Current perspective

Magnetocardiography: current status and perspectives. Part II: Clinical applications

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Magnetocardiography (MCG) is a non-invasive and risk-free technique allowing body surface recording of the magnetic fields generated by the electrical activity of the heart. The MCG recording system allows spatially and temporally accurate measurements of the very weak magnetic fields produced by currents flowing within myocardial fibers during cardiac activity. MCG has now been around for over 30 years, but only recently has progress in instrumentation put the technique on the verge of clinical applicability. This review summarizes the physical principles, instrumentation, main clinical applications and perspectives for the clinical use of MCG. This second part is devoted to the description of the main current clinical applications and perspectives.

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Introduction

During the past 10 years, interest for applications of biomagnetism to the non-invasive study of the brain, the heart and gastrointestinal tract has steadily increased. Because of their intrinsic electrical activity, such organs generate a magnetic activity associated with their electrical currents. Such magnetic activity is detectable, with appropriate instrumentation, on the body surface. Originating in the early '60s[1], magnetocardiography (MCG) has now become a significant application of biomagnetism, and a useful diagnostic tool. The interest of the technique for cardiologists has rapidly increased following the introduction of the superconducting quantum interference device (SQUID) magnetometer, which allows the recording of the very weak magnetic activity generated by the human heart. The distribution of magnetic fields measured over the body surface permits the quantification and the spatial three-dimensional localization of sources within the heart. MCG can now be regarded as an alternative non-invasive and risk-free approach to cardiac electrophysiological phenomena, complementary to the well-known electrocardiographic approach. The clinical validation of MCG is still, however, incomplete, because the technique is not available, with very few exceptions, within clinical and hospital environments. Moreover, most currently available systems are only working in shielded rooms, while, already in 1996, almost every panelist gathered at the round table on MCG at Biomag '96 wished to have a multichannel high critical temperature (T_C) MCG recording system, working outside a shielded room[2]. The introduction of MCG in a cardiological context for a routine use also requires the shortening of examination times, fast data analysis through the use of dedicated software, fast and readily interpretable presentation of results and larger validation studies. The newer MCG systems are multichannel SQUID systems designed for clinical application and routine use and allowing the fast recording of cardiac biomagnetic activity. Recent advances fulfill the clinical needs highlighted above, and now put MCG on the verge of clinical applicability. This part of the review will focus on the current clinical applications of MCG (summarized in table I), the most promising areas of research and the most relevant problems of the field.

Table I. Main clinical applications of magnetocardiography (MCG).

Localization of preexcitation sites in the Wolff-Parkinson-White syndrome
Localization of cardiac arrhythmias (ventricular tachycardia, premature ectopic beats, supraventricular arrhythmias)
Detection of myocardial ischemia (rest and stress MCG) and viability
Risk stratification after myocardial infarction
Detection of ventricular hypertrophy
Ventricular repolarization study (QT prolongation and dispersion)
Fetal MCG
Monitoring rejection after heart transplantation

Localization of preexcitation sites in the Wolff-Parkinson-White syndrome and other arrhythmias

Earlier MCG studies, performed using single-channel instruments, were focused on the evaluation of arrhythmic patients in an attempt at localizing, with sufficient spatial accuracy, the arrhythmogenic sites within the heart[3-6]. Comparisons and validation of MCG measurements were made with standard electrocardiography (ECG) and, soon after, with results of invasive electrophysiological studies[7-9]. MCG appeared to be practical and informative in the diagnosis of cardiac arrhythmias, and had the sufficient spatial accuracy necessary for clinical purposes. The combination of MCG with magnetic resonance imaging (MRI), the development of biomagnetic multichannel systems, the introduction of non-magnetic pacing catheters, the availability of digital subtraction and of high-T_C sensors have recently provided new tools for the investigation of cardiac electromagnetic sources. Patients with various cardiac arrhythmias can now be investigated with the goal of localizing the origin of their disorder[10-15]. The localization of the source of arrhythmias is important for interventions, such as catheter ablation or surgery, when pharmacological therapies are ineffective or inappropriate[16-19]. Catheter or surgical ablation requires the exact localization of the arrhythmogenic substrate. Conventional non-invasive methods for cardiac arrhythmia localization, aimed at mapping accessory pathways or foci of ventricular tachycardia, include 12-lead ECG, the body surface potential mapping (BSPM), vectorcardiography, nuclear phase imaging, computed tomography and MRI. Standard surface ECG can provide useful information but, in many cases, is not efficient in predicting the exact localization and number of arrhythmogenic sites[20]. The 12-lead standard ECG, using 6 channels on the thorax surface, is sensitive for the localization of accessory pathways, but can be used only for the initial evaluation of the patient. Multichannel BSPM, on the other hand, has been attempted since the '70s[21,22], but provided only qualitative classification of ventricular preexcitation sites, with the exception of the work by Lorange and Gulrajani[23-25], who, for the first time, attempted a three-dimensional reconstruction of preexcitation pathways based on a solution of the inverse problem. The accuracy was not however satisfactory[23]. Comparisons of the relative performance of MCG with other techniques, including myocardial scintigraphy[26] and echocardiography[27], have been performed. Other techniques have only yielded a qualitative description of the morphology of the electrical field distribution. In the localization of the site of origin of ventricular tachycardias, none of these non-invasive methods is accurate enough to guide surgical or catheter-based ablative therapies[27]. This is currently achievable only with catheter mapping through an electrophysiological study. However, an electrophysiological study is time-consuming, invasive, uncomfortable for the patient, and associated with considerable X-ray exposure for both the patient and the operator. On the contrary, non-invasive MCG mapping relying on multichannel systems, allows the preoperative accurate localization of the accessory pathway in patients with the Wolff-Parkinson-White (WPW) syndrome who, in case of potentially life-threatening arrhythmias, are candidates for catheter ablation. This therapeutic intervention requires great accuracy in the localization of the preexcitation site. Since 1985, MCG recordings have been focused on the preoperative localization of accessory pathways and the results so obtained have been compared with those of simultaneous invasive catheter localization sites[12,28]. Several groups have studied WPW patients either with a single-channel MCG system acquiring MCG maps by consecutive measurements[12,29-33], or with multichannel systems[13,34,35]. Soon after, MCG algorithms have been applied to attempt a non-invasive localization of the site of origin of atrial and ventricular premature beats and/or tachycardias[34,36-41]. Multichannel systems, not requiring patient repositioning and long acquisition times, are clearly advantageous, especially in case of hemodynamically unstable patients with ventricular tachycardia, or in case of short runs of unsustained arrhythmias[37,39-42].

