Magnetocardiography in clinical cardiology. Status quo and future applications

Magnetokardiografia w kardiologii klinicznej. Stan obecny i przyszłe zastosowania

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Abstract

Magnetocardiography (MCG) is a non-contact, non-invasive technique for the assessment of electromagnetic activity of the human heart. Theoretical considerations and comparative studies indicate different information content between MCG and electrocardiography (ECG). Although many questions about cardiac pathophysiology and electrophysiology can be answered by MCG studies, measurement of biomagnetism is still only marginally recognized as a valuable tool. Although MCG instrumentation (SQUIDs, MSR) and operation (liquid helium) are expensive and not available at the bedside, the gain of information drawn from the cardiac magnetic field is worth the effort. The MCG has superior sensitivity for ischaemic myocardium both at rest and under stress. Therefore, it may change one's ideas of decision making about invasive procedures. Compared to scintigraphy, which is a cumbersome method with the need of radioactivity exposure to the patient, MCG is as easy as bicycle ergometry but with higher sensitivity. In terms of risk stratification for sudden cardiac death, it seems to be possible that MCG in the future will provide additional information as to which patient will not benefit from prophylactic defibrillator implantation. However, appropriate clinical studies are lacking. Most interestingly, MCG appears to be practical and informative in the diagnosis of cardiac arrhythmias, and has sufficient spatial accuracy necessary for clinical purposes. It seems realistic that MCG-based localization of arrhythmogenic spots may guide the operator's ablation catheter, e.g. in patients with relapsing AF after a first successful ablation procedure. There is enough room for fantasy which question in clinical cardiology remains to be answered by MCG.

Key words: magnetocardiography, coronary heart disease, ischaemia, risk stratification, arrhythmia, atrial fibrillation

Streszczenie

Magnetokardiografia (ang. *magnetocardiography*, MCG) jest bezkontaktową, nieinwazyjną metodą pomiaru pola magnetycznego ludzkiego serca. Założenia teoretyczne oraz badania porównawcze wskazują, że MCG i EKG dostarczają odmiennych informacji. Pomiar pola magnetycznego jest nadal w niewielkim stopniu uważany za wartościowe narzędzie, pomimo że badania MCG mogą udzielić odpowiedzi na wiele pytań dotyczących patofizjologii serca i elektrofizjologii. Chociaż oprzyrządowanie konieczne do MCG (SQUIDs, MSR) i jego obsługa (ciekły hel) są drogie i nie są dostępne jako badania przyłóżkowe, to informacja uzyskiwana z badań pola magnetycznego serca jest warta tych wysiłków. Magnetokardiografia charakteryzuje się większą czułością w wykrywaniu niedokrwienia miokardium zarówno w warunkach spoczynkowych, jak i po obciążeniu. W porównaniu z scyntygrafią, która jest metodą niewygodną, związaną z narażeniem pacjenta na promieniowanie radioaktywne, wykonanie badania MCG jest tak łatwe jak wykonanie próby wysiłkowej na ergometrze rowerowym, ale charakteryzuje się większą czułością. W odniesieniu do stratyfikacji ryzyka nagłego zgonu sercowego wydaje się prawdopodobne, że w przyszłości MCG może dostarczyć dodatkowych informacji wskazujących, którzy pacjenci nie odniosą korzyści z wszczepienia defibrylatora w profilaktyce pierwotnej. Nie ma jednak odpowiednich badań klinicznych. Co najbardziej interesujące, MCG wydaje się mieć praktyczne zastosowanie i dostarczać informacji w diagnostyce zaburzeń rytmu serca oraz ma wystarczającą rozdzielczość przestrzenną wymaganą do zastosowania klinicznego. Wydaje się realne, że oparta na badaniu MCG lokalizacja arytmogennych ognisk może służyć operatorowi w trakcie ablacji przezskórnej, np. u pacjentów z nawracającym migotaniem przedsionków po pierwszym skutecznym zabiegu ablacji. Być może wiele problemów w kardiologii klinicznej może być rozwiązane przy użyciu MCG.

