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Qualitative und quantitative Beschreibung von myokardialen Ischämien mittels Magnetokardiographie

Qualitative and Quantitative Description of Myocardial Ischemia by means of Magnetocardiography

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Im Rahmen dieser Arbeit werden quantitative Parameter vorgestellt, mit deren Hilfe aus magnetokardiographischen Aufnahmen, auf eine Ischämie im Herzmuskel geschlossen werden kann.

Die Analyse beruht auf der Untersuchung von 86 Patienten mit instabiler Angina pectoris, von denen 53 mit hoher Wahrscheinlichkeit eine myokardiale Ischämie aufwiesen (angiographisch nachgewiesene Stenose von mindestens 50% einer Koronararterie 1. oder 2. Ordnung bei positivem Troponin; Gruppe I), während dies bei 33 anderen Patienten mit hoher Wahrscheinlichkeit ausgeschlossen werden konnte (angiographisch freies Koronarsystem bei normalen Troponinwerten; Gruppe II).

Der negative Vorhersagewert (die Wahrscheinlichkeit, dass keine myokardiale Ischämie vorliegt, wenn das Magnetokardiogramm negativ ist) beträgt 96,2%, der positive Vorhersagewert 91,2% (die Wahrscheinlichkeit, daß bei positivem Magnetokardiogramm tatsächlich eine koronare Herzerkrankung vorliegt).

Beim gleichzeitig aufgenommenen 12-Kanal-EKG ergibt sich ein positiver Vorhersagewert von 92,8% aber ein negativer Vorhersagewert von 53,4%.

Damit führten die gewählten Parameter mit den hier vorgegebenen Grenzwerten zu einer hohen Trennschärfe zwischen Patienten mit myokardialer Ischämie und solchen ohne. Insbesondere für den Ausschluß einer koronaren Herzerkrankung bei instabiler Angina pectoris erwies sich das MKG dem 12-Kanal-EKG überlegen.

In the framework of this study quantitative parameters are presented which, derived from magnetocardiographic maps, aid in making a conclusion about ischemia in the myocardium.

The analysis is based on the examination of 86 patients with unstable angina, of which 53 exhibit myocardial ischemia with high probability (Group I: angiographically proven stenosis of at least 50% in a coronary artery of first or second order and positive troponin), while in the 33 other patients myocardial ischemia could be ruled out with high probability (Group II: angiographically clean coronary bed and normal troponin values).

The negative predictive value (the probability that there is no myocardial ischemia when the magnetocardiogram (MCG) is negative) is 96.2%; the positive predictive value (the probability that there is actually coronary heart disease when the magneto-cardiogram is positive) is 91.2%.

A 12-lead ECG taken at the same time as the MCG achieved a positive predictive value of 92.8%, but a negative predictive value of 53.4%.

Consequently, the boundary values of the parameters selected lead to a markedly distinct separation between patients with myocardial ischemia from those without. For ruling out coronary heart disease in patients with unstable angina the MCG is superior to 12-lead ECG.

Introduction

The gold standard for the diagnosis of hemodynamically significant lesions in coronary arteries is coronary angiography. Because the process is invasive and is accompanied by heavy doses of radiation, there is demand for alternative methods, especially non-invasive, radiation-free ones, for the determination of myocardial ischemia. The techniques employed to date, such as 12-lead resting ECG, exercise treadmill testing, stress echo or nuclear perfusion imaging, are either not without risk or their predictive value is limited [3, 4, 15, 20, 21, 22].

Magnetocardiography is a non-invasive, radiation-free, non-contact method for the detection of the magnetic field above the heart. With every excitation of a myocardial cell an action current is generated [Hoffmann]. The external membrane of the excited region is always electronegative relative to the non-excited region [8, 12]. The consequence of this biological activity is the creation of electric fields that can be measured as potential differ-

ences by electrodes on the skin surface (electrocardiography: ECG). The distribution of current density in the body tissue simultaneously creates a magnetic field. While the spreading of the electric field depends on the conductivity of the corresponding medium, the magnetic fields pass relatively unattenuated throughout the body.

The use of superconducting quantum interference devices (SQUID) allows the quantitative measurement of these very fine magnetic fields with high temporal resolution. The spatial resolution depends on the number of detectors employed. With multichannel magnetocardiography one can calculate the magnetic field of the heart, for example, every 1 to 10 milliseconds, using mathematical models and interpolation methods. The result are so-called magnetic field maps, which display the entire course of depolarization and subsequent regeneration (repolarization) [9]. In the present study parameters were developed from these field maps, which should permit the determination of myocardial ischemia.