The accuracy of the non-invasive MCG localization of arrhythmogenic substrates has been evaluated by comparison with the results of conventional invasive catheter mapping[28,31-35] and with the amagnetic catheter technique[8,11,43-47]. Table II[12,13,30-35,38,40,48] summarizes some results of the main clinical studies on MCG localization of arrhythmic substrates. As stressed by Moshage et al.[34], one of the most important steps in the MCG evaluation of arrhythmic disorders has been the introduction of multichannel systems. This has allowed the study of patients with premature ventricular contractions and ventricular tachycardia in short times. In 1991, Moshage et al.[34], at the University of Erlangen (Germany), conducted an interesting work aimed at verifying the accuracy of the biomagnetic localization of ventricular arrhythmias. The authors studied 17 subjects with a Siemens Krenikon 37-channel MCG sys-

Table II. Localization results of main biomagnetic studies of ventricular arrhythmias and accessory pathways in the Wolff-Parkinson-White (WPW) syndrome.

Authors/Center	Instrumentation	Comparison method	Arrhythmic disorder	No. patients	Assignment	Mean (± SD) accuracy
Fenici et al.[12], 1989 Rome (Italy)	Single-channel MCG system without shielded room		WPW syndrome	18	X-ray	2.0 cm
Mäkijärvi et al.[30], 1990 Helsinki (Finland)	Single-channel MCG system in shielded room		WPW syndrome	15	X-ray	3.1 cm
Schneider et al.[13], 1990 Erlangen (Germany)	37-channel Krenikon system in shielded room	Invasive catheter mapping and blood pool scintigraphy	WPW syndrome	10	MRI	1-2 cm
Moshage et al.[34], 1991 Erlangen (Germany)	37-channel Krenikon system in shielded room	Bipolar pacing amagnetic catheter	PVC, VT, IPB	17	MRI	Few millimeters
Weissmüller et al.[35], 1992 Ulm (Germany)	37-channel Krenikon system in shielded room	Invasive catheter mapping	WPW syndrome	7	MRI	2.1 (0-5 cm)
Nenonen et al.[31], 1993 Helsinki (Finland)	Single-channel MCG system in shielded room	Intraoperative multicatheter mapping	WPW syndrome	12	MRI	2.1 ± 0.9 cm
Mäkijärvi et al.[32], 1993 Helsinki (Finland)	Single-channel MCG system in shielded room	Invasive catheter mapping	SVT (mostly WPW)	26	MRI	2.0 ± 1.0 cm
Fenici and Melillo[38], 1993 Rome (Italy)	Single-channel MCG system without shielded room	Biomagnetic invasive catheter mapping	VT	35	MRI	1.0 cm
Oeff and Burghoff[40], 1994 Berlin (Germany)	37-channel system in shielded room		PVC, WPW syndrome	25	MRI	0.5-2.0 cm
Nomura et al.[33], 1994 Tokushima (Japan)	7-channel system	BSPM	WPW syndrome	14	MRI	Good correlation
Oeff and Burghoff[40], 1994 Berlin (Germany)	37-channel system in shielded room	Catheter ablation	WPW syndrome	18	MRI	2.1 ± 1.7 cm
Moshage et al.[48], 1996 Erlangen (Germany)	37-channel Krenikon system in shielded room		WPW syndrome	23	MRI	< 2.0 cm

BSPM = body surface potential mapping; IPB = induced paced beats; MCG = magnetocardiography; MRI = magnetic resonance imaging; PVC = premature ventricular contractions; SVT = supraventricular tachycardia; VT = ventricular tachycardia.

tem placed in a magnetically shielded room. They applied the model of the single equivalent current dipole (ECD) in the infinite homogeneous half-space, and transferred the MCG coordinates on previously acquired magnetic resonance images. The MCG recordings of 10 patients with spontaneous premature ventricular complexes, 3 patients with induced ventricular tachycardia, and 4 healthy subjects with induced paced beats (in all 4 cases the site of stimulation was the right ventricular apex) were recorded for 2-15 min. The site of origin of the arrhythmias was localized by examining the magnetic field distribution at the onset of the ectopic beats. To verify the localization accuracy of MCG, a bipolar pacing catheter made of a non-magnetic material was designed and constructed, allowing endocardial stimulation at a given specific site during MCG recording. The catheter tips were filled with a MRI contrast agent to improve their visibility on magnetic resonance images. At the onset of every single ectopic beat, the bipolar magnetic field patterns were examined, thus allowing the three-dimensional localization of an ECD within the heart. The transfer of the site of electrical activity, obtained from the magnetic field distributions during the first milliseconds of the prema-

