Editorial

Treating electrical instability in sudden cardiac death survivors — are we looking at the right side of the coin?

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This editorial refers to “Response of programmed electrical stimulation and clinical outcome in cardiac arrest survivors receiving randomized assignment to implantable defibrillator or antiarrhythmic drug therapy” by Cappato et al. on page 642

The chances of surviving sudden cardiac death (SCD) are low (5–60%) and the recurrence rate is high (40% in the following 2 years). Secondary prevention in SCD-survivors is mandatory. SCD remains the “challenge to contemporary cardiology” as B. Lown wrote in the late 1970s.

In SCD survivors the tool of choice is the implantable cardioverter-defibrillator (ICD), a crude but effective device that increases survival >90%. It prolongs survival, but also reduces the quality of life. However, in view of the 40% recurrence rate of lethal, arrhythmic events, the ICD is implanted in 60/100 patients unnecessarily!

Despite the efficacy of ICD therapy, its high costs are a considerable burden for the community, making a more precise risk stratification necessary to identify patients at the highest risk of recurrence of sudden arrhythmic death among the survivors who would most benefit from ICD.

Programmed ventricular stimulation (PVS) as a risk-stratification tool in SCD survivors

A fascinating model dominated the 1980s and 1990s: the induction of sustained ventricular tachycardia and ventricular fibrillation (VT/VF) using the PVS technique was used to stratify the high-risk group that should undergo secondary prophylaxis with drugs (β-blockers, amiodarone) and/or ICD implantation.

Three major randomised trials examined the efficacy of ICD therapy versus antiarrhythmic drugs for secondary prevention in SCD survivors: The antiarrhythmics versus implantable defibrillators (AVI) trial, the Cardiac Arrest Study Hamburg (CASH) and the Canadian implantable defibrillator study (CIDS). All these trials used all-cause mortality as an endpoint and all demonstrated a definitive survival benefit of ICD compared to antiarrhythmic drugs, suggesting that an ICD should be offered as first-line therapy to all survivors of life-threatening ventricular arrhythmias.

The CASH data have now been reanalysed by experienced authors in light of the unclear value of PVS in survivors of witnessed cardiac arrest that had been treated successfully by advanced cardiac life support and defibrillation. In a 2:1 randomisation to metoprolol or amiodarone versus ICD implantation, the primary endpoint was total mortality and the secondary endpoint, sudden cardiac death (SCD). Among 285 patients, 134 (47%) had inducible sustained VT. The all-cause death rate was significantly higher in inducible patients than in the noninducible subgroup (51.3% vs. 28.8%, p = .0003). Inducibility was the strongest independent predictor of total mortality in a multivariate model but curiously it did not predict SCD. A number of factors may explain this finding, which differs slightly from those of other studies: All-cause death and SCD have previously been rarely investigated independently or, more likely, the relatively small number of patients (n = 285) was insufficient to achieve statistical significance in the present study.

Assignment to the ICD group was associated with a lower risk of all-cause mortality only in the subgroup of noninducible patients with a very low ejection fraction (EF) (<35%). This observation actually suggests that SCD due to ventricular arrhythmias in SCD survivors with a low ejection fraction is more likely to occur among noninducible patients. This subgroup of patients would benefit most from ICD therapy.

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Similar observations about left ventricular function (LVF) were made in a subgroup analysis of the AVID data: ICD therapy showed no advantage over drugs in patients with better preserved left ventricular function (EF 35–40%). A subgroup analysis of the CIDS study also showed a significantly greater benefit of ICD in patients with depressed ventricular function.

These findings point to the importance of impaired left ventricular function as an independent predictor of mortality in SCD survivors and as a potential marker for ICD therapy.

ICDs significantly reduce the risk of arrhythmic death and overall mortality in primary prevention trials like the MADIT I/II and MUST trials compared to antiarrhythmic drug therapy in patients with impaired LVF and inducible sustained ventricular tachycardia. In this context, it is difficult to explain why patients with low EF (<35%) and inducible VT did not benefit from ICD treatment in the CASH study. This seems to suggest that noninducible patients with low EF have a higher risk of SCD due to ventricular arrhythmias, while other causes of death are more prominent in inducible patients.