Słowa kluczowe: magnetokardiografia, choroba wieńcowa, niedokrwienie, stratyfikacja ryzyka, zaburzenia rytmu, migotanie przedsionków

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Introduction

In 1887, Augustus Waller was the first to record the electrical activity of the human heart [1]. Nowadays, the method to measure electric potential differences on the body surface originating from the cardiomyocytes of the beating heart, known as electrocardiography (ECG), is the most important tool for the diagnosis of heart diseases in clinical routine. The same bioelectric activity that generates electric potentials also induces biomagnetic fields, which were recorded from the heart for the first time in 1963 by Baule and McFee [2]. The method was termed magnetocardiography (MCG). However, cardiac magnetic signals are several orders of magnitude weaker than the earth's magnetic field, which is in the order of 10^{-5} Tesla (T), or the urban environmental AC magnetic background (10^{-3} T) (fig. 1) [3]. Therefore, it was not until the introduction of highly sensitive superconducting quantum interference device (SQUID) sensors at the beginning of 1970 that accurate and low-noise detection of cardiac biomagnetism became feasible [4]. For a detailed technical description of SQUIDs the reader is referred to a specific review [5]. The sensors are immersed in liquid helium at the low critical temperature of –269°C necessary to maintain superconductivity, and mounted in a vacuum-isolated container called a dewar [6] (fig. 2). The use of magnetically shielded rooms (mSR) further improved the signal quality during recording by reducing external magnetic noise [4]. Unfortunately, the costs of MSR are high due to the use of aluminium and mu-metal, which is an expensive ferromagnetic material. Further disadvantages are immovability, hence no bedside availability of MCG, and its sensitivity to metal implants or pacemakers. In the last 10 years, different companies have developed MCG systems which are now used under clinical routine conditions (tab. 1). Most of them are large multichannel systems containing more than 60 SQUID sensors covering an area of up to 0.3 m in diameter of the patient's chest. Two of these systems were primarily constructed to record magnetic fields of the brain (magnetoencephalography, MEG), which is, although a most interesting subject, not in the scope of this review.

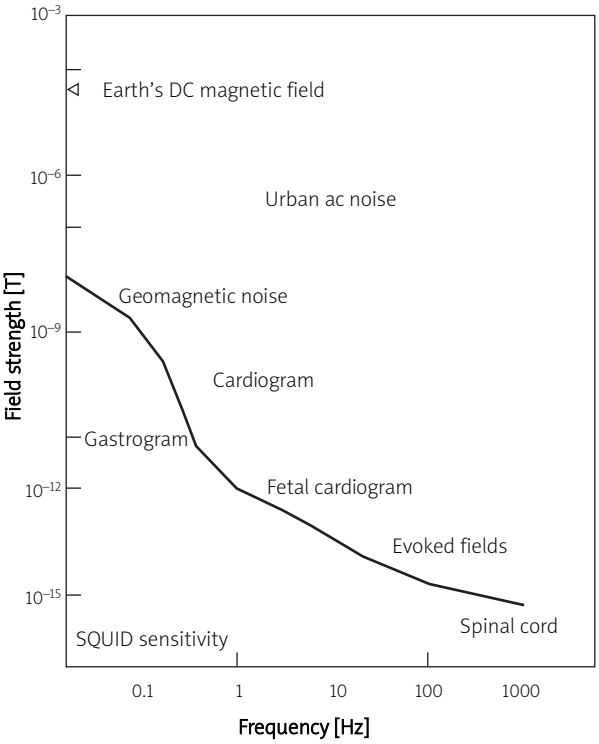

Fig. 1. Signal strength of biomagnetic fields
Ryc. 1. *Wykresy sygnału pola biomagnetycznego*

Biomagnetism

In principle, both electrical and magnetic signals derive from the same ionic currents flowing within myocardial fibres during cardiac activity. The magnetic field generated by an electrical current flowing in a conductor wire (or a heart muscle cell) is characterized by circular and concentric field lines having their centre on the wire and the orientation of a clockwise screw advancing in the same

Fig. 2. Assembly of Dewar, held by the gantry, and the bed
Ryc. 2. *Naczynie Dewara zamontowane na ramie oraz łóżko*

Table 1. Currently available MCG (MEG) systems
Tabela 1. *Aktualnie dostępne systemy MCG (MEG)*

