Clinical Validation of Machine Learning for Automatic Analysis of Multichannel Magnetocardiography[1]

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Abstract. Magnetocardiographic (MCG) mapping measures magnetic fields generated by the electrophysiological activity of the heart. Quantitative analysis of MCG ventricular repolarization (VR) parameters may be useful to detect myocardial ischemia in patients with apparently normal ECG. However, manual calculation of MCG VR is time consuming and can be dependent on the examiner's experience. Alternatively, the use of machine learning (ML) has been proposed recently to automate the interpretation of MCG recordings and to minimize human interference with the analysis. The aim of this study was to validate the predictive value of ML techniques in comparison with interactive, computer-aided, MCG analysis.

ML testing was done on a set of 140 randomly analysed MCG recordings from 74 subjects: 41 patients with ischemic heart disease (IHD) (group 1), 32 of them untreated (group 2), and 33 subjects without any evidence of cardiac disease (group 3). For each case at least 2 MCG datasets, recorded in different sessions, were analysed.

Two ML techniques combined identified abnormal VR in 25 IHD patients (group 1) and excluded VR abnormalities in 28 controls (group 3) providing 75% sensitivity, 85% specificity, 83% positive predictive value, 78% negative predictive value, 80% predictive accuracy This result was for the most part in agreement, but statistically better than that obtained with interactive analysis.

This study confirms that ML, applied on MCG recording at rest, has a predictive accuracy of 80% in detecting electrophysiological alterations associated with untreated IHD. Further work is needed to test the ML capability to differentiate VR alterations due to IHD from those due to non-ischemic cardiomyopathies.

1 Introduction

Magnetocardiographic mapping measures magnetic fields generated by the electrophysiological activity of the heart, and is a promising imaging technology developed for the rapid, non-invasive detection of ventricular repolarization abnormalities. MCG data are usually mapped, simultaneously or sequentially, from

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33-60 locations above the frontal torso, using superconducting quantum interference devices (SQUIDs).

Previous research[1] has shown that, compared to standard ECG, multichannel MCG provides non-invasive evaluation of cardiac electrogenesis, with similar investigation time, but higher spatial and temporal resolution.

The diagnostic potential of MCG mapping ranges from three-dimensional electroanatomical localization of arrhythmias, to the identification of VR abnormalities in patients with myocardial ischemia and non-diagnostic ECG[1,2].

The analysis of VR from MCG mapping can be done visually and/or quantitatively. Quantitative VR parameters can be calculated from the ST interval and/or the T wave[3-10]. Interactive computer-aided analysis of MCG parameters, especially of the ST interval, can be influenced by low signal to-noise ratio (SNR) and by the examiner's experience. Therefore, automatic analysis procedures are needed to speed-up the procedure and to minimize human input.

The aim of this study was to validate automatic classification of Magnetocardiograms using a Machine Learning (ML) approach, developed under the NSF SBIR phase I grant #0232215 and described by Szymanski et al[11]. The performance was compared to computer-aided interactive analysis of MCG mapping, independently performed by two expert cardiologists.

As the ST-segment has usually a low SNR in magnetocardiograms, whereas the T-wave is most likely to show primary abnormalities due to ischemia and has a high SNR, ML was applied to the magnetic field data of the T-wave only.

2 Methods

2.1 Instrumentation and Data Pre-processing

MCG mapping was performed at rest in supine position, with a 36-channel MCG system (*CardioMag Imaging Inc., USA*)[12] based on DC-SQUID sensors coupled to second order gradiometers (baseline: 50-70 mm) with pick-up coils diameter of 19 mm and sensor-to-sensor spacing of 40 mm. The distance between the measuring sensors, kept at liquid helium temperature and arranged in a horizontal plane, and the flat bottom surface of the cryostat is 19 mm^2. With a built-in automatic electronic noise suppression system (ENSS), the instrumentation reaches a sensitivity of about 20 fT/Hz½ at 1 Hz, with balance stability of gradiometers better than 0.01%.

All MCG signals and one reference 12-lead ECG were simultaneously recorded for 90 seconds, at a sampling rate of 1 kHz, in the bandwidth from DC to 100 Hz.

All recordings were performed without electromagnetic shielding, in a room fully equipped for cardiac catheterization and intensive care. Digital low pass filter at 20 Hz was used before ML was applied. To eliminate stochastic noise components, all signals were averaged. For automatic classification, data from a time window between the J point and T peak were used.