1. Materials and Methods

In order to prove that myocardial ischemia can be detected by magnetocardiography (MCG) two groups of patients were studied. In total the data of 86 consecutive patients with unstable angina were entered into a registry. All patients had a 12-lead ECG and a troponin test, an MCG, and then underwent coronary angiography, whereby the 12-lead ECG was taken immediately before or after the magnetocardiograph examination.

Fifty-three (53) patients had pathologically elevated troponin concentrations and concurrent coronary heart disease (50 % or greater stenosis in at least one coronary artery of first or second order). In these patients (Group I) there is a high probability of underlying myocardial ischemia.

As a control group $n=33$ patients were examined who did not exhibit elevated troponin I levels and in whom coronary heart disease could be ruled out (Group II). In Group II patients there is a high probability that myocardial ischemia can be ruled out.

General exclusion criteria were existence of ST elevation MI, left or right bundle branch block, tachycardia with frequency exceeding 150 beats per minute (since in these cases myocardial ischemia can occur [10]), as well as aortic stenosis. Also excluded were, patients with pacemakers and ICDs.

1.1 Magnetocardiograph System

The magnetocardiograph exams were conducted with the „CMI 2409“ (CardioMag Imaging™, Inc., Schenectady, New York, USA) [17]. This system was provided for the study by CardioMag Imaging, Inc.

The „CMI 2409“ magnetocardiograph measures above the thorax of the patient the vertical component ($B_z(t)$) of the time-varying magnetic field $\mathbf{B}(t)$ during the cardiac cycle. The B_z is measured by superconducting quantum interference devices (SQUIDS) under non-shielded conditions. The value of B_z is measured simultaneously at nine (9) points in a plane close to the patient's chest. For the purpose of averaging using an ECG trigger, a 1-channel (lead I) ECG reference measurement was performed. Data from 13 channels (9 MCG sensors, 3 reference sensors, and 1 ECG) were acquired simultaneously at a frequency of 1000 Hz.

1.2 The MCG Test Procedure

Before the MCG test all magnetic, electric, and other large metallic objects (credit cards, watches, keys, bracelets, removable dentures, etc.) are removed from the body or the clothing. Patients with implanted electronic devices like pacemakers or defibrillators are excluded from the MCG tests, since signals from such devices can produce significant artifacts in the MCG traces. During the measurement the patient lies on a bed that can be moved in the x- and y-directions. In total four sepa-

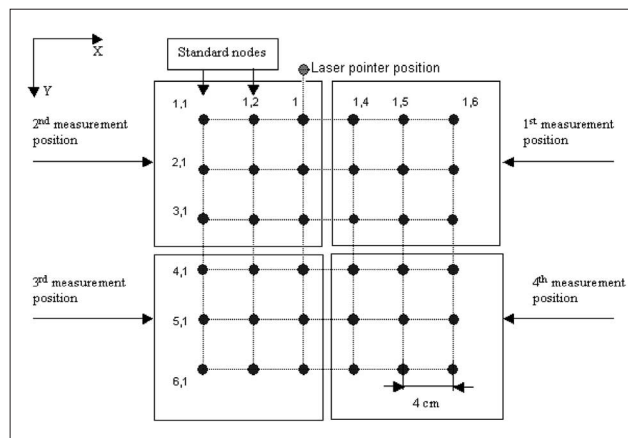


Figure 1. Representation of the measurement positions in the 4-position technique and the resulting 6x6 measurement points

rate measurements are made sequentially in mutually orthogonal positions. Doing so covers a chest area of 20cm x 20cm over the heart with 36 measurement points separated from each other by a distance of 4 cm. Figure 1 illustrates this 4-position technique. The blue point in the matrix represent the center of a detector. The X and Y coordinates are determined by the position of the bed, that assumes each of the four positions. A laser pointer fixed to the side of the detector housing is aimed at the supersternal notch to fix the reference position for the measurements as well as for possible repeat follow-up measurements. After each recording the operator manually sets the bed in the next position.

In order to have enough cardiac cycles for further data processing the measurement in each position lasts 60 seconds. The entire examination, including patient preparation, last about 10 minutes.

