

Programmed Ventricular Stimulation: How Low (with the Coupling Interval) and Aggressive (with the Protocol) Should We Go? No Easy Answers

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Implantable cardioverter defibrillators are used in patients after cardiac arrest or hemodynamic compromise due to ventricular arrhythmia for secondary prevention of recurrent events and death. There has been an increase in the use of ICDs for primary prevention of sudden cardiac death in patients with ischemic and non-ischemic cardiomyopathy at risk of SCD.

ICDs were initially used for this purpose in patients with a history of myocardial infarction, low ejection fraction (< 35–40%), and non-sustained ventricular tachycardia with inducible sustained ventricular arrhythmia during programmed ventricular stimulation [1,2]. Recently, indications for ICD implantation were widened after publication of the MADIT-II trial [3], which showed that patients with a history of myocardial infarction with a left ventricular ejection fraction < 30% – without other markers of arrhythmic risk – have a lower mortality risk with an ICD as compared to patients on medical therapy. Another reason for the extended indications was the SCD-HeFT trial [4], which demonstrated that patients

with LVEF < 35% and heart failure had a lower mortality rate after implantation of an ICD compared to patients with no ICD. The number needed to treat to save one life in 2 years was 18 in MADIT-II and 14 in SCD-HeFT. This number is much higher compared to the first primary prevention trials where it was 4 [1,2]. In addition, implanting ICDs indiscriminately in all patients with LVEF < 30% has a considerable financial and medical cost. The estimated price for a single ICD is between US\$ 20,000 and 35,000. Moreover, these procedures are not risk free and carry a substantial morbidity and mortality risk [5]. Also, a substantial number (11%) of patients receive inappropriate shocks, mainly for supraventricular arrhythmia [6]. Therefore, it seems that while some patients derive benefit from this prophylactic intervention, others do not; the latter may be harmed and at considerable cost.

Better risk stratification of post-MI patients with low EF may achieve two goals: a) identifying most patients who would derive benefit from ICDs, and b) avoiding the implantation of ICDs in patients who would not gain any benefit and may potentially be harmed.

Several methods for risk stratification have evolved over time. Non-invasive markers of increased risk include LVEF, QRS width and the presence of left branch bundle block on the 12-lead elec-

trocardiogram, signal average ECG, T wave alternans, heart rate variability, QT dispersion and others [7]. While some of these methods identify patients at higher risk for VA and sudden death, none has proven sensitive enough to be incorporated as a single-risk stratifier [7].

Programmed ventricular stimulation has long been considered the gold standard for recognizing patients at risk of ventricular arrhythmia and SCD. The theoretical basis for using PVS for risk stratification derives from the substrate of VT in post-MI patients. VT is initiated by means of ventricular extrastimuli; if the substrate for VT exists these ventricular extrastimuli will block one arm of the circuit and will conduct slowly in the second arm and back again over the first arm to initiate reentrant VT. Standard protocol involves delivering a basic train of between five and eight captured beats from two sites (usually right ventricular apex and right ventricular outflow tract) and at two basic cycle lengths (600 and 400 ms) and with delivery of up to three ventricular extrastimuli with a minimum coupling interval of 180 ms. Pacing is usually done at twice the diastolic threshold to ensure local capture and prevent far-field or remote capture. Several landmark studies have shown that patients with low EF, non-sustained VT on Holter monitoring and

CD = implantable cardioverter defibrillator
SCD = sudden cardiac death

LVEF = left ventricular ejection fraction
MI = myocardial infarction

VA = ventricular arrhythmia
PVS = programmed ventricular stimulation
VT = ventricular tachycardia

inducible sustained VA in programmed ventricular stimulation derive survival benefit from ICD implantation [1,2]. Nevertheless, standard PVS fails to identify a substantial number of patients at risk. In the MUSTT registry (patients with a history of myocardial infarction, LVEF < 40%, non-sustained VT and a negative PVS using the standard protocol), the rate of cardiac arrest or death due to arrhythmia was 12% and 24% at 2 and 5 years, respectively [8]. Furthermore, in MADIT-II (82% of patients underwent PVS) the 2 year event rate for VT or ventricular fibrillation was 29.4% for inducible patients and 25.5% for non-inducible patients. Standard inducibility did not predict the combined endpoint of VT or VF ($P = 0.280$, by log-rank analysis) [9], although it was excellent for identifying patients who will develop VT [9]. Moreover, during follow-up, the non-inducible patients had a higher rate of VF compared to inducible patients [9]. Of interest, induction of VF in MADIT II by using three ventricular extrastimuli did not improve prediction [9].

In the current issue of *IMAJ* Belhassen et al. [10] describe a more aggressive protocol of PVS in a MADIT-II-like population (post-MI patients with LVEF < 30%) to increase the sensitivity and specificity of PVS in identifying patients at risk. This method involves a higher output energy (five times the diastolic threshold, but not higher than 3 mA), repeating the shortest captured coupling interval 10 times for double VES and 5 times for triple VES, and no lower limit for coupling interval of VES. Induction of any ventricular arrhythmia was considered positive (unlike the traditional MUSTT and MADIT criteria that designate positive PVS only if monomorphic VT is induced, or VF with up to two VES). The inducibility rate was 75.4% (twice as high as compared to MADIT-II and MUSTT); most were VT and the rest VF and

ventricular flutter. Of note, most of the ventricular fibrillations and ventricular flutter were induced by using triple VES, which would have been considered negative by standard MUSTT criteria. This high inducibility rate could be explained by different patient populations but is more likely related to the more aggressive protocol used in the present study. The article does not mention the actual number of repetitions needed to induce VF or ventricular flutter or to the actual output energy used – which may help put the results in perspective.

The mortality rate in the EPS+/ICD+ group was 10.7% and 14.7% in the EPS-/ICD- group, which was not statistically different. However, this could be attributed to the small number of patients in the EPS-/ICD- group with low statistical power to detect this difference. Importantly, the risk of arrhythmic death or arrhythmic events requiring ICD in the group of patients with negative EPS was very low – 3%, a much lower estimate than the rates in non-inducible patients in MUSTT and MADIT-II [8,9]. This, of course, could be the result of this more aggressive protocol of induction, leaving a smaller number of high risk patients in the non-inducible group, or it could be due to a bias inherent to this type of retrospective analysis with cause of death determined by telephone interviews or chart review [10]. Data showing the number of VA events occurring in the EPS+/ICD+ group and comparing them to the number of VA events in the EPS-/ICD- group is essential to truly appreciate the potential discriminative power of the proposed protocol. In order to appreciate the specificity of this protocol it is essential to know how many patients in the EPS+/ICD+ group were never shocked or received inappropriate shocks.

There are several other limitations worth discussing. It would have been interesting to compare inducibility rates using standard compared to the proposed technique. It would have been

very helpful to see whether prediction of subsequent VA is influenced by the protocol of inducibility. Furthermore, we are not told why those patients were chosen for the study.

Despite these limitations we congratulate the authors for their important efforts to improve risk stratification of post-MI patients. We believe that the next stage should be a study that will compare inducibility rates using this technique vs. the traditional programmed ventricular stimulation protocol followed by an ICD implantation and a follow-up period to appreciate the true predictive difference between the two different protocols – perhaps combining other non-invasive risk stratifiers as well. If proven highly sensitive and specific, then the next stage should be (as proposed by the authors) a trial to compare inducible patients and non-inducible patients who will undergo an ICD implantation vs. non-inducible patients with no ICD.

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VF = ventricular fibrillation
 VES = ventricular extrastimuli

EPS = electrophysiologic study

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