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ICDs and Risk Stratification in Magnetic Field Imaging

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1. Introduction

Sudden cardiac death (SCD) is the main cause of death in the USA with an annual incidence estimated between 184000 and 462000 (Goldberger et al., 2008). The typical therapy for preventing SCD is the use of Implantable Cardioverter Defibrillators (ICDs) in patients with low left ventricular ejection fraction (LVEF). Unfortunately the LVEF has limited sensitivity and specificity: The majority of SCDs occur in patients with preserved LVEF. Furthermore, SCD often occurs in active, outwardly healthy people with no known heart disease or other health problems: Most victims do have heart diseases such as Hypertrophic Cardiomyopathy, although they are unaware of this fact (Figure 1). ICDs are devices capable of terminating

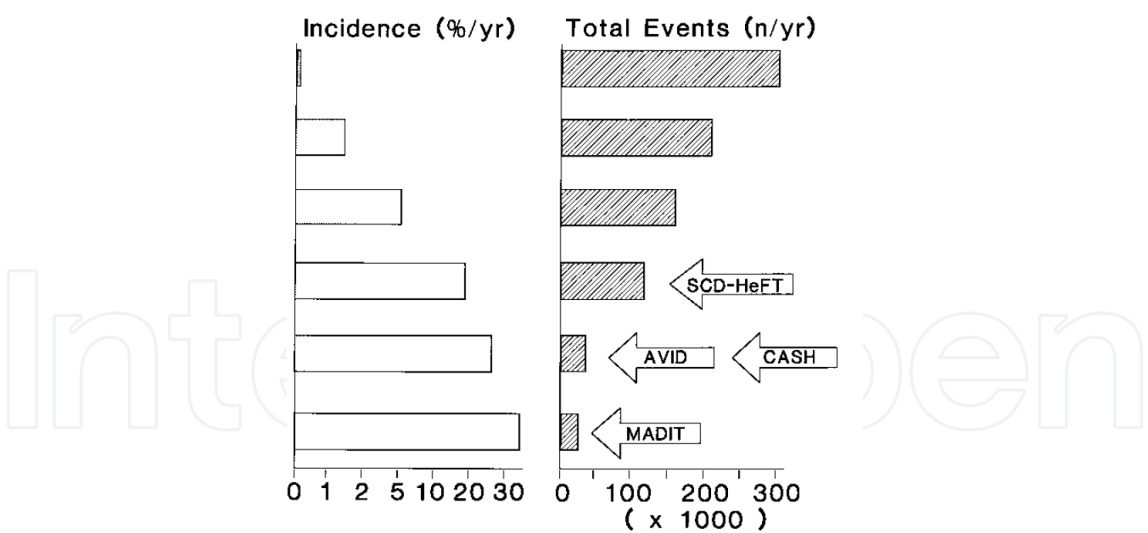


Fig. 1. Estimates of incidences and absolute numbers of SCD. Arrows indicate that trials such as MADIT, AVID and CASH have impact on a small population. SCD-HeFT probably affects a larger population at risk. Anyhow, these subgroups only represent a small part of the patients at highest risk of SCD (Myerburg et al., 1998).

malignant ventricular arrhythmias (Ventricular Tachycardia and/or Ventricular Fibrillation) that have recently been in the focus of large primary prevention studies yielding to an increase of implantation rates (i.e: the SCD-HeFT (Bardy et al., 2005) trial). The substantial number of

patients that fulfill the last trials criteria, in the face of economical constraints and the possible adverse effects, have prompted a research of additional arrhythmia risk markers to further identify patients at highest risk. In fact, the DINAMIT study (Hohnloser et al., 2004) shows that the use of ICDs can reduce the mortality due to arrhythmic events, but on the other hand, the overall mortality increases, due probably to the augmentation of heart failure deaths in the ICD group, presumably due to the ICD interventions. Because of this unprecedented expansion of ICD implantations, that only in few cases (between 21 to 35%) (Bardy et al., 2005) leads to an appropriate therapy (arrhythmic events followed by a shock), there is a continuous interest in a non-invasive predictor for risk-stratification (refer to section 2).

Within the last years, a new methodology is gaining interest in clinical use: Magnetic Field Imaging (MFI) / Magnetocardiography (MCG) (Yamada & Yamaguchi, 2005). Korhonen *et al.* (Korhonen et al., 2006) have performed a pioneer clinical study analyzing the intra QRS-fragmentation in averaged MCG/MFI data (for a mathematical description of the method refers to (Link et al., 1994) and (Mueller et al., 1999)), after attempts made using the high frequencies components of the QRS as marker of risk both in Electrocardiography (ECG) (Cain et al., 1990) and MCG (Leder et al., 2000). The results have showed the superiority of the method in comparison to ECG and, in all-cause mortality, an abnormal MFI score together with a LVEF <30% has shown a positive predictive accuracy (PPA) of 50% and a negative predictive accuracy (NPA) of 91% (Steinberg & Levitt, 2006). The population considered in this work was quite small (158 patients after myocardial infarction- MI) and therefore a bigger perspective clinical study is needed for validating the role of QRS-fragmentation as a risk stratificator.

