Review Article

Does electrophysiological testing have any role in risk stratification for sudden cardiac death?

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Introduction

Implantation of implantable cardioverter defibrillators (ICD) has widely been accepted for secondary prevention of sudden cardiac death (SCD) in cardiac arrest survivors.1 Currently there are increasing interests in primary prevention of SCD in selected high risk patients who have not experienced cardiac arrest.1 Despite extensive investigation for risk stratification, our current ability to accurately identify patients at high risk for SCD remains very poor. The primary reason is probably due to our limited understanding of the mechanisms underlying the pathogenesis of ventricular tachyarrhythmias and sudden cardiac death (Fig.1). Although ventricular tachycardia (VT) or fibrillation (VF) is still considered the most common mechanism of SCD in patients with advanced heart failure, many causes other than VT/VF (such as bradycardia) may account for up to 50% of SCD, particularly in non-ischemic dilated cardiomyopathy (DCM).

Historical review of risk stratification for sudden cardiac death

Approximately 80% of SCD are secondary to coronary artery disease (CAD). Accordingly, our experience on risk stratification is primarily gained from studies in patients with CAD, particularly following myocardial infarction (MI).2 In 1980’s and 1990’s, electrophysiological (EP) testing was widely used for assessment of patients suspected of having ventricular arrhythmias associated with CAD (Table 1).3 At the same time, considerable efforts were also made to investigate the role of several other invasive and non-invasive techniques for risk stratification (Fig. 2). Since the publication of the MADIT II trial in 20024 and particularly after the publication of the SCD-HeFT trial in 2005,4,5 it appears that the predictive value of left ventricular ejection fraction (LVEF) may be over-emphasized and the role of EP testing and other risk factors or techniques are being ignored.6-7 To evaluate clinical value of a given risk factor for risk stratification for SCD, it should be kept in mind that positive predictive value of a risk stratifier rather than its sensitivity or specificity is of much more clinical importance.
Current status of risk stratification for sudden cardiac death

At present, risk stratification for primary prevention of SCD is mainly based on left ventricular function. A low LVEF is recommended to identify patients at high risk of SCD for ICD implantation. This concept is primarily derived from the data of the MADIT II trial and SCD-HeFT trials. The incidence of SCD is highest in patients with more advanced cardiac disease who are at highest risk of all cause mortality. Although a low LVEF is certainly associated with increased risk of SCD, the number of patients needed to treat in order to save a life is relatively high when selecting patients for ICD implantation using LVEF as the only risk stratifier. This leads to a concern regarding the cost-effectiveness of ICD implantation for primary prevention. We personally agree with Dr. Alfred E. Buxton and Dr. Mark E. Josephson on that other risk factors or techniques (including EP testing) in addition to LVEF should be considered to improve cost-effectiveness until a better strategy becomes available.

EP testing in patients with coronary artery disease

There are convincing data showing that induction of VT by programmed electrical stimulation (PES) can be used for risk stratification of SCD in MI patients with non-sustained VT (NSVT) and left ventricular dysfunction (LVEF <40%). In these patients, inducibility of sustained VT ranges between 20% and 40%. Inducibility identifies patients at high risk of subsequent VT and confers a worse prognosis, while the absence of inducibility indicates a low risk with MADIT-type patients. Unfortunately its predictive efficacy is modest (2-year risk for VT or SCD is 18% in patients with inducible VT versus 12% in registry patients, i.e., 50% more risk if inductible). Non-inducible patients are still at relatively high risk of SCD (2-year risk for VT or SCD is 12%). In other words, patients with inducible VT are at higher risk for SCD but non-inducibility does not necessarily exclude the risk of SCD, particularly in patients with a low LVEF (<30%). When a patient’s risk for SCD is assessed, his overall clinical condition should always be considered. It is our experience that the three major risk factors for SCD in patients following MI are residual ischemia, depressed left ventricular function, and ventricular arrhythmias (including inducible VTs by PES). A practical and potentially more cost-effective approach for selection of patients for ICD implantation is firstly to evaluate such patients using non-invasive techniques and further to stratify them using EP testing, as reported by Schmitt and colleagues.

One question that remains to be answered is whether the predictive value of EP testing established in 1980s and 1990s has been altered or not in the era of using percutaneous coronary interventions as the primary therapeutic modality in patients with acute MI.