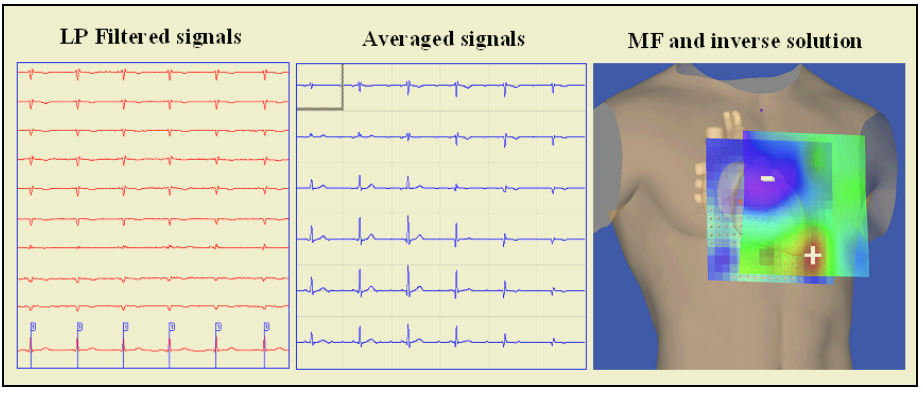

Fig. 1. MCG signal processing

2.2 Signal Processing

To eliminate stochastic noise components, all signals were averaged using the maximum of the R peak as a trigger point (Figure 1).

VR was analyzed according to specific preset parameters, and two ML scores automatically calculated for each subject resulting in an MCG classification of either normal or abnormal (Figure 2).

The tool used for ML is called Direct Kernel partial least squares (**DK-PLS**). Partial least squares (PLS) are one of the standard analysis methods in QSAR and chemo metrics[14]. Kernel PLS (K-PLS) is a recently developed nonlinear version of PLS, introduced by Rosipal and Trejo[15]. K-PLS is functionally equivalent to support vector

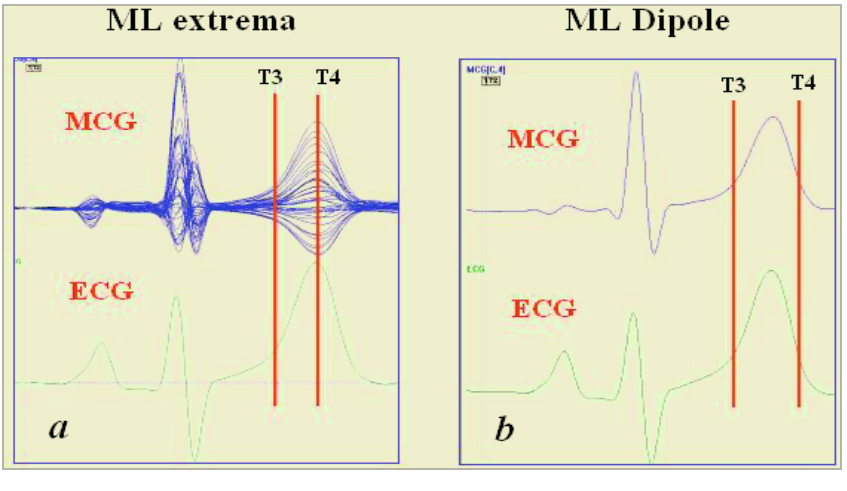

Fig. 2. Time intervals (indicated by T3 and T4 bars) from which the two ML scores were calculated

machines (SVMs) and is currently used to predict binding affinities to human serum albumin. The difference between K-PLS and DK-PLS is that the feature (data) kernel matrix is used in K methods while this matrix is replaced by the (non-linear) kernel-transformed matrix in DK methods[16]. DK-PLS reached a convincing performance in a preliminary preclinical test[11]. The algorithm was trained on data from 73 cases considering MCG patterns of ischemic and non-ischemic patients. Two diagnostic scores were calculated:

1) The "**ML extrema**" score, based on wavelet transformed MCG patterns of the upslope of the T-wave as shown in Figure 2a (abnormal if > 50).
2) The "**ML Dipole**" score, based on parameters delivered by the solution of an inverse problem. This approach assumes that the electrical processes in the heart during repolarization can be approximated by a so-called Effective Magnetic Dipole (EMD), (see Figure 2b, abnormal if > 34).