In Germany one multi center study (MFI-RISTI) is ongoing to prove the utility of this parameter in patients prone to ventricular tachycardia (VT). Although pre-trial data in patients with cardiac dysfunction before implantation of ICDs has been presented, this kind of study is time consuming (in the order of years, if the follow-up phase is considered). An alternative approach is to perform retrospective studies on patients with already implanted ICDs (CORE-AIIM).

2. State of the art

In this section, an overview of the risk stratification methods developed till now is presented (Toennis & Kuck, 2009). These methods were developed in order to have a more precise indicator of Ventricular Fibrillation (VF) and /or Ventricular Tachycardia (VT), both in ischemic and non ischemic patients. The parameters that are used for risk stratification can be divided into different groups:

- conduction system
 - QRS-length
 - late potentials
- heterogeneous ventricular repolarization
 - QT-interval
 - QT-dispersion
 - T-wave alternans (TWA)
- imbalance of the autonomic tonus
 - heart rate variability (HRV)
 - heart rate turbulence (HRT)

- baroreflex sensitivity (BS)
- left ventricular ejection fraction
- ventricular ectopy

2.1 Conduction system

2.1.1 QRS-length

The QRS-length is the easiest parameter to be determined, by measuring the length of the QRS complex on a 12-lead ECG. About 2% of the U.S. population has a QRS-length more than 120 ms and about 5% has either a right or left bundle-branch block (BBB). Among the patients with chronic congestive heart failure, the percentage of those with a QRS-prolongation increases up to 50%. If only those patients with left BBB (LBBB) are taken into consideration, it can be proved that LBBB may be considered an independent predictor of cardiovascular mortality due to SCD. The MADIT-II and the SCD-HeFT studies could not prove a dependence between QRS-prolongation and VT/VF events in patients with ICDs (Buxton et al., 2005).

QRS-length is not recommended, at this stage, for the risk stratification of SCD.

2.1.2 Late-potentials

Late potentials refer to low amplitude signals that occur after the end of the QRS, due to a delay of the conduction system. Low amplitude signals cannot be observed in patient with a BBB since they are hidden; furthermore those signals from regions of scar may also be obscured if the abnormal region is depolarized during the QRS. The validity of this method was proved in the CABG-Patch test. ICD implantation did not improve survivals, although arrhythmic deaths were reduced. Some studies pointed out that late potentials predicted death due to progressive heart failure rather than SCD (Yi et al., 1996).

The use of this parameter for SCD is not adequately supported at this time. Further studies are required to assess the utility of this test (Goldberger et al., 2008).

2.2 Heterogeneous ventricular repolarization

2.2.1 QT-interval

QT-interval is the summation of the ventricular action potentials duration. Since it varies with the heart variability, a corrected definition using the Bazett's formula is used. Although the reproducibility of the QT-interval is very high, the need for correction makes it difficult to compare values of this parameter for different patients. There are controversial studies where the QT-interval was related to higher mortality in patient with low EF, but with different results (Brendorp et al., 2001; Padmanabhan et al., 2003).

The use of this parameter for risk stratification is not supported.

2.2.2 QT-dispersion

QT-dispersion should reflect the dispersion of the myocardial recovery and should be associated with arrhythmia risk. There have been numerous studies that related the QT-dispersion to increased mortality, but no relation was found between QT-dispersion and outcome (Gang et al., 2003).

The use of this parameter for risk stratification is not supported.

2.2.3 T-wave alternans

T-wave alternans (TWA) is a reflection of repolarization alternans at level of the single cells. T-wave alternans is a rate-dependent phenomenon and tends to occur at lower heart rates in

patients prone to ventricular arrhythmias. In order to measure the TWA, a target heart rate with regular R-R (without ectopic beats present) has to be achieved. Because of this, a high percentage (from 12 to 41%) of patients that undergo the test, get an undetermined result. Different studies have been performed, but they have different results (Costantini et al., 2009; Gold et al., 2008).

Furthermore, it is worth to be remembered that TWA cannot be applied in patients with atrial fibrillation (AF- 9-30%) and in those who are not allowed to perform physical test (15%).

Finally, TWA cannot be suggested as parameter for risk stratification.

2.3 Imbalance of the autonomic tonus

2.3.1 Heart rate variability

The Heart rate variability (HRV) can be defined as the variation over time of the period between consecutive heartbeats. It is predominantly dependent on the extrinsic regulation of the heart rate (HR). It reflects the state of the autonomic nervous system that can be divided into two branches: the parasympathetic and the sympathetic nervous system. Normally cardiac arrhythmias occur in patients with enhanced sympathetic and diminished parasympathetic activity; furthermore the parasympathetic effects on the sinus node could predict mortality. The HRV can be calculated over a measurement that lasts between 3 and 8 minutes or using an Holter ECG. Atrial Fibrillation is an exclusion criterion for this method.

