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MAGNETOCARDIOGRAPHY IN ASSESSMENT OF VENTRICULAR ARRHYTHMIA RISK

by
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Academic Dissertation

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"When the press or the radio announces the sudden death of a celebrity from heart disease, a multitude of middle-aged persons runs out to make an electrocardiogram the next morning"

Frank N. Wilson, 1952

To Helena

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ABBREVIATIONS

BSPM	Body surface potential mapping
ECG	Electrocardiogram, electrocardiographic, electrocardiography
HRV	Heart rate variability
LAS	Low amplitude signal duration
LP	Late potential
LVEF	Left ventricular ejection fraction
M	Intra-QRS fragmentation index
MCG	Magnetocardiogram, magnetocardiographic, magnetocardiography
MI	Myocardial infarction
QRSd	Duration of the QRS complex
QT	QT interval
RMS	Root mean square amplitude
S	Intra-QRS fragmentation score
SAECG	Signal-averaged ECG
SCD	Sudden cardiac death
SD	Standard deviation
SQUID	Superconducting quantum interference device
TPE	T wave peak to T wave end interval
VF	Ventricular fibrillation
VPC	Ventricular premature complex
VT	Ventricular tachycardia

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which will be referred to in the text by their Roman numerals.

I Korhonen P, Montonen J, Mäkijärvi M, Katila T, Nieminen MS, Toivonen L. Late fields of the magnetocardiographic QRS complex as indicators of propensity to sustained ventricular tachycardia after myocardial infarction. J Cardiovasc Electrophysiol 2000;11:413-420.

II Korhonen P, Montonen J, Endt P, Mäkijärvi M, Trahms L, Katila T, Toivonen L. Magntocardiographic intra-QRS fragmentation analysis in the identification of patients with sustained ventricular tachycardia after myocardial infarction. PACE 2001;24:1179-1186.

III Korhonen P, Pesola K, Järvinen A, Mäkijärvi M, Katila T, Toivonen L. Relation of magnetocardiographic arrhythmia risk parameters to delayed ventricular conduction in postinfarction ventricular tachycardia. PACE, in press.

IV Korhonen P, Tierala I, Simelius K, Väänänen H, Mäkijärvi M, Nenonen J, Katila T, Toivonen L. Late QRS activity in signal-averaged magnetocardiography, body surface potential mapping, and orthogonal ECG in postinfarction ventricular tachycardia patients. Ann Noninvasive Electrocardiol, in press.

V Oikarinen L, Viitasalo M, Korhonen P, Väänänen H, Hänninen H, Montonen J, Mäkijärvi M, Katila T, Toivonen L. Postmyocardial infarction patients susceptible to ventricular tachycardia show increased T wave dispersion independent of delayed ventricular conduction. J Cardiovasc Electrophysiol 2001;12:1115-1120.

VI Korhonen P, Väänänen H, Mäkijärvi M, Katila T, Toivonen L. Repolarization abnormalities detected by magnetocardiography in patients with dilated cardiomyopathy and ventricular arrhythmias. J Cardiovasc Electrophysiol 2001;12:772-777.

1. ABSTRACT

Introduction Ventricular arrhythmias are, in various cardiac diseases, a common cause of sudden cardiac death (SCD). Although effective methods to prevent SCD have recently emerged, the continuing challenge is to identify the patients at greatest risk. This study investigated whether abnormal delayed conduction manifested as late fields and intra-QRS fragmentation in magnetocardiography (MCG) can identify postinfarction patients with a propensity to sustained ventricular tachycardia (VT) and how these parameters are related to various cardiac variables. The study also investigated how late fields and intra-QRS fragmentation parameters are related to delayed conduction recorded directly in the area surrounding the infarct scar. The association of late fields with abnormal ventricular repolarization and propensity to sustained ventricular arrhythmias was investigated both in patients with remote myocardial infarction (MI) and in patients with idiopathic dilated cardiomyopathy. This study also compared the ability of late fields and late potentials in signal-averaged ECG (SAECG) and body surface potential mapping (BSPM) to identify postinfarction VT patients.

Patients and Methods A total of 205 patients and 17 healthy controls were studied. Late field parameters were compared between postinfarction groups of 38 VT and 62 control patients, and both late field and intra-QRS fragmentation parameters were compared in otherwise similar but larger postinfarction VT and control groups. The relationships of these parameters to cardiac variables, especially left ventricular function, were investigated and the independent discriminative abilities of these parameters assessed. The relation of delayed ventricular conduction to late fields and intra-QRS fragmentation parameters was investigated in 22 patients, each with both a remote MI and a propensity to sustained VT, undergoing surgery to abolish the arrhythmia substrate. The association of late fields with repolarization abnormalities was investigated in 60 postinfarction patients (32 VT and 28 control patients, matched as groups for left ventricular ejection fraction) and in 49 patients with idiopathic dilated cardiomyopathy (18 with VT or ventricular fibrillation and 31 non-arrhythmia controls). The repolarization abnormalities were investigated with both MCG and 12-lead ECG. In 44 postinfarction patients with cardiac dysfunction (22 VT and 22 controls, matched as groups for left ventricular ejection fraction), MCG, SAECG, and BSPM were recorded, and parameter values for late fields (MCG) and late potentials (SAECG and BSPM) were computed and compared in VT identification.

Results In patients with previous MI, both late fields and intra-QRS fragmentation parameters in MCG differed significantly between patients with and without propensity to sustained VT. Differences between the groups were significant also in patients with extensive myocardial damage and low left ventricular ejection fraction. Late field and intra-QRS fragmentation parameters identified patients with VT propensity independently of cardiac variables and in VT patients correlated only modestly with left ventricular ejection fraction. In VT patients undergoing arrhythmia surgery, both late field and intra-QRS fragmentation parameters showed a correlation with delayed epicardial conduction in those patients with an anterior infarction scar. Abolition of the arrhythmia substrate rendered the parameter values almost similar to those of the postinfarction patients without VT propensity. The later part of the T wave interval in MCG was prolonged in patients with sustained ventricular arrhythmias both in those with remote MI and in those with dilated cardiomyopathy, whereas late fields were discriminative only when the arrhythmia propensity was associated with the infarct scar. In ECG, the later part of the T wave interval and conventional QT_{end} dispersion were larger in postinfarction VT patients, whereas none of the repolarization parameters differed between the arrhythmia and control patients in dilated cardiomyopathy. In postinfarction patients with cardiac dysfunction, the late fields performed equally well in comparison to late potentials in SAECG and BSPM in the identification of VT propensity.

Conclusions In conclusion, MCG parameters associated with delayed and inhomogeneous conduction in postinfarction ventricles seem significantly to differ between patients with and without VT propensity. The overlap in parameter values between the groups was in part due to the large infarct scar itself, influencing the parameters towards more abnormal values. Although patients with large infarct scars but without documented VTs are at increased risk for ventricular arrhythmias, complete discrimination between VT and non-VT patients may be impossible. However, combining MCG parameters with other arrhythmia risk indicators such as heart rate variability and measures of abnormal repolarization may improve identification of patients at risk for sustained ventricular arrhythmias. The results of the present study suggest that abnormalities in both depolarization and repolarization periods are important in the genesis of postinfarction ventricular arrhythmias. On the other hand, in dilated cardiomyopathy, only measures of repolarization abnormalities showed any differences between arrhythmia and control groups, thus highlighting their importance in the arrhythmogenesis in this disease.

This was apparently the first series of studies to show that a novel MCG technique can identify propensity to ventricular arrhythmias in two common heart diseases, coronary artery disease and nonischemic dilated cardiomyopathy.

2. INTRODUCTION

Although sudden cardiac death (SCD) can complicate practically any cardiac pathology, in western civilizations a great majority of the cases are due to coronary artery disease, because of its high prevalence. In many of these patients, the cause of SCD is severe transient ischemia or acute myocardial infarction (MI) resulting in ventricular fibrillation (VF). If the patient is successfully resuscitated, and the ventricular function is spared, treatment of myocardial ischemia will usually prevent SCD recurrence (Kehoe et al. 1988). In some of the patients, however, SCD is caused by a ventricular arrhythmia associated with a chronic infarct scar in the absence of significant ongoing ischemia in the spared myocardium. In this patient group, treatment of ischemia will not abolish the propensity to life-threatening ventricular arrhythmias. On the other hand, recent evidence shows that in these patients, implantable defibrillators are effective in preventing SCD (Buxton et al. 1999, Moss et al. 2002). The continuing challenge is how to predict which postinfarction patients will most likely benefit from this treatment.

Both experimental and clinical studies have revealed in these patients the important role of delayed conduction at the border zone of the infarct scar in the genesis of ventricular arrhythmias (Klein et al. 1982, Mehra et al. 1983). Delayed and inhomogeneous conduction can be recorded noninvasively by high-resolution electrocardiographic (ECG) techniques (signal-averaged ECG, SAECG) (Simson 1992). Increased spatial dispersion of ventricular repolarization measured as interlead variability of QT interval in 12-lead ECG is associated with postinfarction ventricular arrhythmias, as well (Pye et al. 1994). Similarly to other noninvasive risk assessment techniques, SAECG and QT dispersion have shown high sensitivity and negative predictive value, while their specificity and positive predictive value have remained low. Consequently, risk prediction methods showing promise at patient-population level do not yield sufficient discrimination at the level of the individual patient. New methods for the assessment of abnormal slow conduction and increased dispersion of repolarization may therefore be of value in postinfarction arrhythmia risk stratification.

Magnetocardiography (MCG) is a noninvasive method which records the magnetic field generated by cardiac electrical activity. Although the first MCG was recorded back in 1963 (Baule and McFee 1963), only the past decade has witnessed the evolution of registering devices suitable for larger-scale patient measurements in the hospital environment. MCG has some interesting features as regards postinfarction arrhythmia risk assessment. The effect on the MCG signal of the tissues lying between the heart and the body surface is smaller than on ECG, which may be advantageous in the registrations of very low amplitude electrical activity. In addition, preliminary data suggest that MCG may be especially sensitive to abnormalities in the repolarization period (Lant et al. 1990).

The aim of the present study was to investigate MCG in the identification of propensity to sustained ventricular arrhythmias among patients with heart disease. The substudies assessed the ability of MCG parameters to dicscriminate between VT and non-VT patients, the parameters' electrophysiological basis, and their relations to several cardiac variables.

3. REVIEW OF THE LITERATURE

3.1. Ventricular arrhythmias and sudden cardiac death

3.1.1. In general

SCD means natural death due to cardiac causes, preceded by sudden loss of consciousness within one hour of the onset of acute symptoms (Myerburg and Castellanos 1997). In many studies, unexpected death during sleep is included in this category, as well. In a recent population-based study, the mean one-year incidence of SCD in the 20- to 75-year age group was approximately 1/1000 and accounted for 18.5% of all deaths. In the same population, only 6% of the resuscitated victims were discharged alive from the hospital, highlighting the importance of risk prediction and of the optimization of out-of-hospital resuscitation (Vreede-Swagemakers et al. 1997). The major cause of SCD is ventricular tachyarrhythmia leading to VF (Kempf and Josephson 1984, Bayés de Luna et al. 1988). In severe cardiac dysfunction, other important mechanisms of death are bradycardia and electromechanical dissociation (Luu et al. 1989).

3.1.2. Mechanisms of ventricular arrhythmias

During normal cardiac rhythm−sinus rhythm−the electrical impulse is generated in the sinoatrial node in the right atrium, from which it spreads to the left atrium. Non-conducting fibrous tissue separates the atria and ventricles except for a specialized conduction system consisting of the atrioventricular node, the bundle of His, the bundle branches, and the Purkinje fibers. From the Purkinje fibers the activation spreads to the ventricular myocardium of the right and left ventricles. Besides the sinoatrial node, other parts of the conduction system also have the potential to fire independently and thus act as pacemakers in case of marked slowing of the sinus rate.

Ventricular arrhythmias can arise in the specialized conduction system distal to the bifurcation of the His bundle, in ventricular myocardium, or in combinations of both tissue types (Shenasa et al. 1993). Three mechanisms are recognized in the genesis of ventricular arrhythmias; *abnormal automaticity*, *triggered activity,* and *reentry*.

Abnormal automaticity refers to a situation in which a group of cells not normally acting as pacemaker cells generates impulses independently. In comparison to normal automaticity, this occurs at markedly less negative resting membrane potentials. This reduction in the potential can be caused by several conditions including ischemia and acidosis, as well as by increased circulating catecholamine levels encountered in such condition as cardiac failure.

Triggered activity is generated by afterdepolarizations, which are oscillations in the membrane potential initiated (triggered) by one or more preceding action potentials. These oscillations are further divided into *early* and *delayed afterdepolarizations*. Early afterdepolarizations occur during the plateau of the repolarization phase of the action potential, and delayed afterdepolarizations after the termination of the repolarization. The amplitudes of early afterdepolarizations tend to increase at slower heart rates, resulting in augmented initiation of triggered arrhythmias (Damiano and Rosen 1984). Early afterdepolarizations are related to a specific type of polymorphic ventricular tachycardia, torsade de pointes, which is a typical arrhythmia in the long QT syndrome (Shimizu et al. 1991). Evidence also stems from animal studies that, after myocardial infarction, triggered activity from both early and delayed afterdepolarizations is a potential VT mechanism (Qin et al. 1996).

Reentry is the mechanism most often involved in postinfarction ventricular arrhythmias. The term “reentry” implies that part of the myocardium (or the entire heart) is reexcited by a circulating impulse. The basic electrophysiologic requirements for reentry are unidirectional conduction block, slow conduction, and a pathway for impulse propagation. A simple form of reentry circuit consists of a fast conducting component with a longer refractory period and a slow conducting component with a shorter refractory period. A properly timed impulse becomes blocked in the fast conducting component and propagates through the slow conducting pathway. By the time the impulse arrives at the distal ends of the pathways, the refractory period of the fast conducting part has expired, allowing the impulse to return to the proximal end of the pathway. A reentrant circuit is thus established. A clinically important feature in reentrant arrhythmias is inducibility following the properly timed extrastimuli which are utilized in electrophysiologic testing (Buxton et al. 2000).

Tachycardias in Wolff-Parkinson-White syndrome are an example of reentrant arrhythmias in which the pathways are fixed anatomical barriers. In contrast to such an *anatomical* reentry, *functional* reentry lacks confining anatomical structures and can be due to dispersion of excitability, refractoriness, and impulse propagation (El Sherif 1995). Several types of functional reentry have been described, including the *figure-of-eight* model, in which the circuit consists of clockwise and counterclockwise wavefronts around two functional arcs of block rejoining into a central common slowly conducting pathway (El-Sherif, 1988). Another model is the *leading circle* hypothesis by Allessie and coworkers, in which the reentrant circle propagates through fibers with shorter refractory periods, constantly blocking in the central area exhibiting longer refractory periods (Allessie et al. 1977). Other models include the *anisotropic* model, featuring variations in conduction velocities and the time course of repolarization, and the *spiral wave model*, relating myocardial spiral wave activity to the onset of reentrant arrhythmias (Davidenko 1994).

3.2. Ventricular arrhythmias and sudden cardiac death in coronary artery disease and in postinfarction patients

Although ventricular arrhythmias and SCD may complicate practically any cardiac disease, in the majority of these, the background is coronary heart disease (Zipes and Wellens 1998). Due to wide application of thrombolytic therapy, improved pharmacological therapy for heart failure,

and specialized units for coronary patients, all in the 1990's, one-year mortality after acute MI has fallen to 5 to 7%, and of all deaths in this patient group, the proportion of SCD is 25 to 30% (Rouleau et al. 1996, Touboul et al. 1997).