Manufacturer	Device	Magnetocardiography		Magnetoencephalography
		Studies at rest	Studies under stress	
Hitachi, Japan	no name	x	?	
AtB, Pescara, Italy	Argos 55	x	x	
Elekta, Stockholm, Sweden	Neuromag			x
4D Neuroimaging, Coquitlam, BC, Canada	no name			x
BMP, Hamburg, Germany	BMP64	x	x	
CMI, Schenedactady, NY, USA	CMI-2409	x		
BMDSys, Jena, Germany	Apollo CXS	x		

direction as the electrical current (fig. 3). The ECG and MCG, therefore, have morphological features such as T-, P-, and Q-waves, and the QRS complex in common. However, the differences of physical properties of magnetic fields compared to electric currents determine the bulk of additional information about the heart, which can be drawn from the reconstruction of cardiac magnetic fields: the magnetic signal is much less influenced by variations of conductance in body tissues than electric currents [7]. Hence, MCG is much more sensitive to very weak signals such as tangential or vortex currents of the heart muscle, which are induced by radial spreading of the wave front from the endocardium towards the epicardium (fig. 3). Moreover, in contrast to ECG, closed loop currents inside the chest can be detected by MCG [8]. The extraordinary sensitivity is best demonstrated by fetal MCG, which is the only reliable diagnostic tool to detect prenatal cardiac rhythm disturbances at certain stages of gestation (for review see [9-11]). Moreover, in healthy males, significant changes of repolarization during pharmacologically induced stress were found with MCG but not with ECG [8, 12]. Also in contrast to ECG, sex and age dependent variation at different time points of the cardiac cycle can be detected with MCG [13]. Due to the fact that no direct body contact is necessary to study biomagnetism, cardiac magnetic field recording is not hampered by false contacts of skin electrodes or variable sensor positions [14]. Thus, excellent reproducibility of MCG findings is clearly a major advantage. The measurement is absolutely passive without any physical interaction or any kind or energy applied to the patient. Nevertheless, although MCG seems to be able to improve non-invasive diagnostics in cardiology, the method is of limited availability and clinical validation is still incomplete.

Coronary artery disease

The diagnosis of haemodynamically relevant coronary artery disease (CAD) is still a clinical challenge. This is true for both asymptomatic patients with numerous cardiovascular risk factors and patients with a first episode of acute chest pain without any clinical signs of CAD. But there is also a dilemma for cardiologists and their patients with known CAD, after multiple coronary interventions and finally coronary bypass grafting, who after a symptom-free period of three years develop angina again. Neither established diagnostic methods such as 12-lead ECG,

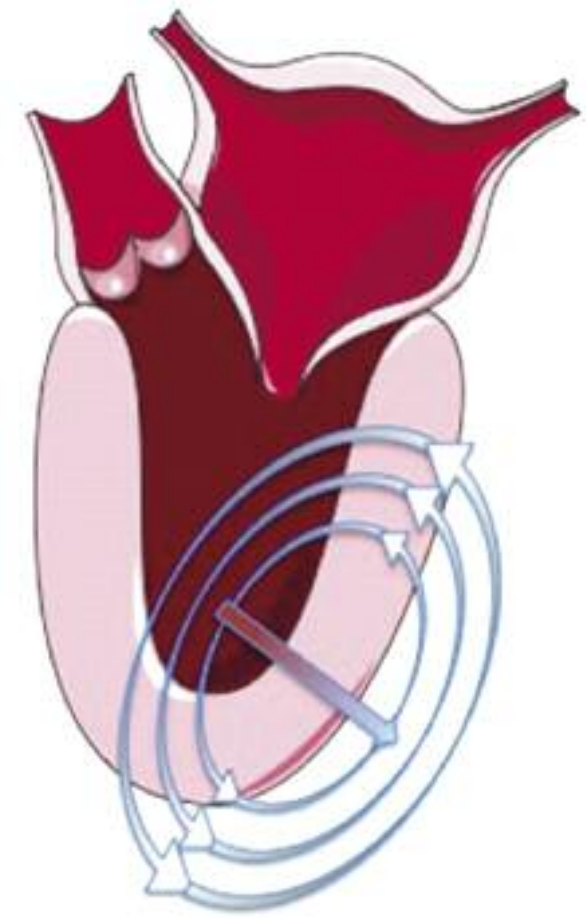

Fig. 3. Schematic drawing of a cardiac current and its corresponding magnetic field lines
Ryc. 3. *Schemat przedstawiający wektor prądu oraz linie pola magnetycznego*