2.3 Validation

To validate ML automatic analysis, two expert cardiologists independently performed **interactive computer-aided analysis** on the same data sets. The interactive analysis of MCG mapping was based on:

- The **T-wave** "**extrema**" Magnetic Field (**MF) dynamics analysis"**, which calculates cardiac magnetic field parameters, in a moving time window of 30 msec duration during the T- wave. Said time window starts at MF strength of 1/3 of that at the Tpeak and ends at the Tpeak. For each millisecond a color contour plot is calculated from the MF and displayed as shown in figure 1. In each map two points are marked indicating the extreme values of the magnetic field. The point indicating the location of the maximal magnetic field strength is labeled "+" ("+ pole"), and the point indicating the location of the minimal magnetic field strength is labeled "-" ("- pole"). Parameters calculated within this time interval are:

  1) Change of angle between + pole and - pole (abnormal if $> 45°$);
  2) Change of distance between + pole and - pole (abnormal if > 20 mm);
  3) Ratio between the strength of + pole and - pole (abnormal if > 0.3)[10];

- The **Quantitative Dipole score** (**Q score**), also based on analysis of EMD parameters calculated at 20 points of the T-wave in the same T3-T4 interval used for the ML Dipole (Figure 2 b), (abnormal if > 0) [8, 9].

- The **magnetic field gradient (MFG) orientation** (**angle**), computed at two time-intervals: 1) the integral of the second quarter from the J-point to the T-wave apex, representing ST-segment, and 2) the T-wave apex[3]. The MF α angle was then calculated as the angle between the direction of the largest gradient and the patient's right-left line. The α angle values were considered normal when in the range between 0-90° (Figure 3).

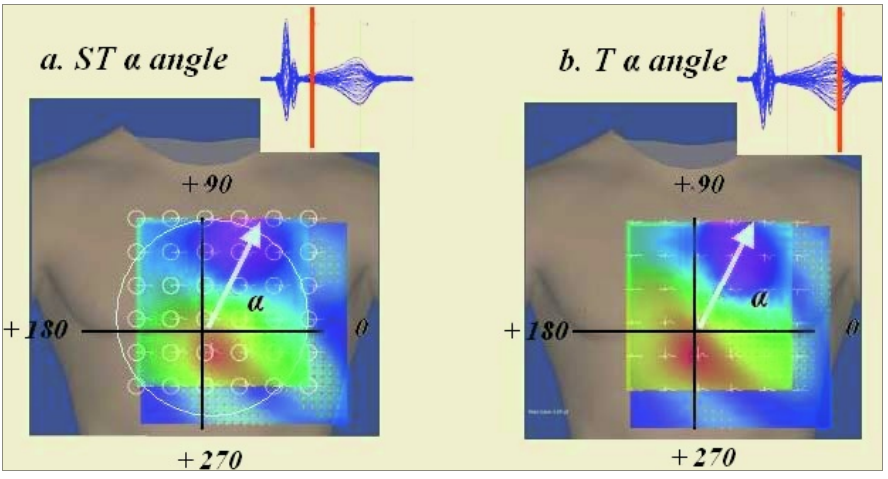

Fig. 3. Example of normal MFG orientation (α angle), at the second quarter of the ST interval (a) and at the apex of the T-wave (b)

2.4 Patients

All MCG studies were performed, after written informed consent, mainly on outpatients, as an additional simultaneous procedure during ECG control.

ML testing was done on a set of 140 randomly analysed MCG recordings belonging to **74 subjects**:

41 patients (Group 1), 26 males and 15 females; 26 with previous MI and 22 with stable class 1 or class 2 angina. Patients were classified as ischemic based on clinical criteria, and on results of exercise ECG testing, nuclear stress testing and/or coronary angiography (CA). CA was available in 31 (29 abnormal). Nuclear stress testing was available in 33 (abnormal in 30). In 9 patients MCG was performed after CA and successful therapy with PTCA. In the 10 patients without CA, nuclear stress testing was abnormal.

All patients were chest pain free at the time of testing, and 27 (67.5%) had a normal or non-specific 12-lead ECG. As 9 patients were studied only after CA, the 32 patients who were studied with MCG before CA were also analysed as a separate group **(Group 2).**

33 subjects, without any evidence of cardiac disease at clinical history, normal physical examination and echocardiography, were included as normal controls **(Group 3)**. The mean age of the investigated subjects was 64.2 ± 9.9 years for group 1 versus 44.4 ± 9.3 years for group 3 ($p<0.0005$).

For each case at least 2 MCG datasets, recorded in different sessions were analysed.

2.5 Statistics

Data are reported as mean ± S.D. Statistical analysis was performed with the unpaired two-tails Student t-test, to evaluate the significance of differences among males and females parameters. A value of $p < 0.05$ was considered significant.