In patients with coronary artery disease but no prior or acute infarction, severe ischemia can provoke ventricular arrhythmias. Severe ischemia results in spatially inhomogeneous metabolic and ionic changes leading into dispersion of excitability and repolarization. These changes, in turn, favor the occurrence of reentrant arrhythmias. Severe ischemia is also associated with acidosis and increased catecholamine levels that may cause arrhythmias by abnormal automaticity and triggered activity. The clinical arrhythmias most often seen in the context of acute ischemia are polymorphic VT and VF.

In patients with an infarct scar, ventricular arrhythmias in the absence of significant ischemia are often reentrant in origin (DeBakker et al. 1988). In the border zone of myocardial necrosis, patchy fibrosis is interspersed with viable myocardial tissue. These structural alterations lead to delayed conduction and to local unidirectional conduction blocks serving as substrates for reentrant VTs. The clinical arrhythmia most often associated with chronic infarct scars is sustained monomorphic VT.

Although either severe ischemia or chronic arrhythmia substrate can be assumed in many instances to be the dominant mechanism, these two mechanisms interact. Using a canine model, Furukawa and coworkers (1991) found that even moderate ischemia increased the inducibility of sustained VT in a 3-week-old experimental MI. Besides ischemia, several other mechanisms may potentially alter the electrical milieu in the stable arrhythmia substrate and precipitate life-threatening ventricular arrhythmias. These include abrupt changes in neurohormonal, in electrolyte, and in acid-base balance, as well as hypoxemia and proarrythmic effects of medications.

3.3. Postmyocardial infarction risk stratification

At present, accurate identification of postinfarction patients at increased risk for ventricular arrhythmias has become increasingly important because implantable defibrillators have proven effective in the prevention of SCD (Moss et al. 1996, Buxton et al. 1999). Several techniques are commonly used in postinfarction arrhythmia risk stratification.

3.3.1. Left ventricular function and infarct artery patency

Although the number of patients with large MIs has diminished in the thrombolytic era, left ventricular function has remained a significant predictor of both total mortality and arrhythmic events. In a study with 68% of 301 MI patients treated with intravenous thrombolysis, left ventricular ejection fraction (LVEF) < 40% was the best predictor of arrhythmic events in the first year after MI (McClements and Adgey 1993). Accordingly, Andresen and coworkers (1999) found that patients with both LVEF > 40% and normal Holter recording had a very low risk for ventricular arrhythmias. The opening of infarct-related arteries has been proposed as one mechanism associated with the greatly improved outcome of MI patients in the thrombolytic era. In fact, in the 1994 study by Hohnloser and coworkers, having patent infarct-related artery was an independent negative predictor of arrhythmic complications. Due to thrombolytic therapy and interventions, however, the patients in their study had well-preserved left ventricular function, and it is not clear whether these findings will apply to patient populations with marked cardiac dysfunction. The data from several studies indicate that low LVEF is a noninvasive marker for increased risk for arrhythmic death with a cut-point value of 40%. A well-defined left ventricular wall aneurysm is an additional indicator for arrhythmia propensity (Meizlish et al. 1984).

3.3.2. Ambulatory ECG

An increased number of ventricular premature complexes (VPC) and runs of nonsustained VTs in ambulatory ECG are recognized as markers of electrical instability after MI. They predict arrhythmic events, especially in patients who also have low LVEF (Schulze et al. 1977). The mechanism explaining the arrhythmogeneity of VPCs is their ability to initiate a reentrant VT by entering a potential reentry circle at a critical moment. Thrombolysis reduces the number of VPCs (Theroux et al. 1989), but in the thrombolytic period their predictive value has remained unchanged. In fact, Statters and coworkers (1996) found VPC frequency more predictive in patients who had received thrombolysis than in those who had not, but that the optimal frequency for dichotomy was higher in the former suggests that their tolerance of VPCs was better. In a large thrombolytic treatment study, VPCs > 10 / hour independently predicted both total mortality and SCD, whereas runs of nonsustained VTs did not (Maggioni et al. 1993). On the basis of the existing data, it is evident that ventricular extrasystoles and runs are related to arrhythmic events, but at present no consensus exists on the critical number of such findings in

the ambulatory ECG. In addition, Senges et al. (2002), in their postinfarction study, found that nonsustained VTs in ambulatory ECG show poor reproducibility, which reduces their value in risk stratification.

3.3.3. Heart rate variability

Heart rate variability (HRV) is widely used as a measure of cardiac autonomic status, and a decreased value reflects either sympathetic dominance or decreased vagal tone. In the chronic phase of MI, a reduced HRV is a strong predictor of mortality independent of left ventricular function and ventricular ectopic activity (Kleiger et al. 1987, Cripps et al. 1991). Both time domain and frequency domain analyses of HRV identify patients with a propensity to sustained VT (Huikuri et al. 1995), and reduced HRV seems to predict both arrhythmic and nonarrhythmic death (Hartikainen et al. 1996). Although the positive predictive accuracy of HRV is not high, it can be improved by combining it with other noninvasive arrhythmia risk parameters (Farrell et al. 1991).

3.3.4. Baroreflex sensitivity

Baroreflex sensitivity evaluates the reflex autonomic responses, in contrast to HRV, which reflects the tonic autonomic control. Vagal reflexes are thought to protect the heart from the arrhythmias precipitated by sympathetic hyperactivity. Depressed baroreflex sensitivity is thus a marker of the reduced cardioprotective effect of the parasympathetic nervous system. The method most often used to evaluate baroreflex sensitivity is correlation of the blood pressure rise induced by an alphamimetic agent, phenylephrine, with the increase produced in cardiac cycle length. Baroreflex sensitivity correlates with the extent of the coronary artery disease but not with LVEF (La Rovere et al. 1988). In postinfarction patients, the reduced baroreflex sensitivity correlates with the inducibility of sustained VT in electrophysiologic study (Farrell et al. 1991). In the ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) study, HRV and baroreflex sensitivity were equally predictive of cardiac death, and the risk was higher when both showed abnormal values. Mortality in that study was relatively low, with no incidence of sudden death reported (La Rovere et al. 1998).

3.3.5. Electrophysiologic study

Because postinfarction ventricular arrhythmias are most often reentrant in origin, the inducibility of a sustained VT in programmed electrical stimulation is considered to indicate the presence of a permanent arrhythmia substrate. In such patients, coronary revascularization alone does not abolish the potential reentrant circuits (Kelly et al. 1990). In general, the inducibility of sustained VT in postinfarction patients has varied between 20% and 40% depending on patient selection and on stimulation protocols. Although the positive predictive value of electrophysiologic study in unselected postinfarction patients is rather low, it is greatly improved when targeted at patients with cardiac dysfunction (Bourke et al. 1991). The negative predictive accuracy in those patient series reported has usually been excellent. Although programmed electrical stimulation is at present the best predictor of arrhythmic events, poor availability and the invasive nature of the study make it unsuitable as a screening method for large patient cohorts. On the other hand, combining data from noninvasive studies may help to identify a high-risk subgroup to undergo programmed stimulation (Pedretti et al. 1993).

3.3.6. Dispersion of ventricular repolarization

Experimental studies have shown that spatial dispersion of ventricular repolarization facilitates induction of ventricular arrhythmias, and the same factors that favor arrhythmia occurrence tend to cause increased dispersion (Han and Moe 1964, Kuo et al. 1983). Adjacent myocardial regions with different repolarization periods may lead to nonuniform conduction and functional conduction blocks, thus giving rise to reentrant arrhythmias. Data from clinical studies suggest that the interlead variability of QT interval in body surface leads may reflect the regional variability in ventricular recovery time (Mirvis 1985). This variability, termed QT dispersion, is usually defined as the difference between the longest and the shortest QT interval. However, recent studies have shown that the time interval between the peak and the end of the T wave serves as an index of transmural dispersion of repolarization (Shimizu and Antzelevitch 1997). Transmural heterogeneities in repolarization are more abrupt than axial ones and may represent a more dangerous substrate for ventricular arrhythmias. Experimental studies have shown that dispersion of monophasic action potential durations correlates more closely with the T-peak to T-end interval than with measures of QT dispersion (Zabel et al. 1995).

Several studies have assessed the value of repolarization abnormalities in postinfarction risk assessment. Pye and coworkers (1994) reported a significantly larger QT dispersion in postinfarction patients with than without sustained VT, although substantial overlap existed between the groups. Perkiömäki and coworkers (1995) compared QT dispersion in healthy controls and postinfarction patients with and without sustained ventricular arrhythmias. QT dispersion in the arrhythmia group was significantly larger than in the non-arrhythmia and control groups and was associated with arrhythmia propensity independently of left ventricular function and other clinical parameters. Notwithstanding these findings, the predictive value of the repolarization heterogeneities is not well established. In a prospective postinfarction study, several repolarization variables in 12-lead ECG including QT dispersion and T-peak to T-end interval failed to predict subsequent arrhythmic events (Zabel et al. 1998). One possible explanation for this lack of prediction may have been the inadequate resolution of local differences in repolarization in 12-lead ECG. However, data from recent studies suggest that novel repolarization descriptors assessing T wave morphology in 12-lead ECG may have value in risk stratification (Zabel and Malik 2001, Zabel el al. 2002).

3.3.7. Signal-Averaged ECG

3.3.7.1. Electrophysiologic basis of ventricular late potentials

Durrer and coworkers in their 1964 postinfarction animal study reported delayed conduction in the normal muscle surrounding transmural infarction, which they termed “postinfarction block.” Later, in 1973, Boineau and Cox demonstrated that prolonged ischemia resulted in nonuniformly distributed delayed and fragmented activity leading to reentrant VPCs. A pioneering study with a canine model of chronic MI showed that the delayed and fragmented activity in the infarct zone could bridge the entire diastolic period, initiating a reentrant VT (El-Sherif et al. 1977). A spontaneous reentrant VT was especially associated with Wenkebach-type conduction in the infarct area. The authors suggested that their electrophysiologic findings could be explained by electrical activity traveling through islands of viable cells interspersed among areas of myocardial necrosis. Viable but partially depressed myocardium could show delayed conduction and unidirectional block at certain sites and at certain cycle lengths, thus providing the prerequisites for reentry. Later, Gardner and coworkers (1985) provided the anatomic basis for these electrophysiologic findings by recording fragmented electrograms in the infarct areas where

individual myocardial fibers were separated by ingrowth of connective tissue, all of this leading to slow and inhomogeneous conduction.

Berbari and coworkers in 1978 were the first to show that delayed potentials in epicardial electrograms could be recorded from the body surface and suggested this as a noninvasive indicator of propensity to VT. Detection of such low-amplitude deflections on a body surface ECG is based on signal-averaging and high-pass filtering. Signal-averaging effectively raises the signal-to-noise ratio, and high-pass filtering suppresses the low-frequency ST segment and T wave while preserving the delayed activity comprising higher frequencies. Later, Simson and coworkers introduced bi-directional filtering to improve the analysis of SAECG and showed strong correlations between the durations of directly recorded ventricular electrograms and QRS in the signal-averaged body surface ECG (Simson et al. 1981). Because abnormal low amplitude activity often extends beyond the end of the non-averaged surface ECG, it is therefore called late potential (LP).

3.3.7.2. Ventricular late potentials in post-myocardial infarction risk stratification

The prevalence of LPs after acute MI ranges from 25 to 45% (Simson 1992). Occluded infarct arteries are associated with the appearance of LPs (de Chillou et al. 1991), and thrombolytic therapy is associated with a reduction in their incidence (Gang et al. 1989). In addition, some studies have associated LPs with the presence of left ventricular aneurysm and reduced LVEF (Zimmerman et al. 1985), whereas others have not (Gomes et al. 1987). In postinfarction patients with ventricular aneurysm and a propensity to sustained VT, aneurysmectomy is associated with the disappearance of LPs and of VT propensity (Rozanski et al. 1981).

In postinfarction patients, the LPs are related to the propensity to sustained VT independently of clinical variables (Kanovsky et al. 1984). The presence of LPs predicts inducibility of sustained VT in the electrophysiologic study, indicating association with propensity to reentrant ventricular arrhythmias (Denniss et al. 1986).

Prospective studies have shown LPs to predict ventricular arrhythmias and SCD after MI independently of left ventricular function and of arrhythmias in Holter ECG (Kuchar et al. 1986, Steinberg et al. 1992). Although the sensitivity and negative predictive accuracy of LPs has usually been good, the positive predictive accuracy has reached only 15 to 20%. On the other hand, combining LPs with other noninvasive methods such as HRV and measures of left

ventricular function has resulted in improved predictability (Farrell et al. 1991, Gomes et al. 2001).

The conventional analysis method in SAECG is *time domain* analysis, in which LPs are quantified by the filtered QRS duration, amplitude of the last 40 ms of QRS, and duration of the low amplitude signal below 40 μV (Breithardt et al. 1991). Invasive data from VT patients has, however, shown that the majority of the myocardium responsible for reentrant VT depolarizes before the last 40 ms of QRS, so that methods limited only to this part fail to detect most of the delayed conduction (Hood et al. 1992). Thus, on the body surface ECG, the abnormal potentials are buried in the QRS complex. Moreover, discrimination between noise and LPs may be difficult, and patients with a bundle branch block in 12-lead ECG are usually excluded from analysis. Analysis methods have therefore been developed that aim at extracting the abnormal fragmented electrical activity from the normal smooth depolarization. Most of these methods are based on the assumption of differing frequency content for the delayed conduction and are thus termed *frequency domain* analysis methods. Combining time- and frequency-domain analyses, Vázquez and coworkers found prediction of arrhythmic events in postinfarction patients improved compared to that of either method used alone (Vázquez et al. 1999). In addition to frequency domain analysis, abnormal intra-QRS potentials detected as notches and slurs during the entire QRS complex have been able to predict arrhythmic events (Lander et al. 1997).

3.3.8. Body surface potential mapping

In comparison to 12-lead ECG, BSPM allows a more accurate description of the thoracic distribution of cardiac potentials. This is attributed to more detailed regional information derived from the unipolar electrodes attached to 30 to 120 thoracic sites often covering the back, as well. The data registered with BSPM can be represented as wave amplitudes, intervals, or morphologies analogous to 12-lead ECG. In addition, the mapping results can be displayed as isopotential and isochrone maps, whose shapes and dynamics may yield information not apparent in the conventional presentation mode.

The first BSPM recordings with fewer than 20 electrodes were performed at the very dawn of the electrocardiographic-technique era more than one hundred years ago. Later, Taccardi (1963) attempted to correlate the body surface potential maxima and minima with the location of depolarization wavefronts in the ventricles. The localization capability of BSPM has proven

useful in the localization of accessory pathways (Dubuc et al. 1993) as well as in the localization of the sites of origin of VTs (Sippensgroenewegen et al. 1994). Studies in patients with transient ischemia and acute MI have shown superior detection with the use of BSPM, with the most sensitive recording locations often being outside the standard precordial lead positions (Kornreich et al. 1993, Hänninen et al. 2001).

3.3.8.1. Body surface mapping of ventricular late potentials

A few studies have investigated the detection of ventricular LPs with BSPM, often comparing it to conventional three-lead SAECG. An experimental study using a canine postinfarction model compared QRS durations in 64-lead BSPM and SAECG to directly recorded epicardial electrograms. QRS durations in BSPM were longer and correlated more strongly with epicardial electrograms, especially in cases with longer electrogram durations (Freedman et al. 1991). That study did not, however, investigate the relation of the QRS durations to spontaneous or inducible ventricular arrhythmias. Accordingly, when Sasaki and coworkers (1994) compared BSPM and SAECG in a postinfarction patient population, they could report that BSPM was superior in identifying patients with fragmented electrograms in ventricular endocardial catheter mapping, but they did not investigate the association of their findings with ventricular arrhythmias. A study comprising postinfarction patients with and without sustained VT or cardiac arrest found BSPM with a 28-lead array able to distinguish between the patient groups with a 70% sensitivity and 84% specificity. The corresponding figures for SAECG were 59% and 86% (Ho et al. 1993).

