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EDITORIAL

The Diminished Role of an Electrophysiology Study in the Current Guidelines for Sudden Cardiac Death

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Abstract

According with the new European and American guidelines, the role of an electrophysiology study (EPS) remains small for risk stratification for sudden cardiac death (SCD), limited to patients with an LVEF >35%, mostly indicated when evaluating symptoms suggestive of ventricular tachyarrhythmias, including palpitations, presyncope and syncope, mainly in those with underlying structural heart disease, particularly coronary artery disease in the setting of a remote myocardial infarction rather than non-ischemic cardiomyopathy. Importantly, there is no indication or need of EPS as a prerequisite for any of the standard indications of implantable cardioverter defibrillator (ICD) for secondary or primary prevention of SCD. ***Rhythmos*** 2018;13(1): 1-5.

Key Words: sudden cardiac death; electrophysiology study; programmed ventricular stimulation; implantable cardioverter defibrillator; cardiac resynchronization therapy

Abbreviations: ARVC = arrhythmogenic right ventricular cardiomyopathy; CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; CRT = cardiac resynchronization therapy; EPS = electrophysiology study; ICD = implantable cardioverter defibrillator; LOE = level of evidence; LV = left ventric-le(-ular); LVEF = left ventricular ejection fraction; MI = myocardial infarction; NICM = non-ischemic cardiomyopathy; NYHA = New York Heart Association; RCTs = randomized controlled studies; RVOT = right ventricular outflow tract; SCD = sudden cardiac death; SVT = supraventricular tachycardia; VA = ventricular arrhythmia; VF = ventricular fibrillation; VT = ventricular tachycardia

Role of EPS for risk stratification

With the completion of randomized controlled trials (RCTs) [1-4] for primary and secondary prevention of sudden cardiac death (SCD) documenting the superiority of implantable cardioverter defibrillator (ICD) over antiarrhythmic drugs with selection of patients based primarily on the type of clinical arrhythmia, the underlying heart disease and the left ventricular (LV) ejection fraction (LVEF) and secondarily on New York Heart Association (NYHA) classification of symptoms, the role of an electrophysiology study (EPS) has markedly been downgraded. [5, 6] Thus, the guidelines solely for the performance of EPS have not been updated since 1995.[7] In the cases of secondary prevention of SCD, there is no need for electro-pharmacological testing any more,[8, 9] while in the instances of primary prevention, the positive predictive value of EPS, similar to that of a bunch of other tests (e.g. signal-averaged ECG, heart rate variability, T-wave alternans, etc.) has remained low and thus their value has been questioned.[10-15] Furthermore, the negative predictive

value of EPS is even lower, while the invasive nature of this test limits its acceptance as a risk stratifier.[16] For secondary prevention, there is no cut-off value for the LVEF, however, for primary prevention an LVEF ≤35% has been adopted by the guidelines as an indication of ICD implantation. A similar cut-off (LVEF≤35%) has been set for implantation of a cardiac resynchronization therapy (CRT) defibrillator (CRT-D) device together with the width (≥120-150 ms) of the QRS complex. LVEF has remained as the best available predictor despite its several limitations in terms of sensitivity and specificity in the absence of a better risk stratifier, either as a single marker or in the form of a risk score. Thus, for all the above instances, there is no need to perform an EPS. However, for greater values (>35%) of LVEF, there is a resurgence of interest in the performance of an EPS for risk stratification in patients with ischemic and non-ischemic cardiomyopathy (NICM)[17, 18] in an attempt to identify more patients at risk for SCD, as it has been poignantly realized for a long time now that many patients with LVEF >35% are also susceptible to the occurrence of SCD.[19] EPS as an old and classical tool of risk stratification combined with newer tools, such as cardiac magnetic resonance imaging (CMR), may offer some hope in expanding the spectrum of risk stratification and SCD protection for more patient categories.

When performing an EPS, only the induction of ***sustained monomorphic ventricular tachycardia (VT)*** is considered a specific finding, while the induction of polymorphic VT or ventricular fibrillation (VF) are nonspecific findings,[15, 20] except perhaps for the induction of VF with ≤2 ventricular extrastimuli in patients with Brugada syndrome.[21] Some may consider that the reproducible induction of polymorphic VT/VF with a low (≤2) number of extrastimuli may be of some clinical significance.[15] In general, induction of polymorphic ventricular arrhythmias (VA) with programmed ventricular stimulation applied at the right ventricular outflow tract (RVOT), particularly with use of 3 ventricular extrastimuli, are always nonspecific findings under any circumstances. The sensitivity and specificity of EPS is always higher in patients with coronary artery disease (CAD) compared with patients with NICM. Finally, although a positive EPS with inducible monomorphic VT may predict the occurrence of clinical monomorphic VT, its ability to predict polymorphic VT or VF is limited.