ture ventricular contraction, to the magnetic resonance image allowed the localization of the site of origin of the ectopic beats. The localization of induced ventricular tachycardia was achieved with a new algorithm based on the reconstruction of the current density distribution ("lead fields"), and showed good topographic agreement with invasive endocardial pace-mapping procedures. The MCG localization of paced beats in healthy subjects showed an error of a few millimeters and related to the catheter tip. After several MCG studies using single-channel devices in WPW patients, Weissmüller et al.[35] in 1992 used a 37-channel SQUID sensor system (with shielding) in 7 such patients. They compared the biomagnetic data with those obtained from standard invasive catheter mapping. The human chest was approximated to a homogeneous infinite half-space, the electrical source within the heart was approximated to the ECD, and all biomagnetic data were matched with anatomical structures obtained by MRI. The site of the ECD was evaluated at the onset of the delta wave, when the ventricles were excited. The MCG localization of the accessory pathways corresponded with catheter mapping results within an average of 2.1 cm (range 0-5 cm). The accuracy of the biomagnetic technique was in the order of 10 mm, as also confirmed in thorax phantoms filled with saline solution[49]. Nenonen et al.[31] studied 12 WPW patients with serious supraventricular arrhythmias refractory to drug therapy. They used a single-channel device having a current dipole source in a realistically shaped digital torso in a shielded room. MCG results were superimposed on magnetic resonance images. All patients also underwent intraoperative multicatheter mapping, now recognized as a standard clinical method for the localization of the accessory pathways prior to ablation or surgical dissection, and were actually submitted to subsequent ablation of the accessory pathway. The accuracy of the MCG localization was compared with the intraoperative mapping. The average three-dimensional difference between the MCG results and those of invasive catheter mapping was 2.1 ± 0.9 cm (mean ± SD). Mäkijärvi et al.[32] studied 26 patients with supraventricular arrhythmias (most suffering from the WPW syndrome) and used a single-channel system in a magnetically shielded room to sample the magnetic field of the heart at 20-60 locations over the anterior chest. MRI images were acquired to provide anatomical landmarks for data analysis. In this study, an ECD source in a realistically shaped torso model was used. An MCG localization of the preexcitation sites was obtained with an average accuracy of 2.0 ± 1.0 cm (mean ± SD) relative to results obtained with invasive catheter mapping. The authors stressed that most of their patients had left inferior or left infero-lateral accessory pathways, theoretically difficult to localize because far from the body surface. Despite this, the MCG localization was satisfactory. A limitation of the MCG method was the presence of multiple pathways, found in 3 out of 26 patients: here the secondary pathways were only demonstrated by means of intraoperative mapping[32]. Fenici and Melillo[38] have also investigated the MCG method in 35 patients with severe ventricular arrhythmias secondary to arrhythmogenic right ventricular dysplasia, dilated cardiomyopathy or ischemic heart disease. They used a single-channel system (necessitating sequential mapping and off-line reconstruction of time-correlated MCG waveforms from a 36-point standard grid) without shielding. The accuracy in the localization of arrhythmogenic foci was found to be in the order of 1.0 cm, as demonstrated by the inverse localization of a biomagnetic catheter. The same study showed the potential usefulness of the relative smoothness index which was found to be lower in patients with cardiomyopathy or sudden death, but which necessitates further clinical investigation[38]. All these studies demonstrate that MCG is capable of localizing preexcitation sites with an accuracy sufficient to provide adequate information for non-pharmacological therapeutic interventions.

MCG mapping has also allowed the localization of ectopic ventricular beats, mostly related to infarct areas of the myocardium, in patients with coronary artery disease. An accuracy in the localization of arrhythmogenic sites in the order of 1.0 cm has been reported in several studies[13,36,37,39-42,48]. Thus, most MCG studies on arrhythmias have been focused on ventricular arrhythmias and on the localization of accessory pathways. Conversely, studies evaluating supraventricular arrhythmias by MCG have been scanty[9,14,32,50,51]. This can be ascribed to the lesser clinical relevance of supraventricular arrhythmias for possible interventional treatments. Other reasons are that atrial excitation is weaker than ventricular excitation and thus more difficult to study with a biomagnetic approach, and that the atria are anatomically located more posteriorly, with a worse signal-to-noise ratio. Mäkijärvi et al.[32] have studied supraventricular arrhythmias with a single-channel system in a shielded room. They used an ECD as the electrical source model and a realistically shaped torso model as the conductor volume. They studied one patient with focal atrial tachycardia. The MCG localization of the onset of the P wave was obtained and the results were related to cardiac anatomy using MRI. The premature atrial activity was located in the right atrium. Subsequent catheter mapping confirmed the localization of the focus, and catheter ablation was finally planned. In the same study, the risk of atrial fibrillation in patients with the WPW syndrome was evaluated. The spatial MCG maps of 26 patients were analyzed. Patients with episodes of atrial fibrillation were found to have a more dispersed distribution of atrial depolarizations during P waves compared to patients without atrial fibrillation. The evaluation of the risk of atrial fibrillation in patients with the WPW syndrome is thus another example of the potential applications of MCG.

The amagnetic catheter technique was first used to attempt an objective evaluation of the MCG localization accuracy of an intracardiac dipolar source[8,11,43,45,47]. The subsequent development of a biomagnetically localizable multipurpose catheter has provided evidence of its potential for MCG-guided intracardiac electrophysiological recordings and ablation[45,52-57]. After the preliminary studies carried out since 1985 in the unshielded electrophysiology laboratory at the Catholic University of Rome (Italy)[8,43,45,47,52], further clinical validation was performed in the shielded room at the University of Helsinki (Finland), where simultaneous multichannel MCG and BSPM recordings were acquired for each patient using standard and patient-specific torso models for the solution of the inverse problem[53,55,58]. Using individually shaped models (including the lungs), the accuracy in localizing source currents within the heart by MCG and ECG methods was investigated in 10 patients. A non-magnetic stimulation catheter inside the heart served as the reference current source. Fluoroscopy was used to localize the position of the catheter. Simultaneous MCG and BSPM recordings were performed during catheter pacing. ECD localization sites were computed from MCG and BSPM data, employing standard and patient-specific boundary element torso models. With an individually shaped torso model, the average MCG localization error of the catheter tip in patients was 7 ± 3 mm (mean ± SD), whereas the average BSPM localization error was 25 ± 4 mm. This result is apparently in contrast with the output of computer simulations published by Hren et al.[59] in 1996, suggesting the better accuracy of BSPM as compared to MCG mapping for cardiac source localization sites. Thus, recent studies, including an overall number of 15 patients, apparently demonstrate that the MCG accuracy in localizing dipolar sources is sufficient for clinical purposes, and that an accurate localization can also be achieved even without the use of individually shaped torso models built for each subject with the help of MRI data[53-55,60]. However, realistic and patient-tailored torso models remain one of the most important factors in determining the accuracy of MCG. In fact, using standard torso models, the average MCG localization error was higher (9 ± 3 mm). Other sources of error are patient's breathing, the signal-to-noise ratio, the adequacy-of-fit of the mathematical models and the lack of appropriate integration of MCG with MRI and/or fluoroscopic images. More recently, effort has been devoted to obtain adequate three-dimensional reconstructions of the patient torso and the heart by using two-dimensional fluoroscopic profiles and a geometric prior model[61,62]. This approach seems promising for the simplification of multimodal MCG imaging, without the need of MRI in each individual patient.