3.4. Nonischemic dilated cardiomyopathy

3.4.1. In general

Dilated cardiomyopathy is a myocardial disease characterized by dilatation and impaired myocardial contractility of the left ventricle or both ventricles (Richardson et al. 1996). The epicardial and intramural coronary arteries are normal or, in cases of stenoses, the ventricular dilation and dysfunction are disproportionate to arteriolar changes. Histologic changes are generally nonspecific, with replacement of myocardial tissue by fibrosis in the majority of patients (Roberts et al. 1987). Intraventricular conduction disturbances, especially left bundle branch block, is a common finding in ECG, with chronic atrial fibrillation common, as well. Prevalence has been estimated as 5 to 8 cases per 100 000 population, but the true number may

be higher due to underreporting of asymptomatic patients (Dec and Fuster 1994). A strong gender association exists, with approximately three-quarters of the patients being male. While in the majority of the cases the etiology is unknown (idiopathic dilated cardiomyopathy), a number of specific causes have been identified, including genetic, viral, and immunological causes, plus alcohol and other toxic factors.

3.4.2. Sudden cardiac death in dilated cardiomyopathy

Although spontaneous improvement in ventricular function is possible (Figulla et al. 1985), the natural course of dilated cardiomyopathy is usually progressive, with increasing left ventricular dilatation and worsening pump failure. The mode of cardiac death in dilated cardiomyopathy is most commonly circulatory failure due to progressive deterioration of left ventricular function or SCD. The proportions of SCD in dilated cardiomyopathy vary widely between different studies. Differences in definitions of SCD, inclusion of nonclassifiable deaths in the sudden death category, patient selection, and pharmacologic interventions probably explain this variation. In a meta-analysis of 14 studies including 1432 patients, the mean mortality rate in a 5-year follow-up was 42%, with 28% of the deaths classified as sudden (Tamburro and Wilber 1992). Although data concerning the mechanisms of SCD in these patients are sparse, VT degenerating into VF or primary VF is considered the most important mechanism.

3.4.3. Mechanisms of ventricular arrhythmias in dilated cardiomyopathy

In dilated cardiomyopathy cases, the ventricular arrhythmia more often is VF or polymorphic VT (Grimm et al. 1998) than in postinfarction patients, in whom a monomorphic VT is the most prevalent form. Irregular myocardial replacement with fibrosis may lead to heterogeneous repolarization, rendering the heart vulnerable to ventricular arrhythmias. Using monophasic action potential mapping in patients with dilated cardiomyopathy, Dinerman et al. (1977) found nonuniformity of total ventricular recovery to be a result of dispersion of both local activation and refractory periods. Increased myocardial fiber stretch in a dilated ventricle, leading to shortening of refractoriness and load-dependent dispersion of refractoriness, may contribute to the occurrence of ventricular arrhythmias (Calkins et al. 1989).

The findings in the long QT syndrome suggest that increased transmural dispersion is a typical finding when the arrhythmia is associated with abnormal repolarization, which results in

polymorphic VT (Shimizu and Antzelevitch 1998). Using human cardiac specimens, Koumi and coworkers reported in 1995 that the late repolarization phase is prolonged in patients with dilated cardiomyopathy compared to this phase in healthy controls and in those with ischemic cardiomyopathy. This prolongation was at least partly due to decreased conductance of the inwardly rectifying K^+ channels.

In patients with congestive heart failure, the sympathetic nervous system is activated, leading to elevated levels of circulating catecholamines (Cohn et al. 1984), which can provoke ventricular arrhythmias. Finally, pharmacologic agents used to treat cardiac diseases may be arrhythmogenic either indirectly (such as diuretics causing hypokalemia), or directly (such as antiarrhythmic agents inducing proarrhythmic electrophysiologic changes).

3.4.4. Assessment of the risk of ventricular arrhythmias and sudden cardiac death in dilated cardiomyopathy

In dilated cardiomyopathy, the diversity of possible mechanisms makes prediction and prevention of sudden death a difficult task. In addition, the progressive nature of the disease, leading to increasing fibrosis and dilatation, may diminish the value of risk stratification. Several clinical features as well as specific arrhythmia risk markers have, however, been applied in attempts at risk stratification. These will be dealt with in more detail in the following chapters.

3.4.4.1. Clinical parameters, ambulatory ECG, and electrophysiologic study

Although in dilated cardiomyopathy, many clinical and hemodynamic factors are related to total mortality, few of them are valuable in prediction of ventricular arrhythmias and of sudden death. The NYHA III-IV functional class is related to total mortality but not necessarily to the risk of sudden death (Romeo et al. 1989). In contrast, Brembilla-Perrot and coworkers (1991) found that syncope was a significant predictor of sudden death in these patients. A high incidence of appropriate shocks was found in those patients with dilated cardiomyopathy and syncope who had received an implantable defibrillator despite a negative electrophysiologic study (Knight et al. 1999). The same report also indicated that syncope in dilated cardiomyopathy is more often due to ventricular arrhythmia than to bradycardia.

In dilated cardiomyopathy, both increased ventricular ectopy and nonsustained VTs are common, with more than 40% of all patients having at least one event of nonsustained VT in a

24-hour Holter recording, and most of these episodes are asymptomatic (Tamburro and Wilber 1992). The prognostic value of spontaneous nonstustained ventricular arrhythmias has been under intensive investigation, and the results are controversial. In a study by Meinertz et al (1984), 93% of patients had an increased number of VPCs, and 36% had runs of nonsustained VTs. The number of VPCs correlated inversely with LVEF. Patients who died suddenly had had significantly more episodes of nonsustained VT, ventricular extrasystoles, and couplets than did patients who died of heart failure. Similarly, Romeo et al. (1989) found complex ventricular arrhythmia to be the only independent predictor of sudden death. Contrary to these findings, von Olshausen et al. (1988) did not report ventricular arrhythmias to predict sudden cardiac death; in fact, VT appeared more often in patients who died of heart failure than in those with SCD.

Thus, it seems that although Holter ECG is a sensitive tool in detecting ventricular arrhythmias in these patients, the significance of Holter findings in assessment of the risk of ventricular arrhythmias and of sudden death remains to be assessed.

Programmed ventricular stimulation, shown to predict future arrhythmic events after myocardial infarction, has not proven useful in dilated cardiomyopathy. Although monomorphic VT is frequently inducible in patients who present with this arrhythmia (Poll et al. 1986), noninducibility in patients with no clinical VT is common and does not indicate low risk for SCD (Meinertz et al. 1985).

3.4.4.2. Signal-Averaged ECG

Although LPs in SAECG have shown prognostic value after myocardial infarction, the results in dilated cardiomyopathy have been less conclusive. The prevalence of LPs has varied markedly between the reported series at least partly due to differing criteria for a positive finding, especially in patients with a bundle branch block. In addition, some studies have excluded patients with previous VTs, whereas others have not. Middlekauff and coworkers (1990) found LPs in only 14% of their dilated cardiomyopathy patients compared to 40% with remote MI. LPs predicted sudden death in neither group. On the other hand, their patients had advanced heart failure, and other mechanisms than ventricular arrhythmias may have been important in the sudden death. Mancini and coworkers reported in 1993 a very low incidence of sustained VT and SCD in patients with normal SAECG. In their study, SAECG was not performed in patients with bundle branch block. Results of a 2001 study by Goedel-Meinem et al. with its 7-year follow-up

showed a high rate of SCD, with the LP as a significant prognostic factor. In 2000 Fauchier and coworkers also had found LPs to predict major arrhythmic events and all-cause mortality. Thus, the most recent evidence suggests that LPs may be useful in risk stratification, but no agreement exists on the criteria for a positive result in dilated cardiomyopathy.

3.4.4.3. Repolarization abnormalities

QT interval dispersion as a risk marker in dilated cardiomyopathy has yielded conflicting results. Grimm and coworkers (1996) found more QT dispersion in patients with than without arrhythmic events but found marked overlap between the groups. In the 1996 study by Fei et al., as well QT dispersion failed to predict sudden death; their incidence of sudden death was very low, at least partly because patients with bundle branch block were excluded. On the other hand, in another prospective study, QT dispersion was the only independent predictor of sudden death (Galinier et al. 1998). Recently, microvolt-level T wave alternans in 12-lead ECG (Adachi et al. 1999) and dispersion of the recovery time (interval from QRS onset to the moment of maximal dV/dT in the ST segment) in BSPM have shown promise in the identification of patients with dilated cardiomyopathy and VT (Aiba et al. 2000).

3.5. Biomagnetism

3.5.1. In general

The movement of charged ions such as Na^+, K^+, and Ca^{2+} across cell membranes generates electrical potentials on the body surface which can be detected by electrographic mapping methods such as ECG. The same ion fluxes also generate electrical currents, which in turn give rise to magnetic fields. These magnetic fields can be registered outside the body, and measurement of the biomagnetic fields generated by the electrical activity of the human body is termed *biomagnetism*. The magnetic field strength is quantified with field density, whose unit is the Tesla (T). In comparison to body surface potential differences, the magnetic fields seem to be less influenced by the conductivity inhomogeneities of body tissues such as skeletal muscle layer (Bruder et al. 1994). This is especially advantageous when the electrical activity in question is of very low amplitude, or when the registration result is used in localization of the electrical activity inside the body that produces the registered external magnetic field (Mäkijärvi et al. 1992). On the other hand, the magnetic fields of the body are weak. For example, the magnetic field of the

heart is < 100 picotesla (1 pT = 10^{-12} T) and that of the brain ~ femtotesla (1 fT = 10^{-15} T) (the earth's magnetic field is ~ 10^{-4} T), and therefore some kind of shielding from external magnetic fields is usually necessary. Biomagnetic measurements have been performed on several organs with electrical activity including the brain (magnetoencephalogram, MEG), eye (magnetooculogram, MOG), and peripheral nerves (magnetoneurogram, MNG).

3.5.2. Magnetocardiography

3.5.2.1. History

Magnetocardiography refers to the registering and interpretation of the magnetic fields generated by cardiac electrical activity; the registration result plotted versus time is called the *magnetocardiogram* (MCG). Baule and McFee registered in 1963 the first MCG using a set of two copper coils and no external shielding. In 1967, Cohen performed MCG measurements in a magnetically shielded room to cancel out the effects of external magnetic fields such as the earth's magnetic field and that of urban traffic. A significant step forward was the invention and implementation of the SQUID (Superconducting Quantum Interference Device) in liquid helium at 4.2 K (-269°C) (Cohen et al. 1970). During the next two decades, MCGs were registered with single channel devices, and mappings were performed by placing the registering sensor at several locations over the thorax and measuring signals from one location at a time. The first reports describing normal MCG patterns were based on such mapping systems (Saarinen et al. 1978). In the 1990's, multichannel devices have emerged, allowing simultaneous recording of the magnetic signals over large precordial areas (Van Leeuwen et al. 1999, Montonen et al. 2000). Today, MCG measurements can be performed with highly sensitive SQUID sensors in specially constructed magnetically shielded rooms, resulting in sensitivities < 5 fT/√Hz at 1-300 Hz. With a modern multichannel device, MCG registration can be performed in 10 to 15 minutes, rendering the method suitable for clinical patient measurements.

3.5.2.2. Magnetocardiographic data presentation

Most groups performing MCG nowadays limit the registration to the component of the magnetic field perpendicular to the anterior chest (the z-component). In MCG, the P, QRS, T, and U waves can be discerned, although their amplitude relationships and morphological details often differ somewhat from those of ECG. For example, the U wave in MCG is often more pronounced than in ECG. In addition to the conventional time domain presentation, it is sometimes more

informative to display the registration results as an isofield map where the registration points with the same field amplitude are connected with lines. These maps can be acquired at specific time instants or as isointegral maps (Figure 1) covering selected time periods such as the QRS complex or QRST interval.

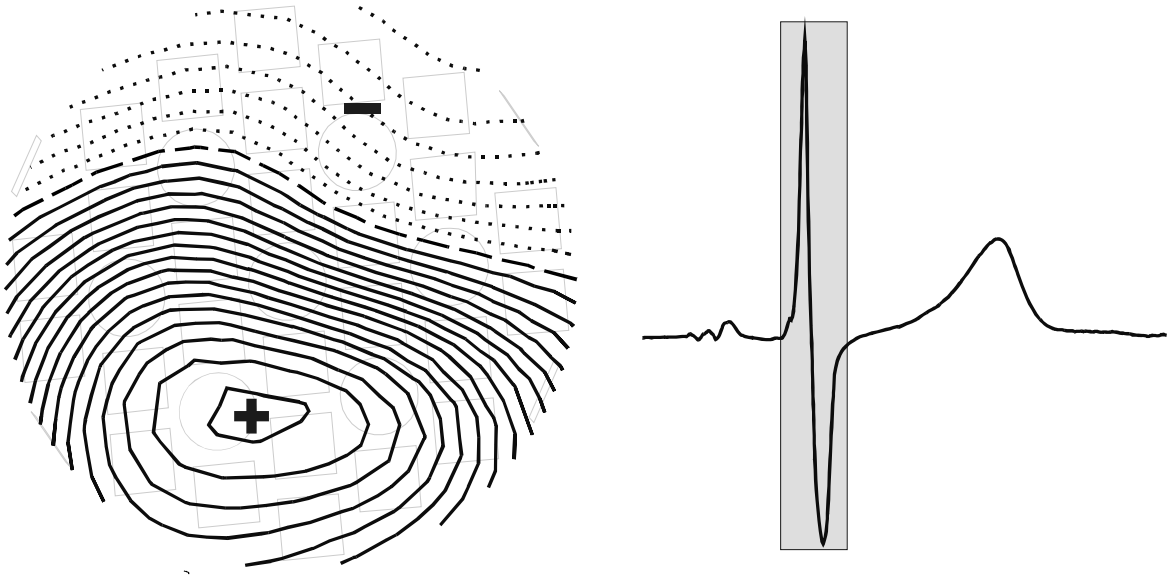

Figure 1. *Magnetocardiographic isointegral map (left) over the entire QRS complex (right, shaded area). Map points with the same integral value are connected with lines. The solid lines indicate regions with a positive integral value (magnetic field directed into the chest) and dotted lines indicate areas with a negative value (magnetic field directed outward from the body). A dashed line marks zero integral value.*

3.5.2.3. Relationship between MCG and ECG

Since the same electrical activity generates both ECG and MCG, the question whether MCG contains information not obtainable from ECG has been a subject of controversy. On the basis of the electromagnetic field theory, ECG is more sensitive to electrical currents radial to the body surface, whereas MCG is more sensitive to currents tangential to it. Normally, the radial currents predominate, but in cardiac diseases interfering with the spread of activation, the contribution of tangential currents may be increased (Siltanen 1989).

Nousiainen and coworkers (1986) compared vector MCG to Frank lead vector ECG (Frank 1956) and found MCG to be more sensitive to the terminal phase of the depolarization when the activation wavefront occurs in a more tangential direction than at the initial part. Accordingly,

Barry et al. (1977) found the angle between magnetic heart vectors of R and T waves to differ markedly from the corresponding electrical vector angle, suggesting that the electrical and magnetic measurements have different sensitivities to some components of cardiac electrical activity. Lant and coworkers in 1990 compared isointegral maps over depolarization and repolarization intervals in both MCG and BSPM in postinfarction patients and in healthy controls; they found that the isointegral BSPM maps in postinfarction patients show abnormalities mainly during the depolarization period, whereas in MCG, better discrimination of postinfarction patients result from use of the abnormalities in the repolarization period.