Indications for EPS

American Guidelines. According with the new (2017) ACC/AHA/HRS guidelines,[22] performing an EPS is recommended in the following instances:

1. ***In patients with ischemic cardiomyopathy, NICM, or adult congenital heart disease who have syncope or other VA symptoms and who do not meet indications for a primary prevention ICD, an EPS can be useful for assessing the risk of sustained VT (Class IIa / LOE B-R)***

2. ***In patients who meet criteria for ICD implantation, an EPS for the sole reason of inducing VA is <u>not indicated</u> for risk stratification (Class III / LOE B-R)***

3. ***An EPS is <u>not recommended</u> for risk stratification for VA in the setting of long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), short QT syndrome (SQTS), or early repolarization syndromes (Class III / LOE B-NR)***

In the text accompanying the Guidelines it is made clear that in the current era of ICD therapy and its proven benefit in the primary and secondary prevention of SCD, the role of EPS is diminished:

- Patients with heart failure and LVEF ≤35% generally will have an indication for an ICD and specific induction of VT/VF before implantation is not necessary.
- Patients with LVEF >35% and unexplained syncope or near-syncope may benefit from an EPS to determine if VT/VF is the cause of symptoms and to guide further therapy.
- Induction of VT/VF is often attempted before *catheter ablation* of the arrhythmia substrate to guide the procedure and to determine the success of the intervention after ablation is performed.
- An EPS can be used to determine the mechanism of a wide complex tachycardia.

It is further emphasized that in patients who meet criteria for ICD implantation (i.e., heart failure and LVEF ≤35%), data do not support the routine use of EPS solely for risk stratification, as such patients have been shown to derive survival benefit from the ICD.

An EPS may be helpful, however, in selected patients suspected to have preexcitation or supraventricular arrhythmias as the cause of symptoms or wide complex tachycardias that warrant definitive diagnosis and management. Supraventricular tachycardia (SVT) leading to VT/VF or aberrantly conducted SVT may also be suspected in younger patients or those with a preserved LVEF. Induction of SVT and ablation may then be curative, with no need for an ICD. In such cases, failure to induce VT/VF after elimination of the substrate for SVT would be expected.

Finally, it is pointed out that risk stratification for channelopathies is generally made on the basis of symptoms, the ECG, exercise treadmill testing, and the results of genetic testing. The EPS (i.e., programmed

ventricular stimulation) does not have prognostic value for risk stratification in these patients.

European Guidelines. However, one may argue that European countries should abide by the ESC guidelines. According to these guidelines, last updated in 2015,[23] an EPS is recommended as follows:

1) In patients with CAD for diagnostic evaluation of patients with remote myocardial infarction (MI) with symptoms suggestive of VAs, including palpitations, presyncope and syncope (class I, LOE B).

2) In patients with syncope when bradyarrhythmias or tachyarrhythmias are suspected, based on symptoms (e.g. palpitations) or the results of non-invasive assessment, especially in patients with structural heart disease (class I, LOE C)

3) EPS may be considered for the differential diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC) and benign RVOT tachycardia or sarcoidosis (class IIb, LOE B)

In particular, for patients with unexplained syncope, the indication for EPS is phrased as follows: ***"Programmed ventricular stimulation (PVS) should be considered in survivors of an MI with preserved LV function and otherwise unexplained syncope (class IIa, LOE C).***"

In the text, the guidelines emphasize that in patients with cardiomyopathies and inherited primary arrhythmia syndromes, EPS might play a role in ARVC or NICM patients, while ***it does not contribute to identifying high-risk patients in hypertrophic cardiomyopathy (HCM) (class III).*** Among the channelopathies, EPS is not indicated in LQTS, CPVT and SQTS, while its utility is debated in Brugada syndrome. With regards to the latter group, the article that accompanies the American guidelines[24] reviews the evidence from 6 studies of 1138 asymptomatic patients with Brugada syndrome about the value of EPS. Inducible VA on EPS was identified in 390 (34.3%) patients. Primary analysis limited to 5 of the 6 studies found an odds ratio of 2.3 (p=0.2) for major arrhythmic events (sustained VAs, SCD, or appropriate ICD therapy) in asymptomatic patients with Brugada syndrome and inducible VA on EPS versus those without inducible VA.

In patients with syncope, it is noted that EPS is useful in patients with LV dysfunction due to a previous MI (LVEF <40%) but is not sensitive in patients with NICM.

Induction of polymorphic VT or VF, especially with aggressive stimulation techniques, is not specific. In CAD, the diagnostic yield may reach 50%.

Table 1. Current Indications for an Electrophysiology Study (EPS) for Sudden Cardiac Death (SCD) Risk Stratification

- ***patients with underlying structural heart disease and an LVEF >35% or who do not meet indications for a primary prevention ICD, when evaluating symptoms suggestive of ventricular tachyarrhythmias, including palpitations, presyncope and syncope***
- ***before catheter ablation of the arrhythmia substrate to guide the procedure and to determine the success of the intervention after ablation is performed***
- ***to determine the mechanism of a wide complex tachycardia***
- ? may be considered for the differential diagnosis of ARVC and benign RVOT tachycardia
- ? asymptomatic patients with Brugada syndrome

ARVC = arrhythmogenic right ventricular cardiomyopathy; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; RVOT = right ventricular outflow tract

ICD for secondary Prevention of SCD

It is clear from the guidelines that <u>EPS is not indicated and not needed</u> when a patient suffers from documented VT/VF (in the absence of reversible causes or within 48 h after MI) wherein an ICD is recommended for secondary prevention of SCD.