2.3.1.1 Short-term HRV

The short-term HRV is not reproducible, especially in patients with congestive heart failure. Moreover, there is a very strong interindividual variation in the relationship between short-term HRV and parasympathetic effect (Goldberger et al., 2001). For these reasons it cannot be used as parameter for the risk stratification of SCD.

2.3.1.2 Long-term HRV

In case the long-term HRV is used, the circadian rhythm has to be taken into account as well as the changes in HR according to the daily activity: This means that the power spectrum (PS) in the PS analysis is not stationary. In many studies it has been proved that there is an increase in mortality in those patients with a low HRV, but there is no evidence of a relation between low HRV and SCD (Gerritsen et al., 2001).

For this reason it cannot be used as parameter for risk stratification of SCD.

2.3.2 Heart rate turbulence

The term Heart Rate Turbulence (HRT) describes short-term fluctuations in sinus cycle length that follows spontaneous ventricular premature complexes (VPCs) (Schmidt et al., 1999). In normal subjects, it consists of a short initial acceleration followed by a deceleration of the heart rate compared with the pre-VPC rate. In order to use this method, at least 15 premature beats have to be analyzed in patients without AF. It was demonstrated that there is an increase in mortality in post-MI patients with low HRT.

HRT is a very attractive parameter for risk stratification, but a study involving the relation between low HRT and SCD has not been performed yet.

2.3.3 Baroreflex sensitivity

The baroreflex mechanism is a central part of the regulation of the cardiovascular system, particularly in the control of vagal and sympathetic outflow to the heart and the peripheral circulation. Baroreflex sensitivity (BRS) can be quantified by the analysis of the changes in

heart rate in response to changes in blood pressure. It has been demonstrated that there is a close link between reduced BRS and increased risk for serious ventricular tachyarrhythmias (Schwartz et al., 1992).

Although there are studies that suggest the utility of BRS as parameter for risk stratification of SCD in patients with CHD, further studies and a method to get a more reproducibility parameter are needed.

2.4 Left Ventricular ejection fraction

LVEF, that measures the left ventricular systolic function, is the most used parameter for the indication of implantation of an ICD. Reduced LVEF is considered a risk factor for overall mortality and SCD in the heart failure population. Although the LVEF has been demonstrated as the strongest independent predictor of SCD, its sensitivity and specificity are very low. In fact, if, on the one hand, those persons with low EF have a higher probability to die from SCD, on the other hand, there is a considerable amount of people that die from SCD and have a preserved EF.

2.5 Ventricular ectopy and NSVT

Ventricular ectopic beats (VEBs) and non-sustained ventricular tachycardia (NSVT) are common arrhythmias that appear on the surface electrocardiogram (ECG) as a profound disturbance of normal cardiac rhythm (Campbell, 1993). In order to study them an Holter-ECG is necessary. Ectopy beyond 10 VPBs per hour does not affect the risk of mortality. The positive predictive value of VEBs after MI for predicting VT/VF or death is between 5% and 15% and the predictive value increases if it is combined with a low LVEF. Furthermore, patients with non ischemic cardiomyopathy are at increased risk of SCD and frequently have high grade ventricular ectopy and NSVT (Kron et al., 1988), but the relationship is not valid in case of ischemic cardiomyopathy. The method has low sensitivity (Toennis & Kuck, 2009).

3. Magnetic field imaging

3.1 Materials

Magnetic field imaging (MFI) is a new non-invasive modality that is able to combine the recording of external magnetic field (MF) generated by the electrical activity of the heart using a multi channel magnetic sensor array with its clinically applicable spatio-temporal visualization. Since heart MFs are very small when compared with the earth magnetic field (see Figure 2 for comparison), the acquisitions were in the past normally carried out in very heavy and expensive shielding rooms. With the advent of new technologies it is possible to redistribute the workload between hardware and software and this makes it possible the use of MFI in a daily clinical routine. Figure 3 shows an example of MFI acquisition system (Apollo CXS system). The sensor system is a 55-channels SQUID gradiometer system arranged in a hexagonal matrix, which covers an area of approximately 28 cm. The patients lie in a supine position during the recording. The sensor system is placed at approximately 1 cm distance from the anterior chest wall above the heart. For the details concerning the acquisition and the preprocessing please refer to (Di Pietro Paolo et al., 2011).

