Programmed Ventricular Stimulation: Not Dead

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How easy it is to make people believe a lie, and how hard it is to undo that work again!

- Mark Twain in Eruption

Medicine, like most other human endeavors, goes through fads. These fads are often initiated by persuasive, well-meaning persons who have incomplete grasp of fundamental pathophysiology. Because ideas underlying fads may sound plausible, the fad is perpetuated and accepted as gospel until a randomized controlled trial or other well-designed study proves the concept faulty.

One example of this phenomenon is seen in the evolution of efforts to prevent sudden cardiac death in survivors of acute myocardial infarction (MI). Widespread study of sudden cardiac death (SCD) was aided by development of technology permitting real-time ECG monitoring, resulting in proliferation of the CCU in the 1960s and 1970s. Patients who developed primary ventricular fibrillation (VF) with acute MI in the CCU were often observed to exhibit progressively frequent and “complex” ventricular ectopy in the minutes leading up to VF. At the same time, randomized trials demonstrated that antiarrhythmic agents such as lidocaine, procainamide and quinidine could reduce the occurrence of VF in this setting. These observations then gave rise to the following assumptions: 1. SCD late after MI is due exclusively to VF, 2. the presence of frequent ventricular ectopy and nonsustained ventricular tachycardia (VT) 2-4 weeks after onset of acute infarction would identify patients at risk of SCD, and 3. suppression of ventricular ectopy by antiarrhythmic drugs would prevent post infarction SCD. As a result, it became common for physicians to perform a 24-hour ambulatory monitor in patients with recent MI, and then prescribe chronic antiarrhythmic drugs in patients with “complex” ectopy. This continued for 20 years until the Cardiac Arrhythmia Suppression Trial (CAST) proved this practice killed more patients than it helped. Among others, 2 faults with
this line of reasoning were failure to recognize that the pathophysiology of sudden cardiac death (SCD) after MI differs from the pathophysiology (sudden ischemia) of SCD in the acute phase of MI, and failure to recognize that SCD following MI is multifactorial, often resulting from VT, not VF.

At the same time that most cardiologists were enthusiastically suppressing PVCs in MI survivors, another trend developed among electrophysiologists. In the 1970s it was recognized that monomorphic sustained VT following MI was usually due to a reentrant mechanism, and programmed ventricular stimulation (PVS) could induce sustained VT in over 90% of patients who presented with spontaneous sustained VT.3 Knowing that sustained monomorphic VT could precipitate cardiac arrest, in the 1980s electrophysiologists then began performing PVS in patients who had never experienced spontaneous sustained VT, presuming that the presence of inducible sustained VT was a marker for SCD risk. Several single center observational studies demonstrated significantly increased risk of SCD in patients with inducible sustained VT compared to patients without inducible VT. Additionally, suppression of inducible VT by antiarrhythmic drugs seemed to reduce SCD risk. In 2000, results of the Multicenter UnSustained Tachycardia Trial (MUSTT) were reported, evaluating the ability of electrophysiologic studies (PVS) to guide antiarrhythmic therapy and reduce risk for SCD after MI. This trial enrolled 2202 coronary disease patients with EF ≤40% and nonsustained VT.4,5 Thirty-five percent of patients had inducible VT and were randomized either to receive no antiarrhythmic therapy or to electrophysiologically (EP)-guided therapy. Those randomized to EP-guided therapy underwent repeated EP studies on antiarrhythmic drugs. Patients whose inducible VT was suppressed on antiarrhythmic drugs were discharged on those drugs. Those whose VT remained inducible underwent ICD implantation. After a median follow-up of 39
months this trial provided 2 major findings: 1. patients with inducible VT randomized to EP-guided therapy and discharged on antiarrhythmic drugs had significantly higher mortality than patients discharged with an ICD, while mortality of patients with inducible VT discharged with no antiarrhythmic therapy was not significantly different than that of patients treated with pharmacologic antiarrhythmic therapy, and 2. patients with inducible sustained VT had significantly higher risk for SCD and total mortality than patients without inducible sustained VT.

These results, together with those of the Multicenter Automatic Defibrillator Implantation Trial (MADIT) and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) resulted in abandonment of pharmacologic antiarrhythmic therapy (in the US) for primary prevention of SCD in patients with coronary artery disease and reduced ejection fraction (EF).6,7 Thus, electrophysiologic testing proved inaccurate to predict antiarrhythmic drug effects. The second major finding of the MUST Trial was the value of electrophysiologic testing for risk stratification for SCD: at 2 years 12% of patients without inducible sustained VT versus 18% of patients with inducible VT (randomized to no therapy) experienced SCD or cardiac arrest (adjusted p<0.001, HR=0.66)! In spite of these findings, and the fact that the ACC/AHA/ESC Ventricular Arrhythmia/Sudden Death Guidelines Committee endorsed the use of PVS for risk stratification of patients with coronary disease and EF ≤40%,8 it is little used in the US today. Thus, we have an example of trial results not logically influencing practice. Why? Many were disappointed that PVS did not identify every single patient in the MUSTT that died suddenly. Some vocal physicians voiced the opinion that PVS had no value – basically, they threw out the baby with the bath water. However, it is noteworthy that no other risk stratification test, except T-wave alternans (which proved inferior to PVS9), has ever been evaluated for utility in a
randomized controlled trial. This holds true for EF. The fault here lies with the expectation that one test (in this case, PVS) can identify all patients at risk for SCD. We now understand far better than we did in 1990, when MUSTT and MADIT were begun, that multiple mechanisms can lead to ventricular arrhythmias that cause SCD. If multiple arrhythmia mechanisms can precipitate SCD, how can we expect one test to identify all persons at risk? Furthermore, not all SCD in the post-MI population results from arrhythmias.10