1.3 Data Format

Raw data are stored and can be retrieved at any time. Filtered and preprocessed data (spectral analysis and digital filtering) are represented as temporal traces of magnetic

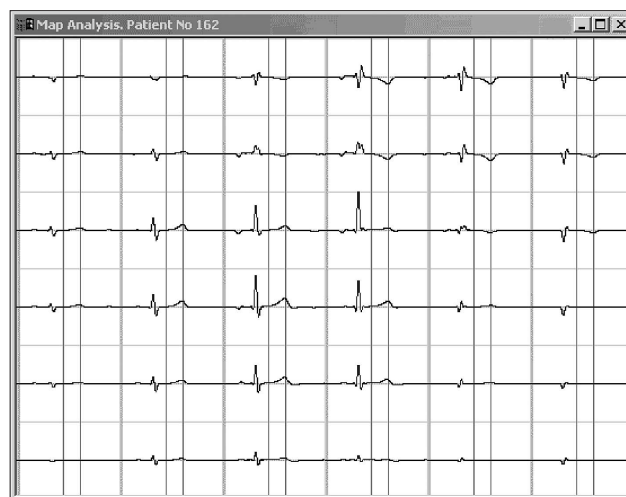


Figure 2. Filtered and averaged MCG data measured at 36 points over the period of one cardiac cycle.

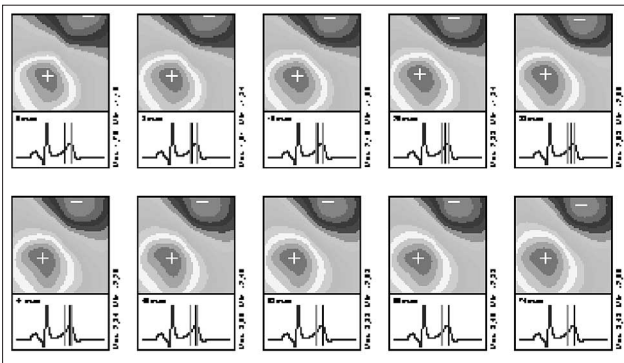


Figure 3. Cardiac magnetic field of a patient without myocardial ischemia (Group II), generated at various time points in the interval between $T_{max}/3$ and T_{max}

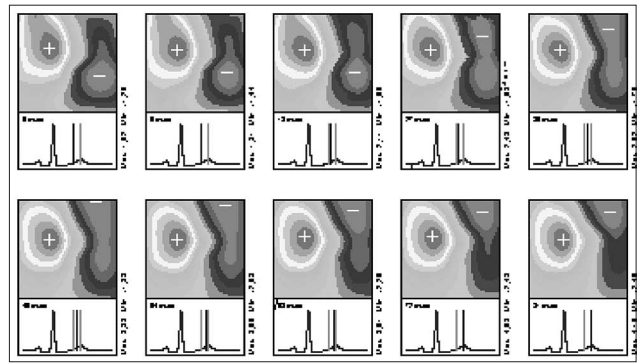


Figure 4. Cardiac magnetic field of a patient with acute myocardial ischemia (Group I), generated at various time points in the interval between $T_{max}/3$ and T_{max}

field intensity in a horizontal plane above the thorax where the magnetic detectors are located.

These temporal traces of the magnetic field intensity look similar to those of conventional electrocardiography. The MCG data of every channel are displayed like an averaged ECG with P- and T-waves, as well as QRS complexes and ST segments. Figure 2 shows an example of averaged data. By means of interpolation among the 36 discrete measurement points the magnetic field distribution at any arbitrary time in the cardiac cycle can be displayed (magnetic field maps). Figure 3 shows different phases of the magnetic field distribution of a patient without myocardial ischemia, and Figure 4 the same phases of a magnetocardiogram for a patient with myocardial ischemia.

1.4 Data Analysis and Diagnostics

Before data analysis can begin, in every case one must examine whether an analysis is possible. For this one must be certain that the T-wave in the recorded raw data is clearly greater than the noise.

From the changes in the magnetic field during a cardiac cycle parameters can be determined which aid in establishing a diagnosis of „ischemia“. The question arises which part of the cardiac cycle appears suited to the diagnosis of ischemia. Here experience from the area of electrocardiography provides some distinct clues.