MCG has shown promise in the localization of sources of cardiac electrical activity such as accessory pathways in Wolff-Parkinson-White syndrome (Mäkijärvi et al. 1992). Comparing MCG and BSPM in the localization of a pacing catheter in the heart, Pesola et al. (1999) found the localization accuracy of MCG to be superior to that of BSPM.

It seems, therefore, that although the electrophysiologic basis of MCG and of ECG is the same, each method produces information that is not readily available from the other one. These methods thus act as complementary tools in the assessment of cardiac electrical activity.

3.5.3. Magnetocardiography in postinfarction arrhythmia risk assessment

3.5.3.1. High-resolution magnetocardiography and magnetic late fields

In comparison to ECG, MCG is less influenced by intervening tissues between the heart and the registering device (Nenonen et al. 1996). In addition, MCG registering does not require skin-electrode contact, which is prone to noise. In MCG, noise is mostly instrumental or ambient in nature, and thus can be reduced by effective shielding. These features have made MCG an interesting tool in the detection of small-amplitude cardiac electrical phenomena such as ventricular LPs. Findings at autopsy in patients with postinfarction VT include areas of thin, ribbon-like spared subendocardium (Bolick et al. 1986). These kinds of myocardial structures could possibly show predominantly tangential currents more readily detectable with MCG than with ECG.

Erné and coworkers first described in 1983 *late fields* in signal-averaged MCG in three of four postinfarction patients who had LPs in SAECG. The presence of late fields after the QRS complex was judged by visual inspection, and they did not report whether those three patients

had ventricular arrhythmias. The late fields were of the order of 1 pT in amplitude and in two patients extended beyond the LPs. A study by Stroink et al. (1989) compared late fields and LPs in the identification of postinfarction VT propensity: in a population of 15 VT patients (11 post-MI), 12 postinfarction non-VT patients, and 14 healthy controls, LPs in SAECG showed better discrimination between the groups than did late fields. With the ratio of the maximum amplitude of the R wave to the last 40 ms of QRS serving as their criterion of abnormality, they reported 67% sensitivity and specificity for MCG. Another study with 10 postinfarction VT patients and 10 postinfarction controls showed a sensitivity and specificity of 80% in VT identification, with the QRS duration > 115 ms serving as the criterion of abnormality (Mäkijärvi et al. 1993). In comparison to the work of Stroink et al., their registrations had lower noise levels and longer recording times together with different criteria for abnormality. Thus far, the studies on late fields have included patient populations very limited in numbers, and the VT and control groups have not been matched as to clinical parameters such as LVEF. In addition, no criteria exist for a positive finding in late fields.

A few studies have attempted to localize the origins of late fields in the postinfarction myocardium (Weismüller et al. 1993, Leder et al. 1998). Although the first results have been encouraging, the significance of these findings remains to be confirmed.

3.5.3.2. Intra-QRS fragmentation analysis in magnetocardiography

Concurrently with the studies on late ventricular activity in MCG, parameters describing abnormal delayed conduction during the entire magnetic QRS have emerged. Intra-QRS fragmentation analysis applying binomial filtering to detect polarity changes inside QRS have shown promise in the discrimination between VT and non-VT patients after MI (Endt et al. 1998, Müller et al. 1999). Using a slightly different fragmentation analysis, Brockmeier and coworkers in 1997 reported increased intra-QRS fragmentation values also in patients with type I diabetes, and the values correlated with left ventricular mass index. The authors postulated that these findings may be due to intraventricular conduction disturbances and may serve as early signs of diabetes-associated cardiomyopathy.

3.5.3.3. Magnetocardiography and postinfarction repolarization abnormalities

MCG has shown promise in the detection of repolarization abnormalities both in postinfarction patients (Lant et al. 1990) and in patients with left ventricular overloading (Fujino et al. 1984). A

few studies have investigated repolarization inhomogeneities and postinfarction VT propensity. Stroink and coworkers (1992) compared MCG isointegral maps for QRS, QRST, and ST-T intervals between 15 VT patients (11 with remote MI) and 15 postinfarction controls. That the maps during the repolarization period in VT patients showed significantly more multipolarity suggests inhomogeneous repolarization. Trajectory plots investigating the spatial route of the map extrema showed even better discrimination between the groups. Another study comparing these sophisticated analysis methods suggested that MCG is slightly more sensitive than BSPM in the assessment of the repolarization abnormalities associated with VT propensity (Stroink et al. 1999).

Few studies have investigated dispersion of the QT intervals in MCG. Using a 37-channel MCG, Van Leeuwen and coworkers compared conventional QT dispersion (the difference between the longest and the shortest QT interval) to a newly developed index better describing local variations of QT intervals. Their 1996 results showed that the parameter they termed smoothness index was superior in discriminating postinfarction patients from healthy controls. Unfortunately, their study did not include VT patients, and so the value of the method in postinfarction risk stratification remains to be assessed.

Manual measurements in clinical practice of QT intervals from multichannel registrations are tedious. Oikarinen et al. presented in 1998 an automated method for QT interval analysis in MCG registrations. In a postinfarction population with 10 VT and 8 control patients, they discovered by use of several dispersion parameters increased QT dispersion in the VT patients. The differences were significant both in manual and in automated measurements. The automated measurements correlated strongly with the manual measurements as regards QT apex dispersion and less strongly but yet significantly with QT end dispersion.

3.5.4. Magnetocardiography and arrhythmia risk in other heart diseases

Few studies have investigated MCG in arrhythmia risk assessment in other than ischemic heart disease, and the populations studied have been small. The relative smoothness score describing temporal fluctuation in magnetic field distribution during the ST segment revealed more fluctuations in patients with diverse cardiomyopathies associated with ventricular arrhythmias than in patients with no severe arrhythmias (Schmitz et al. 1989). In contrast, another study showed the sensitivity of the relative smoothness score in identifying cardiomyopathy patients

with ventricular arrhythmias to be only 40%, with 50% specificity (Fenici and Melillo 1993). The patient groups in both studies were inhomogeneous, comprising various cardiomyopathies and in the Fenici and Melillo study the criterion for a severe ventricular arrhythmia was Lown grade 3 or higher, with only a few patients having sustained VT.

Repolarization disparities related to idiopathic long QT syndrome seem to be detectable with MCG, as well. Rovamo and coworkers (1995) investigated 13 children with long QT syndrome, both with and without symptoms. All patients showed beat-to-beat variability in T wave morphology. When the isofield maps during the T wave were analyzed with eigenvectors for data reduction, the symptomatic patients displayed more disparity in their maps, suggesting more heterogeneous repolarization. The relative smoothness score has also shown lower values in this patient group (Brockmeier et al. 1989).

4. AIMS OF THE STUDY

This thesis aimed at examining MCG in assessment of ventricular arrhythmia risk in heart disease. More specifically, the aims of the six substudies were to investigate:

1. The ability of MCG late fields to identify patients after MI who show a propensity to sustained VT.
2. Whether fragmentation of the QRS complex in MCG is increased in patients with postinfarction VT.
3. In postinfarction patients, relationships of the MCG arrhythmia risk parameters to other cardiac variables, especially left ventricular function and infarct location.
4. In patients with postinfarction VT undergoing arrhythmia surgery, the relationships of MCG arrhythmia risk parameters to delayed conduction recorded in the area surrounding the infarct scar.
5. Both in patients with remote MI and in patients with dilated cardiomyopathy, how MCG parameters describing delayed conduction and abnormal repolarization are associated with a propensity to sustained ventricular arrhythmias.
6. The comparison between MCG late fields and LPs in orthogonal three-lead SAECG and BSPM in the identification of a propensity to postinfarction sustained VT.

5. PATIENTS AND METHODS

5.1. Study patients

The study population comprised an overall total of 205 patients admitted to the Department of Cardiology of Helsinki University Central Hospital during the period between August 1995 and January 2001. Of these, 156 had a remote MI, and 49 had nonischemic dilated cardiomyopathy. The patients with remote MI were subdivided into those with (62 patients) and without (94) documented VT or VF. Postinfarction patients with VT or VF were admitted to undergo electrophysiologic studies, and the non-arrhythmia controls had come for diagnostic coronary arteriography. Accordingly, the cardiomyopathy patients were divided into those with (18) and without (31) documented sustained ventricular arrhythmias. The arrhythmia patients were referred to electrophysiologic studies, and most of the controls were hospitalized due to

worsening heart failure. In addition, 17 healthy controls with no history or signs of cardiovascular disease were studied; each had a normal echocardiogram and performed a bicycle exercise test without either chest pain or ischemic ST segment changes.

The aim in patient selection was consecutive recruitment, but for administrative reasons it was not always possible to follow this principle strictly. Furthermore, at the later stage of the study, only postinfarction patients with LVEF ≤ 40% were recruited, to furnish a subgroup with characteristics comparable to those of arrhythmia patients. The patient population was further distributed among six substudies (Table 1). Patients with a permanent pacemaker were excluded because the moving pacemaker lead causes significant artifacts in the MCG signal. In addition, patients with a complete bundle branch block in 12-lead ECG were excluded from the postinfarction population.

Table 1. *Distribution of 205 study patients among 6 substudies*

Substudy	Heart disease	VT patients	Non-VT patients	Study recordings
Study I	Postinfarction	38	62	MCG, SAECG
Study II	Postinfarction	53	83	MCG
Study III	Postinfarction	22	-	MCG, intracardiac
Study IV	Postinfarction	22	22	MCG, BSPM, SAECG
Study V	Postinfarction	32	28	MCG, 12-lead ECG
Study VI	Dilated cardiomyopathy	18	31	MCG, 12-lead ECG

MCG = magnetocardiography, SAECG = signal-averaged ECG, BSPM = body surface potential mapping

Study I

These study groups comprised patients having suffered a remote MI. The VT group comprised 33 patients with a history of documented sustained (over 30 seconds) monomorphic VT and 5 with a history of VF not related to acute MI and inducible to sustained monomorphic VT. In the

electrophysiologic study, sustained monomorphic VT was inducible in 30 (79%) patients. Non-sustained VT was inducible in three (8%) and VF in two (5%) patients. The control group comprised 62 patients who had suffered an MI more than 6 months previously and had no history of sustained ventricular arrhythmias.

Study II

The VT group comprised 53 patients who had suffered a remote MI: 46 had a history of documented sustained (over 30 seconds) monomorphic VT and 7 a history of VF not related to acute MI and inducible to sustained monomorphic VT. Such sustained monomorphic VT was inducible in 44 (83%) patients, including all who had presented with VF. Polymorphic VT was inducible in 3 (6%) patients and non-sustained VT in one (2%).

Those in the VT group were slightly older than controls (Table 2). They had a significantly lower LVEF (31 ± 9 vs. $41 \pm 15\%$, $p < 0.001$) and more often had a left ventricular aneurysm. The control group comprised 83 patients with an MI more than 6 months previously and with no history of sustained ventricular arrhythmias.

There were 94 patients (46 in the VT group and 48 in the control group) who had LVEF ≤ 40% and thus comprised a subgroup, each with a large infarction and marked left ventricular dysfunction (Table 2).

Study III

The study population comprised 22 patients with a remote MI who were subjected to arrhythmia surgery because of a sustained ventricular arrhythmia late after infarction. The presenting arrhythmia was sustained monomorphic VT in 19 and VF in 3 patients. The infarct location was anterior in 15 (68%) and inferior in 7 (32%), and 15 (68%) patients had a left ventricular aneurysm. In the electrophysiologic study, sustained monomorphic VT was induced in 20 (90%) patients including all 3 with VF as their presenting arrhythmia. All patients were in sinus rhythm.

Study IV

The study population comprised 44 patients with a history of MI and cardiac dysfunction defined as LVEF ≤ 45%. These patients were divided into two groups based on a history of sustained VT. The VT group comprised 22 patients with a remote MI and who were referred to electrophysiologic study: 17 patients had a history of documented sustained (over 30 seconds)

monomorphic VT and 5 had a history of VF. Sustained monomorphic VT was inducible in all patients.

The control group comprised 22 consecutive patients having had an MI more than 6 months previously but with no history of sustained ventricular arrhythmias. All had been admitted for diagnostic coronary arteriography. In a follow-up of 31 ± 12 months, 20 of 22 (91%) of the control patients remained free of sustained ventricular arrhythmias and sudden death.

Table 2. *Characteristics of postinfarction patients in Study II. Characteristics for both the whole study population (n=136) and for the subgroup of patients with left ventricular ejection fraction ≤40% (n=94) are given.*

	VT Group	**Non-VT Group**	**P-value**
All patients	N = 53	N = 83	
Age (years)	62 ± 8	59 ± 9	0.038
Gender (M/F)	47/6	70/13	0.48
LVEF (%)	31 ± 9	41 ± 15	< 0.001
Infarct location: anterior/inferior/both	27/16/9	36/36/9	0.47
Arteriography: 1/2/3 vessel disease	8/22/23	21/20/41	0.10
Left ventricular aneurysm	24 (45%)	6 (7%)	< 0.001
Patients with LVEF ≤ 40%	N = 46	N = 48	
Age (years)	62 ± 7	61 ± 8	0.28
Gender (M/F)	40/6	43/5	0.69
LVEF (%)	29 ± 7	31 ± 8	0.19
Infarct location: anterior/inferior/both	25/12/9	23/20/5	0.20
Arteriography: 1/2/3 vessel disease	5/19/22	3/15/29	0.38
Left ventricular aneurysm	21 (46%)	5 (10%)	< 0.001

LVEF= left ventricular ejection fraction, VT= ventricular tachycardia

Study V

The VT group comprised 32 patients with a remote MI and either a clinical history of documented sustained monomorphic VT (n = 26) or a history of cardiac arrest not associated

with acute MI and inducible into sustained monomorphic VT in the electrophysiologic study (6). The postinfarction control group comprised 28 patients with a history of remote MI, but with no history of sustained ventricular arrhythmias. The MI controls were matched as a group with the VT group in regard to LVEF. The healthy controls comprised 13 (12 men; mean age 55 ± 7 years) non-smoking volunteers with no history or signs of cardiovascular disease.

Study VI

The study population comprised 49 consecutive patients with nonischemic dilated cardiomyopathy hospitalized for life-threatening ventricular arrhythmias or cardiac dysfunction. Patients with a history of sustained VT or VF (18) comprised the arrhythmia group, and patients without such arrhythmias or syncope (31) comprised the control group. Coronary arteriography was performed in 16/18 patients in the arrhythmia group; in 12 patients no stenoses were present. Four patients showed ≥ 50% luminal narrowing in one or two main coronary artery branches, but the global ventricular dilatation and dysfunction were disproportionate to arteriographic findings. In the control group, coronary arteriography was performed in 16/31 patients, and two of them had ≥ 50% luminal narrowing.

In the arrhythmia group, the presenting arrhythmia was VF in 12 patients (67%), with sustained VT in 6 (33%). In the electrophysiologic study, sustained monomorphic VT was induced in 5 (29%), polymorphic VT in 3 (18%), and VF in one (6%), whereas 8 patients (47%) were noninducible.

Six patients in the arrhythmia group and four in the control group (p = NS) were in atrial fibrillation during the study, and six arrhythmia patients and eight controls had a complete bundle branch block in 12-lead ECG (p = NS).

