

# Increased Intra-QRS Fragmentation in Magnetocardiography as a Predictor of Arrhythmic Events and Mortality in Patients with Cardiac Dysfunction After Myocardial Infarction

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**MCG Intra-QRS Fragmentation After MI.** *Introduction:* Increased intra-QRS fragmentation score (FRA) in magnetocardiography (MCG) has shown association with sustained ventricular arrhythmias in post-MI patients suggesting its relation to arrhythmia substrate. The aim of this study was to investigate whether increased FRA in MCG predicts arrhythmic events and mortality after acute myocardial infarction (MI) with cardiac dysfunction.

*Methods and Results:* A series of 158 patients with acute MI and left ventricular ejection fraction (LVEF) <50% were studied. Their age was  $60 \pm 10$  years and LVEF  $40 \pm 6\%$ . MCG was registered and FRA was computed. For comparison, QRS duration in 12-lead ECG was measured. In a mean follow-up of  $50 \pm 15$  months, 32 (20%) patients died and 18 (11%) had an arrhythmic event. Both arrhythmic event rate and all-cause mortality were significantly higher in patients with increased FRA ( $P < 0.001$  for both). In contrast, increased QRS duration in ECG predicted all-cause mortality ( $P < 0.05$ ) but not arrhythmic events. In multivariate analysis, FRA was an independent predictor of both arrhythmic events and all-cause mortality. Using a combined criterion of increased FRA and LVEF < 30% yielded positive and negative predictive accuracies of 50% and 91% for arrhythmic events.

*Conclusion:* In post-MI patients with left ventricular dysfunction, increased intra-QRS fragmentation in high-resolution magnetocardiography predicts arrhythmic events, whereas QRS duration in 12-lead ECG predicts all-cause mortality. Analysis of intra-QRS fragmentation by MCG may assist in guiding therapy of post-MI patients, for example, by selecting those who would benefit most from prophylactic implantable cardioverter-defibrillator therapy. (*J Cardiovasc Electrophysiol*, Vol. 17, pp. 1-6, March 2006)

*magnetocardiography, intra-QRS fragmentation, myocardial infarction, cardiac dysfunction*

## Introduction

Sudden cardiac death (SCD), often late after acute MI, remains an important cause of death especially in patients with left ventricular dysfunction.<sup>1,2</sup> Implantable cardioverter-defibrillators (ICD) capable of terminating malignant ventricular arrhythmias have recently been in the focus of large primary prevention studies and the implantation rates have increased especially after the results of MADIT-II (Multicenter Automatic Defibrillation Implantation Trial II).<sup>3-5</sup> The substantial number of patients fulfilling MADIT-II criteria in the face of economical constraints and possible adverse effects<sup>6,7</sup> has prompted a search of additional arrhythmia risk markers to further identify patients at highest risk.

Magnetocardiography (MCG) is a completely noninvasive method to register cardiac electromagnetic activity with

high resolution. Previous case-control studies in post-MI patients have related increased fragmentation in magnetocardiographic QRS complexes to a propensity to develop sustained ventricular arrhythmias.<sup>8</sup> The aim of this prospective study was to examine if increased intra-QRS fragmentation detected by MCG predicts arrhythmic events and all-cause mortality in patients after acute MI and substantial myocardial damage. In particular, its aim was to examine whether MCG analysis could provide prognostic information in addition to that yielded by low LVEF alone.

## Methods

### Patients

The study was conducted in five hospitals in the Helsinki district. Patients who had acute MI were screened consecutively from May 1997 to June 2000, and the study follow-up extended till June 2003, 3 years after the last enrollment. To obtain a cohort of patients with large myocardial damage, only patients with LVEF <50% and at least one local hypokinetic or akinetic region was included in the study. The diagnosis of acute MI was confirmed by typical chest pain or electrocardiogram (ECG) changes together with diagnostic elevation (twice the normal value) of serum troponin T, troponin I, or MB fraction of creatine kinase. All patients had left ventricular cineangiography or echocardiography performed

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at stable convalescent phase. Altogether, 158 patients fulfilled the inclusion criteria and were recruited to the study. MCG and conventional ECG registrations were performed 1-2 weeks after the acute MI at stable convalescent period.