The part of the ECG sensitive to ischemia is the ST-T Segment [13]. The ST segment alone in the magnetocardiogram appears to be of limited utility, since it is often difficult to distinguish the biological signal from the noise. It is not easy to separate ST-depressions and ST-elevations from fluctuations in the baseline.

The part of the ECG interval most sensible from the standpoint of ischemia is the end phase of the ST segment or the beginning of the T-wave. Unfortunately the initial phase of the T-wave also does not ensure a good analysis since the signal to noise ratio here does not allow a guaranteed analysis for all patients.

In order to ensure a reliable and reproducible analysis for all patients an arbitrary cut-off value of 1/3 of the maximum of the T-wave was specified, from which the analysis of the changes in the magnetic field would begin. Since

no qualitative differences in the magnetic field changes between patients with and without ischemic myocardium could be found in the descending part of the T-wave, we confined diagnosis of ischemia to the ascending part of the T-wave between $T_{max}/3$ and T_{max} .

In the selected MCG interval between $T_{max}/3$ and T_{max} the magnetocardiograms of patients without ischemia exhibit qualitatively a temporally very stable magnetic field (Figure 3). The direction of the main vector, the pole positions, the pole strengths, as well as the pole separation change slowly or remain over the period for the most part constant. A „pole“ is either the maximum or minimum of the magnetic field at any point in time. The plus pole designates the place of maximum field strength where the field is directed into the measurement plane. Analogously the minus pole designates the place of minimum field strength where the magnetic field direction comes out of the plane.

Patients with myocardial ischemia present a completely different picture. Here we see pronounced temporal instability of both poles. Figure 4 shows an example. This patient had angiographically proven coronary heart disease (70% stenosis of the left coronary artery, single vessel disease) and elevated troponin levels with symptoms consistent with unstable angina.

For the characterization of myocardial ischemia we chose the following parameters in the time interval described above: direction of the vector (from plus pole to minus pole), change in the angle of this vector, change in the distance between plus and minus poles, and change in the ratio of the pole strengths. Rapid changes in these parameters in a time interval of 30 msec in the MCG interval between $T_{max}/3$ and T_{max} were characteristic of ischemia. Therefore, we defined the following values as parameters for ischemia:

- P1:** the direction of the main vector lies between -20 and +110 degrees
- P2:** a change in the angle of the main vector of more than 45 degrees inside a time interval of 30 msec between $T_{max}/3$ and T_{max}
- P3:** a change in the distance separating the plus and minus poles of more than 20 mm inside a time interval of 30 msec between $T_{max}/3$ and T_{max}

Figure 5. Typical example for the change in angle of the magnetic main vector of greater than 45 degrees within 30 msec in the interval between Tmax/3 and Tmax (Group I) (Criterion P2)

Figure 6. Typical example for the change in distance between the plus and minus poles of more than 20 mm degrees within 30 msec in the interval between Tmax/3 and Tmax (Criterion P3)

Figure 7. Typical example for a change in the ratio of the plus and minus poles of more than 0.3 within 30 msec in the interval between Tmax/3 and Tmax (Criterion P4)

P4: a change in the ratio of the plus and minus pole field strengths of more than 0.3 inside a time interval of 30 msec between Tmax/3 and Tmax

A diagnosis of myocardial ischemia is made when at least one of these four parameters exceeds the corresponding critical value. Several examples follow which illustrate the calculation of these parameters.

The angle of the main magnetic vector is quantitatively described over the entire time interval and is displayed graphically as a function of time. Sudden strong changes – as in Figure 5 – characterize an ischemia of the heart muscle (Criterion P2).

Figure 6 shows an example of changes in the distance separating the magnetic poles (Criterion P3). Changes in the distance between the plus and minus poles of more than 20 mm inside a time interval of 30 msec between Tmax/3 and Tmax are evaluated as myocardial ischemia.

Criterion P4 cannot be easily recognized in the figures since the pole strengths are only shown as gradients in color. Accordingly quantitative changes are only noticeable in graphs. Figure 7 provides an example.

Changes in the ratio of the plus and minus pole strengths of more than 0.3 inside a time interval of 30 msec between Tmax/3 and Tmax are evaluated as myocardial ischemia (Criterion P4).

2. Patients

Included in the study were a total of 86 patients with symptoms of unstable angina: 53 patients, who were determined angiographically to have coronary heart disease and at the same time exhibited elevated troponin levels, and 33 patients with normal troponin levels in whom coronary heart disease was ruled out. The patients fulfilling the inclusion and exclusion criteria were consecutively entered into the registry.