5.2. Magnetocardiographic recording and data processing

High-resolution MCG recordings were made within a few days before or after the electrophysiologic study (arrhythmia patients), and any antiarrhythmic medication was discontinued for at least five half lives before the recording. In Study III the postoperative registration was performed one to two weeks postoperatively, at the time of hospital discharge. The measurements were performed in a magnetically shielded room (Euroshield Ltd., Eura, Finland) in the BioMag laboratory of Helsinki University Central Hospital. A 67-channel

cardiomagnetometer (Neuromag Ltd., Helsinki, Finland) was employed. This cardiomagnetometer is equipped with 7 coaxial and 60 planar dc-SQUID gradiometers, arranged on a slightly curved surface with a diameter of 30 cm (Figure 2). The gradiometers record the component of the magnetic field perpendicular to the bottom of the instrument. The patient lay on a non-magnetic bed, and the center of the gradiometer grid was placed in a position 15 cm caudally from the jugular notch and 5 cm left of the midline with a slight tilt towards the left side of the anterior chest. The grid was always brought as close to the chest as possible without touching it. The MCG signal was recorded at rest for 5 minutes.

Recordings were band-pass filtered at 0.03-300 Hz, digitized with a sampling frequency of 1 kHz, and stored on a computer disc. An automatic signal averaging 150 to 250 cardiac cycles was performed offline to reduce the noise level. The root mean square noise level was determined during a 40-ms time interval in the ST segment of a 40-Hz high-pass filtered signal, and channels with a mean noise level ≥ 35 fT were rejected from analysis.

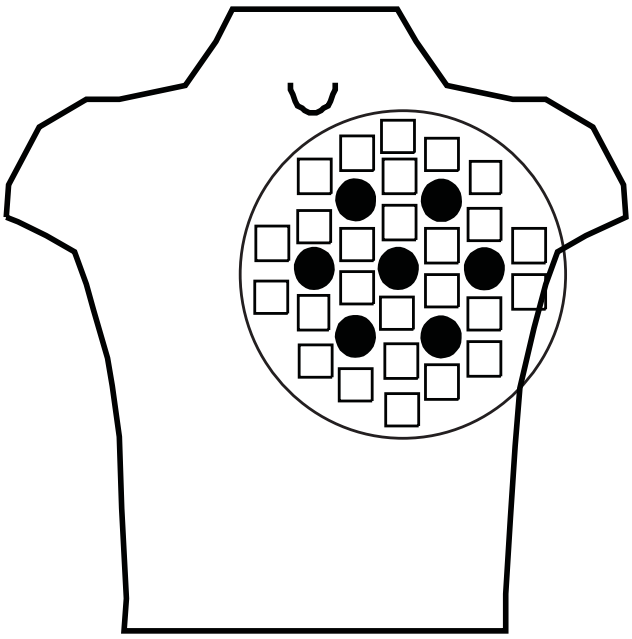

Figure 2. *Schematic illustration of channel positions in the cardiomagnetometer. Original axial channels utilized in late field and intra-QRS fragmentation analyses (●). Each pair of planar channels (□). In repolarization analyses, data from each planar channel pair were transformed to correspond to data recorded from a single axial channel in the same position, resulting in 33 axial channels (7 original + 26 transformed).*

5.2.1. Time domain analysis in magnetocardiography

Before time domain analysis, the averaged QRS complexes were high-pass filtered to suppress the low frequency ST segment and T wave. A bi-directional infinite impulse response filter (type Butterworth, fourth order) with a 40 Hz cut-off frequency was utilized. After high-pass filtering, an envelope complex was formed, utilizing a Hilbert-transform realized by a finite impulse response filter (Montonen et al. 1988).

The beginning and end of the QRS complex were automatically defined following the guidelines published by Simson based on the noise levels of the filtered signal both before and after the QRS complex (Simson 1981). The following indexes for MCG late field parameters were computed: QRS duration (QRSd), root mean square amplitude (RMS) of the magnetic field strength during the last 40 ms of the QRS complex (RMS_{40}), and duration of the low amplitude signal (LAS) below 300 and 500 fT (LAS_{300} and LAS_{500}) at the end of the filtered QRS (Figure 3). In the final analyses, the average values of the 7 (Studies I-V) or 33 transformed axial channels (Study VI, described in section **5.4**) were used.

5.2.2. Intra-QRS fragmentation analysis in magnetocardiography

The same averaged QRS complexes were used as described for time domain analysis (Studies II, III). A binomial high-pass filter of the 90^{th} order with a cut-off frequency of 37 Hz was implemented. Next, high-frequency components were removed by application of a binomial low-pass filter with a 90 Hz cut-off frequency. To quantitate the intra-QRS fragmentation of these bandpass-filtered signals, the number of polarity changes or extrema ***M*** inside the QRS complex was computed. A Fragmentation score of ***S*** describes intra-QRS notching by covering the number of amplitude extremas and their magnitudes within the QRS complex (Figure 4). The computations were performed with custom-made software according to the guidelines of Müller (1999).

5.3. Reproducibility and high-pass filtering cut-off frequency

In order to find the optimal cut-off frequency for high-pass filtering of the averaged MCG signals, a comparison was made between 25 and 40 Hz. Both reproducibility and ability to identify postinfarction VT patients were investigated. Previously, Mäkijärvi and coworkers, in a 1993 report comprising 10 VT and 10 postinfarction controls, found that 25 Hz was superior to

40 Hz in separating the groups. They also applied infinite impulse response filters, but these were of a high order and of the Chebysev type, in comparison to the fourth order Butterworth type filter of the present study. The effects of the cut-off frequencies are therefore not identical between these filter types. Butterworth type filters are most frequently applied in SAECG analysis, and applying them in MCG may facilitate comparison between the methods. The Butterworth, like other infinite impulse response filters, has sharp transitions at the cut-off frequencies, but this type of filter may cause a phenomenon known as filter ringing, which can distort the analysis of late fields. Therefore, in the analysis of late fields, bi-directional filtering by the guidelines of Simson (1981) is advantageous.

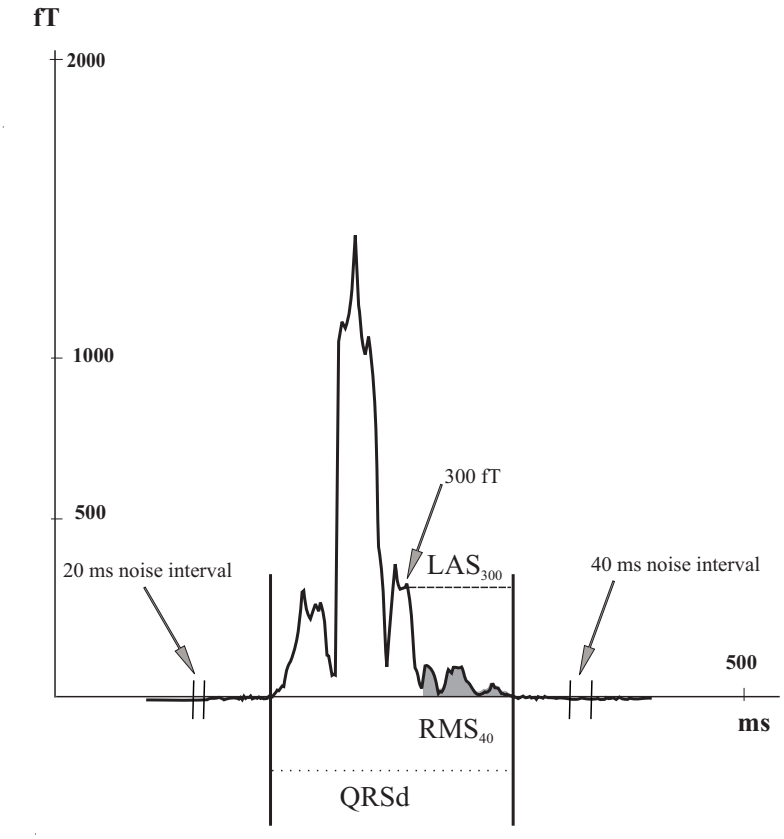

Figure 3. *Principles of calculating magnetocardiographic late field parameters from the high-pass filtered QRS complex. QRSd (dotted line between vertical bars) denotes duration of the QRS complex. The beginning and end of the QRS are defined on the basis of noise intervals both before and after the QRS complex. LAS300 (dashed line) denotes duration of later part of the QRS with amplitude < 300 fT. RMS40 (shaded area) is root mean square amplitude during the last 40 ms of the QRS complex.*

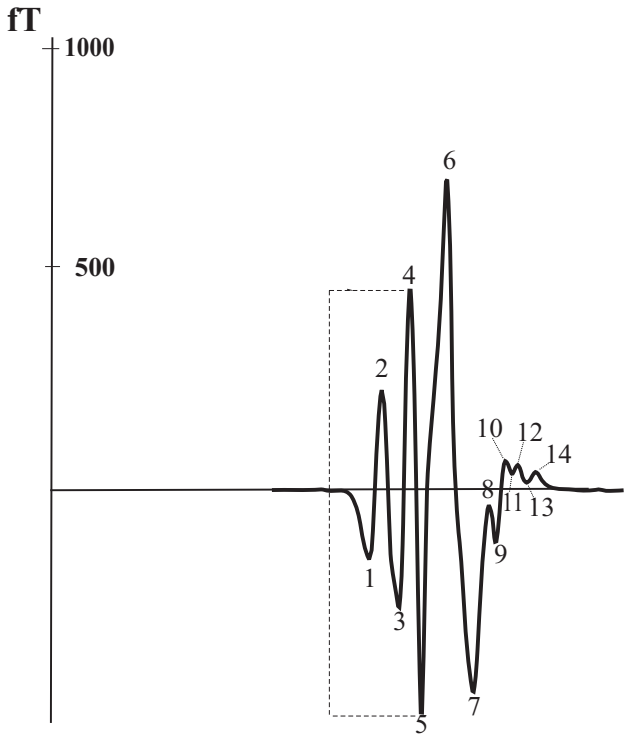

Figure 4. *Principles of intra QRS fragmentation analysis. Number of polarity changes (=fragmentation index M, 1-14) is computed. Polarity change refers to the change in the direction of the amplitude transformation from growth to reduction or vice versa. Next, the amplitude difference of each adjacent extrema is computed, and differences are summed (difference between fourth and fifth extrema is indicated with a dashed line). Finally, the difference between first and last extrema is added to this sum to yield the fragmentation score S.*

Besides comparing the reproducibility of different filter settings in time domain analysis, the reproducibility of intra-QRS fragmentation parameters was investigated in the same patient population. Intra-QRS fragmentation analysis was preceded by binomial filtering 37-90 Hz as in section **5.2.2**.

Of the 18 subjects (12 male, age 49 ± 16 years) studied, 11 had coronary artery disease (one with remote MI) with no documented sustained VTs, 3 suffered from postinfarction sustained monomorphic VTs, and 4 were healthy controls. Each subject was registered twice by the protocol described in section **5.2.** After signal averaging, high-pass filtering was performed with both 25 and 40 Hz cut-off frequencies utilizing a bi-directional filter (Butterworth, fourth order). Time domain and intra-QRS fragmentation parameters were computed as described in sections **5.2.1.** and **5.2.2**.

The reproducibility of the numeric results was determined separately for each variable of time domain and intra-QRS fragmentation analyses. For each subject and variable studied, the mean and SD of the two measurements were computed. Next, the coefficient of variation for each parameter was calculated as SD divided by the mean value; higher values indicate lower reproducibility. Finally, the average value of the coefficient for each parameter in the test population was computed. The coefficients of corresponding time domain parameters in 25 and 40 Hz cut-off frequencies were compared, and the significance of the differences was tested with a two-tailed Wilcoxon signed rank test.

QRSd was the most reproducible of the time domain parameters at both 25 and 40 Hz cut-off frequencies, with a mean coefficient of variation of 3 ± 2% and 4 ± 2%, respectively (p = NS for difference) (Figure 5). RMS_{40} was the least reproducible time domain parameter at both cut-off frequencies with a mean coefficient of 18 ± 21% in 25 Hz and 17 ± 28% in 40 Hz high-pass filtering (p = NS). The LAS parameters were more reproducible at 40 Hz, although the difference was statistically significant only at LAS_{300} (12 ± 8% at 25 Hz and 8 ± 7% at 40 Hz, p = 0.015).

The fragmentation index M displayed good reproducibility with a coefficient of variation of 5 ± 3%; the reproducibility of fragmentation score S was also adequate, with a coefficient of variation of 10 ± 6%.

5.3.1. Comparison of 25 and 40 Hz high-pass filtering in identification of VT propensity

A subset of 44 patients with remote MI was studied, 22 with and 22 without sustained VT. MCG recording, signal-averaging, and time domain analyses were performed as described in **5.2**. QRSd, RMS_{40}, and LAS_{300} were computed in both groups. To compare 25 and 40 Hz cut-off frequencies, receiver operating characteristic (ROC) curves characterizing VT identification were created for each parameter at both cut-off frequencies as described in section **5.11**. The areas under the ROC curves were calculated.

The area under the curve was 0.72 for QRSd both at 25 and at 40 Hz cut-off frequencies and 0.74 for RMS_{40} at both frequencies. In LAS_{300}, the area under the curve was 0.72 at 25 Hz and 0.77 at 40 Hz cut-off frequency.

On the basis of the comparisons above, a 40 Hz cut-off frequency was therefore applied in all the time domain analyses of this study.

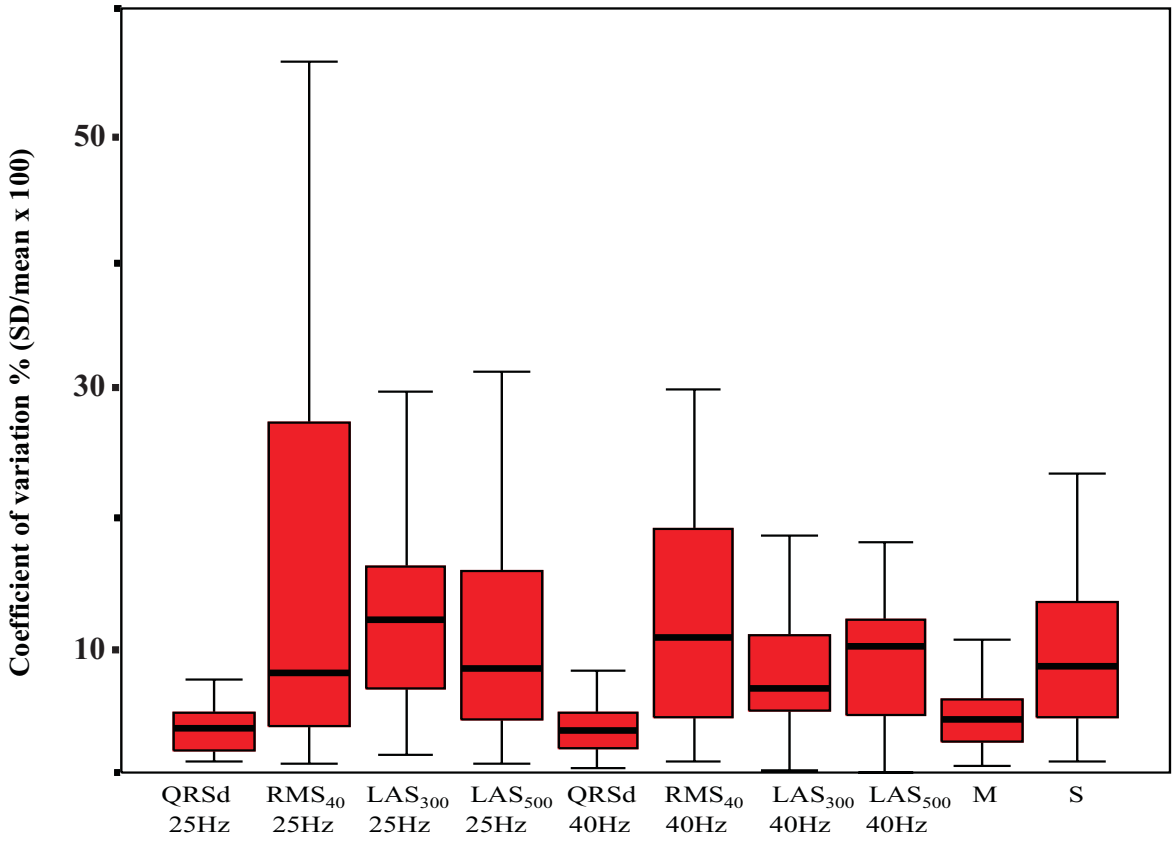

Figure 5. *Reproducibilities of the magnetocardiographic parameters. Each box shows median, upper and lower quartiles, and extreme values of the coefficient of variation of each parameter within the study group. Higher value = lower reproducibility*

5.4. Analysis of repolarization parameters in magnetocardiography

For measurements related to ventricular repolarization (Studies V, VI), the averaged MCG signals from 7 axial and 60 planar gradiometers were transformed to correspond to the data of 33 axial channels (Figure 2). This validated approach makes the MCG channels comparable to each other and enables comparison of MCG data recorded with different multisensor systems (Numminen et al. 1995, Burghoff et al. 2000). The QT interval analyses were performed automatically with a computer-based algorithm (Oikarinen et al. 1998). In brief, in each channel the peak of the T wave was determined as the peak of a parabola fitted to the highest amplitude deviation from the T-P baseline. The end of the T wave was determined by finding the intersection of the steepest tangent fitted to the descending limb of the T wave and the T-P baseline (slope-intercept method). Channels with a T wave amplitude < 600 fT were

automatically excluded from analysis as were channels with a QT_{end} interval < 200 ms or > 600 ms and channels with a QT_{peak} interval < 200 ms or > 550 ms.