The here mentioned MFI recordings were carried out at the Asklepios Hospital St. Georg in Hamburg (Germany) using an Apollo CXS system (BMDSys Production GmbH, Germany). Magnetic signals of 172 subjects were recorded: The control group consisted of 20 healthy volunteers and 44 subjects with normal coronary and normal LVEF, whereas the other group

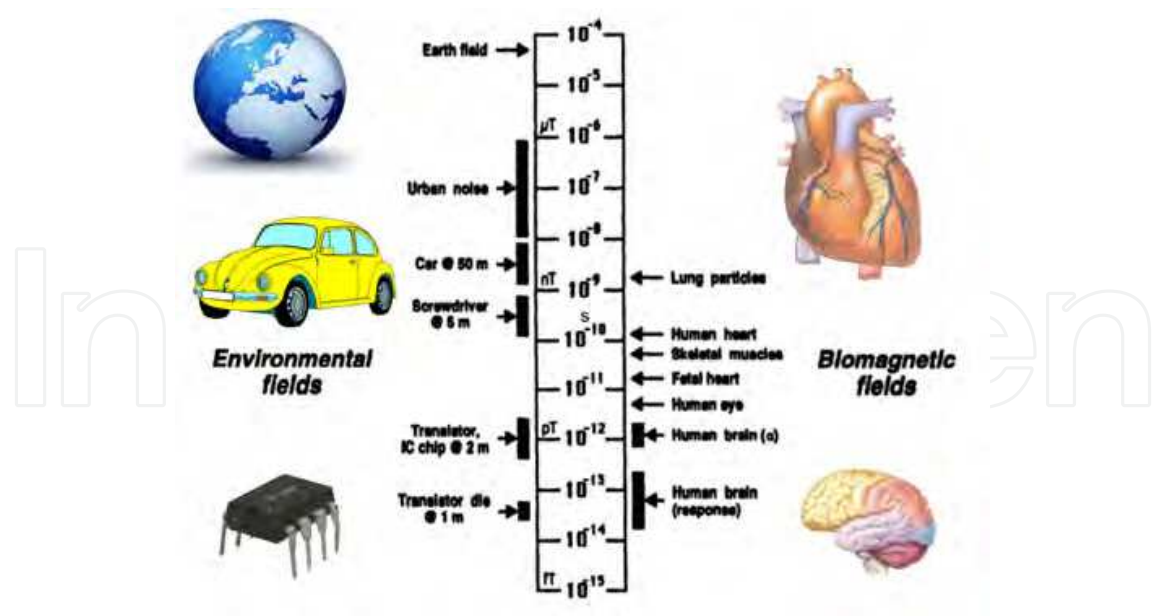


Fig. 2. Comparison of selected biomagnetic fields (heart, brain) and environment disturbances.



Fig. 3. Apollo CXS system: view from the preparation room into the acquisition room soon before the acquisition is carried out. The patient lies on the bed as close as possible under the dewar bottom.

consisted of 108 patients with primary prevention indication for ICD implantation, before the implantation.

The acquisition lasted about 5 minutes. All patients were followed up after implantation. The primary endpoint was the occurrence of ventricular arrhythmias.

Further information concerning the subjects characteristics can be found in the tables 1 and 2.

	ICD-group	volunteers	no CHD
N	108	20	44
Male	88(81%)	5(25%)	26(59%)
Female	20(19%)	15(75%)	18(41%)
Age	64 ± 12	39 ± 11	61 ± 11
Diabetes Mellitus	29(27%)	0	9(20%)
Hypertension	76(70%)	0	31(70%)
AF	35(32%)	0	7(16%)
LBBB	32(30%)	0	2(5%)
QRS	120 ± 33	90 ± 18	95 ± 18
LVEF	27 ± 7%	n.a.	61 ± 9% ¹
β-Blockers	88(81%)	0	25(57%)
Amiodarone	25(23%)	0	2(5%)

Table 1. Subjects Characteristics: number of subjects, sex, medicaments, QRS-length, percentage of persons with Atrial Fibrillation (AF), Left Bundle Branch Block (LBBB) and Left Ventricular Ejection Fraction (LVEF).

	ICD-group
N	108
Isch. CM	74(69%)
DCM	31(29%)
Other (Brugada, Myocarditis,HOCM)	3(3%)
CABS	29(27%)
NYHA I	17(16%)
NYHA II	47(44%)
NYHA III	43(40%)
NYHA IV	1(1%)
ICD	100(93%)
VR	44(41%)
DR	25(23%)
CRT	31(29%)
no ICD	8(7%)

Table 2. ICD-Patients Characteristics: number of patients with Ischemic Cardiomyopathy (Isch. CM), Dilated Cardiomyopathy (DCM), Hyper-trophic obstructive cardiomyopathy (HOCM), Coronary artery bypass surgery (CABS), New York Heart Association (NYHA) Class I, II, III, and IV, ICDs in different typology (single chamber (VR), dual chamber (DR) and Cardiac Resynchronization Therapy (CRT)).

3.2 Methods-the Fragmentation Index (FI)

As aforementioned, QRS-fragmentation can be very useful for the risk stratification of SCD. A new parametrization of QRS- fragmentation has been introduced based on the findings of the past decades in order to make it possible to apply MFI using standardized equipments used in clinical environment and under clinical routine conditions. Until now, parameterization of

¹ data not available for all subjects

the fragmentation was based on the quantification suggested by (Endt et al., 1998) which in principle is a measure of the magnitude and number of extrema of the averaged and bandpass filtered QRS-complex signal. This direct approach has some intrinsic limitations:

- the weighting over the number of extrema makes the parameter very sensitive to the total noise.
- it only concentrates on one aspect of the fragmentation: the level difference.
- the score is clearly designed as a local quantity, since it refers to the signal of one channel

Furthermore, as already reported by (Mueller et al., 1999) the elementary parameters referring to a single channel have to be evaluated over all the available sensors with the goal to extract global values which are typical for the spatio-temporal evolution of the QRS-complex.