echocardiography, and radionuclide imaging at rest and under stress, nor innovative cardiac imaging based on magnetic resonance imaging or computed tomography have sufficient accuracy to reliably rule out de novo or relapsing myocardial ischaemia [15-20]. Transient myocardial ischaemia, however, causes well-recognizable changes in a variety of MCG parameters, first described by Cohen and Kaufman in 1975 [21]. The action potential is affected in different ways, e.g. reduction of cellular membrane potential (ST depression [22-24], ST-T signal amplitude [25], QRS and ST-T integrals [26, 27]) or conduction velocity, followed by changes of time intervals (QT interval [28]). Ischaemia also leads to repolarization disturbances. The resulting QT dispersion can be spatially evaluated with MCG.

With the first 9-channel MCG system developed for clinical use without an MSR (CMI, Cardiomag Imaging, USA), Park and Jung were able to define criteria for ischaemia within the T-wave and to identify myocardial ischaemia in patients with unstable angina with a positive predictive value of 91% and a negative predictive value of 96% [29]. However, due to the use without an MSR only a poor signal-to-noise-ratio could be achieved. In a following clinical study it could be demonstrated that MCG on admission in patients presenting with acute chest pain and without ST-segment elevation was superior for the detection of CAD compared to ECG, ECHO, and troponin-I. Owing to the unshielded environment, the magnetic field recording of 63 out of 264 patients (24%) could not be interpreted [30]. Tolstrup *et al.* published comparable results using the same device and software [31]. Interestingly, a multivariate regression analysis after a 3-year follow-up revealed the highest mortality risk for patients with diabetes mellitus and an abnormal MCG at admission (RR = 18.0; 95% CI: 2.49-133.3) [32]. By the use of a shielded 55-sensor multichannel MCG system (ATB, Italy), allowing the recording of the heart's entire magnetic field every 2 ms, a further clinical study showed that MCG can be performed together with a standard dobutamine/atropine stress protocol [33]. Assuming an ischaemia-induced reduction of epicardial current density and strength, the study compared the epicardial current distribution at the time point of maximal QRS strength at rest or under stress conditions. Figure 4 shows the epicardial current distribution of a patient with a high-grade stenosis of the posterior descending artery. Using this analysis the authors were able demonstrate that dobutamine stress (DS) MCG yielded significantly higher accuracy for the detection of significant coronary artery stenosis (sensitivity 98%, specificity 83%, positive predictive value 80%, negative predictive value 98%) than DS-ECG in patients with intermediate pre-test probability for CAD [33]. Moreover, in most cases spatial resolution of MCG allows assignment of the ischaemic myocardial area to the corresponding coronary artery.

Fig. 4. Epicardial current distribution of a patient with a high-grade stenosis of the posterior descending artery (schematically indicated as a black line) at rest (left) and under dobutamine-induced stress (right)

Ryc. 4. *Rozkład prądów nasierdziowych u pacjenta z ciasnym zwężeniem gałęzi tylnej zstępującej (przedstawiony schematycznie jako czarna linia) w spoczynku (po lewej) i po obciążeniu dobutaminą (po prawej)*

A different algorithm for CAD identification calculating the maximum amplitude and maximum current-arrow magnitude of the subtracted ST-T waveform was published by Kanzaki *et al.*, showing a sensitivity and specificity of detecting CAD and normal control patients of 74.6% and 84.1%, respectively [34]. Van Leeuwen *et al.* used a spatio-temporal analysis of the MCG data and demonstrated that disturbances in cardiac electrogenesis resulting from CAD may be assessed using MCG signal analysis [35]. In a pathophysiological study using a 49-channel system from Physikalisch Technische Bundesanstalt, Berlin, Germany, together with a multiple time and area analysis, Morguet *et al.* showed that an accurate patient classification with regard to the extent of myocardial scar within the viable tissue in comparison to PET analysis was possible [36]. Last but not least, a very active Finnish group around Hänninen and Takala contributed substantially to the knowledge about the detection of myocardial ischaemia or healed myocardial infarction by analysing cardiac magnetic fields [25, 37-39].

