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, Mark Twain in Eruption

Medicine, like most other human endeavors, goes through fads. These fads are often initiated by persuasive, well-meaning people who have an 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 (SCD) in survivors of acute myocardial infarction (MI). Widespread study of SCD was aided by the development of technology permitting real-time ECG monitoring, resulting in proliferation of the cardiac care unit in the 1960s and 1970s. Patients who developed primary ventricular fibrillation with acute MI in the cardiac care unit were often observed to exhibit progressively frequent and “complex” ventricular ectopy in the minutes leading up to ventricular fibrillation. At the same time, randomized trials demonstrated that antiarrhythmic agents such as lidocaine, procainamide, and quinidine could reduce the occurrence of ventricular fibrillation in this setting. These observations then gave rise to the following assumptions: (1) SCD late after MI is due exclusively to ventricular fibrillation; (2) the presence of frequent ventricular ectopy and nonsustained ventricular tachycardia (VT) 2 to 4 weeks after the onset of acute infarction identifies patients at risk of SCD; and (3) suppression of ventricular ectopy by antiarrhythmic drugs prevents postinfarction SCD.1 As a result, it became common for physicians to perform a 24-hour ambulatory monitor in patients with recent MI and then to prescribe long-term antiarrhythmic drugs in patients with complex ectopy. This continued for 20 years until the Cardiac Arrhythmia Suppression Trial (CAST) proved that this practice killed more patients than it helped.2 Among others, 2 faults with this line of reasoning were failure to recognize that the pathophysiology of SCD after MI differs from the pathophysiology (sudden ischemia) of SCD in the acute phase of MI and failure to recognize that SCD after MI is multifactorial, often resulting from VT, not ventricular fibrillation.

At the same time that cardiologists were enthusiastically suppressing premature ventricular contractions in MI survivors, another trend developed among electrophysiologists. In the 1970s, it was recognized that monomorphic sustained VT after MI was usually due to a reentrant mechanism, and programmed ventricular stimulation (PVS) could induce sustained VT in >90% of patients who presented with spontaneous sustained VT.3 Knowing that sustained monomorphic VT could precipitate cardiac arrest, in the 1980s, electrophysiologists 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 with 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 electrophysiological studies (PVS) to guide antiarrhythmic therapy and to reduce the risk for SCD after MI. This trial enrolled 2202 coronary disease patients with an ejection fraction (EF) ≤40% and nonsustained VT.4,5 Thirty-five percent of patients had inducible VT and were randomized to receive either no antiarrhythmic therapy or electrophysiologically guided therapy. Those randomized to electrophysiologically guided therapy underwent repeated electrophysiological studies on antiarrhythmic drugs. Patients whose inducible VT was suppressed on antiarrhythmic drugs were discharged on those drugs. Those whose VT remained inducible underwent implantable cardioverter-defibrillator (ICD) implantation. After a median follow-up of 39 months, this trial provided 2 major findings. First, patients with inducible VT randomized to electrophysiologically guided therapy and discharged on antiarrhythmic drugs had significantly higher mortality than patients discharged with an ICD, whereas the mortality of patients with inducible VT discharged with no antiarrhythmic therapy was not significantly different from that of patients treated with pharmacological antiarrhythmic therapy. Second, 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 pharmacological antiarrhythmic therapy (in the United States) for the primary prevention of...
SCD in patients with coronary artery disease and reduced EF.\textsuperscript{7,8} Thus, electrophysiological testing proved inaccurate in predicting antiarrhythmic drug effects. The second major finding of MUSTT was the value of electrophysiological testing for risk stratification for SCD: At 2 years, 12\% of patients without inducible sustained VT compared with 18\% of patients with inducible VT (randomized to no therapy) experienced SCD or cardiac arrest (adjusted $P<0.001$; hazard ratio, 0.66). Despite these findings and the fact that the American College of Cardiology/American Heart Association/European Society of Cardiology ventricular arrhythmia/sudden death guidelines committee endorsed the use of PVS for risk stratification of patients with coronary disease and EF $\leq 40\%$,\textsuperscript{9} it is little used in the United States 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 MUSTT who 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 experienced SCD or cardiac arrest (adjusted $P<0.01$; hazard ratio, 0.66). Over a median follow-up of 42 months, 2 of the 80 patients who had no inducible sustained VT experienced SCD or cardiac arrest >40 days after MI. This is reflected in their relatively young age (58 years). Although data on the distribution of New York Heart Association 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 the MUSTT, MADIT, and SCD-HeFT study populations. Those multicenter trials enrolled patients an average of $>3$ years after acute MI, and the average age of post-MI patients was $>6$ years greater than that of patients in the present report. Two thirds of patients in MUSTT and MADIT-II had symptomatic heart failure, which could have contributed to SCD by mechanisms not detected by PVS. The present study population is more akin to the patients enrolled in the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) and the Immediate Risk Stratification Improves Survival (IRIS) trial.\textsuperscript{17,18} 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 requires the consideration of multiple risk factors.\textsuperscript{10,19,20}

Finally, there is one other critical observation of the present study that bears on current guidelines for the 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 the use of ICDs to prevent SCD are deeply flawed. EF is a good predictor of total mortality but has no direct relation to the 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 who will not benefit...
and withholding them from patients whose survival could be improved with ICD treatment.

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