Editorial

Less Heart Is More

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The study by St John Sutton et al1 in this issue of Circulation provides additional information on the importance of the myocardial substrate for the genesis of cardiac arrhythmias, in this instance, ventricular arrhythmias in the postinfarction remodeled human left ventricle (LV). The authors demonstrate significant relationships between ventricular arrhythmias and LV size, mass, and function at baseline, and at 1 and 2 years after infarction in a subset of 263 patients who received both echocardiographic and Holter evaluations in the Survival And Ventricular Enlargement (SAVE) trial. They found a greater preponderance of ventricular arrhythmias in those individuals with the largest LV mass, leading the authors to conclude that postinfarction remodeling is an important substrate for triggering ventricular arrhythmias.

What does this important study teach us? Basically, we learn that the bigger the heart and the poorer its function, the more likely it is to manifest ventricular arrhythmias and, by inference, cause sudden cardiac death (SCD). The latter must be inferred because the endpoints used by the authors, premature ventricular complexes (PVCs) singly or 3 in a row (the definition they used for ventricular tachycardia [VT]), generally do not cause SCD in and of themselves. In fact, one can argue against accepting these endpoints, no doubt chosen as surrogates for the really important outcome, SCD. We know from the Cardiac Arrhythmia Suppression Trial (CAST)2 that abolition of asymptomatic ventricular arrhythmias in some circumstances can be deceiving, as such suppression by encainide, flecainide, and moricizine occurred in CAST, but so did an increase in mortality. Also, elevating 3 PVCs in a row to the status of VT, though almost universally used, is based on an arbitrary classification made many years ago. It is time to replace such a definition with clear, concise descriptions of the actual ventricular arrhythmias observed. Nevertheless, despite these limitations and the fact that only a single 24-hour ECG was obtained at each evaluation, the endpoints chosen correlated with LV size and function.

Variations on the theme presented by the authors have been noted before, but now we have prospective quantification and correlation in a controlled fashion. That is useful. However, what can we take away that impacts future care and improves postinfarction patient survival, particularly as it relates to SCD? The first message would be to try and prevent postinfarction remodeling. That is a given. How can we use the concept of postinfarction remodeling to reduce SCD? It is here that this editorialist has a problem, although through no fault of the authors. They have carried their inquiry as far as they could. My predicament comes from being an electrophysiologist struggling with our inability to fully understand the mechanisms responsible for clinically occurring ventricular arrhythmias leading to SCD and to identify those individuals at risk for that event.

The authors note that “ventricular tachycardia is believed to be due to anisotropic re-entry, consequent on slowed impulse propagation velocities through myocardium partially replaced by fibrosis” that “may be facilitated in hearts undergoing progressive dilatation in which there is dynamic imbalance between distending forces and the stretch-resistant extra-cellular collagen scaffold during postinfarction LV remodeling.”1 What they in essence are positing is that the LV, remodeled after myocardial infarction, causes the cardiac impulse to “zigzag” slowly in the abnormal myocardium and that ventricular dilatation exaggerates such abnormal conduction, promoting re-entrant ventricular arrhythmias. Although such a hypothesis nicely fits the authors’ data1 and is certainly well founded on solid electrophysiological evidence from a variety of animal models, as of yet, the concept has not helped us treat arrhythmias better in the postinfarction patient or more accurately identify the patient at risk of having life threatening ventricular arrhythmias. The reason is because the clinical mechanisms are far more complex and multifactorial. Such animal studies that have provided the foundation for this reasoning, of which our group is “guilty” of performing as well,3 remind me of the person who has lost his watch in a dark alley but searches for it under the street lamp. When asked why, he responds, “Because I can see here.” We study what we can “see,” and in this situation, what we see is only a part of the problem. The scarred myocardium is the static substrate upon which are staged a variety of activities that culminate in the episode of SCD. The latter, which is really nothing more than a common mode of death, represents the final outcome of a complex interplay of clinical and pathophysiological events that have their source in metabolic, biochemical, primary electrophysiological, and pathological entities, leading to the ultimate destabilization of the cardiac rhythm.4,5