The mean age of the study patients was  $60 \pm 10$  (range: 34-79) years. The LVEF was  $40 \pm 6\%$ . Bundle branch block in ECG was present in 6%, QRS duration  $> 120$  msec in 12%, and atrial fibrillation in 4% of the patients. Of the patients, 82% were male and 22% had diabetes. Fifty-eight (37%) patients had suffered at least one previous MI. The noninvasive tests were performed before hospital discharge. Coronary arteriography was performed in 92 (58%) patients, 48 (30%) patients underwent percutaneous coronary intervention, and 25 patients (16%) underwent coronary bypass surgery. Both in-hospital and subsequent medical therapy was given according to current guidelines. Beta-blockers and aspirin were prescribed to all patients (100%) and angiotensin converting enzyme (ACE) inhibitors to patients with marked left ventricular dysfunction. At the end of the study follow-up, 95 % of the patients were on beta-blockers, 94% on aspirin, and 72% on ACE inhibitors. Patients were excluded if they were unable to give informed consent or if they had a significant noncardiac comorbidity likely to shorten their survival markedly. Also, patients with a cardiac pacemaker were excluded. All patients gave their written informed consent and the study protocol was approved by the institutional ethical review board.

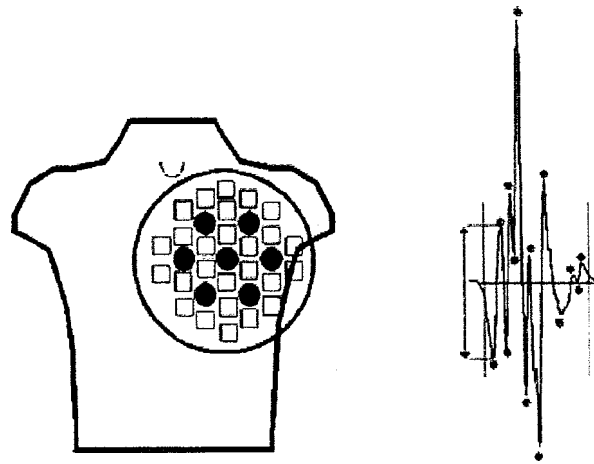
#### MCG Registration and Intra-QRS Fragmentation Score

MCG recordings were performed in a magnetically shielded room (Euroshield Ltd., Eura, Finland) in Helsinki University Hospital. A high-resolution cardiomagnetometer (Neuromag Ltd., Helsinki, Finland) was employed. The cardiomagnetometer was equipped with seven coaxial dc-SQUID (Superconducting Quantum Interference Device) gradiometers, which record the component of the magnetic field perpendicular to the chest. During the 5-minute recording, the patient lay on a nonmagnetic bed and the cardiomagnetometer was placed as close as possible to the chest on the left side without touching the skin (Fig. 1).

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 of 150-250 cardiac cycles was performed to reduce the noise level below 35 fT (femtotesla,  $10^{-15}$  Tesla). The beginning and end of the QRS complex were automatically defined based on the noise levels both before and after the QRS complex.<sup>9</sup> Next, a binomial high-pass filter of 90th order with a cut-off frequency of 37 Hz was implemented. High-frequency components were removed by applying a binomial low-pass filter with 90 Hz cut-off frequency. The intra-QRS fragmentation score (FRA) of these magnetocardiographic QRS complexes was computed by calculating the number of extrema and their magnitudes within the QRS complex (Fig. 1). For a mathematical description of the FRA method, see reference.<sup>10</sup> In the final analysis, the average of the seven coaxial channels was used. All the MCG analyses were performed by researchers blinded to patient outcomes.

#### QRS Duration in 12-Lead ECG

Standard 12-lead ECG was recorded at a paper speed of 50 mm/sec. The onset and offset of QRS were determined manually with calipers by one of the researchers (PK) unaware



**Figure 1.** A: The Position of magnetocardiographic (MCG) registration dewar during the measurements with the seven co-axial channels (black dots). B: The principle of the intra-QRS fragmentation score analysis in MCG. After binomial filtering the number of polarity changes or extrema (\*) is computed. Next, the differences of each adjacent extrema are computed and the differences are summed. As an example, the difference between the first and second extrema is shown with a thin arrow. Finally, the difference between the first and the last extrema is added to this sum, yielding the intra-QRS fragmentation score. The horizontal bars indicate the onset and offset of the filtered QRS.