Here, the parameterization of the fragmentation without the weighting with the number of extrema has been proposed. Three parameters were calculated for each QRS interval in each channel:

1. The signal magnitude between the extrema: *step*

$$s_{step,i} = |y(t_{i+1}) - y(t_i)| \quad (1)$$

2. The sum over the slopes (derivative): *slope*

$$s_{slope,i} = \frac{|y(t_{i+1}) - y(t_i)|}{t_{i+1} - t_i} \quad (2)$$

3. The length of the linearized signal curve: *trace*

$$s_{trace,i} = \sqrt{(y(t_{i+1}) - y(t_i))^2 + (t_{i+1} - t_i)^2} \quad (3)$$

In Equation 1 and 2 the time intervals were normalized to an idealized QRS length of 80 ms. In this way a set of 3 indicators (step, slope and trace), each of them related to the sensor position was obtained. Mueller *et al.* (Mueller et al., 1999) pointed out that the availability of a large array of sensors is important because:

- only channels with high signal to noise ratio (> 40 % of the maximum QRS amplitude) are worth to be considered.
- channels "close" to the zero line in the dipolar pattern are more easily contaminated by breathing artifacts.

As a consequence, the maximum (MAX) and the root mean square (RMS) of the calculated parameters of all sensors satisfying the above mentioned conditions (signal amplitude > 40 % of the maximum QRS amplitude, sensor "far" from zero line) lead to 6 global parameters, 2 (MAX and RMS) for each of the 3 indicators (step, slope, and trace). The final goal was to obtain a unique scalar parameter. In order to perform the average of the 6 parameters defined above, a homogeneous metric had to be used. Therefore all parameters were normalized by the corresponding quadratic mean calculated averaging over a control group defined previously (eq. 4 and 5). Finally, all values were merged to one global, one dimensional scalar parameter: the Fragmentation Index (FI). In order to get the normalization parameters

required before, the *RMS* was calculated for all six parameters ($\text{indicator}_{MAX,RMS}$) on the basis of the data of the control group:

$$RMS = \mu_{ind} = \sqrt{\frac{1}{N} \sum_{i=1}^N S_{ind}^2(i)} \quad (4)$$

where N is the number of subjects contributing to the normalization. That way, normalized parameters were obtained

$$S_{ind}^*(i) = \frac{S_{ind}(i)}{\mu_{ind}} \quad (5)$$

A set of 6 normalized parameters, showing the parameterization of the fragmentation, was defined using the signal averaged and band-pass filtered QRS-complex of the selected MFI channels. The Fragmentation Index was determined as the averaged value of the six above introduced parameters.

$$FI = \frac{1}{6} \sum S_{ind(MAX,RMS)}^* \quad (6)$$

Figure 4 shows a graphical view of the three parameters in a filtered QRS-complex. Figure 5

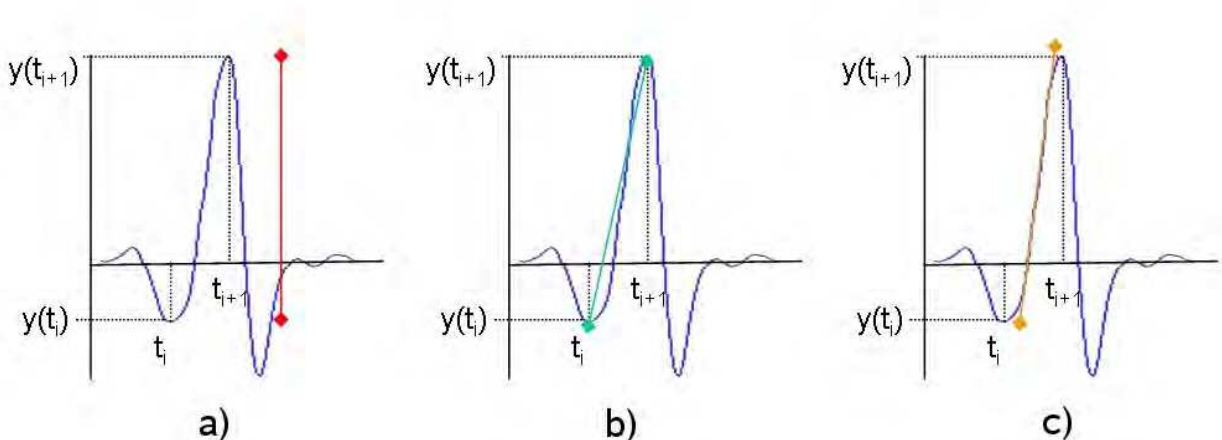


Fig. 4. Schematic explanation of the different fragmentation parameters: a) the difference between extrema: *step*, b) the length of the curve: *trace*, c) the derivative: *slope* (eq. 1, 2, and 3).

shows an example of channels that are used in the calculation of the global Fragmentation Index in a patient with low EF. The QRS-fragmentation Index was determined using the analysis software of Apollo CXS.

