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EDITORIAL COMMENT

Eliminating Triggers of Ventricular Fibrillation

The Past, Present, and Future*

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The importance of ventricular ectopy and its causal relationship to induction of ventricular arrhythmias has been recognized for many years. The frequency and complexity of ventricular ectopy is related to risk, yet it is not an accurate predictor of sustained ventricular arrhythmias for individual patients. The practice of suppressing ventricular ectopy during the management of acute coronary syndromes has been abandoned in the coronary care unit because treatment with antiarrhythmic medications has no survival benefit. Numerous trials were conducted to test the hypothesis that suppression of ventricular ectopy by antiarrhythmic medications would improve survival. Josephson (1) correctly predicted that attempts to suppress ventricular premature beats (VPBs) with medication would fail to improve survival, and the results of the CAST (Cardiac Arrhythmia Suppression Trial) study (2) convincingly demonstrated the futility of that strategy.

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The recent body of work refocuses attention on the relationship between ventricular ectopy and recurrent ventricular fibrillation (VF). In 2002, Haïssaguerre et al. (3) reported the initial observation that VPBs arising from the Purkinje system had an important role in the induction of idiopathic VF. In 2003, they described the same approach with good results in a small number of patients with long QT syndrome or Brugada syndrome who had frequent VPBs and episodes of VF or polymorphic ventricular tachycardia (4). Later that year, Bansch et al. (5) reported 4 patients with combinations of repetitive VF, polymorphic ventricular tachycardia, or monomorphic ventricular tachycardia who benefited from ablation of ventricular ectopy that arose from the Purkinje system. Similar results have been reported by others (6) in a small series of patients or as isolated case reports, and Bogun et al. (7) demonstrated the role of Purkinje fibers in re-entrant ventricular tachycardia after myocardial infarction.

In this issue of the *Journal*, Knecht et al. (8) from Bordeaux provide long-term follow-up of patients with idiopathic VF who have undergone ablation of VPBs that was presumed to have a causal relationship. In most cases, the VPBs appeared to arise from the Purkinje system. As viewed from the surface electrocardiogram, neither the morphology of the VPBs nor the coupling interval was unique. Most patients underwent ablation of more than one origin. The procedure diminished the risk of recurrent VF, yet late recurrence was observed, and some patients appeared to benefit from treatment with antiarrhythmic medications. Among patients with recurrent VF, some had recurrence of the original VPBs and others developed a new focus. Despite the clear benefit derived from ablation of VPBs, the fact that 18% experienced recurrent VF attests to the need for an implantable cardioverter-defibrillator, and the late recurrences at 3 to 5 years raise the possibility that with even longer follow-up the event rate may increase over time.

A practical consideration is that Knecht et al. (8) performed many of the ablations electively, and the time required was not exceptional compared with most ablation procedures. Nonetheless, the procedures are likely to be more prolonged in less-experienced centers. Although the patients needed to have VPBs at the time of ablation or recordings of VPBs to compare with pace mapping, most of the patients did not require emergency procedures. This distinction is important because the logistic issues for ablation of VPBs in patients with VF "storm" are challenging. The schedule in busy laboratories is replete with other long elective procedures that cannot be interrupted or readily canceled and rescheduled. When protracted cases are performed in the middle of the night, they exact a toll on the physicians and supporting staff. Few electrophysiology laboratories are equipped to deal with this challenge on a routine basis.

Clinical electrophysiologists should not extend the results of this study beyond its intended population. This is a select group of patients for whom the evidence was compelling that VPBs triggered VF. Although ablation of ventricular ectopy can be of benefit in patients with recurrent VF, there is no evidence that we should pre-emptively ablate ventricular ectopy in patients who have not experienced sustained ventricular arrhythmias. To do so would lead us into the same line of reasoning that supported the CAST study.

Although the lack of benefit from treatment with antiarrhythmic medications may be related in part to the adverse effects of the drugs, it is likely that in most patients there simply is no benefit from suppression of the ventricular ectopy. Aggressive intervention by catheter ablation is associated with certain risks that would outweigh the benefits in most patients. Even among patients with struc-

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tural heart disease who have survived isolated VF, ablation of VPBs may not have the same impact as it does in patients with idiopathic VF or VF "storm." The causal relation between VPBs and VF in these groups may not be applicable to all patients with VF.

Several laboratories have explored the role of Purkinje fibers in the initiation and maintenance of VF or polymorphic ventricular tachycardia. In 1998, Berenfeld and Jalife (9) used a 3-dimensional model to test the hypothesis that re-entry involving the Purkinje muscle junction may be a mechanism of focal subendocardial activation. In addition to the capacity for triggered activity, the differences between Purkinje fibers and myocardium in upstroke velocity, intracellular coupling, and action potential duration may provide the conditions for initiating or sustaining VF. Their model supported the possibility that Purkinje fibers are involved in the evolution and maintenance of re-entry with variable surface electrocardiogram morphology that reflects changes in epicardial activation.

Three studies from Dr. Idecker's laboratory (10–12) at the University of Alabama in Birmingham demonstrate the potential role of the Purkinje system in VF. Dosdall et al. (10) showed that the Purkinje system is active during the early post-shock activation cycles, but further study is required to determine whether early activation initiates in the Purkinje system as opposed to the myocardium. In a second study by Dosdall et al. (11), ablation of the Purkinje system by Lugol solution hastened spontaneous VF termination and altered AF activation. Li et al. (12) recorded electrical activity of induced VF and found that over time the incidence of re-entry in myocardium decreased but there was an increased incidence of intramural foci. It is not clear yet whether these arise from Purkinje fibers.

Aside from the immediate benefit that ablation of VPBs offers to selected patients with VF, the work by Knecht et al. (8) and Bansch et al. (5) raise a number of important questions. Most center on why these patients are so prone to VF. Many patients with ventricular ectopy do not develop VF, so what makes the susceptible patients different? It appears that VPBs arising from the Purkinje system may be particularly malignant, yet we do not know how many people who never experience VF have VPBs arising from the Purkinje system. It may be more common than we appreciate. Perhaps there is something different about the interface between the Purkinje system and the myocardium that predisposes these individuals to micro–re-entry and the initiation of VF. One might speculate that tissue damage associated with either ischemic or nonischemic cardiomyopathy would provide the substrate for this mechanism, but why does it occur in patients without any evidence of structural heart disease? Are there characteristic features detected from the body surface that are unique identifiers of risk? Can a noninvasive technology such as analysis of T-wave alternans or electrocardiographic imaging shed additional light on why these patients are prone to VF? Why does a patient with complex ectopy do well for months or years and suddenly experience recurrent VF? What changed on that day? Is it the development of a different VPB origin that arises from the Purkinje system? Are there autonomic or metabolic factors that we do not recognize?

Advances in medicine often raise more questions than they answer. I believe the observations from both clinical and basic science studies have important implications for the way we manage patients with recurrent VF, but even more important is the interest they inspire and the insights we will gain in future work to determine why patients develop VF or why the ablation is so beneficial. The answers to these questions may extend our horizon and pave the way for new strategies to prevent VF.

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Key Words: ablation ■ ventricular fibrillation ■ ventricular tachycardia ■ Purkinje fibers.