Several clinical observations point out the inadequacy of animal models, and therefore the incompleteness of the hypothesis. For example, consider the asymptomatic postin-
The infarction patient, who is apparently stable (say, 2 years after the infarction) and develops ventricular fibrillation (VF) at 7 AM on a Tuesday, but not on the Monday before. Surely the fixed substrate studied by the authors has not changed very much in 24 hours in an asymptomatic patient. Yet one must postulate a change, or else why did the VF start? Therefore, there must be a dynamic factor(s), possibly transient, that interacts with the fixed substrate to precipitate the arrhythmia, which can then be maintained by the abnormal ventricle. The possibilities fill a long list and include things as transient ischemia, pH and electrolyte changes, inflammation, hypoxia, stretch, ion channel abnormalities, neuroendocrine actions, drugs, and so forth, all of which are capable of modulating that zigzag conduction in ways we mostly don’t understand. \(^{4,5}\) More permanent changes could also have occurred, such as a plaque rupture.

Consider also the role of genetics. The Paris Prospective Study I analyzed more than 7000 men followed-up for an average of 23 years. They found that a parental history of SCD increased the relative risk of SCD for offspring to 1.8 without elevating the risk for myocardial infarction. When both parents had SCD, the relative risk for SCD in offspring was 9.4. \(^{6}\) A retrospective study performed on cardiac arrest survivors in King County, Washington, also reported family history to be a significant, independent risk for SCD, with an odds ratio of 1.57. \(^{7}\) Thus, genetic influences also play a role in modulating the fixed substrate, perhaps by affecting atherothrombosis, electrogenesis, and impulse propagation, as well as neural regulation and control. \(^{4,5}\)

Another bothersome fact is that, if the primary problem were only electrical, ie, zigzag conduction, or a form of it leading to reentrant ventricular arrhythmias and SCD, one would think that an antiarrhythmic drug that affected the electrophysiological substrate, for example by prolonging the refractory period to cause a block in the pathway, would prevent the arrhythmia. However, most of the traditional antiarrhythmic agents worsen outcomes, and at best may be neutral. Amiodarone may be the exception, at least according to data from a meta-analysis,\(^ {8}\) in which it was shown to reduce total (13\%) and arrhythmic (29\%) mortality. Although one could argue that we have not found the “right” antiarrhythmic agent, in fact, it is drugs not thought of as traditionally antiarrhythmic, such as angiotensin-converting enzyme inhibitors and receptor blockers, aspirin, β-blockers, spironolactone, statins, and even fish oil,\(^ {9,10}\) that have been shown to reduce SCD and, by inference, ventricular arrhythmias. Because these drugs do not exert a primary electrophysiological action, they must be working “proximal” to the arrhythmia as modulators of the substrate and precipitating factors noted above.

Finally, it is troubling to note that the endpoints proffered in this study cannot be used to help identify the patient at risk for SCD with sufficient predictive accuracy to intercede with an established antiarrhythmic intervention, the implantable cardioverter-defibrillator, as primary therapy. In fact, we are able to identify such patients in only a minority of at-risk individuals. \(^{11}\) The usual epidemiological or anatomic risk factors identify at-risk populations but have poor utility for individual risk prediction. \(^{12}\) So, although studies such as the one reported by St John Sutton and colleagues\(^ {1}\) are welcome, they do not lead to identification of the implantable cardioverter-defibrillator candidate before an event and do not help us select therapeutic options. We still struggle with reducing the horrendous toll taken by SCD on the vast majority of patients. At best, for most victims, all we can offer are various stratagems for prompt resuscitation. In fact, it is our failure to develop an inexpensive, noninvasive, accurate, specific marker(s) to identify the SCD candidate that has led to the emphasis on resuscitation. \(^{13}\) For the fortunate survivor, secondary prevention becomes straightforward, \(^{14}\) but it is primary prevention that must be our goal.

In summary, the authors\(^ {1}\) are to be congratulated on a fine study about postinfarction remodeling, a concept they formulated from the very beginning. \(^{15}\) We electrophysiologists are to be urged to continue our search for the elusive events that modulate that remodeled substrate.

### References