Electrophysiological studies

In patients with arrhythmias surgical or catheter ablative strategies can be considered when antiarrhythmic medication is not effective or unfeasible. These procedures require previous exact localization of the arrhythmogenic substrate, which is currently achievable only with an electrophysiological (EP) study. However, besides being invasive and uncomfortable for the patient, EP studies are considerably time consuming and associated with relevant X-ray exposure for both the patient and the operator. Since 1985, magnetocardiographic mapping has been carried out in patients with severe ventricular arrhythmias, related to primary cardiomyopathy and ischaemic heart disease, for the purpose of non-invasive localization of the

arrhythmogenic focus or evaluation of patients at risk of sudden cardiac death. The first review about the localization of arrhythmogenic substrates was published in 1993 [40]. At that time, either single channel MCG or the first 4-channel system was used. However, in 1998, using the Helsinki multichannel system with an acceptable signal-to-noise ratio, Fenici *et al.* demonstrated that MCG is an effective clinical tool for non-invasive three-dimensional electro-anatomical imaging [41]. Accurate localization of the accessory pathway has been successfully performed in patients with Wolf-Parkinson-White (WPW) syndrome [42-46]. In these studies the accuracy of the non-invasive MCG localization of arrhythmogenic substrates has been evaluated by comparison with the results of conventional invasive catheter mapping.

Further electropathophysiological entities which can be detected by MCG are long-QT syndromes (LQTS) and Brugada syndrome (BS). Kandori *et al.* calculated current arrow maps from MCG signals of fetuses and adults and identified spatial current dispersions in both the QRS complex and T-wave, which could be used to make a prenatal diagnosis and to distinguish between different LQTS forms in adults [47-49]. It was also the group around Kandori who used a whole-heart electrical-activation diagram (W-HEAD) model for visualization of the spatial time-variant activation of the whole heart. They described activation of R-peak and posteromedian left ventricle excitation with half the amplitude of RBBB, as well as a low electrical conduction rate to the posterosuperior septum area as to be typical for BS [50]. Joung *et al.* showed that during depolarization the horizontal spatiotemporal activation graph location and maximum current angle of the r' wave were useful to distinguish BS from either right bundle branch block (RBBB) or normal findings. The magnetic dispersion was a more frequently observed finding in BS patients than in RBBB and normal patients during late repolarization [51].

Atrial fibrillation (AF) as the most common cardiac arrhythmia in clinical practice may be the most interesting field to be developed for MCG. The number of invasive ablative procedures is increasing but despite recent progress in techniques, current catheter ablation success rates fall short of expectations [52, 53]. Pioneering work using a single-channel system concerning MCG as a valuable tool for detection of supraventricular arrhythmias was done by Mäkijärvi *et al.* [54]. Twelve years later, multichannel systems demonstrated superior sensitivity compared to ECG for evaluation of atrial depolarization features [55]. Kim and associates introduced a novel beamforming method named Separative Surface Potential Activity Beamformer (sSPAB) for MCG source localization. This method, particularly useful for localization of rhythmic activities, obtained f-waves showing periodic oscillatory behaviour. By using the sSPAB, the f-waves were separated from other activations and the position of a re-entry circuit corresponding to the f-wave was localized. By separating the f-wave time-by-time and visualizing the activity map for action potentials for each time-separated waveform, the propagation trace of the AF could be inferred. After the MCG map-guided minimal AF surgery, the patient converted to sinus rhythm, well preserved after several follow-ups [56]. Finally, Jurkko *et al.* contributed substantially to refinement of MCG studies in AF. They described clinical subclasses of lone AF possessing distinct signal profiles of atrial depolarization, which may reflect pathogenetic variations and could have implications on diagnostics and therapy [57]. Moreover, with a 99-channel system, this group of researchers could show that MCG mapping is capable of distinguishing intra-atrial conduction pathways. In 27 patients undergoing catheter ablation of paroxysmal AF, MCG was recorded prior to determination of the LA activation sequence during sinus rhythm using invasive electroanatomical mapping. The MCG was able to identify three different pathways, the Bachmann bundle, the margin of the fossa ovalis, and the coronary sinus ostial region, as breakthrough of electrical activation from the right to the left atrium [58]. It could be further shown that susceptibility to paroxysmal lone AF is associated with propagation of the atrial signal to the LA via the margin of the fossa ovalis or multiple pathways. When conduction occurs via the Bachmann bundle, it is related to prolonged atrial activation. Thus altered and alternative conduction pathways may contribute to pathogenesis of lone AF [59]. Interestingly, in patients with persistent AF after cardioversion, MCG but not signal-averaged ECG or echocardiography identified electrophysiological alterations with incomplete recovery after 1 month in stable sinus rhythm [60].