Figures 6 shows the QRS-fragmentation into two subjects: Figure 6a shows an example of QRS-fragmentation in a healthy volunteer whereas figure 6b in a patient with an ischemic cardiopathy.

4. Results

4.1 Results - MFI before ICD implantation

Preliminary results of the method have been presented in 2010 at the Herbsttagung und Jahrestagung of the German society of cardiology (Nuernberg) by Toennis et al (Toennis et al., 2010).

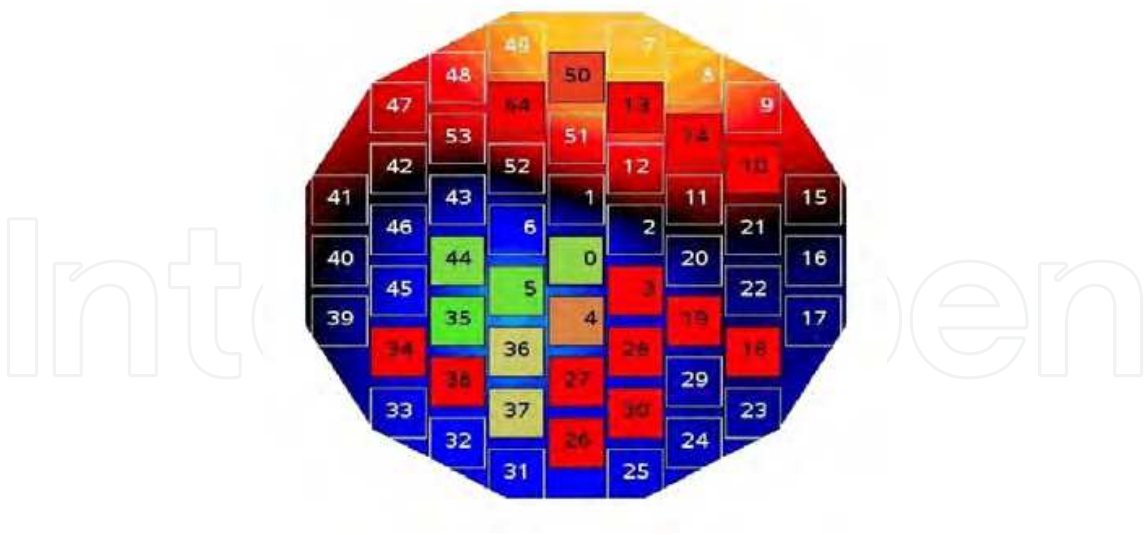


Fig. 5. Magnetic field map with channels position: The different colors of the channels correspond to different values of FI from green (low FI) to red (high FI): the transparent channels correspond to unused channels since too noisy (i.e 29) or too close to the 0 line (i.e: 1).

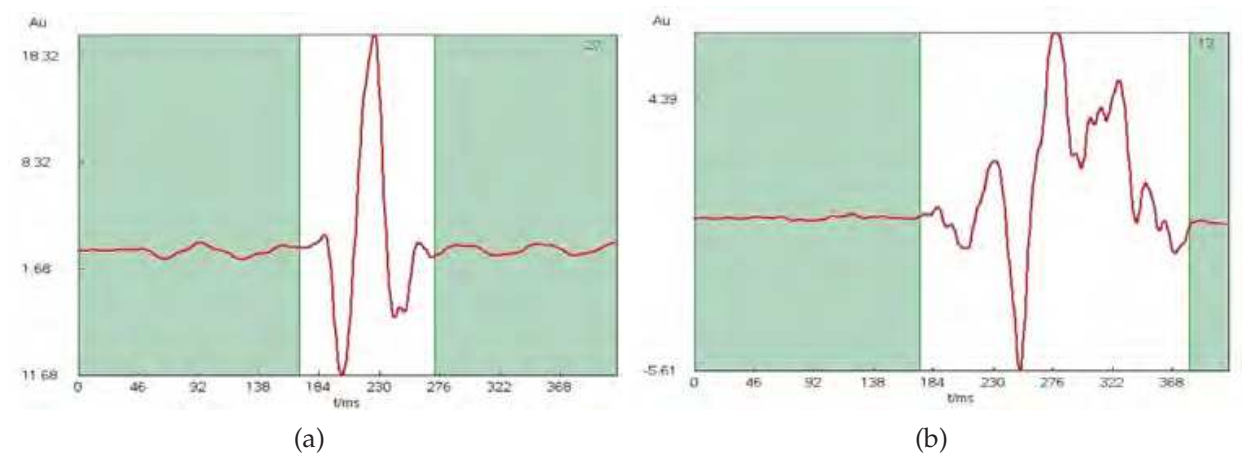


Fig. 6. a) QRS-fragmentation of one healthy volunteer (FI=0.994), b) QRS-fragmentation in a patient with ischemic cardiomyopathy with EF=25% before ICD implantation (FI=2.10).