After automatic determination of the T wave time instants, all channels were visually inspected on the computer screen, where checkmarks were used to mark the peak and the end of the T wave. If the checkmarks were clearly misplaced, the channel was excluded from further analysis. The number of accepted channels in Studies V and VI ranged from 27 to 31 in the arrhythmia groups and from 26 to 30 in the control groups. Since the QRS-T complex averaged in each channel was formed with the same simultaneously recorded beats, a common onset of the QRS (Q onset) for QT interval measurements was defined as the median of all the QRS onsets in the 33 channels, determined as described above for time domain analysis.

Finally, in each channel, QT_{peak} interval was calculated as the time interval between Q onset and T wave peak, and QT_{end} interval was calculated as the time interval between Q onset and T wave end. The T wave peak to T wave end (TPE) interval was calculated in each channel as the time interval from T wave apex to T wave end. From the transformed 33 axial channels, the QT_{peak} dispersion was calculated as the difference between maximal and minimal QT_{peak} intervals, and the SD of all QT_{peak} intervals. The corresponding variables were computed for QT_{end} intervals. QT intervals were rate-corrected by the nomogram method (Karjalainen et al. 1994) (Study V) or according to the Bazett equation (Bazett 1920) (Study VI). QT dispersion, SD, and TPE interval did not show a significant correlation with heart rate and were thus calculated from noncorrected data.

5.5. Analysis of repolarization parameters in ECG

ECG recordings were performed a few days before or after the electrophysiologic study (arrhythmia patients), and any antiarrhythmic medication was discontinued for at least five half lives before the recording (Studies V, VI). Standard 12-lead electrocardiograms were recorded at a paper speed of 50 mm/s. The ECGs were measured in a blinded fashion on a digitizing board. Time from the onset of the QRS complex to the peak and to the end of the T wave was measured with calipers from two consecutive complexes. T wave end was defined as the return to the T–P baseline. In cases with U waves, the T wave end was measured to the nadir of the curve between the T and U waves. Any lead where the T wave could not be reliably identified was excluded.

The repolarization parameters were calculated analogous to MCG data. In the final analysis, the average of the two measurements in each lead was used.

5.6. SAECG recordings and data analysis

SAECG recordings were performed a few days before or after the electrophysiologic study, and any antiarrhythmic medication was discontinued for at least five half lives before the recording (Studies I, IV). The measurements were performed at rest to record 150 to 250 complexes. In Study I, a commercial registering device (MAC 12®, Marquette Electronics Inc., Milwaukee, WI., USA) with modified Frank leads (Frank 1956) and disposable Ag/AgCl electrodes were used for data registration and signal averaging. In Study IV, the SAECG leads were derived from the BSPM electrodes at positions corresponding to modified Frank leads, and the registration and signal averaging were performed with a custom-made data collection and signal averaging system (Simelius et al. 1996).

Signals were band-pass filtered at 0.03 (Study I) or 0.16 (Study IV) -300 Hz and digitized at a sampling frequency of 1 kHz. High-pass filtering of the averaged signal from each bipolar lead was performed off-line at the same filtering software and cut-off frequency of 40 Hz as for the MCG data. The filtered leads were combined in a vector magnitude $(X^2+Y^2+Z^2)^{1/2}$. The onset and offset of the QRS complex were determined analogous to the MCG data. The root mean square noise level was analyzed during a 40 ms time interval in the ST segment, and recordings with a mean noise level ≥ 1 μV were rejected. Finally, QRSd, RMS_{40}, and LAS_{40} were computed from the vector magnitude.

5.7. BSPM recordings and data analysis

BSPM recordings were performed a few days before or after the electrophysiologic study, and any antiarrhythmic medication was discontinued for at least five half lives before the recording (Study IV). With Wilson's central terminal as a reference (Wilson et al. 1934), 63 unipolar leads covering the anterior thorax were applied. The Ag/AgCl electrodes were used at a vertical interelectrode distance of 5 cm. The electrodes were attached to nine flexible plastic strips, each containing seven electrodes. These strips were attached to the anterior torso vertically with the highest electrode density on the left (Figure 6). The horizontal distances between the electrode

strips were determined individually according to the dimensions of the thorax. BSPM was recorded in the supine position at rest for 5 minutes to collect 150 to 250 complexes. Recordings were band-pass filtered and digitized analogous to SAECG data (Study IV). Signal averaging, time domain analysis, and determination of QRS onset and offset were performed correspondingly. QRSd, RMS_{40}, and LAS_{40} were computed for each lead separately.

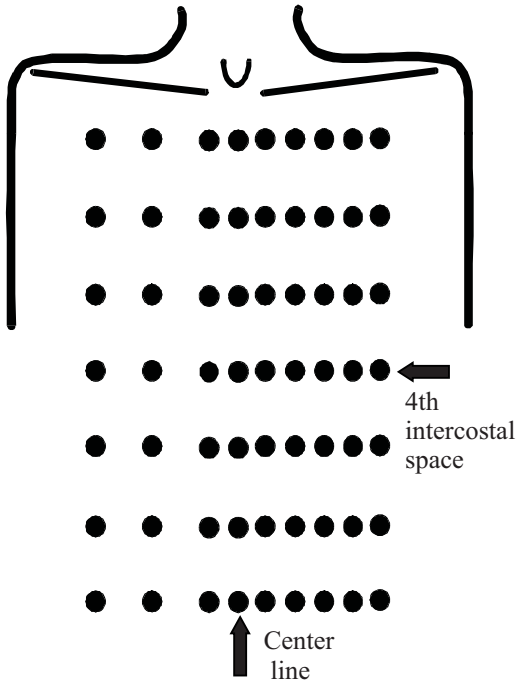

Figure 6. *Body-surface sites of 63 BSPM electrodes.*

5.8. Coronary arteriography, left ventriculography, and electrophysiologic study

Coronary arteriography was performed and LVEF calculated from cineangiograms in right anterior oblique projection by the area-length method (Studies I-VI). In Study VI, LVEF was determined in some patients by 2-dimensional echocardiography. A significant coronary artery stenosis was defined as ≥ 50% narrowing of the vessel diameter. Left ventricular aneurysm was defined as a left ventricular wall region with paradoxical systolic motion.

Programmed ventricular stimulation was performed by use of 600 and 400 ms drive cycle lengths and with up to three extrastimuli in the right ventricular apex and outflow tract. Sustained monomorphic VT was defined as monomorphic VT lasting over 30 seconds or requiring cardioversion for hemodynamic instability.

5.9. Intraoperative cardiac mapping and data analysis

Local cardiac electrograms were registered in sinus rhythm with commercial hardware and software (CardioMap®, Prucka Engineering Inc., Houston, TX, USA). The epicardial electrograms were registered by means of an epicardial electrode jacket with 102 bipolar electrodes arranged in 12 strips each containing 7 or 10 bipolar electrodes with a 4-mm interval between the electrodes in each pair. This jacket is stretchable in order to cover even grossly dilated ventricles, and the interelectrode distance thus varies slightly depending on heart size. Sinus rhythm electrograms were typically registered for 5 to 10 seconds. Next, VT was induced by programmed stimulation via epicardial temporary leads. The site of the earliest epicardial activation during VT was recognized in the activation sequence maps according to the standard procedure. To register endocardial electrograms, left ventriculotomy via the infarct scar was performed, and an inflatable endocardial electrode balloon was inserted in the ventricular cavity. The balloon consists of 72 bipolar electrodes arranged in 12 strips, each containing six bipolar electrodes with a 4-mm interval between each bipole pair. The anatomical distance between the electrodes varies by chamber size. Registration of the sinus rhythm electrograms and VT mapping were performed as for the epicardial data.

Although it was impossible to place all the electrodes in contact with the epicardium and endocardium, care was taken to ensure adequate contact in the infarct area and in neighboring areas. For the final analysis, electrograms with artifactual signals were excluded. Nine surface ECG leads were registered simultaneously with local electrograms for time reference.

The time when the depolarization signal returned to baseline was determined for each local electrogram. The onset of the QRS complex on surface leads served as a reference. The latest epicardial and endocardial excitations were examined separately and combined for the latest overall excitation. The end of ventricular excitation was found to be epicardial in the majority (14/22) of cases.

5.10. Definition of remote myocardial infarction

The diagnosis of remote myocardial infarction was based on a history of typical chest pain together with new q-waves in 12-lead ECG. Alternatively, a significant increase in the plasma

creatine kinase cardiac isoenzyme level, or an akinetic or dyskinetic ventricular wall in an area supplied by a stenosed coronary artery was required for infarct diagnosis (Studies I-V).

5.11. Statistical methods

Continuous variables are presented as mean ± SD values and discrete variables as frequencies and percentages. Comparisons between any two groups were made by the Student t-test or Mann-Whitney U-test for continuous variables and the Chi-square test or Fisher's exact test for discrete variables. Paired-samples t-test was used to compare the MCG parameter values before and after the operation (Study III). Comparison of continuous variables between multiple groups was performed with the Kruskal-Wallis test.

Spearman's rank correlation test or Pearson's correlation coefficient served to study the correlations between various variables.

Multivariate analyses were performed to evaluate the relative information content of individual variables in classifying patients to VT and control groups using stepwise logistic regression analysis and a p-value of 0.05 as the limit to entry into the equation and a p-value of 0.10 as the limit to be removed from the equation.

Sensitivity was defined as the percentage of abnormal test results in the patient group and specificity as the percentage of normal test results in the control group. ROC curves were created for various parameters to assess their performances in the identification of patients with a propensity to VT. The areas under the curves are given in fractions of the maximum value 1, which would be the result of a test yielding a 100% sensitivity and specificity. Cut-off values were dichotomized for various parameters by selecting the parameter value resulting in the maximum sum of sensitivity and specificity in classification of patients to VT or control groups. Positive predictive value was defined as the percentage of patients with abnormal test results who were correctly diagnosed as VT patients, and negative predictive value as the percentage of patients with normal test results who were correctly diagnosed as non-VT controls.

A two-tailed p-value < 0.05 was considered statistically significant. SPSS for Windows (version 8.0 or 10.0) biostatistic software was used.

6. RESULTS

6.1. MCG late field parameters in patients with postinfarction ventricular tachycardia

Time domain parameter values differed significantly between VT and control patients. QRSd was 137 ± 26 ms in the VT group and 110 ± 18 ms in controls ($p < 0.001$). RMS_{40} and LAS_{300} also differed between the study groups (Table 3) (Study I).

Table 3. *Magnetocardiographic late field parameters in postinfarction VT and non-VT patients in Study I.*

Parameter	VT Patients	Non-VT patients	P-value
	N = 38	N = 62	
QRS duration (ms)	137 ± 26	110 ± 18	< 0.001
RMS_{40} (fT)	260 ± 170	510 ± 360	< 0.001
LAS_{300} (ms)	42 ± 19	27 ± 11	< 0.001

VT = ventricular tachycardia, fT = femtotesla (10^{-15} Tesla)

The dichotomized cut-off values in a larger patient population (n = 136) yielded sensitivities between 72% and 87% and the specificities between 70% and 72%, with LAS_{300} as the most strongly discriminating parameter (Table 4). The combination of the dichotomized parameter values (at least two of the following: QRSd > 121, RMS_{40} < 250 fT, LAS_{300} > 32 ms) did not result in any better discrimination than did LAS_{300} alone (Study II).

Table 4. *Sensitivity and specificity of time-domain late field parameters in classification to ventricular tachycardia group among postinfarction patients (Study II).*

Parameter	Cut-off Value	Sensitivity	Specificity
QRS duration (ms)	≥ 121	72%	72%
RMS_{40} (fT)	< 250	81%	72%
LAS_{300} (ms)	> 32	87%	70%

6.2. MCG intra-QRS fragmentation in postinfarction ventricular tachycardia

Both fragmentation index M and score S differed significantly between VT and control patients (Study II). M was 12 ± 3 in the VT group and 9 ± 2 in the control group ($p < 0.001$), and the corresponding figures for S were 83 ± 42 vs. 56 ± 21 ($p < 0.001$). The dichotomized cut-off values yielded 75% sensitivity and 69% specificity for M in VT identification, and the corresponding values for S were 77% and 61%. The combination of the dichotomized values (M > 9.5 *or* S > 57.5 as the criteria for abnormality) resulted in a sensitivity of 87% and specificity of 61%.

The fragmentation parameters correlated with time domain parameters, the strongest correlation being between QRSd and fragmentation score S ($r = 0.81$, $p < 0.001$). Since a longer QRS complex might manifest more polarity changes than a shorter one also in a control patient, the discriminative ability of the fragmentation parameters was tested by limiting the analysis to the last 40 ms of the QRS. In addition, VT identification was further tested with the indexes M and S normalized by dividing them by the corresponding QRSd. Neither approach resulted in any better discrimination.

6.3. Relation of late field and intra-QRS fragmentation parameters to cardiac variables

In the subgroup with a large infarction and LVEF ≤ 40%, parameter values in the arrhythmia-free control patients were closer to those of the VT patients than in the entire study group. Yet the differences between groups remained significant (Table 5). The infarct location also had an impact on parameter values; the parameters showed larger differences between VT and control patients in the subgroup with an anterior infarction, although the parameters differed also in the inferior MI group (Study II).

The criteria based on combinations of dichotomized cut-off values yielded sensitivities of 75 to 89% for both time domain and intra-QRS fragmentation parameters in all subgroups. On the other hand, the specificities were lower, especially in the subgroup with LVEF ≤ 40% (56% with time domain and 42% with intra-QRS fragmentation criteria).