The accuracy of non-invasive MCG localization of arrhythmogenic foci will turn out to be the crucial point for acceptance in clinical electrophysiology. Pioneering work concerning the exactness of biomagnetic localization was done by Moshage *et al.* [61]. The authors studied patients with ventricular arrhythmias by combining MCG data with magnetic resonance imaging (MRI). Analysing the magnetic field distribution at the onset of ectopic action potentials could localize the ectopic focus. In order to verify the exactness of orientation, MRI-visible non-magnetic pacing catheters were used for endocardial stimulation during MCG recording. Likewise, the orientation of stimulated ectopic beats was calculated from the magnetic field distribution and verified by MRI. The authors concluded that multichannel magnetocardiographic studies enable the completely non-invasive localization of ventricular arrhythmias [61]. The results were obtained in parallel by other investigators [62]. Given the data of Jurkko mentioned above, preoperative MCG may also be helpful for the interventional electrophysiologist going in for ablation of atrial fibrillation or flutter.

Another aspect of electropathophysiology is worth mentioning, which is identification of patients with cardiomyopathy or ischaemic heart disease at risk for ventricular arrhythmias. In 2000, Korhonen *et al.* published a first clinical MCG study in 100 patients with remote myocardial infarction (MI), 38 with and 62 without history of ventricular tachycardia (VT). High-resolution MCG and signal-averaged ECG as a comparative method were recorded. It could be shown that late fields of the MCG QRS complex indicate propensity to life-threatening VT in post-MI patients. This discriminative ability persists in the presence of severe left ventricular dysfunction, where ECG late potentials lose their informative value [63]. The authors completed the concept of risk prediction in patients with dilated cardiomyopathy, showing that the prolongation of the end part of the T wave was related to malignant ventricular arrhythmias [64]. In terms of ischaemic heart disease, the results were in line with smaller studies on MCG late potentials done by other groups [65-67]. However, the clinical value of late potential analysis is under discussion [68] and analysis with MCG appears not to be of significant advantage when compared to high-resolution ECG recordings [69]. In contrast, fragmented electrograms in infarcted myocardium, generated by viable cells within fibrotic regions, seem to be of higher predictive value [70]. Gödde *et al.* published one of the first studies on MCG mapping of QRS fragmentation [71]. They found patients with a history of VT characterized by increased QRS fragmentation and large areas of high fragmentation in 2D contour maps. In parallel, the group around Korhonen could show that in post-MI patients with left ventricular dysfunction, increased intra-QRS fragmentation in high-resolution magnetocardiography predicted arrhythmic events. They concluded that the analysis of intra-QRS fragmentation by MCG might assist in guiding therapy of post-MI patients, for example, by selecting those who would benefit most from prophylactic implantable cardioverter-defibrillator therapy [72].

Conclusions and future prospects

The MCG is a non-contact, non-invasive technique for the assessment of electromagnetic activity of the human heart. Theoretical considerations and comparative studies indicate different information content between MCG and ECG. Although many questions about cardiac pathophysiology and electrophysiology can be answered by MCG studies, measurement of biomagnetism is still only marginally recognized as a valuable tool.

Although MCG instrumentation (SQUIDs, MSR) and operation (liquid helium) are expensive and not available at the bedside, the gain of information drawn from the cardiac magnetic field is worth the effort. The MCG has a superior sensitivity for ischaemic myocardium both at rest and under stress. Therefore, it may change one's ideas of decision making about invasive procedures. Compared to scintigraphy, which is a cumbersome method with the need of radioactivity exposure to the patient, MCG is as easy as bicycle ergometry but with higher sensitivity. In terms of risk stratification for sudden cardiac death, it seems to be possible that MCG in the future will provide additional information as to which patient will not benefit from prophylactic defibrillator implantation. However, appropriate clinical studies are lacking. Most interestingly, MCG appears to be practical and informative in the diagnosis of cardiac arrhythmias, and has sufficient spatial accuracy necessary for clinical purposes. It seems realistic that MCG-based localization of arrhythmogenic spots may guide the operator's ablation catheter, e.g. in patients with relapsing AF after a first successful ablation procedure. There is enough room for fantasy which question in clinical cardiology remains to be answered by MCG.

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