Seventeen (17) patients in Group I had Diabetes mellitus (15 NIDDM, 2 IDDM); of whom 12 were insulin dependent, 7 in Group II (all NIDDM, of whom 4 were insulin dependent). There was arterial hypertension in 35 patients in Group I and in 21 patients in group II; 18 patients in Group I and 13 patients in Group II had hypercholesterolemia.

There were 13 heavy smokers in Group I (29 ex-smokers, 21 never smoked). In group II there were 3 heavy smokers, 12 ex-smokers, and 18 never smoked.

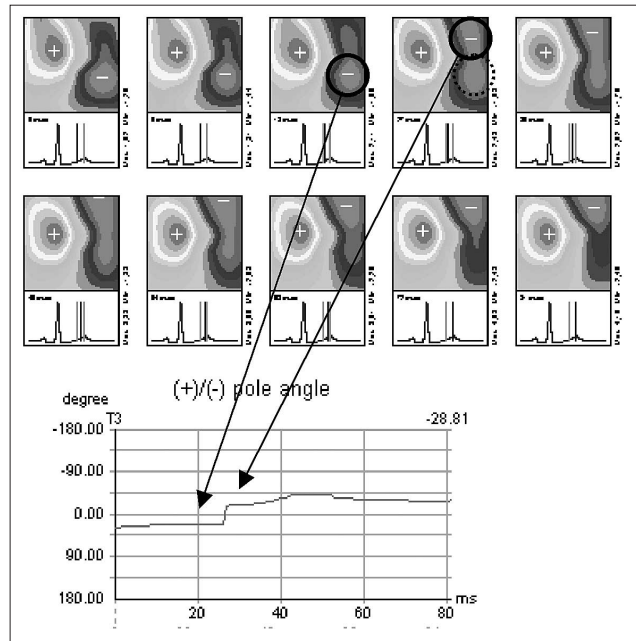


Figure 5

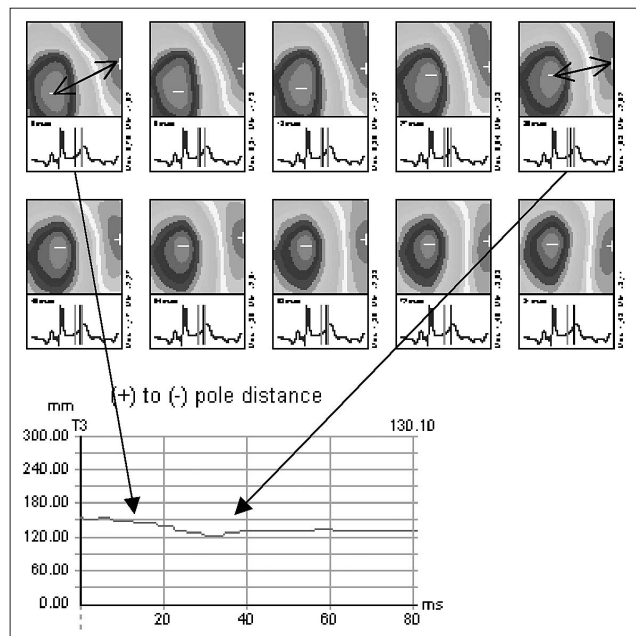


Figure 6

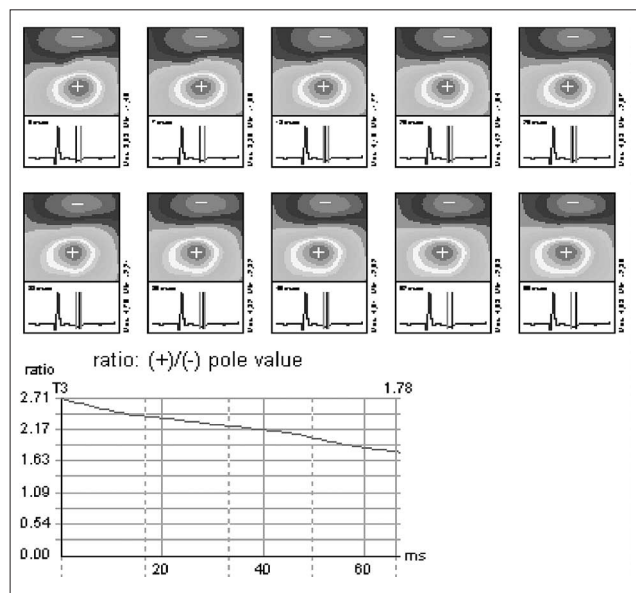


Figure 7

Table 1 lists selected demographic and clinical information of both groups.