In view of these results, there is little need for additional electrophysiologic studies in SCD survivors to determine the likelihood of recurrence of an arrhythmia, as most patients will receive a prophylactic ICD.

PVS as a tool for evaluating antiarrhythmic therapy in SCD survivors

The second part of the above-mentioned model was that PVS could be used to evaluate the efficacy of an antiarrhythmic drug therapy.

However, it was soon clear that PVS was not useful for proving the effectiveness of a drug therapy. Again, the inducibility of arrhythmia during PVS under a sufficient antiarrhythmic therapy in about half of the drug-treated patient cohort did not improve prognosis compared to noninducible patients. This has been confirmed in SCD survivors, demonstrating that 52.7% of patients remained inducible despite adequate antiarrhythmic therapy. In addition, 21.7% of patients who were noninducible at baseline became inducible under drug treatment.

PVS is not an instrument of choice to evaluate the efficacy of secondary prevention using antiarrhythmic drugs in SCD survivors.

The nature of sudden cardiac death — are we looking at the right side?

The current understanding of SCD reflects a variety of "Coumel triangles," including several contributing factors like electrical instability, ischaemia, electrolyte imbalance, the autonomic nervous system, haemodynamic LVF impairment, and others. Until now, rhythmologists have found it difficult to accept the value of factors other than arrhythmias, such as LVF and the morphologic substrate. They accept them only as adjuncts to premature ventricular beats (PVB), VT, and VF. Counting PVBs or setting up criteria for "therapeutic success" were just too enticingly simple to examine this model more critically. However, ventricular arrhythmias do not specifically predict SCD in patients with reduced LVF (≤35%).

Beyond the ICD, the prevention of SCD is based on drugs that do not have a predominant antiarrhythmic profile, such as β-blockers, ACE-inhibitors, lipid-lowering agents, polyunsaturated fatty acids, aldosterone receptor antagonists, etc. In patients with impaired LVF, neurohumoral blockade significantly reduced the rate of SCD.

It is obvious that the most common cause of SCD is arrhythmia, VT, and VF due to acute ischaemia or left ventricular dysfunction. But where are the chicken and the egg in the causal chain? What is the relation between LVF and arrhythmias? Are arrhythmias only bystanders, as was obviously proven in MADIT II? Reduced LVF was enough for ICD implantation. Nonsustained VT, or PVBs recorded on ambulatory ECG or induced by PVS did not have a significant predictive value for risk stratification after acute myocardial infarction.

Let us set aside the life-threatening arrhythmias and examine LVF more closely. ACE-inhibitors work, but until now there has been no study proving their antiarrhythmic effect, which is similar to that of the β-blockers, according to rhythmology criteria. Accept the crude but successful work of the ICD, but don’t think that it is the last word!

No study has been made of secondary prevention in SCD-survivors to compare neurohumoral blockade with the above-mentioned "protective arrhythmia suppression" concept.

In summary, PVS in survivors of cardiac arrest seems to be back and could become more prominent. The inducibility of VF and/or VT stratifies a cohort with a higher cardiac mortality, especially if EF is >35%.

What are the consequences for the clinician, especially when under economic pressure to implant an expensive device that in many cases is unnecessary?

Should we implant ICDs in the high-risk group, thus preventing sudden arrhythmic death, although these patients more frequently have cardiac, nonsudden, and nonarrhythmic deaths?

Would it be desirable to avoid ICD or Amiodarone in the low-risk cohort because it is costly overtreatment?

What is a reasonable risk in these patients?

The ICD is a "hammer" that turns everything into a nail, but works. Will we need this "hammer" when future studies have investigated neurohumoral blockade (ACE inhibitors, β-blockers) and/or the re-establishment of synchronicity between and within the ventricles (cardiac resynchronisation therapy), at first with, and eventually possibly without, ICD protection to reduce cardiac deaths?
References