It is current recommendation that prophylactic antiarrhythmic therapy is not indicated for patients who do not have symptomatic arrhythmias, without prior MI, and those with prior MI whose LVEF is greater than 40% since their SCD risk is not sufficiently high to warrant prophylactic therapy. EP testing may be performed in these patients for management of VTs rather than for risk stratification of SCD only.

EP testing in patients with idiopathic dilated cardiomyopathy

Risk stratification is difficult in patients with idiopathic DCM although these patients usually have a poor prognosis (5-year mortality is estimated at 20% with SCD accounting for approximately 30% of deaths). Many stratifiers that predict overall outcome also predict SCD. They generally reflect severity of disease (such as a low LVEF). Therefore, they do not specifically predict arrhythmic SCD. For example, a low LVEF (<20%) may not have high positive predictive value for SCD. This is further supported by the negative results of ICD implantation for primary prophylaxis, such as in the CAT, AMIOVERT, and DEFINITE trials. It appears that syncope is associated with a higher risk of SCD in these patients.

The predictive value of EP testing remains controversial in patients without CAD, such as idiopathic DCM. It has generally been thought that EP testing has limited role for risk stratification in patients with idiopathic DCM due to relatively low inducibility, low reproducibility, and low predictive value of induced VT. We reviewed 102 patients with idiopathic DCM underwent ICD implantation prior to MADIT II publications aimed at assessing the predictive role of EP testing. We found that in these patients inducible VT (using a more aggressive stimulation protocol) was associated with more appropriate ICD therapies during a median follow-up period of 20.6 months (Fig.3). It seems that in patients with idiopathic DCM, inducible patients are at increased risk of spontaneous arrhythmic events and potentially cardiac arrest (with positive predictive value of 84% and specificity of 91%) but less sensitive compared to that in patients with CAD for risk stratification (with sensitivity of 59%).

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Table 1 Clinical outcomes during the first year of follow-up in 1209 patients according to the electrophysiological testing at hospital discharge

<table>
<thead>
<tr>
<th></th>
<th>Inducible (n=75)</th>
<th>Not inducible (n=1134)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reinfarction</td>
<td>5(7%)</td>
<td>60(5%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Electrical event</td>
<td>14(19%)</td>
<td>35(3%)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Spontaneous VT/VF</td>
<td>10(13%)</td>
<td>20(2%)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Instantaneous death</td>
<td>5(7%)</td>
<td>16(1%)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Other death</td>
<td>10(13%)</td>
<td>46(4%)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>After reinfarction</td>
<td>3(4%)</td>
<td>0(0%)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Other</td>
<td>7(9%)</td>
<td>46(4%)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Alive</td>
<td>60(80%)</td>
<td>1072(95%)</td>
<td>&lt;0.0005</td>
</tr>
</tbody>
</table>
EP testing in other patients at increased risk for SCD

Risk stratification for SCD in other relatively less common clinical settings (such as hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, and Brugada syndrome) has been difficult, partially due to limited number of patients available for large clinical trials. Proposed risk factors usually include prior history of cardiac arrest or unexplained syncope, spontaneous sustained VTs (possibly including NSVT as well), and more severe pathological changes (for example, left ventricle thickness $>30$ mm in hypertrophic cardiomyopathy). Again the predictive value of EP testing remains controversial in these patients. In general, inducible VTs in these patients might be considered to be associated with higher risk for SCD, especially in patients with other risk factors.

Summary

It is current practice that ICD implantation is indicated in patients with a low LVEF. Other risk factors are to be sought to increase the cost-effectiveness of ICD for primary prevention of SCD. EP testing can be used for risk stratification for SCD in patients with CAD. This may improve predictive accuracy in patients stratified using other risk factors, including a low LVEF. Based on the data from MADITT II and MUSTT trials, it is class I indication for ICD implantation in patients with nonsustained VT due to prior MI, LVEF $<40\%$, and inducible VF or sustained VT at EP testing.$^1$ EP testing is reasonable for risk stratification in these patients (class IIa indication).$^{12}$ In patients at increased risk for SCD without CAD (including idiopathic DCM), EP testing may also provide useful predictive information (Class IIb indication). In conclusion, EP testing might be considered in selected patients for further risk stratification for SCD in order to improve cost-effectiveness of expansive ICD implantation. It should be kept in mind that the predictive value of combination of multiple risk factors is always superior to any of a single factor, including LVEF.$^1$

References