n	Group I 53	Group II 33
Gender M/F	31/22	18/15
Age [years]	68.2±11.9	61.2±9.6
RR, systolic [mmHg]	144±24	138±16
RR, diastolic [mmHg]	77±13	80±10
Pulse [beats/min]	87±24	73±12
Coronary status		
1-vessel disease	8	-
2-vessel disease	13	-
3-vessel disease	32	-

Table 2 shows the ischemia parameters determined for both groups.

	Group I	Group II	P
	N=53	N=33	
P1 [degree]	177.9±108.1	282.5±58.6	0.0001
P2 [degree]	41.7±108.1	10.8±13.7	0.0171
P3 [cm]	20.7±108.1	10.5±6.1	0.0014
P4 [-]	0.41±108.1	0.19±0.18	0.0104

In thirty (30) of the 53 patients in Group I coronary intervention followed coronary angiography, and in 14 others, urgent heart surgery.

3. Statistics

The results are stated as mean values with standard deviation. For the uncoupled 2-tailed problem the Student t-test was used. Probabilities smaller than $p=0.05$ were evaluated as significant. Since the evaluation of the magnetocardiogram was made prior to coronary angiography without knowledge of the troponin value, the calculation of sensitivity, specificity, as well as predictive values took place without pretest probability [5]. The sensitivity is calculated by dividing the number of true positive results by the number of patients with disease; the specificity is calculated by dividing the number of true negative results by the number of patients without disease. With help of bayes formula one can calculate the probability that the disease to be diagnosed is actually present after a positive diagnostic test result (pV).

$$pV = \frac{\text{True positive results}}{\text{(True positive results + false positive results)}}$$

Likewise one can calculate how large the probability is, that a disease is absent when a test result is negative. This takes place with help of the negative predictive value (nV):

$$nV = \frac{\text{True negative results}}{\text{(True negative results + false negative results)}}$$

4. Results

Thirty-three (33) of the 53 patients exhibited a pathologic angle orientation of the vector, 12 pathologically elevated angle deviations, 18 pathologically elevated pole distance variations, and 24 pathologically elevated changes in the pole strengths.

In Group I 50 of 53 patients (94.3%) were recognized as true positive, 3 as false negative (5.7%). In Group II 31 of 33 patients (93.9%) were recognized as true positive, 2 as false positive (6.1%)..

The sensitivity of magnetocardiography for the diagnosis of myocardial ischemia without pretest probability in the unstable angina patient group selected here was 94.3% and the specificity 93.9%. The negative predictive value (the probability that there is no myocardial ischemia when the magnetocardiogram is negative) was 96.2%, the positive predictive value 91.2%.

In Group I 26 patients had a pathologic ECG (in 27 cases unremarkable), while in Group II 31 of the 33 patients had an unremarkable ECG. The specificity in these patients was 93.9% and the sensitivity, on the other hand, only 49%. The corresponding positive predictive value was 92.8% and negative predictive value 53.4%.

5. Discussion

The aim of the study was to prove whether myocardial ischemia, which is associated with characteristic changes in the cardiac magnetic field during a cardiac cycle, can be described by simple quantitative parameters. To this end we studied patients with and without myocardial ischemia at rest with a 9-channel magneto-cardiography system without shielding. By observing magnetic field maps of patients without manifest coronary heart disease and comparing these with those of patients with symptoms of acute angina pectoris and manifest coronary heart disease, we formulated four parameters first qualitatively or descriptively, then quantitatively. It was shown that the analysis with a combination of these four parameters led to a very high positive predictive value: the probability that a patient with a pathologic MCG has myocardial ischemia at the time of the examination was 91.2% (positive predictive value), that with a physiological MCG has no ischemia was 96.2% (negative predictive value).

A high negative predictive value is especially important to avoid as much as possible the inadvertent discharge of the patient who truly has myocardial ischemia. Of the patients who are mistakenly discharged from a „Chest Pain Center“ as healthy, 4 to 5% develop a myocardial infarction and 11 to 20% enhanced morbidity.