The QRS-fragmentation index was calculated in the 172 subjects and the 108 patients with primary prevention indication for ICD implantation had a follow-up of 6.6 months (median 10). There was no event (VT/VF) in the normal group and in those patients with a FI less than 1.25 (normal until light fragmentation). In the ICD group 2 patients died, one for an electrical storm and the other one for a progressive heart failure. Six patients had ventricular episodes (6%), 2 of them terminated the episode by means of a DC-shock, 2 by using a anti-tachycardia pacing (ATP) therapy, 1 had one episode before the ICD was implanted (external shock) and the last one had nsVT that is without therapy. Five had an inadequate therapy (5%) caused in 4 out 5 cases by AF. An histogram of the results is in Figure 7.

This prospective study for validating the use of QRS-fragmentation as predictor for arrhythmic events needs time. A faster way for evaluating this method is doing retrospective studies on patients with already implanted ICDs.

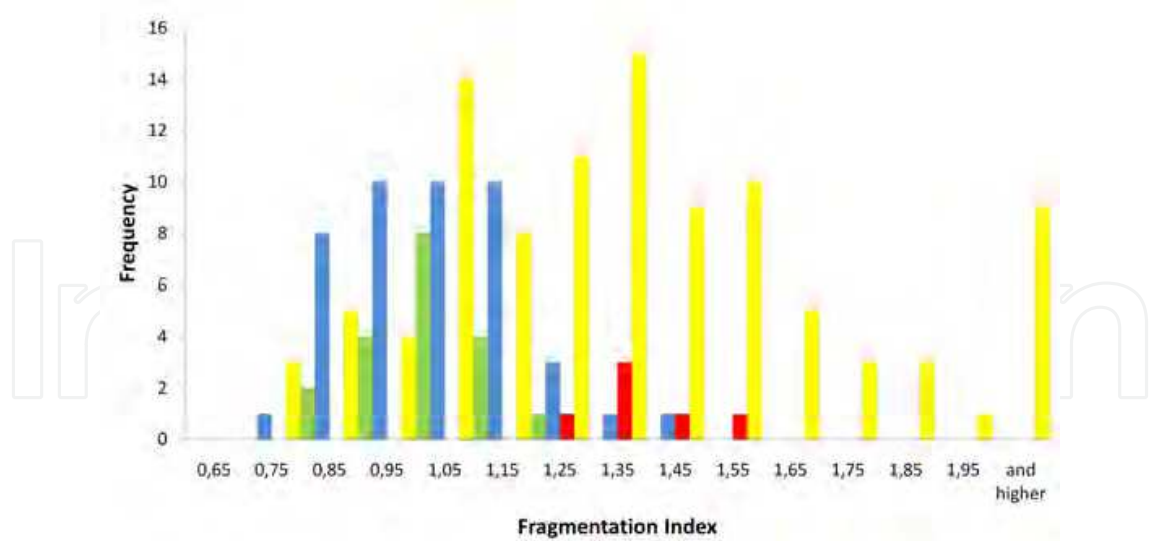


Fig. 7. QRS Fragmentation-Distribution according to the different groups: volunteers (green), Patients without coronary artery disease and normal EF (blue), patients with primary indication for ICD (yellow) and patient with ventricular arrhythmia episodes (red).

4.2 Results - MFI after ICD implantation

A preliminary study is presented using follow up data of 10 patients (10 males-0 females, age 54 ± 8) with already implanted ICD using a post-processing method based on Blind Source Separation (BSS) in order to extract the cardiac signals from biomagnetic signals that are disturbed by an ICD (Di Pietro Paolo et al., 2009). Until now, it has not been possible to perform biomagnetic measurements in patients with ICDs. In fact, the presence of this device in the thorax (normally located inside the chest on the left shoulder) of the patient leads to very strong interferences, that are orders of magnitude larger than the biomagnetic signal of the heart. For this reason, ICDs and pacemakers are among the exclusion criteria for studies concerning MFI. Di Pietro Paolo et al. (2009) extracted for the first time cardiac signals from measurements disturbed by an ICD, offering the possibility for a QRS-fragmentation analysis in such patients. Two out of the 10 patients had a ventricular arrhythmic event and both of them had a higher fragmentation level when compared to a patient that did not shock (Figure 8). On the basis of these results, a first retrospective study (MFI-COREAIM), enrolling patients with already ICD implanted, has been started.

5. Discussion and conclusion

The gold standard to evaluate the risk to suffer from a VT/VF in future and for the implantation of an ICD is based on LVEF. LVEF does not directly measure arrhythmogenic substrate and statistics also show that only about 20% of those individuals, being evaluated to be at risk on the basis of LVEF, suffer from life threatening VT/VF within two years after diagnosis, respectively ICD implantation. On the other hand, looking at those persons that die from SCD there is consent that about 75% of them suffer from a preceding VT/VF episode before dying suddenly. This means that the LVEF has a small sensitivity and specificity: As already pointed out previously, the persons that die from SCD knowing to be suffering from a cardiac disease are only a small percentage when compared to the total number of persons dying from SCD every year (1/1000/y in the U.S).