3 Results

3.1 Automatic Classification of MCG

ML classification of MCG mapping was highly reproducible. In Group 1, the combination of two ML scores, obtained by considering "pathological" any patient with at least one of the two scores abnormal, gave: 61% sensitivity, 85% specificity, 83% positive predictive value, 64% negative predictive value, and 72% predictive accuracy (Table 1). However, if only patients of Group 2 were considered (Table 2), the predictive accuracy of the combined ML scores increased to 80%.

Table 1. ML results of 41 IHD patients (Group 1) vs 33 Normals (Group 3)

	ML extrema	**ML Dipole**	**Combination of 2 ML scores**
41 IHD patients	46,4 ± 36,1	46 ± 32,3	-
33 Normals	12,9 ± 17,2	8,8 ± 16,3	-
p value	***< 0.001***	***< 0,001***	-
Sensitivity	41,4	54	61
Specificity	94	88	85
Positive PV	89	85	83
Negative PV	56	60	64
Predictive Accuracy	**65**	**69**	**72**

Table 2. ML results of 32 IHD patients (Group 2) vs 33 Normals (Group 3)

	ML extrema	**ML Dipole**	**Combination of the 2 ML scores**
32 IHD patients	53,6 ± 36,8	53,5 ± 31	-
33 Normals	12,9 ± 17,2	8,8 ± 16,3	-
p value	***< 0.001***	***< 0,001***	-
Sensitivity	47	63	75
Specificity	94	88	85
Positive PV	88	83	83
Negative PV	65	71	78
Predictive Accuracy	**71**	**75**	**80**

3.2 Validation by Comparison with Interactive Quantitative Analysis

For comparison the predictive values of computer-aided interactive estimate of VR parameters (T-wave extrema MF dynamics analysis, Q score analysis and MFG orientation) were calculated.

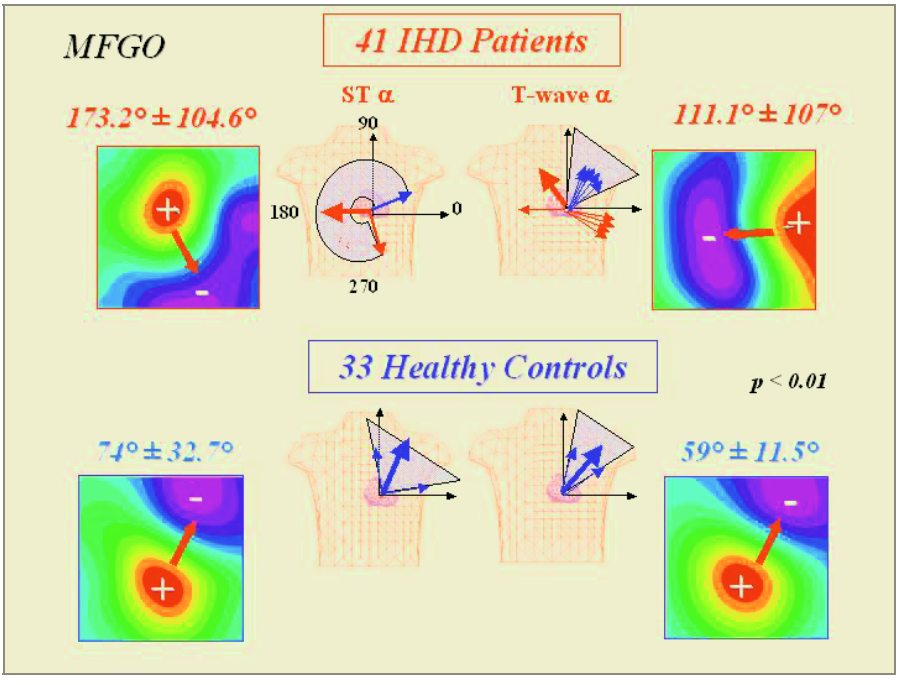

Fig. 4. Examples of typical MF distribution and of average values of MF field gradient orientation (α angles), computed during the ST interval and at the T-wave peak, are shown for Group 1 patients and for controls (Group 3)