The ECG in this study exhibited similar specificity and positive predictive values, but the sensitivity of 49% and negative predictive value of 53.4% were considerably inferior.

The reason for this lies probably in the different information which these two physical processes contain [19]. The ECG describes potential differences on the surface of the skin of the patient, and is not sensitive to closed cur-

rent paths inside the body. According to Trahms [18] the surface potential $U(\underline{r})$ can be represented as a function of the location r (Equation 1):

$$U(r) = \sum_{\substack{n=1,\infty \\ m=0,n}} U_{nm}(\underline{r}, a_{nm}, b_{nm}) \quad (1)$$

Here the terms a_{nm} and b_{nm} describe sources and sinks of the current fields. Contrary to this the MCG is a recording of the magnetic fields that arise also because of these closed currents inside the body. The magnetic field $B(r)$ is described by the following formula (Equation 2) [18]:

$$\underline{B}(r) = \sum_{\substack{n=1,\infty \\ m=0,n}} \underline{B}_{nm}(\underline{r}, a_{nm}, b_{nm}) + \underline{B}'_{nm}(\underline{r}, \alpha_{nm}, b_{nm}) \quad (2)$$

Here a_{nm} and b_{nm} describe closed current paths. Both equations are constructed similarly in the first summations, however in Equation 2 there is an additional summation which is not present in Equation 1. That this physical difference is of special significance, especially for ischemic states, could be demonstrated on healthy patients by Trahms and his co-workers: while the ECG remained nearly unchanged before and after pharmacologically induced cardiac stress, the cardiac magnetic fields displayed significant differences [18].

The MCG measurement is, in contrast to the ECG measurement, completely non-contact. Therefore artifacts caused by insufficient and/or variable electrode-skin contact, which happens not so seldom during ECG recording, as a rule do not exist. Furthermore the sensor configuration is – different from the ECG measurement – fixed. Therefore, the precision of the technical signal transfer and the reproducibility of the MCG measurement is superior to the ECG [16].

Similar to the ECG the early repolarization phase, in which the ischemia-sensitive changes in the MCG are observed, is most likely caused by altered ion transfer in relation to the metabolic status of cardiac cells [2]. A change in the angle of the magnetic field vector during ischemia was already described by other groups [6, 7]. However, only the combination of various instabilities which appear in the magnetic field in the case of myocardial ischemia during a cardiac cycle leads to the high degree separation achieved in this work. In a recently published study by Hailer et al. a semi-quantitative analysis using a 1-channel MCG system could show that there is a significant difference in the magnetic fields of patients with coronary heart disease and of healthy controls [7]. Here the magnetic field maps were qualitatively grouped into five categories, and the frequency of these categories was compared between the two groups.

6. Limitations of the Study

The ability of this study to make a statement is limited for a variety of reasons. The number of patients evaluated is

too small to draw definitive conclusions. Moreover, one has to bear in mind that a 9-channel system was used in the current case, so that four measurements had to be made sequentially. In so doing, the recordings in the four quadrants differ in time.

In all patients the MCG examination took place after initial care in the intensive care unit. Therefore, all patients at the time of the MCG examination were under medication (heparin, nitrates, calcium antagonists, beta blockers, aspirin/clopidogrel/GpIIbIIIa blockers). At this time it is not known to what extent these have influenced the results.

The diagnostics selected in this study (symptoms, coronary angiography, Troponin I concentration) can identify patients with myocardial ischemia with high probability. Of course, one must keep in mind that troponin can also become elevated in patients with hypertension, cardiac insufficiency, kidney insufficiency, myocarditis, etc. On the other hand, myocardial ischemia is also possible in the patients of Group 2, since, for example, coronary vasospasm or a coronary microangiopathy can also result in ischemia. Simply by the temporal delay between the diagnostics carried out (with the exception of the ECG) and the MCG in individual cases it is possible for ischemia to occur, or the ischemia can be relieved by stabilization of the coronary blood flow.

7. Conclusions

The selected parameters with the cut-off values given above lead to a very distinct separation between patients with myocardial ischemia and those without. A multicenter trial is in preparation in which the parameters will be evaluated in a large cohort of patients. How well the predictive values of the defined ischemia parameters can be improved further will be tested through ROC analysis.

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