In conclusion, clinical studies performed so far have indicated a good spatial accuracy of the biomagnetic technique (below 10 mm for the localization of superficial cardiac sources), with a decrease in accuracy (up to 20 mm) for deeper sources[29,39,41,52]. The amagnetic catheter technique has demonstrated that such a three-dimensional accuracy can be improved substantially, and even reach 2 mm, when systematic errors are avoided[57,60]. In spite of such promising results and after having been around for almost two decades, MCG is still not accepted for routine clinical use. This is likely to be due to the need of additional examinations and of time-consuming procedures for data analysis and presentation. The current availability of low-cost fast computer processing has completely solved the problems of the time-consuming procedures of MCG data analysis for the three-dimensional localization and imaging of cardiac electrophysiological phenomena and myocardial ischemia. Indeed, the most recent instruments can perform imaging procedures almost in real time[63,64]. New multicenter trials are now investigating the clinical reliability of MCG as a valuable clinical tool. MCG can thus fairly compete with, or rather be complementary to, other available techniques (Tables III and IV).

Ischemic heart disease

Rest magnetocardiography. The ability to study the three-dimensional localization of cardiac electrical activity makes MCG a potentially useful tool in the evaluation of the presence and localization of coronary artery disease[65], the identification of viable myocardium after myocardial infarction[66,67], and the risk stratification of patients with infarcts[68-72]. Myocardial ischemia induces changes in the electrophysiological properties of the myocardium, resulting in a decrease in resting membrane potential and conduction velocity, with a dispersion of the activation wavefront. The electrophysiological features of an ischemic area are quite different from those of an infarcted area. The detection of myocardial ischemia is commonly achieved at standard surface ECG, at echocardiography or at myocardial scintigraphy, at rest and under stress. Coronary

Table III. Advantages and disadvantages of magnetocardiography compared with other cardiological techniques.

Advantages	Disadvantages
Non-invasive	Expensive
Spatially and temporally accurate	Magnetically shielded room necessity for many multichannel SQUID systems
Risk-free	No bedside availability
Contactless	Not portable
Fast	Requires realistic torso models
Allows beat-to-beat analysis	Sensitive to metal objects and pacemakers
No tissue interference	
Allows three-dimensional	
Allows three-dimensional reconstruction of cardiac electrical activity	

Table IV. Main features of magnetocardiography compared with standard surface electrocardiography.

Analogies
Non-invasive
Based on the same ionic currents
Risk-free
Similar morphological aspects (P-QRS-T waves)
Fast
Differences
Expensive
Magnetically shielded room necessity for many multichannel SQUID systems
No bedside availability
Not portable
Requires specific electric sources and torso models
Sensitive to metal objects and pacemakers
Uses multichannel system on thorax surface and not only six surface leads
Measures the magnetic field produced by cardiac electrical activation; not sensitive to differences in electrical potential on the body surface
Less influenced by electric conductivity of interposed tissues
Contactless, does not use skin electrodes
Sensitive to vortex currents not detectable with electrocardiography
More sensitive to tangential currents
Limited number of clinical studies
Results can be superimposed on magnetic resonance images for three-dimensional reconstruction of current density distribution
Great accuracy in the localization of accessory pathways in Wolff-Parkinson-White syndrome and ventricular tachycardia foci

anatomy is usually defined by angiography. Positron-emission tomography and MRI are also increasingly used in tertiary centers for the non-invasive functional imaging of the heart, mostly to detect myocardial ischemia and viable tissue. MCG allows the non-invasive clinical detection and localization of abnormal current flows associated with cardiac ischemia, and allows the correlation of such events with the arrhythmogenic potential of that area[73]. Transient acute myocardial ischemia causes well-recognizable changes in the MCG on the ST segment and the T wave: the orientation of the maximum spatial gradient of the magnetic field can be used as a parameter to determine these changes[74]. Such changes strongly depend on ischemic regions and can also be detected with BSPM, but not with 12-lead ECG[75]. A beat-to-beat analysis method for MCG recording during interventions has also been developed and can be applied for the on-line analysis of MCG data and detection of myocardial ischemia[76]. Indeed, the latter method, which provides heart rate adjustment of the magnetic field map rotation, improves the performance of MCG in ischemia detection, by the analysis of the ST and T magnetic fields.

MCG detection of ischemia has been attempted at rest and under physical or pharmacological stress. A first experimental study on the MCG detection of acute myocardial infarction was reported by Cohen and Kaufman[77] in 1975 who found ST-segment shifts during the experimental occlusion of the coronary artery in the dog.