In contrast to US practice, for 30 years the electrophysiology group in Westmead, Australia has diligently studied and reported on the use of electrophysiologic testing for risk stratification of patients with recent MI.11-13 In the current issue of Circulation, these investigators provide an update on their experience using programmed stimulation for risk stratification of patients surviving MI from 1999-2008.14 In this report, the investigators performed programmed stimulation 8 days (median) after MI in 128 STEMI survivors with EF \(\leq 35\%\). They induced sustained monomorphic VT (cycle length \(\geq 200\) msec) in 37\% of patients. Ninety percent of those with inducible VT had an ICD implanted 13 days (median) after MI.

The focus of this study is the 80 patients that had no inducible sustained VT. The latter patients were not given any specific antiarrhythmic therapy, except 3 cases in which the attending physician implanted ICDs based solely on reduced EF (protocol violations). Over a median follow-up of 42 months 2 (2.5\%) of the non-inducible untreated patients experienced SCD or resuscitated cardiac arrest \(> 40\) days post-MI.

In order to interpret these results appropriately, we have to place them in context. There are several noteworthy aspects of this experience that require comment. One-quarter of the study population had an EF \(\leq 40\%\). This is high in comparison to current US figures, but may be explained in part by the fact that the range of cases dates to 1999. Second, the median follow-up
is only 3.5 years. While relatively long in comparison to studies like MADIT-II (mean follow-up 20 months), there are increasing reports of patients treated with primary prevention ICDs not experiencing an appropriate therapy until after replacement of the initial ICD (i.e., greater than 5 years after implant). It is critical to remember that healing and remodeling after acute MI is an evolutionary process, and not a static situation. Patients with low-risk characteristics early after MI, may develop recurrent ischemia, heart failure, or other issues that require reassessment of SCD risk during follow-up.

Also noteworthy is the fact that the non-arrhythmic management of these patients was excellent. Ninety-six percent received beta-blocking agents, 87% received an ACE-inhibitor or angiotensin-receptor blocker, and 99% were given a statin! These figures far exceed the use of these agents in MUSTT, MADIT, MADIT-II, or SCD-HeFT. The excellent pharmacologic management undoubtedly contributed to the low mortality observed. However, there are other factors that likely contributed to the low observed mortality of all three patient groups in the Australian study. In 79% of the patients without inducible VT the qualifying MI was the first coronary event. This is reflected in their relatively young age 58 years. Although data on the distribution of NYHA class and renal function are not provided, I suspect that the study population did not include many patients with advanced heart failure or renal failure, both important prognostic indicators. This may explain in part why PVS performed so well.

How should we interpret and use the results of this report in practice today? It should be with caution, in view of the small study population, with few events over a relatively short follow-up. However, there are a number of useful take home points. First, it is important to contrast the study population with that of the MUSTT, MADIT and SCD-HeFT study populations. Those multicenter trials enrolled patients an average of more than 3 years after
acute MI, and the average age of post-MI patients was about 6 years greater than that of patients in the current report. Two-thirds of patients in MUSTT and MADIT-II had symptomatic heart failure that could have contributed to SCD by mechanisms not detected by PVS. The current study population is more akin to those enrolled in the DINAMIT and IRIS trials. In light of this, one wonders whether the 5 patients with inducible VT who had arrhythmic events within 40 days of acute MI survived. The results of this study suggest that judicious application of PVS should be considered a standard part of the process we use to stratify patients for risk of SCD after MI. However, lessons from previous trials warn us that risk stratification cannot rely on single tests alone, but require consideration of multiple risk factors. Finally, there is one other critical observation of the current study that bears on current guidelines for primary prevention of SCD. In this study, more sudden deaths occurred in the “low risk” control group of patients whose EF was >40%. This is not a novel finding, replicating previous observations. However, once again we are reminded that the current guidelines for use of ICDs to prevent SCD are deeply flawed. EF is a good predictor of total mortality, but has no direct relation to development of arrhythmias. Until we find ways to move past the current fad of EF-based guidelines, we will continue to waste money and harm patients, implanting ICDs in many that will not benefit, and withholding them from patients whose survival could be improved with ICD treatment.

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**References:**


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