There is, for this reason, still the need of non-invasive parameters for risk stratification of

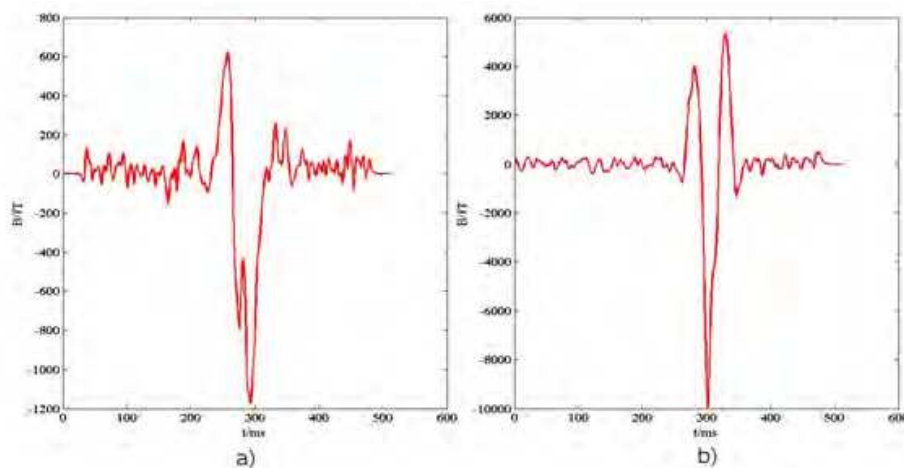


Fig. 8. Illustration of QRS-fragmentation recorded in two patients with implanted ICD, after post-processing: a) QRS fragmentation of a shocked patient, b) QRS-fragmentation of a patients that did not shock: Note the difference in the fragmentation level into the two cases.

patients at highest risk to die from SCD. In this chapter the main non invasive parameters introduced in the last period have been briefly described, but none of them was able to get better results when compared to LVEF. Another important point that should be consider is that most of the non-invasive parameters correlate with all cause of mortality, but the correlation with SCD is still unclear.

Magnetic Field Imaging can provide another parameter for SCD: the QRS-fragmentation. The easy application of a 5 minutes MFI examination and the lack of any risk or negative side-effects for the patient support the suggestion to use MFI as an efficient method to evaluate individuals risk. QRS fragmentation has already been shown to be a reasonable predictor for arrhythmic events and mortality in patients with cardiac dysfunction after myocardial infarction (Korhonen et al., 2006). The QRS-fragmentation was then parameterized to obtain a stable reproducible and operator-independent parameter: the Fragmentation Index. This method could complement the new risk stratification guidelines, as stability and reproducibility of the FI detected by means of non-invasive MFI have been shown. Based on these findings, two studies are ongoing: one is a prospective study (RISTI) that shows the correlation between high QRS-fragmentation (calculated before ICD implantation) and arrhythmic ventricular events whereas the other one is a retrospective study (CORE-AIIM) that investigates the relation between QRS-fragmentation and events in patients with an already ICD implanted.

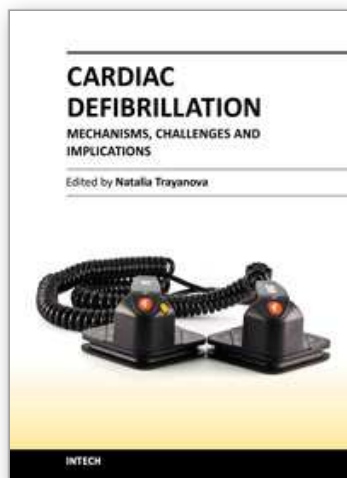
Preliminary results of two ongoing studies have been referred, showing that high Fragmentation Index correlates (at this point of the trial) with an higher probability to suffer from a VT/VF.

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The only known effective therapy for lethal disturbances in cardiac rhythm is deï-brillation, the delivery of a strong electric shock to the heart. This technique constitutes the most important means for prevention of sudden cardiac death. The efficacy of defibrillation has led to an exponential growth in the number of patients receiving implantable devices. The objective of this book is to present contemporary views on the basic mechanisms by which the heart responds to an electric shock, as well as on the challenges and implications of clinical defibrillation. Basic science chapters elucidate questions such as lead configurations and the reasons by which a defibrillation shock fails. Chapters devoted to the challenges in the clinical procedure of defibrillation address issues related to inappropriate and unnecessary shocks, complications associated with the implantation of cardioverter/defibrillator devices, and the application of the therapy in pediatric patients and young adults. The book also examines the implications of defibrillation therapy, such as patient risk stratification, cardiac rehabilitation, and remote monitoring of patient with implantable devices.

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