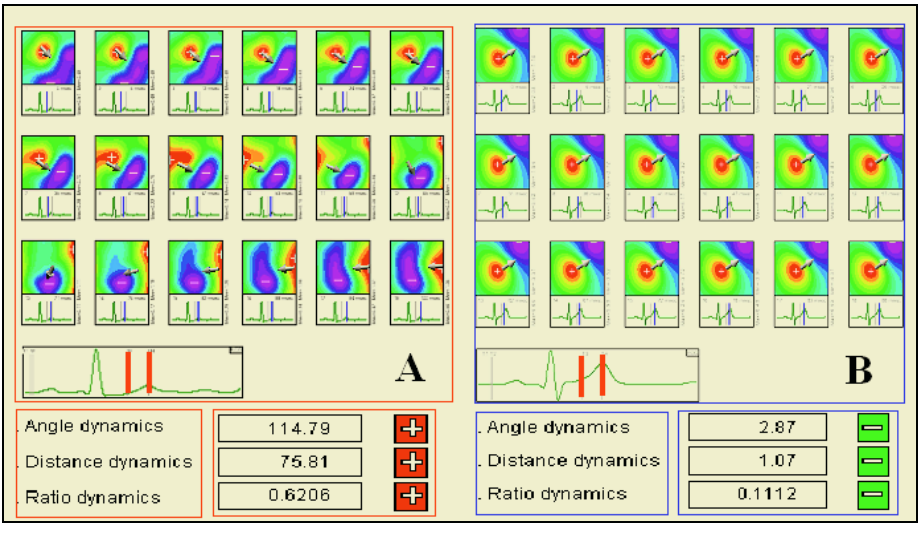

Fig. 5. Example of interactive computer-aided analysis of the MF dynamics during the ascending phase of the T-wave (vertical bars on the ECG). In A, abnormal pattern of an IHD patient. In B, a normal subject is shown for comparison

An example of typical MF distribution during the ST interval and at the T-wave peak in IHD patients and in normal controls is shown in Figure 4, where the average values of MF gradient orientation (α angles) are also included.

An example of MF dynamics analysis is shown in Figure 5.

Interactive computer-aided quantitative estimate of VR parameters (Table 3) was in good agreement with the results of automatic classification, although none of the calculated parameter reached the same predictive accuracy obtained with a combination of the two ML scores, especially in Group 2 patients.

Table 3. Interactive computer-aided analysis

	41 IHD patients (Group 1)					**32 IHD patients w/o PTCA (Group 2)**				
%	**ST α angle**	**T-wave extrema ***			**Q score**	**ST α angle**	**T-wave Extrema ***			**Q score**
Sensitivity	69	22	39	46	56	81	25	47	50	66
Specificity	70	100	91	79	79	70	100	91	79	79
PPV	74	100	84	73	77	72	100	83	70	75
NPV	64	51	55	59	59	79	58	64	62	70
Pred Acc	**69**	**57**	**62**	**61**	**66**	**75**	**63**	**69**	**65**	**72**

** T-Wave extrema parameters: Change of angle between + pole and - pole; Change of distance between + pole and – pole; Ratio between the strength of + pole and - pole (see page 4). Pred Acc: Predictive accuracy.*

4 Conclusions

The possibility of accurate, rapid, and no risk diagnosis of ischemia in an emergency room setting may have a great impact on health care. Truly ischemic patients would benefit from a significant reduction of time for diagnosis while in non-ischemic subjects unnecessary admissions and more invasive testing could be avoided.

This study was performed in an unshielded hospital room fully equipped for intensive cardiac care and interventional cardiology. The MCG data and mapping quality was sufficiently high to detect ventricular repolarization abnormalities in IHD patients.

Automatic classification of rest MCG recording provided quick detection of electrophysiological alterations associated with ischemic heart diseases, with sensitivity ranging between 60 and 70%, specificity of about 85% and predictive accuracy higher than 70%, thus better than that of rest ECG, which was 50 % in Group 1 patients (Table1). Interestingly, when patients successfully treated with PTCA before MCG mapping were excluded from the statistic evaluation (Group 2), the sensitivity, specificity, and predictive accuracy improved to 75%, 85%, and 80%, respectively (Table 2). Thus, although the number in investigated patients is limited, our results confirm that, as for patients with acute chest pain and normal or non-specific 12-lead ECG and normal troponin[8-10] magnetocardiographic imaging is a

promising alternative with the capability of detecting repolarization abnormalities at rest in patients presenting with class 1 and 2 angina, in the absence of significant ECG alteration. The predictive accuracy of the ML method was comparable with that obtained blindly with interactive computer-aided analysis by two expert cardiologists, or even better in untreated patients (Group 2) (Tables 2–3).

In order to improve the predictive accuracy of the method one could incorporate so-called domain knowledge into the machine learning process. Information about the patient, e.g. history, risk factors, results from other tests, could be considered as additional parameters if available. An interesting challenge will be the automatic differentiation of magnetocardiographic abnormalities due to different cardiac diseases by solving a non-ordinal multi-class classification problem[13].

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