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**Controversies in the Prevention of Sudden Death**

M. Santini, C. Pignalberi, R. Ricci

Implantable cardioverter defibrillators (ICDs) have been demonstrated to be the best tools to improve survival in patients with prior cardiac arrest due to ventricular fibrillation or poorly tolerated sustained ventricular tachycardia [1-4]. In sudden death primary prevention, ICD efficacy has been tested and demonstrated only in very selected high-risk populations [1]. Identification of patients at high risk for sudden death in larger cohorts who may benefit from ICD implantation is a major challenge to deal with. Furthermore, risk related to device implantation and psychological impact on daily life has to be considered. Although technologic improvements allow us to obtain increasingly smaller and safer ICDs, their costs obviously relate to economic determinants, requiring a careful cost-effectiveness evaluation. Invasive electrophysiological study combined with depressed LVEF and unsustained ventricular tachycardia selected very high risk patients in MADIT and MUSTT trials. In spite of that, in the MUSTT registry not inducible patients showed a 24% sudden death rate after 5 years. As a matter of fact, the major challenge for the future is the improvement of sensitivity in patient stratification, considering that the actual number of deaths is higher in the so called “low risk” groups. *J Clin Basic Cardiol* 2001; 4: 273-8.

**Keywords:** sudden cardiac death, implantable defibrillators, heart failure, unsustained ventricular tachycardia, electrophysiological study

**Spontaneous Ventricular Arrhythmias**

Incidence of spontaneous ventricular arrhythmias in the post-infarction period has been demonstrated to be as high as 85% for Premature Ventricular Complexes (PVC) and 11% for Non-Sustained Ventricular Tachycardia (NSVT) [5, 6]. In these patients, the risk of sudden death was classified high in case of PVC > 10/h. In the thrombolytic era [7] a fair decrease of ventricular arrhythmias incidence has been demonstrated (PVC 64% and NSVT 7%). In the GISSI-2 study [5], the PVC number was directly related to the mortality rate; in particular, PVC > 10/h was associated with a 6% mortality and the occurrence of NSVT had a prognostic value similar to that of PVC > 10/h. However, multivariate analysis did not show a significant independent predictive value of these parameters. The different prognostic value in pre- and post-thrombolytic era is probably related to the reperfusion therapy, which leads to changes of the myocardial substrate. In the CAMI study [8], patients not thrombolysed (previously enrolled in MPRG study [9]) were compared with thrombolysed patients. In patients treated with conventional therapy, a linear correlation between PVC number and mortality rate was detected, with a statistical significance in the case of more than 10 PVC/h. In patients treated with thrombolytic therapy an analogous correlation arose; nevertheless, only in patients complaining of more than 30 PVC/h was there a statistically significant correlation with mortality. In conclusion, in the pre-thrombolytic era, the presence of more than 10 PVC/h was a significant risk index, while, in the thrombolytic era, the number of PVC/h with a prognostic significance increased to 30.

![Figure 1. Survival of ICD versus conventional therapy in MADIT trial patients subdivided according to the median value of left ventricular ejection fraction (0.26)](image-url)
Left Ventricular Ejection Fraction (LVEF)

LVEF is the most powerful predictor of total mortality and sudden death. In both the pre-thrombolytic and thrombolitic [8, 9] era a LVEF < 40 % was associated with a severe increase of mortality rate. In a recently published MADIT trial revision [10], the patients with very depressed LVEF proved to be at the highest risk of sudden death. In fact, in the MADIT study [1] the eligibility criterion was a LVEF < 0.35. When the 196 enrolled patients were divided into two groups according to LVEF median value (0.26), the ICD therapy expressed its benefit almost exclusively in those with the lower LVEF (< 0.26) (Fig. 1). This finding is exactly the contrary of what was thought when the 4 major trials [1–3, 11] on ICD were planned. ICD therapy was expected to be less effective in case of more advanced left ventricular failure, whereas such experience demonstrated that the sickest patients may benefit the most.