QRSd showed moderate inverse correlation with LVEF ($r = -0.60$, $p < 0.001$), whereas RMS_{40} ($r = 0.41$, $p < 0.001$) and LAS_{300} ($r = -0.40$, $p < 0.001$) showed weaker correlations.

When the VT group was analyzed separately, however, the correlation between QRSd and LVEF was poor ($r = -0.33$, $p = 0.014$), and neither RMS_{40} nor LAS_{300} showed any correlation. Similarly, the fragmentation parameters M and S showed a correlation with LVEF in the entire patient population ($r = -0.53$ and -0.54), whereas in the VT group the correlations were negligible ($r = -0.28$ and -0.27). None of the time domain or intra-QRS fragmentation parameters showed any correlation with age.

In stepwise logistic regression analysis, QRSd, RMS_{40}, and the presence of left ventricular aneurysm showed independent discriminative value in assessment of the propensity to VT (Study II). In univariate analysis, LAS_{300}, M, and S all showed high χ^2 values, but due to correlations between variables they did not enter the model (Table 6). In the otherwise similar but smaller series (Study I), logistic regression analysis was performed with several clinical variables and with QRSd as the only MCG parameter. In that study, QRSd, left ventricular aneurysm, and also age showed independent discrimination.

6.3.1. Relation of late field and intra-QRS fragmentation parameters to delayed ventricular conduction

The overall end of ventricular excitation showed moderate correlation with QRSd ($r = 0.45$, $p = 0.035$), but not with RMS_{40} and LAS_{300}. Fragmentation index M ($r = 0.64$, $p = 0.001$) and score S ($r = 0.73$, $p < 0.001$) correlated with excitation more strongly. When investigated separately, the latest epicardial excitation correlated strongly with QRSd, M, and S ($r = 0.74$, 0.74, and 0.80, $p < 0.001$ for each) and weakly with LAS_{300} ($r = 0.32$, $p = 0.005$), whereas RMS_{40} showed no correlation. The latest endocardial activation correlated with none of the parameters (Study III).

The correlations were strong in patients with anterior infarction; $r = 0.87$, 0.91, and 0.82 for QRSd, M, and S, respectively ($p < 0.001$ in each), and also RMS_{40} ($r = -0.65$, $p = 0.008$) and LAS_{300} ($r = 0.73$, $p = 0.002$) showed correlation in this subgroup.

Table 5. *Magnetocardiographic time-domain late field and intra-QRS fragmentation parameters in postinfarction subgroups with cardiac dysfunction and anterior and inferior infarcts.*

	VT Group	Non-VT Group	P-value
LVEF≤ 40%	N = 46	N = 48	
QRS duration (ms)	148 ± 31	124 ± 18	< 0.001
RMS_{40} (fT)	168 ± 106	381 ± 322	< 0.001
LAS_{300} (ms)	49 ± 18	32 ± 13	< 0.001
Fragmentation index M	12 ± 4	10 ± 2	0.002
Fragmentation Score S	87 ± 43	65 ± 22	0.010
Anterior infarction	N = 27	N = 36	
QRS duration (ms)	148 ± 35	111 ± 17	< 0.001
RMS_{40} (fT)	180 ± 131	545 ± 381	< 0.001
LAS_{300} (ms)	48 ± 16	26 ± 9	< 0.001
Fragmentation Index M	12 ± 4	9 ± 2	< 0.001
Fragmentation Score S	90 ± 51	57 ± 23	0.002
Inferior infarction	N = 16	N = 36	
QRS duration (ms)	142 ± 30	119 ± 22	0.010
RMS_{40} (fT)	172 ± 78	365 ± 310	0.001
LAS_{300} (ms)	45 ± 16	34 ± 12	0.007
Fragmentation Index M	12 ± 3	9 ± 2	0.020
Fragmentation Score S	79 ± 32	57 ± 21	0.020

LVEF = left ventricular ejection fraction

Table 6. *Results of stepwise logistic regression analysis in postinfarction patients with ventricular tachycardia as the dependant variable.*

Parameter	χ^2	Univariate P-value	Stepwise Logistic Regression Analysis
QRS duration	33.1	< 0.001	< 0.001
LAS_{300}	31.0	< 0.001	0.12
Fragmentation index M	26.0	< 0.001	0.97
RMS_{40}	26.0	0.001	0.003
Left ventricular aneurysm	25.7	< 0.001	<0.001
Fragmentation score S	20.1	< 0.001	0.79
LVEF	16.0	< 0.001	0.43
N of diseased vessels	5.0	0.081	0.20
Age	4.6	0.031	0.13
Infarct location	4.4	0.353	0.55

LVEF = left ventricular ejection fraction

Of the 21 patients studied postoperatively, only one remained inducible to VT; others were noninducible. In the postoperative MCG, the time domain and intra-QRS fragmentation parameters were modified significantly (Table 7). The postoperative values resembled those of postinfarction patients with large infarctions but with no history of VT, as seen in Table 5.

Table 7. *Effect of arrhythmia surgery on magnetocardiographic arrhythmia risk parameters in postinfarction patients with sustained ventricular tachycardia.*

Parameter	Preoperative value	Postoperative value	P-value
QRS duration (ms)	138 ± 27	120 ± 19	0.003
RMS_{40} (fT)	156 ± 126	385 ± 226	0.010
LAS_{300} (ms)	50 ± 18	32 ± 12	0.006
Fragmentation Index M	11.4 ± 2.2	9.3 ± 2.0	< 0.001
Fragmentation Score S	75 ± 22	58 ± 18	0.004

6.4. Relation of MCG late fields to late potentials in BSPM and orthogonal three-lead SAECG

In MCG, the average of the three channels with the most abnormal values discriminated between the groups better than did the average of all channels. In contrast, in BSPM the average of all channels yielded better VT identification in comparison to the average of five or ten channels with the most abnormal values. The data are therefore given as averages of the three channels with the most abnormal values for MCG, and as the averages of all the channels for BSPM (Study IV).

Between patient groups all parameters in MCG, BSPM, and SAECG differed significantly (Table 8). The ROC curves showed that the differences between the three methods were small as regards all time domain parameters, with the areas under the curves ranging between 0.72 and 0.81 (Figure 7). LAS_{300} in MCG showed the best discrimination with the area under the curve of 0.81. A dichotomized cut-point for LAS_{300} yielded sensitivity and specificity of 77% and 82%.

All the time domain parameters correlated markedly between MCG and BSPM. The correlation coefficient was 0.86 for QRSd ($p < 0.001$), 0.67 for RMS_{40} ($p < 0.001$), and 0.69 for LAS ($p < 0.001$). On the other hand, the correlations between MCG and orthogonal SAECG parameters were weaker; the correlation coefficient for QRSd was 0.57 ($p < 0.001$), 0.24 for RMS_{40} ($p = 0.114$), and 0.28 for LAS ($p = 0.065$). The correlation coefficient values for BSPM and SAECG parameters were intermediate among these. Since the LAS parameters in MCG and SAECG showed no mutual correlation, their combination was tested in classification to the VT group; the criteria of LAS_{300} in MCG > 47 ms or LAS_{40} in SAECG > 42 ms yielded 95% sensitivity and 68% specificity.

Table 8. *Parameter values in signal-averaged MCG, BSPM, and SAECG in postinfarction VT and non-VT patients.*

	VT Group N = 22	Non-VT Group N = 22	P-value
MCG			
QRS duration (ms)	153 ± 39	124 ± 16	0.003
RMS_{40} (fT)	127 ± 144	226 ± 162	0.038
LAS_{300} (ms)	59 ± 22	37 ± 13	< 0.001
BSPM			
QRS duration (ms)	149 ± 22	128 ± 18	0.006
RMS_{40} (μV)	9 ± 6	17 ± 10	0.002
LAS_{40} (ms)	77 ± 22	56 ± 19	0.002
SAECG			
QRS duration (ms)	149 ± 27	127 ± 26	0.009
RMS_{40} (μV)	11 ± 8	25 ± 19	0.004
LAS_{40} (ms)	60 ± 24	39 ± 22	0.005

MCG = magnetocardiography, BSPM = body surface potential mapping, SAECG = signal-averaged ECG

In the larger series (n=100), MCG late fields were compared to orthogonal SAECG late potentials in VT identification. In that study using commercial data acquisition and a signal averaging program, the MCG late fields showed superior discrimination, especially in the subgroup with marked cardiac dysfunction (Study I).

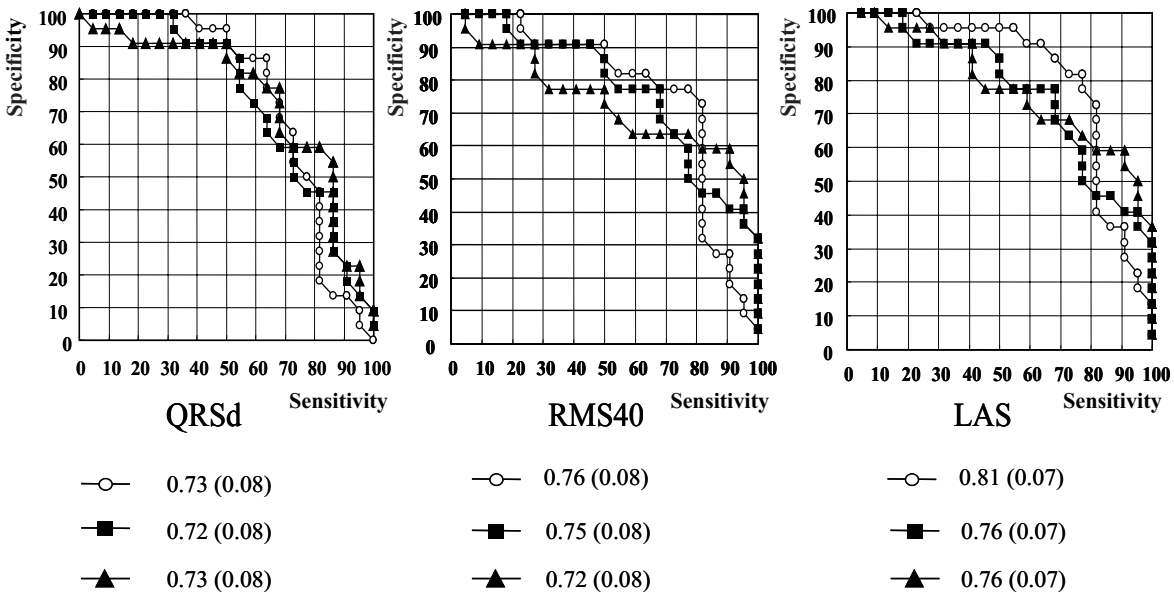

Figure 7. *Receiver operating characteristic curves illustrating discriminative powers of time domain parameters in signal-averaged MCG (—○—), -BSPM (—■—), and orthogonal three-lead ECG (—▲—). Areas under the curves with their standard errors appear under each chart.*

6.5. Repolarization abnormalities in magnetocardiography

6.5.1. Repolarization abnormalities in patients with a propensity to postinfarction ventricular tachycardia

In MCG, the later part of the T wave intervals (TPE) (maximum, average of the six longest, and the mean of all channels) in 33 axial channels yielded significantly higher values in the VT group than in the MI and control groups (Table 9). On the other hand, conventional QT dispersion measures in MCG did not discriminate between VT and MI patients. In contrast, in ECG only the mean TPE interval was increased in VT patients in comparison to the MI group (80 ± 11 vs. 74 ± 9 ms, $p < 0.05$), but the conventional QT_{end} dispersion values were significantly larger in the VT group (Study V).

Mean QRSd was longer in the VT than in the MI group (Table 9). Mean QRSd correlated with the maximum TPE interval in the MI group ($r = 0.40$, $p = 0.037$) but showed no correlation with any of the TPE measures in the VT group.

Table 9. *Magnetocardiographic measures of depolarization and repolarization in postinfarction ventricular tachycardia (VT), myocardial infarction (MI), and healthy control groups.*

	Controls (N = 13)	**MI group (N =28)**	**VT group (N = 32)**	**P-value**
Mean QRS duration, 7 axial channels		114 ± 22	135 ± 34#	
TPE interval, 7 axial channels				
Maximum	83 ± 9	86 ± 13	93 ± 16	0.054
Mean	71 ± 6	71 ± 7	75 ± 10	0.111
TPE interval, 33 axial channels				
Maximum	91 ± 12	104 ± 19	117 ± 23¶#	0.001
6 longest (average)	82 ± 9	88 ± 11	100 ± 16¶**	< 0.001
Mean	72 ± 6	70 ± 6	78 ± 9§††	0.001
QT_{peak} interval, 33 axial channels				
Maximum (rate corrected)	343 ± 20	366 ± 26†	378 ± 35¶	0.001
Dispersion	44 ± 18	74 ± 25†	74 ± 24¶	0.001
SD	9 ± 4	17 ± 6‡	17 ± 7‖	0.001
QT_{end} interval, 33 axial channels				
Maximum, (rate corrected)	417 ± 26	441 ± 28*	467 ± 38¶#	< 0.001
Dispersion	55 ± 22	81 ± 26†	93 ± 32¶	0.001
SD	11 ± 4	18 ± 7†	22 ± 10¶	< 0.001

Values are mean ± SD (in ms). P values in the right column are from the Kruskal-Wallis test. * $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$ between Controls and MI group; § $p < 0.05$, ‖ $p < 0.01$, ¶ $p < 0.001$ between Controls and VT group; # $p < 0.05$, ** $p < 0.01$, †† $p < 0.001$ between MI and VT groups.

A cut-off value > 81 ms for mean TPE interval in MCG distinguished between VT and MI groups with a sensitivity of 31% and a specificity of 96%, whereas a cut-off value of > 140 ms for QRSd yielded a sensitivity and specificity of 41% and 89%. A combination of these criteria (mean TPE interval > 81 ms and / or QRSd > 140 ms) increased sensitivity to 63% with 89% specificity.

6.5.2. Repolarization abnormalities in patients with dilated cardiomyopathy and ventricular arrhythmias

None of the QT dispersion parameters in MCG showed any difference between VT and control groups. The TPE interval tended to be longer in VT patients, but the difference lacked statistical significance. On the other hand, in the subset of patients in sinus rhythm, the TPE interval was larger in the arrhythmia group: 87 ± 15 vs. 73 ± 12 ms, p = 0.005), whereas other dispersion parameters failed to show any difference (Table 10). A cut-point value of > 84 ms yielded 67% sensitivity and 85% specificity. In the subgroup without bundle branch block, the TPE interval discriminated between arrhythmia and control patients. TPE interval did not correlate with LVEF (Study VI).

None of the repolarization parameters in 12-lead ECG differed between the arrhythmia and control groups regarding the whole patient population or subgroups in sinus rhythm or without bundle branch block. Nor did MCG late field parameters differ between groups; QRSd was 126 ± 27 ms in the arrhythmia group and 129 ± 43 ms for the controls (p = NS). Nor were late fields discriminative in patients without bundle branch block.