In the normal myocardium, the current flow is almost uniform during ventricular repolarization. When ischemia is present, the current flow becomes less uniformly oriented, and the associated magnetic field becomes weaker. This results in a decrease in the maximum integral value in the iso-integral maps obtained for the two more relevant time intervals (QRS and ST-T) defined from the MCG waveforms. This has been reported by Sato et al.[78] in a recent study on ischemic patients. In 25 such patients with severe (≥ 75%) coronary stenosis as assessed at angiography, MCG, performed using a 64-channel SQUID system in a shielded room at the Tsukuba University Hospital in Japan, has been compared with standard resting 12-lead ECG and echocardiography. Abnormal mapping patterns were found during the repolarization phase in 22 out of 25 (88%) of these patients. Resting ECG showed ischemic changes, such as an abnormal Q wave or ST-T changes, in 18 patients but no ischemic alterations were detected in the remaining 7 patients. Echocardiography revealed an abnormal left ventricular wall motion (asynergy) in 16 patients. MCG abnormalities during the repolarization phase were detected in all patients with severe coronary lesions in vector arrow maps and iso-integral maps, the two kinds of MCG data analysis used by the authors.

Chaikovsky et al.[79] have performed MCG measurements in 49 control healthy subjects and in 51 patients with coronary artery disease and symptoms of stable angina but without a previous myocardial infarction. Eighteen patients were affected by three-vessel disease, 17 by two-vessel disease, and 16 by single-vessel disease. MCG recordings were obtained using a single-channel instrumentation in an unshielded environment, simultaneously acquiring the electrocardiogram on lead II. MCG data were analyzed in current density vector maps and current line maps. Maps from healthy subjects showed a homogeneous distribution of currents; in contrast, maps from patients with coronary artery disease showed additional current areas with a deviated direction. The position of additional currents might reflect the anatomy of ischemic areas and may be considered as a footprint of the area served by the diseased coronary artery. In 81% of cases there was a good correlation between the location of additional current areas and the angiographic localization of coronary stenosis. The localization of myocardial ischemia by MCG has also been successfully attempted using a current density reconstruction method[80].

Another interesting study has analyzed the role of MCG in the detection of electrophysiological changes in patients with coronary artery disease after percutaneous transluminal coronary angioplasty. In these patients, successful relief of the obstruction is followed

by a more homogeneous current density distribution in the MCG map as early as 1 month after the procedure. This aspect might be exploited for the follow-up of coronary angioplasty patients[81].

MCG offers information complementary to that provided by standard surface ECG and BSPM obtained with 32 leads on the thorax surface[82] (Tables III and IV). BSPM allows a better spatial analysis of ECG information than the standard ECG; in particular, the iso-integral maps offer the possibility of rapidly identifying those areas in which QRST abnormalities are detectable. Magnetic field mapping adds complementary information through the spatial and temporal reconstruction of the magnetic field generated within the heart. The MCG study of ventricular repolarization, in patients with previous myocardial infarction, has also allowed a recording of T wave abnormalities in the iso-magnetic maps, in some cases at a time when T waves in the standard ECG had returned to normality[68]. In 1990 Lant et al.[82] have proposed the comparison of BSPM and magnetic field mapping with the aim of differentiating patients with infarcts and normal subjects. They studied 22 patients with infarcts (11 with a non-Q wave myocardial infarction and 11 with a Q wave myocardial infarction, anterior in 4 cases and inferior in 7) and 9 normal subjects. MCG was recorded with a single-channel system acquiring data on a 56-point grid in a shielded room. Time integrals were defined, both for MCG and BSPM, for every QRST time interval. Maps were constructed in iso-contour lines connecting the points with the same integral values. Analyzing magnetic field maps, the most profound abnormalities in anterior myocardial infarction were found in the QRS complex, while in inferior infarction, abnormalities were found during the entire repolarization period. In contrast, examination of the mean iso-integral BSPMs revealed significant differences between anterior and inferior infarctions during the QRS complex only, without any alterations in the repolarization phase. The authors concluded that magnetic field mapping and BSPM are complementary in the evaluation of ischemic heart disease[82]. Similar conclusions have been more recently reached by Adams et al.[83].

In summary, MCG methods appear promising in diagnosing myocardial ischemia, infarction and viability[84,85], but it has to be appreciated that clinical results in this area are still quite scanty and less extensive than in the area of arrhythmias.

Stress magnetocardiography. In stress MCG, the subject undergoes biomagnetic measurements during physical exercise or pharmacological stress. The ECG exercise test is commonly used in the assessment of patients with angina pectoris and coronary artery disease, mostly through the assessment of ST segment depression. Cohen et al. conducted the first stress MCG study in man in 1983. They detected abnormalities of ventricular repolarization, including ST segment depression and baseline QT segment elevation[86]. Changes in ventricular depolarization can be already observed in healthy subjects during stress testing comparing MCG and ECG signals[86-89]. Brockmeier et al.[90] have acquired BSPM and magnetic field mapping before and during pharmacologically-induced stress. They found significant stress-induced differences during ventricular repolarization in magnetic field mapping, not present in BSPM. They suggested that vortex components of the current density distribution were responsible for the changes observed in MCG maps under stress. The vortex components of the current density distribution generate a magnetic field, without any detectable surface electric potential. MCG is sensitive to these vortex currents, as shown by the detection of ST-T shifts during the exercise test[87]. These variations in healthy subjects have been considered as a physiological phenomenon. The origin of the vortex components under stress is still however uncertain. Further information will be available by larger comparisons of healthy subjects and patients.

MCG recordings during physical exercise also show very few artifacts due to breathing or muscular contraction. Conversely, these are common in stress ECG. Stress MCG is not influenced – contrary to ECG – by changes in skin resistance occurring because of the increased transpiration during exercise.

MCG appears thus feasible during exercise, and possibly more sensitive than ECG in detecting early ST segment shifts in patients with ischemic heart disease[91]. In these patients, electrophysiological changes during ventricular repolarization under stress are well evident both in BSPM[92] and in magnetic field mapping, even in patients with single-vessel disease[93]. However, the real advantages of MCG over ECG in ischemic patients have to be further evaluated before any definite conclusions are reached.