Ventricular Late Potentials (LPs)

LPs originate from areas of myocardium where islands of viable tissue alternate with scars. In these areas the impulse spreading is fragmented, producing high frequency potentials, directly recordable on these zones. In many studies [12–14], the prognostic value of LPs has been found significant: however, while the negative predictive power was good (96–99 %), the positive predictive power was very low (7–27 %). In the CABG-patch trial [15] patients who were candidates for coronary artery bypass with left ventricular ejection fraction less than 35 % and positive LPs were enrolled. The 2-year overall mortality in the control group was 18 %, inferior to that of MADIT [1] (32 %) and AVID [2] (24 %). This difference could be related to the surgical treatment; however, a critical difference could have been the arrhythmia risk indicator used for patient enrolment in these trials. The AVID study required spontaneous sustained ventricular tachyarrhythmias, the MADIT trial inducible sustained ventricular tachyarrhythmias not suppressible by intravenous procainamide and, finally, the CABG-patch trial the presence of LPs on a Signal Averaged Electrogram (SAECG). These results showed that sustained ventricular arrhythmias, either spontaneous or induced, are a better marker for risk of sudden death than abnormalities on the SAECG. Patients without LPs on SAECG have a low mortality risk, while those with LPs need further analysis to have appropriate risk stratification.

Autonomic Nervous System

Many studies demonstrated that parasympathetic stimulation has a protective power, while the sympathetic system has a pro-arrhythmic action in patients at high risk for ventricular arrhythmias [16–18]. Using Heart Rate Variability (HRV) and Baroreflex Sensitivity (BRS) analysis may evaluate the balance in the autonomic nervous system.

HRV evaluates heart rate beat-to-beat in time and frequency-domain, while BRS analyses heart rate control by arterial baroreceptor. The first study on HRV [19], confirmed by late evidences [20], demonstrated, in 808 patients from MIRF trial [9], that those with depressed HRV had a mortality rate nearly 6 times higher than others with normal HRV. If LVEF was included in the analysis, patients with depressed left ventricular function and normal HRV had a mortality rate similar to those with normal LVEF and low HRV. The authors concluded that the two prognostic parameters have the same weight. Nevertheless, more recent studies did not confirm these findings. In patients with recent myocardial infarction, where all HRV parameters were evaluated, Lanza et al. [21] demonstrated that only ‘very low frequency’ parameter was able to significantly discriminate patients at high risk. However, multivariate analysis showed that only LVEF and PVC (10/h), and not HRV, could identify an increased risk of sudden death.

BRS has been evaluated in the ATRAMI trial [22]. 1284 patients with recent myocardial infarction were prospectively followed to evaluate the predictive role of HRV, BRS, LVEF and spontaneous tachyarrhythmias. Both HRV and BRS significantly discriminated patients at high and low risk and the association of the two factors allowed an increase in sensitivity power; multivariate analysis confirmed the predictive role of HRV and BRS. Anyway, due to uncertain and non consistent data, HRV and BRS should be used only in association with other risk stratification parameters.

Invasive Electrophysiological Study (EPS)

In patients with previous myocardial infarction, the inducibility of ventricular arrhythmias at EPS considerably declines when myocardial infarction has been treated with thrombolytic therapy (from 88 to 8 % [23] and from 67 to 20 % [24]). In patients with not complicated myocardial infarction [25], inducibility rate is very low (6 %). Anyway, inducibility is associated to higher occurrence of spontaneous ventricular arrhythmias after 12 months (19 % versus 3 %). MADIT [1] and MUSTT [11] trials included EPS in population screening. In both, EPS was performed in patients with depressed LVEF (< 0.35 MADIT and ≤ 0.40 MUSTT) and spontaneous ventricular arrhythmias. The association of these three parameters was able to predict a high number of clinical events. In fact, in this setting ICD implantation was associated with improved survival when compared with antiarrhythmic drug therapy or no therapy. In the MADIT trial, 2-year all cause mortality decreased by 54 % in the ICD group; in the MUSTT trial 2-year mortality decreased from 28 % (control group) to 9 % (ICD group). In the MADIT the individual weight of EPS in patient screening could not be adequately investigated; the authors did not collect long-term data on all screened patients. Differently, in the MUSTT 2202 patients with LVEF ≤ 0.40 and spontaneous NSVT were assigned to EPS. In 1438 patients, no sustained ventricular arrhythmias could be induced; they were followed without any antiarrhythmic therapy in a registry. In these patients the 5-year mortality rate for sudden cardiac death was 24 %. 704 patients showed as inducible at EPS study and agreed to undergo randomisation; they were assigned to receive EPS-guided therapy (antiarrhythmic drugs or ICD) or no therapy. In the subgroup without any therapy the 5-year mortality rate for sudden cardiac death was 32 % (p < 0.01 versus non-inducible). These data demonstrate that EPS was able to increase the sensitivity of the algorithm used to select high risk patients (the 5-year mortality rate for sudden cardiac death was 32 % versus 24 %); however, the negative predictive power of EPS alone did not appear excellent (24 % of high risk patients, out of a cohort of 1438, not detected). In conclusion, EPS is a useful tool in screening high risk patients, but other parameters, in particular LVEF and spontaneous ventricular arrhythmias, need to be taken into account for appropriate risk stratification.