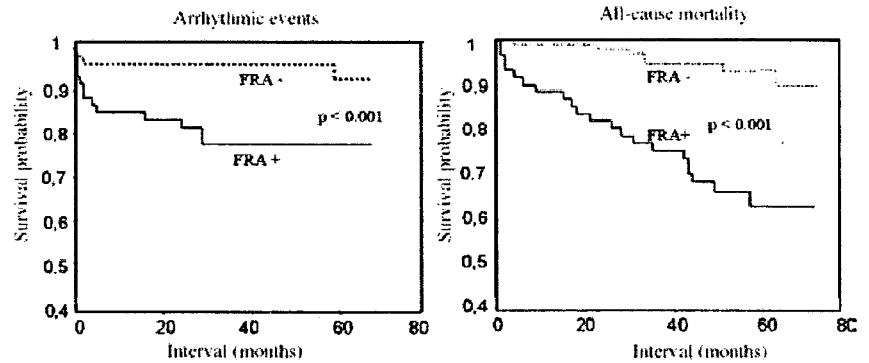
of the clinical history and outcome of the patients. The mean of two consecutive beats was computed. In the final analysis, the mean value of the QRS durations in leads V3-V6 was used.

#### Follow-Up and Study Endpoints

During follow-up, all data concerning hospital admissions were obtained. In addition, at the end of the study the patients or their relatives were contacted by phone. In cases of death, all available information regarding the circumstances and causes of death was obtained from hospital files and autopsy records. In cases of ventricular tachycardia (VT) or fibrillation (VF), a 12-lead ECG or a monitor strip was required to confirm the diagnosis. The study endpoints were arrhythmic events and all-cause mortality. The classification of cause and mode of death was based on the method used in the AIRE (Acute Infarction Ramipril Efficacy) study.<sup>11</sup> Accordingly, death was established as arrhythmic if VT or VF was documented during attempted resuscitation without evidence of progressive heart failure or acute MI, or if in the case of witnessed sudden death there were no preceding new symptoms. For the purpose of this study, an arrhythmic event was defined to include arrhythmic death, resuscitation from VF, or documented sustained VT.

#### Statistical Analysis

Continuous variables are presented as mean  $\pm$  SD values and discrete variables as percentages. Comparisons between the groups were made using the Student's t-test or Mann-Whitney U-test. For FRA we used a predefined cut-point value 57.5, which in our previous study optimally separated post-MI patients with history of VT from those without sustained ventricular arrhythmias.<sup>8</sup> For QRS duration the



**Figure 2.** Kaplan-Meier actuarial curves for arrhythmic events and all-cause mortality based on intra-QRS fragmentation score (FRA). FRA+ = intra-QRS fragmentation score >57.5, FRA- = intra-QRS fragmentation score ≤57.5.

cut-point value chosen was 120 msec. Kaplan-Meier curves were generated to describe the cumulative incidences of arrhythmic events and all-cause mortality for each FRA and QRS duration group. The equality of the event distributions for each risk parameter was assessed with log-rank test. To study the independent predictive values of the same risk variables, a Cox proportional hazards analysis was performed together with several clinical variables including age, sex, atrial fibrillation, bundle branch block, LVEF ≤30%, and diabetes. The hazard ratios (HR) with their 95% confidence intervals (CI) for each variable were calculated.

Positive predictive accuracy (PPA) was defined as the percentage of patients with abnormal test results who had an event at follow-up, and negative predictive accuracy (NPA) as the percentage of patients with normal test results and no events at follow-up. Statistical significance was defined as a P value <0.05. The SPSS for Windows (version 11.5. 1, SSPS Inc., Chicago, IL, USA) biostatistic software was used.

**Results**

Thirty-two patients (20%) died during a mean follow-up time of 50 ± 15 (range: 1-72) months. Of the deaths, 17 (53%) were classified as cardiac deaths. Death was caused by a stroke in 7(22%) patients, 7 patients died of other noncardiac causes, and the cause of death for 1 patient could not be defined. Eighteen (11%) patients had a defined arrhythmic event during follow-up. Of these patients, 7 suffered SCD and 11 had a documented VT or VF without recurrent MI.