Risk analysis in ischemic patients

Late field analysis. MCG has also been used as a prognostic tool after myocardial infarction, with some evidence about the possibility of the early identification of ischemic subjects at high risk for ventricular arrhythmias[94]. The duration of the QRS complex in the magnetocardiogram was significantly longer in patients with ventricular tachycardia after an old myocardial infarction compared to patients with infarcts but without ventricular tachycardia (144 vs 109 ms). The sensitivity and the specificity of MCG in identifying ventricular tachycardia patients were found to be both around 80%, and the positive and negative predictive values were 78 and 86% respectively. High-resolution ECG recorded during the same session performed slightly better, showing sensitivity, specificity, positive and negative predictive values all around 90%. The ECG signal-to-noise ratio was higher than for MCG. This study nevertheless concluded that MCG is helpful in screening pa-

tients at risk of ventricular arrhythmias after myocardial infarction[69]. In another study, the sensitivity and specificity of MCG in the assessment of the risk for ventricular arrhythmias after myocardial infarction were found to be 90 and 100% respectively[95]. However, this study had some limitations including the fact that it was conducted on a few patients, without the establishment of clearly defined cut-off points, and that a myriad of different MCG systems were used.

MCG recordings have also been applied for risk stratification evaluating the risk of ventricular tachycardia after acute myocardial infarction in ischemic patients. In a recent work, Korhonen et al.[71] have proposed the MCG late field analysis in 100 subjects with remote myocardial infarction as a marker of the propensity to sustained ventricular tachycardia. Late fields of the MCG QRS complex are a potential new method for the non-invasive risk assessment in post-myocardial infarction patients even in the presence of severe left ventricular dysfunction. In the latter case, ECG late potentials loose their informative and prognostic value. However, studies in this area are limited, and show no significant advantage of MCG when compared to high-resolution ECG recordings.

Prolongation of the QT interval and QT dispersion. It is well known that prolongation of the QT interval reflects an alteration in cardiac electrical properties and that it is a predictor of malignant ventricular arrhythmias. Prolongation of the QT interval, as detected by ECG, is associated with life-threatening ventricular arrhythmias and sudden death after myocardial infarction[96]. Arrhythmogenesis seems here to be correlated more with the inter-lead differences in QT duration than with the absolute value of the QT interval. QT dispersion is therefore measured as the difference between the maximum and the minimum value of the QT duration in a standard 12-lead ECG, and is associated with an increased risk of ventricular arrhythmias and sudden death in subjects with a previous myocardial infarction[97,98]. MCG has been applied as an alternative to ECG for the evaluation of QT dispersion. In contrast to standard ECG, multichannel MCG (but also BSPM) measurements permit the determination of QT intervals at numerous locations above the heart and also the reconstruction of the spatial distribution of QT dispersion.

At standard ECG, healthy subjects generally show shorter QT intervals than those with an infarct. van Leeuwen et al.[99] have shown that MCG offers the capability of examining the spatial distribution of the QT interval duration and that such analysis seems to be more sensitive than the QT dispersion based on standard 12-lead ECG. Oikarinen et al.[100] studied whether MCG measurements of the QT dispersion can distinguish post-myocardial infarction patients with and without a susceptibility to sustained ventricular tachycardia. Ten patients with a history of ventricular tachycardia and 8 patients without ventricular tachycardia were studied after a remote infarction. In this study, a single-channel MCG system was used, and QT dispersion was defined as the range and the standard deviation of the measured QT intervals. The ventricular tachycardia group showed more QT and JT dispersion than controls. MCG mapping may thus provide a useful method to detect and localize differences in ventricular repolarization. Hailer and van Leeuwen[72] used a 37-channel Siemens Krenikon MCG system to evaluate the temporal and spatial aspects of QT dispersion in a study including 20 healthy subjects as well as 42 patients after myocardial infarction. Eleven of the latter had documented ventricular tachycardia. Healthy subjects demonstrated a very similar spatial pattern of QT values, while the pattern of the patients showed marked differences in terms of the local and global variability of QT duration and higher values of QT dispersion. The ECG was not able to distinguish healthy subjects from patients using the QT dispersion as the temporal parameter. Although all these data are promising, it has to be pointed out that most studies have been conducted on small populations, with different recording systems and without standardization of methods for data analysis. Proper comparisons with the rivaling technique of BSPM are also lacking.

Ventricular hypertrophy, cardiomyopathies and myocarditides

Cardiac hypertrophy is characterized by an increase in ventricular mass which can be primitive or caused by pressure overload, such as in subjects with arterial hypertension or aortic valve stenosis. Echocardiography is the diagnostic technique of choice for the evaluation and quantification of the myocardial mass. Less-routine techniques, such as MRI or the invasive ventriculography, can also be used for the same purpose. Some studies have suggested a potential role of MCG in the clinical evaluation of cardiac hypertrophy, both primitive and secondary, and cardiomyopathies, comparing MCG results with those of well-established techniques such as echocardiography and ECG[101]. MCG tracings may show an increase in the QRS complex amplitude and an inversion of the T waves[102]. A superior sensitivity and specificity of MCG compared to ECG in the detection of left ventricular hypertrophy has been claimed[103]. Nikitin et al.[104] studied 18 patients with arterial hypertension, and compared the diagnostic potential of MCG, ECG and echocardiography. Left ventricular hypertrophy was detected at echocardiography, MCG (from the abnormalities of ventricular repolarization) and ECG in 11 (61%), 16 (84%) and 7 (34%) patients respectively. Left atrial hypertrophy was detected primarily by echocardiography and MCG. Alterations in ventricular repolarization were detected by MCG in 39% of patients. Although further investigations including larger patient populations are needed to better

evaluate these aspects, the above results might suggest that MCG can be used as an additional tool for the investigation of cardiac hypertrophy.

MCG mapping can also be applied to the study of the evolution of myocarditis. Myocarditis is commonly diagnosed and monitored by myocardial biopsy, but MCG seems a revolutionary and non-invasive approach for the diagnosis of this disease. It provides useful magnetic parameters (such as the "electrical circulation" describing the correlation between the instantaneous current dipole and its localization in consecutive heart beats) which seem to be related to the lymphocytic infiltration occurring in myocarditis[105]. Finally, MCG in the early diagnosis of arrhythmogenic right ventricular dysplasia seems to be promising[106].