Conclusions

LVEF is the best known risk predictor for sudden death. No ‘electrophysiologic’ parameter is individually so powerful as to be used alone in routinely stratification of arrhythmic risk. A combination of invasive and non-invasive tests should allow...
the best stratification; however, an algorithm globally accepted is not available yet. Tested algorithms are only those used during enrolment of patients in trials on ICD [1–4, 11, 15]. LVEF is always present; spontaneous or induced ventricular tachyarrhythmias are used in all studies, except for the CABG-patch trial, where LPs were employed. Tested algorithms were able to identify different percentages of events during the follow-up (2-year all cause mortality rate in the control groups ranging from 32 % and 18 %). Nevertheless, using very selective algorithms, a very high risk population would be individualised, while an elevated number of patients, who will experience an acute event, would be excluded. A very explicative example of that can be obtained from the CIDS study [26], where the effectiveness of ICD therapy was tested in patients with depressed LVEF and spontaneous major tachyarrhythmias. Using multivariate analysis (Fig. 2), only 3 variables significantly predicted overall mortality (increasing age, decreasing LVEF and NYHA class III or IV). Dividing all patients into 4 quartiles of ascending risk of death, according to the 3 predictors, a significant benefit of ICD therapy arose just in the highest risk quartile, where a 50 % reduction of mortality/year was documented. Therefore, a patient with a very high, very near to the number of deaths in the fourth quartile, during enrolment of patients in trials on ICD [1–4, 11, 15]. LVEF is always present; spontaneous or induced ventricular tachyarrhythmias are used in all studies, except for the CABG-patch trial, where LPs were employed. Tested algorithms were able to identify different percentages of events during the follow-up (2-year all cause mortality rate in the control groups ranging from 32 % and 18 %). Nevertheless, using very selective algorithms, a very high risk population would be individualised, while an elevated number of patients, who will experience an acute event, would be excluded. A very explicative example of that can be obtained from the CIDS study [26], where the effectiveness of ICD therapy was tested in patients with depressed LVEF and spontaneous major tachyarrhythmias. Using multivariate analysis (Fig. 2), only 3 variables significantly predicted overall mortality (increasing age, decreasing LVEF and NYHA class III or IV). Dividing all patients into 4 quartiles of ascending risk of death, according to the 3 predictors, a significant benefit of ICD therapy arose just in the highest risk quartile, where a 50 % reduction of mortality/year was documented. Therefore, a population at very high risk, with a 50 % mortality/year rate could be detected; however, a large number of patients who will actually experience an acute event would not have been found. In fact, in this population, while the sudden death incidence is low in percentage, the actual number of deaths is high, very near to the number of deaths in the fourth quartiles. Ongoing trials, testing new algorithms to identify patients who may benefit from ICD implantation, will hopefully answer some of the open questions.

References

Figure 2. CIDS trial. Left: mortality rate in quartiles of ascending risk of death, according to increasing age, decreasing LVEF and NYHA class III or IV; right: actual number of deaths according to quartiles of risk and treatment randomisation; conv. = conventional


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