Patients with FRA >57.5 were older (63 ± 9 vs 59 ± 11 years, P = 0.03) and they had lower LVEF (37 ± 6 vs 42 ± 5%, P < 0.001) compared with those with FRA ≤57.5. In addition, they had more often bundle branch block in ECG (15% vs 0%, P < 0.001), and they more often had a history

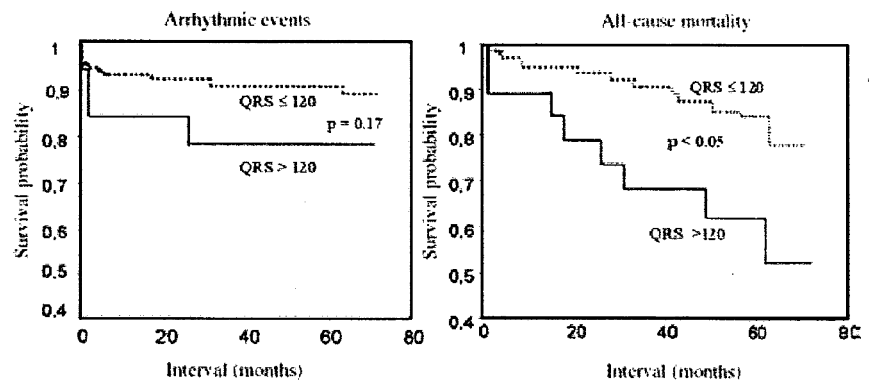
of previous MI (56% vs 25%, P< 0.001). The patient groups did not differ with regard to gender and presence of diabetes or atrial fibrillation.

Patients with arrhythmic events at follow-up had significantly higher FRA values compared with those who did not (67.8 ± 24.3 vs 55.4 ± 26.3, P = 0.006). Patients having FRA exceeding the previously defined limit of >57.5 had significantly higher rate of arrhythmic events compared with those with FRA ≤57.5 (Fig. 2). Also, patients who died during follow-up showed markedly higher FRA values compared to survivors (76.3 ± 34.2 vs 51.8 ± 21.3, P < 0.001) and FRA >57.5 was a significant predictor of all-cause mortality in Kaplan-Meier analysis (Fig. 2). In contrast, QRS duration > 120 msec in ECG did not predict arrhythmic events, but it was a significant predictor of all-cause mortality (Fig. 3).

In multivariate analysis, FRA was the strongest predictor of arrhythmic events with HR 5.1 (95% CI: 1.7-15.9), and only LVEF ≤30% with HR 3.1 (1.1-8.8) could add any predictive value after FRA had entered the model. In regard to all-cause mortality, FRA was also the strongest independently predicting variable with HR 4.4 (1.8-10.4) while diabetes, LVEF, and patient's age showed predictive value, as well.

FRA was >57.5 in 61(39%) patients. Of these patients 24 died and 14 had an arrhythmic event, yielding 23% PPA and 96% NPA for arrhythmic events (Table 1). Respective figures were 39% and 92% for all-cause mortality. Fifteen patients (9%) had LVEF ≤30% and 7 of them died, while 5 suffered an arrhythmic event resulting in 33% PPA and 91% NPA for arrhythmic events. Respective figures were 47% and 83% for all-cause mortality.

The combined criteria of FRA >57.5 and LVEF ≤30% identified a subgroup of 10 (6%) patients, of whom 5 had an arrhythmic event and 7 death from any cause. In them, PPA



**Figure 3.** Kaplan-Meier actuarial curves for arrhythmic events and all-cause mortality based on QRS duration in standard 12-lead ECG.

TABLE I

Positive and Negative Predictive Accuracies of LVEF  $\leq$ 30%, FRA  $>$ 57.5, and Their Combination in Prediction of Arrhythmic Events and All-Cause Mortality

Arrhythmic Events	All-Cause Mortality		All-Cause Mortality		
	PPA	NPA	PPA	NPA	
LVEF $\leq$ 30%	33%	91%	LVEF $\leq$ 30%	47%	83%
FRA $>$ 57.5	23%	96%	FRA $>$ 57.5	39%	92%
LVEF $\leq$ 30% + FRA $>$ 57.5	50%	91%	LVEF $\leq$ 30% + FRA $>$ 57.5	70%	83%

LVEF = left ventricular ejection fraction; FRA = intra-QRS fragmentation score; PPA = positive predictive accuracy; NPA = negative predictive accuracy.

and NPA of the combined criterion for arrhythmic events were 50% and 91%, respectively.

### Discussion

The principal finding of the present study was that increased intra-QRS fragmentation detected by high-resolution MCG predicted arrhythmic events and all-cause mortality in post-MI patients with left ventricular dysfunction. The predictive ability of the FRA parameter was independent of clinical variables, and when FRA was combined with low LVEF it was possible to identify a subgroup of patients with a high propensity to arrhythmic events.