Fetal magnetocardiography

The application of MCG to the study and monitoring of fetal cardiac activity is novel and promising. Fetal MCG has been applied to the study of the cardiac time intervals, heart rate variability, congenital heart disease and fetal arrhythmias. MCG measurements can usually be made starting from the 20th-22th week of gestation, and provide information about fetal health and normal growth[107]. Magnetocardiograms can be acquired already at the 16th week, but such early recordings are often inadequate. Tissues interposed between the fetal heart and the recording system (such as the *vernix caseosa*) do not influence the biomagnetic signal, and this offers an extra advantage with respect to fetal ECG. In addition, the availability of digital subtraction, also used in ECG, allows the removal of maternal artifacts. A fetal MCG was successfully recorded for the first time in 1974 by Kariniemi et al.[108], and was soon considered as a new and promising tool in the prenatal evaluation of several fetal parameters. During fetal growth, the signal amplitude of fetal MCG progressively increases, with a wide interindividual variability. Even consecutive recordings in the same fetus show considerable intraindividual variability, which can probably be ascribed to changes in the intra-abdominal position of the fetus. Indeed, the morphology and polarity of the QRS complex at fetal MCG highly depend on the fetal intra-abdominal position with respect to the detector.

Fetal MCG allows the recording of all parts of the P, QRS, and T waves from the second trimester onwards, and makes the determination of the cardiac time intervals possible[109]. According to Menendez et al.[110], the cardiac time intervals and amplitudes of fetal MCG increase in parallel with fetal growth from the 10th week onwards. The mean P wave duration increases from 31 to 49 ms, the PQ interval from 95 to 107 ms, and the QRS duration from 36 to 52 ms. In the same study, several fetal arrhythmias, including episodes of ventricular and supraventricular tachycardias and atrioventricular blocks, were recorded after the 26th week. During fetal growth, the cardiac time intervals increase, and several studies have been performed with the aim of establishing the normal values for different gestational ages. Horigome et al.[111] have recently assessed the developmental changes in the PQ, QRS and QT intervals in 150 healthy fetuses > 20 weeks in gestational age. The QRS, P and T waveforms were successfully recorded in 85, 68 and 43% of the subjects respectively. The QRS intervals, ranging from 32 to 74 ms, showed a positive linear relationship with the gestational age, which probably reflects an increase in the number and size of myocardial cells. The PQ interval was rather constant and showed a poor correlation with the gestational age (average value 100 ms); the QT interval, ranging from 180-302 ms, tended to be slightly shorter during early gestation. During pregnancy, the duration of the P wave and of the QRS complex increase, while the PQ and the QT intervals remain quite constant. Fetal MCG however does not allow the unambiguous determination of the T wave[112]. Recently, a database with normal values of fetal ECG and fetal MCG parameters has been created, with the collaboration of a number of international centers (available on line at: http://bct.tn.utwente.nl). Here, the normal fetal time intervals registered at either ECG or MCG from uncomplicated pregnancies have been reported[113].

The high sensitivity of fetal MCG offers a new method for fetal surveillance and allows the study of fetal cardiac activity not otherwise available with current methods, such as fetal echocardiography or Doppler ultrasound. These methods are widely used to monitor fetal heart rate and to diagnose fetal suffering, but do not allow the recording of QRS complexes. In addition, fetal ECG is recorded with an adequate signal only in about 50% of cases. From the 20th week onwards fetal MCG reaches a success rate close to 100% in obtaining good-quality QRS complexes in normal pregnancies[109]. Fetal MCG also has a potential for the detection and classification of fetal arrhythmias[114], the prenatal diagnosis of the long QT syndrome[115], congenital heart diseases[116], the study of fetal heart rate variability – which increases with gestational age –, and the maturation of the autonomic nervous system during pregnancy[117,118].

Rejection reactions after heart transplantation

The acute graft rejection is the major complication after heart transplantation. The standard monitoring of this serious postoperative complication is obtained with serial myocardial biopsies. MCG monitoring of rejection reactions after heart transplantation was first attempted in Berlin by Schmitz et al. in the late '80s (unpublished data). In 1992 Schmitz et al.[119] reported a high sensitivity (91%) and specificity (93%) for the detection of acute rejection in 15 patients after cardiac

transplantation using the MCG strength of the ECD localized at the peak of the R wave. This strength increased in patients with acute rejection, perhaps due to changes in myocardial impedance. In 1991, Fenici et al.[36] reviewed the 10-year MCG activity at the Catholic University of Rome, and preliminarily reported about a single patient studied at MCG every week after cardiac transplantation, starting from the 4th month. In this period, three endomyocardial biopsies were performed, all of which were negative for a rejection reaction. MCG data (an almost 2-fold increase in the maximal magnetic field and the ECD intensity) were however highly suspicious for an acute rejection reaction. Plasma levels of cyclosporine were very low in that patient because of an interaction with a cholesterol-lowering drug. MCG would thus appear to be a promising technique for the early diagnosis of cardiac transplant rejection reactions, and the increase in amplitude of the magnetic index, a parameter which can be considered as a reflection of the magnetic signal intensity, seems to be an early sign of rejection, which is comparable to histology. Achenbach[120] has subsequently reported a sensitivity of 83% and a specificity of 84% for the diagnosis of graft rejection in 12 patients (1 to 4 years after transplantation) and 6 controls. This application of MCG has not however been further investigated so far.

Conclusions and future perspectives

Areas of MCG application are expanding, and now include the study of supraventricular and ventricular arrhythmias, preexcitation syndromes and the accurate localization of arrhythmogenic substrates and accessory pathways for catheter ablation or surgery. Preoperative MCG can provide the interventional electrophysiologist with useful information to address catheter placement for the ablation of arrhythmogenic substrates. Furthermore, MCG mapping during electrophysiologic studies has the potential to three-dimensionally image and guide an amagnetic ablation in contact with the arrhythmogenic target, with minimal use of fluoroscopy[42,47,56].