ICD for primary prevention of SCD

According to both American and European guidelines, an ICD is indicated for primary prevention of SCD in the following instances, <u>without the need for an EPS</u>:

1) ICD therapy is recommended to reduce SCD in patients with symptomatic heart failure (NYHA class II–III) and LVEF ≤35% after ≥3 months of optimal medical therapy who are expected to survive for at least 1 year with good functional status: *class I/LOE A* for ischemic etiology (at least 6 weeks after MI), *class I / LOE B* for non-ischemic etiology.

The European guidelines state that currently there are no RCTs demonstrating the value of an ICD in asymptomatic patients (NYHA class I) with systolic dysfunction (LVEF ≤35–40%) or in patients with heart failure and preserved LVEF >40–45%, thus ICDs are not recommended for primary prevention in these patients.

However, the American guidelines provide the following criteria for ICD implantation in patients with NYHA class I and LV dysfunction, based on the two MADIT trials:[2, 3, 22] an ICD is recommended in patients with ischemic heart disease and LVEF of <u>≤</u>30% who are at

least 40 days' post-MI and at least 90 days post-revascularization (*class I / LOE A*); while in patients with NICM, an ICD is recommended when LVEF is ≤35% (*class IIb, LOE B-R*), based on the DEFINITE trial.[25] The criteria differ for patients with NICM due to a *Lamin A/C* mutation, whereby an ICD is recommended if they have ≥2 risk factors (non-sustained VT, LVEF <45%, non-missense mutation, and male sex) (*class IIa/ LOE B-NR*).

Importantly, no EPS is recommended as a prerequisite for any of the above indications of ICD for primary prevention. The only group that the American guidelines indicate the usefulness of an EPS to determine the need for an ICD includes patients fitting the group of the MUSTT trial,[26] i.e. patients with non-sustained VT due to prior MI, LVEF of ≤40% and inducible sustained VT or VF at EPS (*class I / LOE B-R*). Practically, based on all the above indications, *EPS may be of use for ischemic patients with 35%<LVEF<40%*.

Conclusion

Despite a resurgence in the interest for performing an EPS for risk stratification of cardiac patients for SCD, according to the new European and American guidelines, the role of EPS remains small, limited to patients with an LVEF >35%, particularly indicated when ***evaluating symptoms suggestive of ventricular tachyarrhythmias, including palpitations, presyncope and syncope*** mainly in those with underlying CAD (remote MI) rather than NICM. Importantly, there is no indication or need for EPS as a prerequisite for any of the standard indications of ICD implantation either for primary or secondary prevention of SCD. EPS is not recommended for risk stratification of patients with primary electrical disease (channelopathies), except perhaps for asymptomatic patients with Brugada syndrome, nor for patients with hypertrophic cardiomyopathy. Rarely, may EPS be useful in the differential diagnosis of ARVC and benign RVOT tachycardia. Finally and plausibly, the invasive nature of EPS is a major obstacle for its wider acceptance as a risk stratifier.

Perspective

The development of optimal risk-stratification tools that can identify patients specifically at risk for SCD who could maximally benefit from ICD implantation remains a vexing challenge. Unfortunately, most of the broadly adopted and widely used risk stratification tools and scores are not specific for SCD. Decreased LVEF is a prime example of a problematic risk stratifier that has no ability to explicitly predict SCD; it mainly identifies patients at overall high cardiac mortality risk. However, even the more sophisticated tools, like heart rate variability, T-wave alternans, signal-averaged ECG, etc., are also only useful at sorting out high mortality risk patients, without specifically predicting arrhythmic risk, while all of them are suffering from low predictive values. Combining these tests may increase the predictive value but the number of patients having some or all of them positive sharply diminishes.

Among all of these imperfect tools, EPS appears to be the only well-established risk stratification tool specifically for SCD, but this test also suffers from relatively low predictive values, while its major drawback is its invasive nature. Thus, better noninvasive tools are urgently needed. In this direction contrast-enhanced CMR detecting myocardial fibrosis and scar with late gadolinium enhancement (LGE) appears to be a powerful risk stratifier for patients with NICM.[17, 18] This apparently relates to the fact that myocardial scar promotes VAs via mechanisms of heterogenous myocardial conduction and electrical reentry that may lead to SCD. Importantly, this non-invasive risk stratifier seems to be also useful in patients with LVEF >35%, where there is greater and more dire need for SCD risk stratification, as there are currently no guidelines applied and no means to predict and prevent SCD in this patient population. The ongoing randomized CMR_Guide trial (https://clinicaltrials.gov/ct2/show/NCT01918215) will test whether a routine CMR-guided management strategy of ICD insertion (in LGE-positive patients) is superior to a conservative strategy of standard care among patients with mild-moderate LV systolic dysfunction (LVEF 36%–50%).

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