Based on the electromagnetic theory, MCG is more sensitive than ECG to myocardial currents tangential to body surface. Findings during autopsy in patients with post-MI VT have revealed areas with thin strands of spared myocardium,<sup>12</sup> which could show predominantly tangential currents more readily detectable by MCG. This, together with MCG's sensitivity to signals of small amplitude, makes it an interesting technique for arrhythmia risk evaluation. With modern multichannel registering devices, MCG can be recorded in 5-10 minutes, rendering the method suitable for clinical studies.<sup>13,14</sup> However, up to the present time, prospective data on MCG variables in post-MI patients have been lacking.

Previously, MCG late fields analogous to late potentials in signal-averaged ECG describing electrical activity extending beyond QRS complex have been associated with post-MI VT propensity.<sup>15,16</sup> However, invasive data from VT patients have shown that a major part of the myocardium responsible for reentrant VT is depolarized before the last 40 msec of QRS, limiting the ability of the methods examining the end of QRS deflection.<sup>17</sup> Moreover, discrimination between noise and late QRS activity may be difficult, and patients having bundle branch block are usually excluded from risk assessment studies. Therefore, methods extracting fragmented electrical activity during the entire depolarization phase of QRS deflection have been developed. Using a signal-averaged ECG method, which calculates various notches and slurs in the QRS complex, Lander and coworkers found these abnormal intra-QRS potentials superior to conventional time domain parameters in the prediction of post-MI arrhythmic events.<sup>18</sup> Our previous studies showed that intra-QRS fragmentation in MCG correlates with invasively registered slow conduction in post-MI VT patients and that in-

creased fragmentation discriminates VT patients from those without sustained ventricular arrhythmias.<sup>8,19</sup> In comparison to time domain late field analysis, an obvious advantage of FRA analysis is its decreased sensitivity to noise, since the exact definition of beginning and end of QRS is not critically important.

Although a variety of post-MI risk assessment methods have been introduced, none of them have reached widespread clinical use, mostly due to poor PPA or failure to effectively guide therapy.<sup>20-22</sup> For example, signal-averaged ECG has high NPA, but the PPA is relatively low. In addition, the technique has not been applicable to patients with bundle branch block, who are known to have elevated risk of arrhythmic events.<sup>23</sup> T-wave alternans has shown promise in risk stratification<sup>24,25</sup> although the technique may lose predictive power when post-MI patients are on beta-blocker medication,<sup>26</sup> and is not applicable in atrial fibrillation. In contrast, the FRA parameter analyzed with MCG technique could predict arrhythmic events even when including patients with bundle branch block or atrial fibrillation and in patients treated with beta-blockers.

The incidence of sudden death after myocardial infarction has presently decreased when residual ischemia is actively treated with coronary artery revascularization and neurohormonal activation is counteracted with use of beta-adrenergic antagonists and ACE inhibitors or angiotensin receptor blockers.<sup>27,28</sup> These therapies may have decreased the influence of arrhythmia modifiers<sup>29</sup> and left the arrhythmia substrate as the major determinant for genesis of ventricular arrhythmias. Our observations emphasize the value of looking for slow inhomogeneous ventricular conduction, indicating the arrhythmia substrate as a risk stratifier after MI.

QRS duration  $>$  120 msec in the standard 12-lead ECG did not predict arrhythmic events in the present study. Preliminary results from MADIT-II substudies showed a trend toward increased mortality in patients with longer QRS, after which QRS duration  $>$  120 msec was suggested as an additional criterion for ICD implantation. Later, further analyses on MADIT-II patients testing several QRS duration cut-points did not support those observations,<sup>30</sup> which is in agreement with the present results. Our findings are congruent with previously observed association of prolonged QRS duration with increased overall cardiac mortality in left ventricular dysfunction.<sup>31,32</sup>

### Limitations of the Study

The study patient population was relatively small, which reduces the power of the study. Also, follow-up time was long, covering a period of 3 years since the last enrollment, which to some extent balances the limited number of patients. Although aiming to obtain a patient cohort with remarkable myocardial damage, the number of patients with LVEF  $\leq$ 30% was low, weakening the observations in this subgroup. Therefore, larger studies perhaps including other noninvasive tests are warranted. Yet, the combined criterion of FRA and LVEF could show significant predictive value also in this high-risk subgroup. Furthermore, prediction was achieved adapting the dichotomizing FRA value that was found optimal in a previous case-control study<sup>8</sup> and not using any cut-point value derived from the present study data.

