studies. This will potentially make MCG a rapid, non-invasive, and cost-effective screening test for patients with suspected myocarditis [24]. Brala *et al.* reported that MCG can detect the response to immunosuppressive therapy in patients with myocarditis within 7 days. However, improvement was not detectable by echocardiography until after 30 days of immunosuppressive therapy in patients who responded to treatment. In patients with myocarditis, changes in MCG were significant at day 7 of immunosuppressive therapy (effect size: 30%) [25]. MCG demonstrates high sensitivity in detecting patients with myocarditis in terms of clinical improvement. This suggests that MCG is more advantageous for the screening, diagnosis, individualized treatment, and prognostic assessment of patients with myocarditis.

5. Technological advances in MCG

In conventional MCG, a SQUID magnetometer is used to record the weak magnetic field generated by the heart, requiring liquid helium to maintain the necessary ultra-low temperature. However, liquid helium is a scarce and expensive resource, which is not conducive to clinical dissemination [26]. The advantages of the optical pump

magnetometer (OPM), which does not require Dewar bottles as a cryogenic coolant, make system miniaturization possible and increase the flexibility of the sensor array arrangement for multichannel measurements [27]. The spin-exchange relaxation free (SERF) magnetometer belongs to the vector OPM, a type of OPM [28]. Recently, Yang *et al.* developed a wearable multichannel human MCG system based on a SERF magnetometer array. This MCG system comprises a magnetic shielding device, a wearable SERF magnetometer array, and a computer for data acquisition and processing, which denoises MCG data using independent component analysis and empirical mode decomposition [29]. Tao *et al.* proposed an end-to-end deep learning architecture (referred to as MCG-Net), which integrates a convolutional neural network with transformer-based global context blocks for the fine-grained segmentation and diagnostic classification of Q-, R-, S-, and T-waves from MCG data [30]. A new analysis system with an MCG with a resting 90-s scan demonstrates considerable potential for assessing coronary artery stenosis in patients with chest pain between observation units in the emergency room [31]. Overall, technological advances in MCG are significant, and the future of MCG will largely depend on the continued advancement of new sensor technologies and improved data processing and analysis methods. These advances may soon provide more compact, cost-effective, portable, and wearable devices for unshielded MCGs or ambulatory patients in hospital settings.

6. Challenges and perspectives in the clinical application of MCG in CVDs

Despite the progress made in the clinical application of MCG in CVD, some challenges remain. For example, the cost of MCG remains high. Furthermore, professional technicians are needed for interpreting and analyzing the imaging results. In the future, studies should be undertaken to further optimize the MCG imaging technique to improve its feasibility and accuracy in the clinical application of CVDs.

MCG is an emerging non-invasive examination with broad research and clinical application prospects. With the continuous improvement of technology and methods, MCG will continue playing an important role in the diagnosis and research of CVDs and can provide more accurate and personalized diagnosis and treatment strategies for clinical settings.

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Disclosure statement

The authors declare no conflict of interest.

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