Controversies in the Prevention of Sudden Death

Santini M, Pignalberi C, Ricci R

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M. Santini, C. Pignalberi, R. Ricci

Implantable cardioverter defibrillator (ICD) has been demonstrated effective in preventing sudden cardiac death in high risk patients. However, individual prognostic stratification is needed in order to optimise cost-effectiveness ratio. Depressed left ventricular ejection fraction (LVEF) is the most powerful predictor of total mortality and sudden death. In particular, subgroup analysis of ICD trials demonstrated that the patients with very low LVEF (< 0.26) may benefit the most from ICD implantation. Among other risk indexes in the post-infarction period, the occurrence of premature ventricular complexes > 10/h in the pre-thrombolytic era and > 30/h in the thrombolytic era were associated to significantly increased risk. Ventricular late potentials showed an high negative predictive power, while the positive predictive power was very low. Heart rate variability and baroreflex sensitivity, individually or in combination, significantly discriminated patients at higher or lower risk. However, only inclusion of LVEF in the analysis allowed identification of patients at very high risk. 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

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)
**Left Ventricular Ejection Fraction (LVEF)**

LVEF is the most powerful predictor of total mortality and sudden death. In both the pre-thrombolytic and thrombolytic [8, 9] era a LVEF $\leq 0.35$ 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 trial [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 [2] on ICD therapy could not be adequately investigated; the authors did not collect long-term data on all screened patients. Differently, in the MUSTT [11] trials included EPS in population screening. In both, EPS was performed in patients with depressed LVEF ($\leq 0.35$ MADIT and $\leq 0.40$ 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 $\leq 0.40$ and spontaneous NSVT were assigned to EPS. In 1348 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 ‘electrophysiological’ 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 tachyarrhythmia are used in all studies, except for the CABG-patch trial, where LVEPs 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 in 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 very high-risk population 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


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