We found that FRA predicted not only arrhythmic events but also all-cause deaths, of which 22% were sudden. This implies that FRA in itself is not a very specific predictor of arrhythmias, which is also reflected as a relatively low PPA in the whole study group. On the other hand, PPA of increased FRA was markedly higher in patients with low LVEF. In addition, this may also in part reflect the difficulties in discriminating between arrhythmic and nonarrhythmic deaths in general.

The present study included patients soon following the acute phase of MI. Therefore, the observations may not be readily applicable to patients with remote myocardial infarctions. Therefore, confirmatory studies are needed to examine whether FRA analyzed with MCG or other techniques could assist in targeting therapy in patients with remote MI and cardiac dysfunction.

### Conclusion

The findings of the present study underline the importance of the assessment of the arrhythmia substrate in post-MI risk stratification. Increased intra-QRS fragmentation in magnetocardiography predicts arrhythmic events and mortality in post-MI patients with cardiac dysfunction. Thus, it could be used as an additional criterion to target preventive therapies including ICD implantation for those patients who would benefit most.

### References

- Myerburg RJ, Interian A Jr, Mitrani RK, Kessler KM, Castellanos A: Frequency of sudden cardiac death and profiles of risk. *Am J Cardiol* 1997;10F:19F.
- Huikuri HV, Castellanos A, Myerburg RJ: Sudden cardiac death due to cardiac arrhythmias. *N Engl J Med* 2001;345:1473-1482.
- Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M: Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmias. *N Engl J Med* 1996;335:1933-1940.
- Buxton AE, Lee KL, DiCarlo L, Gold MR, Greer GS, Prystowsky EN, O'Toole MF, Tang A, Fisher JD, Coromilas J, Talajic M, Halley G: Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. *N Engl J Med* 2000;342:1437-1445.
- Moss AJ, Zareba W, Hall J, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown M, Andrews ML, for the Multicenter Automatic Defibrillation Implantation Trial II Investigators: Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877-883.
- Rosenqvist M, Beyer T, Block M, den Dulk K, Minten J, Lindemans F: Adverse events with transvenous implantable cardioverter-defibrillators: A prospective multicenter study. *Circulation* 1998;98:663-670.
- Maisel W, Sweeney M, Stevenson WG, Ellison K, Epstein L: Recalls and safety alerts involving pacemakers and implantable cardioverter-defibrillator generators. *JAMA* 2001;286:793-799.
- Korhonen P, Montonen J, Endt P, Mäkijärvi M, Trahms L, Katila T, Toivonen L: Magnetocardiographic intra-QRS fragmentation analysis in the identification of patients with sustained ventricular tachycardia after myocardial infarction. *PACE* 2001;24:1179-1186.
- Montonen J, Katila T, Leiniö M, Madekivi S, Mäkijärvi M, Nenonen J, Siltanen P: Time and frequency domain analyses of cardiac micropotentials. In: Atsumi K, Kotani M, Ueno S, Katila T, Williamson SJ, eds. *Biomagnetism '87*. Tokyo: Denki University Press, 1988, pp. 278-281.
- Müller H-P, Gödde P, Czerski K, Oeff M, Agrawal R, Endt P, Kruse W, Steinhoff U, Trahms L: Magnetocardiographic analysis of the two-dimensional distribution of intra-QRS fractionated activation. *Phys Med Biol* 1999;44:105-120.
- Cleland JG, Erhardt L, Hall AS, Winter C, Ball SG: Validation of primary and secondary outcomes and classification of mode of death, among patients with clinical evidence of heart failure after a myocardial infarction: A report from the Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. *J Cardiovasc Pharmacol* 1993;22(Suppl 9):S22-S27.
- Bolick DR, Hackel DB, Reimer KA, Ideker RE: Quantitative analysis of myocardial infarct structure in patients with ventricular tachycardia. *Circulation* 1986;74:1266-1279.
- Van Leeuwen P, Haupt C, Hoormann C, Hailer B, Mackert BM, Stroink G: A 67-channel biomagnetometer designed for cardiology and other applications. In: Yoshimoto T, Kotani M, Kuriki S, Karibe H, Nakasato N, eds. *Recent Advances in Biomagnetism*. Sendai: Tohoku University Press, 1999, pp. 89-92.