Table 10. *Magnetocardiographic repolarization parameters in dilated cardiomyopathy patients with and without ventricular arrhythmias in subgroups with sinus rhythm and without bundle branch block*

	Patients in sinus rhythm			***Patients without bundle branch block***		
Parameter	**Arrhythmia Group (N = 12)**	**Control Group (N = 26)**	**P-value**	**Arrhythmia Group (N = 12)**	**Control Group (N = 23)**	**P-value**
QT_{end} (ms)	432 ± 38	429 ± 38	0.826	404 ± 53	419± 32	0.310
QT_{end} dispersion (ms)	81 ± 36	70 ± 31	0.351	85 ± 36	71± 32	0.263
QT_{peak} dispersion (ms)	66 ± 20	66± 27	0.997	67 ± 20	62 ± 23	0.532
TPE interval (ms)	87 ± 15	73 ± 12	0.005	80 ± 16	69 ± 10	0.040

TPE= T wave peak to T wave end

7. DISCUSSION

7.1. Main findings

Magnetocardiographic late field parameters differed between those postinfarction patients with a propensity to sustained VT and those who were non-VT patients. In postinfarction patients with cardiac dysfunction, the differences between these groups were smaller but significant. However, that the parameter values in VT and non-VT groups overlapped turns risk assessment for any one individual patient into a difficult task. The performances of different late field parameters in VT identification were roughly equal, but the lower reproducibility of RMS may reduce its utility in clinical practice. In patients with nonischemic dilated cardiomyopathy, late field parameters did not discriminate between patients with and without arrhythmia susceptibility, probably because in these patients delayed conduction is not as important in arrhythmogenesis.

In addition to late fields that concentrate at the end of the QRS complex, MCG parameters describing abnormal electrical activity during the whole depolarization period also showed differences between VT and non-VT patients after MI. These, however, did not outperform time domain late field parameters.

In postmyocardial infarction VT patients, MCG arrhythmia risk parameters did not correlate with the extent of left ventricular dysfunction. This implies that fragmented and slow conduction in the surviving muscle fibers is a more likely cause of abnormal parameters than is the large infarction alone. In classification of patients into VT and non-VT groups, both late field and intra-QRS fragmentation parameters showed discriminative ability that was independent of clinical parameters.

Both time domain and intra-QRS fragmentation parameters showed better VT identification in patients with anterior infarction, although VT patients with inferior MI also showed parameter values different from those of controls.

MCG arrhythmia risk parameters correlated with delayed ventricular conduction in postinfarction patients with anterior infarction and VT propensity. Surgical abolition of the arrhythmia substrate reduced the abnormalities in MCG parameters.

In patients with postinfarction VT propensity and cardiac dysfunction, MCG late fields, as markers of slow and inhomogeneous propagation of conduction, were at least as sensitive as LPs in SAECG and BSPM. The combination of LAS parameters in MCG and SAECG may yield additive information in postinfarction arrhythmia risk assessment.

In comparison to non-arrhythmia controls, the later part of the T wave in MCG was prolonged in patients with a propensity to ventricular arrhythmias both in those with remote MI and those with nonischemic dilated cardiomyopathy. This prolongation was independent of delayed conduction.

7.2. Contribution to previous knowledge

MCG late field parameters and postinfarction VT propensity

In a previous study on MCG late fields in postinfarction VT patients, a sensitivity and specificity of 80% resulted from use of QRSd > 115 ms as the criterion (Mäkijärvi et al. 1993). Those results are comparable to the present ones, although the previous study utilized a single channel cardiomagnetometer in which each channel was registered sequentially. Stroink and coworkers reported in 1989 a sensitivity and specificity of 67% in VT identification using as their criterion for abnormality the ratio of R wave maximum over the average signal during the last 40 ms of the QRS. Besides different criteria for abnormality, their measurements also had higher noise levels and shorter recording times in comparison to those of the present study. Their study population of 15 VT patients and 12 postinfarction control patients was more heterogeneous, also including VT patients with no previous infarction.

MCG intra-QRS fragmentation parameters in postinfarction ventricular tachycardia

Müller and coworkers in their 1999 MCG study found that fragmentation score S adequately identified VT propensity, whereas QRSd did not. In contrast to the present study, QRSd was measured by visual inspection and VT patients with no previous MI were also included.

The findings of the present study are also concordant with those in SAECG, in which the abnormal notching and altered frequency content of the QRS complex in postinfarction patients were associated with ventricular arrhythmias (Lander et al. 1997, Kelen et al. 1991).

Relation of MCG arrhythmia risk parameters to cardiac variables and delayed conduction

No previous study seems to have attempted to correlate MCG arrhythmia risk parameters with cardiac variables. A few studies have, however, investigated the relationship between LPs in SAECG and left ventricular dysfunction. While some studies show a relationship between LPs with left ventricular function and wall motion abnormalities (Breithardt et al. 1982, Zimmerman et al. 1985), others found no similar associations (Pollak et al. 1985, Gomes et al. 1987). Different patient populations, recording techniques, and criteria for abnormality in SAECG are probably the most important reasons for these discrepancies. The results of the present study with MCG late fields resemble those of Kanovsky et al., indicating that the low-amplitude late QRS activity in SAECG originates from a true arrhythmia substrate and is not merely a marker of cardiac dysfunction (Kanovsky et al. 1984).

This is the first study to investigate the electrophysiologic correlates of MCG arrhythmia risk parameters. In 1983, Simson and coworkers reported that the fragmented, delayed endocardial activity corresponds in time with LPs in SAECG. Their results with catheter endocardial mapping also showed prolonged ventricular activation times in postinfarction patients with a propensity to VT. Our findings with late fields resemble theirs, although our endocardial registrations failed to show a correlation, probably due to a non-optimal data collection method (endocardial electrode ball vs. separately placed endocardial catheter).

Studies using SAECG have also found that the abolition of the arrhythmia substrate normalizes the arrhythmia risk parameters and that this modification seems to predict the success of the arrhythmia surgery (Breithardt et al. 1982). Our findings were similar, although with only one patient remaining inducible postoperatively, the ability of MCG to predict the efficacy of the surgery cannot be assessed.

Relation of magnetocardiographic late fields to LPs in BSPM and SAECG

The results of this study showed that in the detection of the late QRS activity associated with VT propensity, the new methods in late activity recordings, MCG and BSPM, were at least as good as orthogonal SAECG. Sasaki et al. (1994) studying patients with ischemic heart disease, showed that LP parameters in multi-lead BSPM more strongly correlates with fragmented intracardiac electrograms than does three-lead SAECG. When applied to postinfarction risk stratification, however, BSPM does not outperform SAECG in the identification of VT propensity, although BSPM could better assess the extent of the body surface area positive with LPs (Sasaki et al. 1995).

In contrast to the present study, Ho and coworkers showed in 1993 greater sensitivity without loss of specificity in a 28-lead BSPM than in SAECG. Their control patients, however, had only slightly impaired left ventricular function, which may have reduced the number of false-positive findings. Our results indicate that patients with considerably reduced left ventricular systolic function display abnormal LP values even without a propensity to ventricular arrhythmias.

Repolarization abnormalities in patients with a propensity to postinfarction ventricular tachycardia

In a previous prospective postinfarction study, a number of repolarization parameters in 12-lead ECG–including QT_{end} dispersion and TPE interval–failed to predict arrhythmic events. The reason for that lack of predictive accuracy may have been the inability of the 12-lead ECG to detect regional dispersions in ventricular repolarization (Zabel et al. 1998). The present study suggests that multi-channel MCG mapping does detect regional disparities in postinfarction patients with a propensity to VT. Since the repolarization data from the 7 original axial channels only failed to discriminate VT from MI groups, it is probable that the detection of repolarization abnormalities was not merely due to MCG's good sensitivity to myocardial currents, but was also a result of detailed multichannel mapping.

A previous MCG study investigating repolarization heterogeneity in postinfarction patients found both QT_{peak} and QT_{end} dispersion to identify patients with a propensity to sustained VT (Oikarinen et al. 1998). However, contrary to the present study, those VT patients had a markedly lower LVEF than did the controls; this may have affected results.

Repolarization abnormalities in MCG in patients with dilated cardiomyopathy and ventricular arrhythmias

Fei and coworkers (1996) found no increased QT dispersion in 12-lead ECG to predict sudden death in dilated cardiomyopathy, whereas Galinier et al. (1998) reported QT dispersion to predict arrhythmic events. Although the results of these 12-lead ECG studies are conflicting, Aiba and coworkers in 2000 reported dispersion of recovery times in BSPM but not in 12-lead ECG to identify patients with dilated cardiomyopathy and sustained VT. Thus, mapping a larger precordial area may improve the detection of repolarization abnormalities in ECG. Interestingly, their study showed neither conventional QT dispersion in BSPM or 12-lead ECG to identify VT patients.

No previous MCG study has investigated the relation of late fields to arrhythmia propensity in dilated cardiomyopathy. MCG late fields revealing delayed conduction showed no difference between patients with and without ventricular arrhythmias, even when patients with bundle branch block were excluded from analysis. However, a few studies have investigated the role of SAECG in risk stratification. In a prospective 2000 study, Yi and coworkers applied both time domain and wavelet decomposition analysis of SAECG in risk prediction; neither method predicted ventricular arrhythmias or sudden cardiac death. Conversely, both Fauchier et al. (2000) and Goedel-Meinem and coworkers (2001) found LPs to associate with ventricular arrhythmias in patients with dilated cardiomyopathy.

7.3. Methodological considerations and study limitations

Study patients

Bundle branch block was an exclusion criterion in the postinfarction studies (I-V). Intra-QRS fragmentation analysis may be applicable even in this patient group, since some methods extracting information from the whole QRS complex in SAECG have shown promise in risk stratification, despite conduction blocks (Lindsay et al. 1988, Haberl et al. 1988). On the other hand, this study excluded only those patients with a typical bundle branch block; those with nonspecific intraventricular conduction diseases were included.

Electrophysiologic study was not performed in the non-arrhythmia patients. Further, except in Study IV, the control group was not followed up after the study registrations. Their arrhythmia propensity cannot, therefore, be completely ruled out, although they had been free of any sustained ventricular arrhythmias for at least 6 months after the acute MI**.** On the other hand, data from prospective postinfarction studies have shown that a major portion of the arrhythmic events occurs during the first 6 months; thereafter, the risk diminishes markedly (Newby et al. 1998).

In arrhythmia patients, the registrations were usually performed within a week after the clinical arrhythmia. Since most of the patients received an implantable defibrillator precluding MCG registration or underwent arrhythmia surgery, it was impossible to repeat the recordings later. The fact cannot, therefore, be ruled out that the acute arrhythmia might have caused changes in the MCG signal recorded soon after the acute phase.

As Study IV included only patients with cardiac dysfunction, the results may not be directly transferable to patients with small infarcts and normal left ventricular function. In addition,

the low correlation between LAS parameters in MCG and SAECG does not necessarily mean that they provide independent predictive information. Other factors, including large interindividual variation in parameters, may have reduced correlations between them.

MCG recordings

That the MCG registering grid was not positioned according to the site of the infarct scar may have limited the detection of late fields. In addition, a recording grid with more channels covering an even larger precordial area could have added to the accuracy.

In Study III, the postoperative registration was performed one to two weeks postoperatively. At this early postoperative stage, there may have been local inflammation at the resection area to affect local conduction and the registered MCG signal.

Criteria for abnormality in late fields

No generally accepted criteria for abnormality exist for late fields nor for intra-QRS fragmentation or MCG repolarization parameters. Therefore, in each study the cut-point values for individual parameters were created by maximizing the sum of sensitivity and specificity. Naturally, these cut-point values may not be optimal in another patient population. Moreover, the values found optimal from these case control studies may not be directly transferable to prospective risk assessment studies.

Intracardiac registrations

In Study III, during the arrhythmia surgery, all the individual epi- and endocardial electrodes could not be brought into contact with the epicardium and endocardium. Although the electrodes were always placed so that the infarct area and the neighboring areas were covered, no information on the exact locations of individual electrodes was collected. However, this study aimed to examine the relation of MCG parameters to the latest ventricular activation, with the location of the latest activation being less important.

7.4. Clinical implications

Since MCG parameters describing both depolarization and repolarization periods yielded significantly different values in postinfarction patients with and without VTs, they may be considered promising tools in postinfarction risk assessment. Overlap existed in parameter values between arrhythmia patients and others. This was especially true for patients with left ventricular dysfunction, which is the postinfarction patient subgroup at which risk

stratification strategies should be targeted. On the other hand, MCG parameters mainly indicate the presence of the arrhythmia substrate, and modifying mechanisms and triggers are also important for the manifestation of the clinical arrhythmias. This may in part explain why some patients with abnormal late fields had not suffered from sustained ventricular arrhythmias. Furthermore, patients with no documented VTs have an increased propensity to ventricular arrhythmias when myocardial damage is great, and complete discrimination between VT and non-VT patients may thus be impossible. However, combining MCG with other noninvasive risk stratification methods such as measures of cardiac autonomic function may be of value in the identification of patients at the highest risk for ventricular arrhythmias.

MCG arrhythmia risk parameters have not been tested in a prospective manner. Although this study indicates that several MCG parameters can serve to identify patients with a propensity to postinfarction VT, a prospective study in postinfarction patients is warranted to assess their predictive value.

Among patients with nonischemic dilated cardiomyopathy, the later part of the T wave was more prolonged in those with ventricular arrhythmias than in those without. However, the progressive nature of the disease makes the timing of the risk assessment very difficult in practice. The results of this study suggest that in the arrhythmogenesis of these patients repolarization abnormalities are important. Whether these findings have clinical value in clinical arrhythmia risk assessment remains to be assessed.

The sensitivity of MCG to changes in the repolarization period suggests that the development of analysis methods to extract subtle abnormalities from the magnetic T wave may be valuable in arrhythmia risk assessment of both postinfarction and nonischemic cardiomyopathy patients.

Modern multichannel MCG is a promising tool in noninvasive arrhythmia risk assessment. It is already evident that good quality MCGs can be quickly registered in a hospital environment, making the method suitable for clinical settings. Although at present, instrumentation and maintenance are costly, in future, the application of high temperature SQUIDs will probably reduce expenses markedly.

8. CONCLUSIONS

In conclusion, the new MCG technique can identify propensity to ventricular arrhythmias in heart disease. In arrhythmia patients, abnormalities in both depolarization and repolarization periods are detectable with MCG. Although the parameters detect ventricular arrhythmia propensity independently of clinical variables, their values overlap between arrhythmia and non-arrhythmia patients, reducing their specificity and indicating the need to combine them with other arrhythmia risk stratification methods in clinical decision making. More specifically, the substudies showed that:

1. In patients with remote MI, MCG late fields significantly differ between patients with and without a VT propensity. The difference between VT and non-VT patients exists also among patients with marked cardiac dysfunction.
2. MCG parameters detecting fragmented electrical activity during the entire depolarization period distinguish between VT and non-VT patients among postinfarction populations. Their performance is almost as good as that of late fields.
3. Both late fields and intra-QRS fragmentation parameters correlate with LVEF. However, when VT patients were analyzed separately, the correlations were weak, indicating that abnormal parameter values are more strongly associated with VT propensity than with cardiac dysfunction. Both late fields and intra-QRS fragmentation parameters can discriminate between VT and non-VT patients independently of left ventricular function and infarct location.
4. In patients with postinfarction VT undergoing arrhythmia surgery, both late fields and intra-QRS fragmentation parameters show correlations with the latest epicardial activation in patients with an anterior infarct scar. Surgical eradication of the arrhythmia substrate reduces the abnormalities in MCG parameters.
5. Both in patients with previous MI and ones with nonischemic dilated cardiomyopathy, the later part of the T wave interval, a marker of transmural repolarization inhomogeneity, is longer in those with a propensity to sustained ventricular arrhythmias in comparison to those without. In postinfarction patients, the later part of the T wave interval is independent of delayed conduction, although both are associated with the arrhythmia

propensity. In nonischemic dilated cardiomyopathy, abnormal repolarization rather than delayed conduction seems to be the key mechanism in arrhythmogenesis.

6. In postinfarction patients with cardiac dysfunction, late fields identify propensity to VT equally well in comparison to LPs in SAECG and BSPM. Delayed ventricular conduction in MCG and SAECG may have additive value in classifying VT and non-VT patients.

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