MCG is definitely "unique", in that it makes it possible to acquire, with a single non-invasive and quick procedure, a great amount of information about cardiac function. Indeed MCG simultaneously provides three types of information, combining the electrophysiological evaluation (useful in arrhythmia localization), the "metabolic" evaluation (useful in case of myocardial ischemia), and a spatial-temporal correlation between the ischemic and arrhythmogenic areas (useful in the estimation of the risk of sudden death)[121]. All this information can be otherwise acquired, in clinical practice, only with separate and surely more expensive investigations such as an invasive catheter electrophysiologic study, BSPM, or nuclear cardiology investigations such as single photon emission tomography and positron emission tomography. Compared to electrocardiographic BSPM which detects the electrical aspects of the same physiological and pathophysiological currents detected by MCG, the latter is faster and does not necessitate direct contact. Besides, it probably offers a better spatial reconstruction.

Some disadvantages of MCG have also, however, to be considered (Table III). The SQUID recording system is cumbersome, and the liquid helium, required as a coolant in the cryostat for low-T_C SQUID systems, is very expensive. In addition, a shielded room is necessary for accurate measurements, e.g. for the evaluation of the ST segment and in high-resolution MCG. The magnetic shielding is also very expensive and may pose difficulties in installation, because it requires a large space (Fig. 1). Recordings are also sensitive to metal objects and pacemakers, which inevitably produce magnetic noise. MCG instrumentation is not bedside-available and not portable. A new generation of SQUID systems, the so-called high-T_C SQUID, not requiring liquid helium (at a temperature of 4.2 K) as a coolant, but liquid nitrogen, at the much higher (and, in practice, easier to achieve) temperature of 77 K, has been recently introduced. These systems, such as the 16-channel high-T_C SQUID used by Nagaishi et al.[122], although less performing at present than low-T_C SQUID, are less expensive to maintain, and may be adaptable, in the near future, to bedside use. This has been recently reported from the Biomagnetism Center of the University of Jena (Germany), where a single-channel equipment, movable from bed to bed, was used[123]. One important limitation is that, electromagnetic shielding being mandatory for the majority of MCG multichannel systems, the integration of MCG, invasive electrophysiologic, MRI and/or fluoroscopic data, by necessitating a change in the patient's position from one study to another, might significantly affect the accuracy of the spatial localization of intracardiac sources. Thus, being the

Figure 1. *Magnetically shielded room installed at the University of Ulm (Germany).*

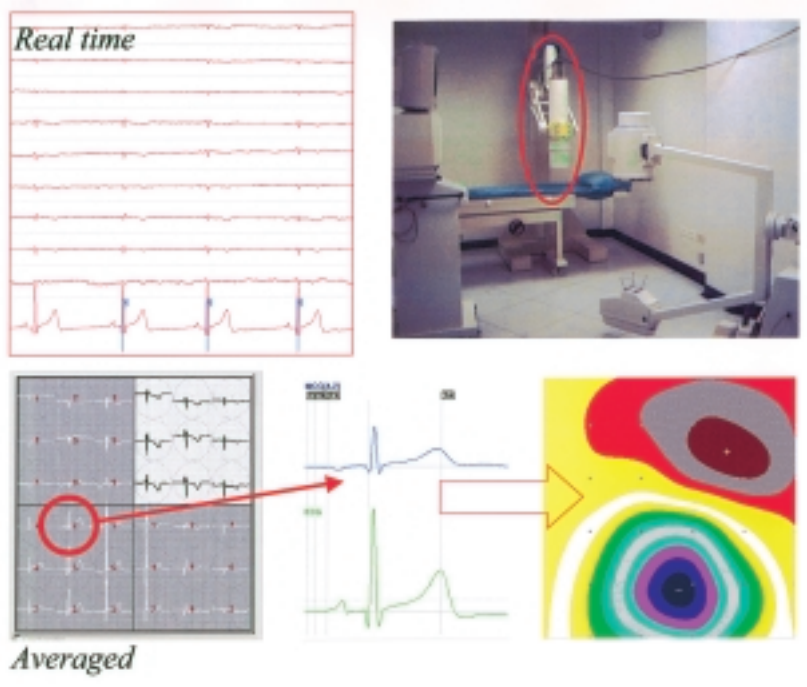

Figure 2. *Example of a normal 36-point magnetocardiographic recording, carried out with the 12-channel system in the unshielded electrophysiology laboratory of the Biomagnetism Center-CNR at the Catholic University of Rome (Italy). Real time and averaged recordings are shown with the magnetic field distribution computed at the apex of the T wave. The size and space required for the whole magnetocardiographic system, highlighted on the picture of the laboratory, is minimal when compared with that of a shielded room (see Fig. 1).*

present trend directed towards the multimodal functional imaging and "electroanatomical integration" of cardiac electrophysiology, the development of new MCG instrumentation, working with sufficient sensitivity in unshielded electrophysiology laboratories, seems to be the most convenient approach. Until a few months ago this was considered a remote future opportunity, unreachable with the present technology. The recent installation of the 12-channel system in the unshielded electrophysiology laboratory of the Biomagnetism Center-CNR at the Catholic University of Rome (Italy)[63,64] (Fig. 2), demonstrates that unshielded MCG is nowadays possible and opens a new way for the development of low-cost widespread clinical MCG.

This is also reinforced by the recent progress in high-T_C SQUID technology, which will probably simplify the daily use of superconducting instrumentation and facilitate novel advanced applications for the bedside use of MCG, such as fetal MCG, risk stratification after myocardial infarction, and the characterization of viable myocardium susceptible to revascularization. In the future, the introduction of more realistic models, both for the torso and the cardiac electrical source, will also likely lead to further improvement.

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