- Montonen J, Ahonen A, Hämäläinen M, Ilmoniemi R, Lame P, Nenonen J, Paavola M, Simelius K, Simola J, Katila T: Magnetocardiographic functional imaging studies in Biomag laboratory. In: Aine C, Okada Y, Stroink G, Swithenby S, Wood C, eds. *Biomag96, Proceedings of the 10th International Conference on Biomagnetism*. New York: Springer, 2000, pp. 494-497.
- Mäkijärvi M, Montonen J, Toivonen L, Siltanen P, Nieminen MS, Leiniö M, Katila T: Identification of patients with ventricular tachycardia after myocardial infarction by high-resolution magnetocardiography and electrocardiography. *J Electrocardiol* 1993;26:1171-124.
- 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.
- Hood MA, Pogwizd SM, Peirick J, Cain ME: Contribution of myocardium responsible for ventricular tachycardia to abnormalities detected by analysis of signal-averaged ECGs. *Circulation* 1992;86:1888-1901.
- Lander P, Goyal P, Goyal R, Berbari EJ, Caminal P, Lazzara R, Steinberg J: Analysis of abnormal intra-QRS potentials. Improved predictive value for arrhythmic events with the signal-averaged electrocardiogram. *Circulation* 1997;95:1386-1393.
- Korhonen P, Pesola K, Järvinen A, Mäkijärvi M, Katila T, Toivonen L: Relation of magnetocardiographic arrhythmia risk parameters to delayed ventricular conduction in post-infarction ventricular tachycardia. *Pacing Clin Electrophysiol* 2002;25:1339-1345.
- Huikuri H, Mäkiälä T, Raatikainen P, Perkiömäki J, Castellanos A, Myerburg R: Prediction of sudden cardiac death. Appraisal of the studies and methods assessing the risk of sudden arrhythmic death. *Circulation* 2003;108:110-115.
- Bigger TJ Jr: Prophylactic use of implanted cardiac defibrillators, in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. *N Engl J Med* 1997;337:1569-1575.
- Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatake R, Fain E, Gent M, Connolly SJ: DINAMIT Investigators: Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med* 2004;351:2481-2488.
- Zimetbaum PJ, Buxton AE, Batsford W, Fisher JD, Halley GE, Lee KL, O'Toole MF, Page RL, Reynolds M, Josephson ME: Electrocardiographic predictors of arrhythmic death and total mortality in the multicenter unsustained tachycardia trial. *Circulation* 2004;110:766-769.
- Bloomfield DM, Steinman RC, Namerow PB, Parides M, Davidenko J, Kaufman ES, Shinn T, Curtis A, Fontaine J, Holmes D, Russo A, Tang C, Bigger JT Jr: Microvolt T-wave alternans distinguishes between patients likely and patients not likely to benefit from implanted cardiac defibrillator therapy. *Circulation* 2004;110:1885-1889.
- Ikeda T, Saito H, Tanno K, Shimizu H, Watanabe J, Ohnishi Y, Kasamaki Y, Ozawa Y: T-wave alternans as a predictor for sudden cardiac death after myocardial infarction. *Am J Cardiol* 2002;89:798-802.
- Tapanainen JIM, Still AM, Airaksinen KEJ, Huikuri HV: Prognostic significance of risk stratifiers of mortality, including T wave alternans after acute myocardial infarction: Results of a prospective follow-up study. *J Cardiovasc Electrophysiol* 2001;12:645-653.
- Hjalmarson A, Fagerberg B: MERIT HF mortality and morbidity data. *Basic Res Cardiol* 2000;95(Suppl 1):198-1103.
- Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, Smid R, Dunkman WB, Loeb H, Wong M: A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;325:303-310.
- Muller JE, Kaufmann PG, Luepker RV, Weisfeldt ML, Deedwani W, Willerson JT: Mechanisms precipitating acute cardiac events:

- Review and recommendations of an NHLBI workshop. *Circulation* 1997;96:3233-3239.
30. Moss AJ: MADIT-II. Substudies and their implications. *Card Electrophysiol Rev* 2003;7:430-433.
31. Shamim W, Yosufuddin M, Cicoria M, Gibson DG, Coats AJS, Hencin MY: Incremental changes in QRS duration in serial ECGs over time identify high risk elderly patients with heart failure. *Heart* 2002;88:4751.
32. Bode-Schnurbus L, Bocker D, Block M, Gradaus R, Heinecke A, Breithardt G, Borggreffe M: QRS duration: A simple marker for predicting cardiac mortality in ICD patients with heart failure. *Heart* 2003;89:1157-1162.