Editorial Comment

Electrically Induced Ventricular Tachyarrhythmias in the Experimentally Infarcted Canine Model*

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In clinical electrophysiologic circles, the search continues for the optimal protocol of programmed electrical stimulation as a predictor of sudden death, or as a prognosticator of future spontaneous occurrences of sustained ventricular tachycardia. The opening paragraph of the introduction in the paper by Garan et al. (1) in this issue of the Journal might suggest to the cursory reader that the authors' emphasis was on specifically clarifying these clinical questions. It should be pointed out, as alluded to by the authors, that this contribution could not and did not presume to directly address these questions. This should not detract from the fact that their contribution offers valuable insights. Studies at 1, 2, 4 and 6 weeks after infarction to more explicitly constrain temporal and technical variables when applying programmed stimulation on the substrate of canine experimental infarction offers one of the most comprehensive scans of both time and electrical response currently available.

Although the time frame was different and the exact emphasis different, the reader is directed to their earlier reports utilizing this canine model (2–4). Also, for perspective's sake, it should be noted the studies by Wolf et al. (5) marked the beginning of interest in electrically induced ventricular tachycardia in experimental animals. This work was followed by that of Kaplinsky et al. (6), while the studies of Wellens (7) represented the opening chapter in these applications to patients. The work of Josephson et al. (8) beginning in the late 1970s marked the beginning of a series of extensive and in depth contributions addressing questions on the clinical meaning of inducible ventricular arrhythmias. Michelson et al. (9) further addressed the question of the anatomic substrate and sustained arrhythmias in a chronic dog model. El-Sherif et al. (10,11) studied early and late reentrant arrhythmias in the canine model.

The present report by Garan et al. (1) provides additional insurance that well constrained models produce the most meaningful results. In the infarct group, three extrastimuli resulted in inducibility of sustained monomorphic ventricular tachycardia that was relatively high, ranging from 45 to 50% at each test period; immediate reproducibility was maximal at 95% with three extrastimuli used during ventricular pacing. After 2 weeks, reproducibility of induction during the same study reached 100%. In contrast to sustained monomorphic ventricular tachycardia, nonsustained polymorphic ventricular tachycardia and ventricular fibrillation induction was lower and slightly decreased further as the age of the infarct increased. However, the reproducibility of these latter arrhythmias was still between 70 and 75% at 6 weeks. The fact that reproducibility of sustained monomorphic ventricular tachycardia was high at 2 weeks, was 100% by 4 weeks and continued to be 100% reproducible at 6 weeks brings a comforting sense of order to the reader and reassures us that the reentrant loop, once established, may remain the same under stable conditions. As expected, a larger infarct and lower ejection fraction increased the inducibility of sustained monomorphic ventricular tachycardia.

Possible limitations of the study. However, a major gap remains and that is the ability to extrapolate from this study human clinical meaningfulness, or more specifically, to predict sudden death or the spontaneous occurrence of sustained ventricular tachycardia on the basis of prospective programmed stimulation studies. In the clinical setting, many investigators have found that the application of triple extrastimuli, a requirement for the best yield in the present study, resulted in a loss of diagnostic specificity, that is, the ability to predict future spontaneous occurrences of ventricular arrhythmias. Likewise and certainly not unique to the study of Garan et al., the fact exists that any canine model suffers from the problem of lack of similarity to the anatomic substrate of clinical coronary artery disease. In general, the animals have no atherosclerotic heart disease, and in most instances have sustained single infarction procedures. On the other hand, most patients at risk for sudden death or sustained ventricular tachycardia have a milieu of multivessel coronary artery atherosclerosis and have often sustained more than one infarction. They have dynamic intermittent ischemia, often with electrically inhomogeneous border zones with the propensity for current flow. Even in the experimental animal, work by Myerburg et al. (12) using a cat model suggests that interaction between infarcts of different ages creates an even more unstable electrical environment. It is recognized that all things cannot be contained in one study, but this model might make further

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contributions at a later stage if the sites of the slowly conducting portion of the reentrant circuit could be specified (4,13–17).

**Clinical implications.** The authors are very careful in cautioning the reader against over-extrapolation of their data into the clinical setting. For example, it is important for the reader to keep clearly in mind the difference in the application of the term "specificity" when it is used in the clinical setting in implying correlation between laboratory-induced ventricular arrhythmias and spontaneously occurring ventricular arrhythmias or sudden death in the same individual at some subsequent time. In this study, the high specificity of inducible sustained monomorphic ventricular tachycardia referred to its 100% absence in the animals without infarction compared with its 45 to 50% presence in the group with infarction.

Thus, these investigators, using serial studies at 1, 2, 4 and 6 weeks encompassing the convalescent phase of infarction, attempted to determine evolution of the response elicited by different modes of programmed stimulation and the characteristics of the induced arrhythmias during this period. The results demonstrated that electrically induced sustained monomorphic ventricular tachycardia was an arrhythmia that was specific for the postinfarction state and was never encountered in the control animals, regardless of mode of programmed stimulation and the age of the infarction. The arrhythmia was most inducible using three programmed extrastimuli. Large infarcts with low left ventricular ejection fraction predisposed the canine heart to the electrically inducible arrhythmia. This elaboration of their particular preparation of infarction was amenable to a high yield of inducible and reproducible sustained monomorphic ventricular tachycardia, most likely due to reentrant mechanisms. They have shown maximal reproducibility of the induced arrhythmia beginning after 2 weeks postinfarction and extending to the end of the 6 week study period, suggesting that such a model could be quite useful in testing the efficacy of various antiarrhythmic agents.

The general principle that could be extrapolated to the human analog is that postinfarction ventricular arrhythmias should be assessed by carefully adhered to protocols using modes of programmed stimulation associated with the highest immediate reproducibility of response. In the human situation, two rather than three extrastimuli may prove to offer the best compromise between sensitivity and specificity.

Finally, it is appropriate to acknowledge the fact that my views have been enriched immensely through the years by the opportunity to study the work of and frequently communicate with other investigators interested in this area. Among those are Mark Josephson and Al Buxton, Ben Scherlag and Ed Berbari, Bob Myerburg, Neil Moore and Nabil El-Sherif.

**References**