EDITORIAL COMMENT

Gap Junctions, Slow Conduction, and Ventricular Tachycardia After Myocardial Infarction*

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Over the past 30 years, the cumulative results of clinical, experimental, and theoretical studies have validated the concept that slow conduction, related at least in part to changes in intercellular coupling via gap junctions, plays an important role in the pathogenesis of ventricular tachycardia (VT) after myocardial infarction. Long before the major cardiac gap junction protein, connexin43 (Cx43), was first cloned by Beyer et al. (1) in 1987, the basic relationship between electrical coupling and the speed of impulse propagation had been recognized through the pioneering work of Barr, Dewey, Lieberman, Kootsey, Johnson, Spach, and many others (2–5).

As early as 1961 (6) and certainly by the early 1980s, it had been shown that “fractionated electrograms” and “continuous electrical activity” could be identified in myocardial regions bordering healed infarcts, and they became manifest as fibrous tissue accumulated during infarct healing (7–10). Although it was also understood that slow conduction could be related to factors independent of those responsible for producing fractionated electrograms, the presence of fractionated electrograms in the setting of chronic ischemic heart disease was consistently linked to slowing of impulse propagation (7–10). At the same time, it was becoming apparent that fractionated electrograms persisted in healed infarct border zones once acute post-infarct derangements in resting membrane potential and active ionic currents had normalized (7–10). Taken together, these observations led to the conclusion that fractionated electrograms and slow conduction in the chronic infarct border zone were the result of diminished intercellular electrical coupling, associated with separation of fibers by peri-infarct scar tissue. This concept, articulated most lucidly by Josephson and Wit in the early 1980s (9,10) and later by de Bakker et al. (11), had its origins in seminal experimental work by Spach (4,5), Waldo and Kaiser (12), Boineau and Cox (13), El-Sherif et al. (14), Spear (15,16), Spear et al. (15,16), and others. It has since been strengthened by morphometric and immunohistochemical studies documenting gap junction remodeling in viable cardiac myocytes bordering healed infarcts (17–19) and ever more powerful in vitro and computational studies defining specific structural and electrophysiological determinants of slow conduction under various conditions and elucidating their pathophysiological consequences (20–22). Although it is true that these studies have differed in terms of the animal species, experimental protocols, and theoretical models used and have involved different types of measurements at different intervals after infarction, they have all converged on the idea that gap junction remodeling can reduce intercellular coupling and thereby slow conduction in ways that contribute importantly to the pathogenesis of re-entrant VT after myocardial infarction. Recognition of this concept has also raised the obvious possibility that preservation or enhancement of intercellular coupling in the infarct border zone might decrease the risk for re-entrant VT, an idea originally proposed in studies pre-dating the modern era of molecular biology and genetic engineering.

Of course, ventricular arrhythmias are complex phenomena, often thought of as arising from multiple input determinants and initiated by stochastic events. It has been challenging, therefore, to apply conventional reductionist approaches to identify the specific contributions of any individual factor, and without such knowledge, the development of rational mechanism-based therapies becomes even more challenging. The advent of genetic engineering has made possible gain-of-function or loss-of-function studies that have certainly advanced our understanding of the key determinants of arrhythmogenesis, but most of these studies have been performed in vitro or in mice, which have unavoidable limitations as models of arrhythmias in human heart disease. Precise genetic interventions in a large animal model would be of great potential value, therefore, in elucidating the role of specific molecules in VT after myocardial infarction.

Now, in this issue of the Journal, Greener et al. (23) report the use of a state-of-the-art targeted gene transfer approach in a large animal model to provide an important new demonstration of the critical role of Cx43 expression and, by inference, cell-cell coupling, in the development of fractionated electrograms, slow conduction, and VT inducibility in the healed infarct border zone. Greener et al. (23) subjected Yorkshire pigs to transient left anterior descending coronary artery occlusion to produce infarction and then monitored arrhythmia inducibility as the infarcts healed.
Most animals exhibited repeatedly inducible, sustained monomorphic VT 4 weeks after infarction, by which time infarct healing was largely completed, and the area previously occupied by necrotic myocardium was composed of maturing scar tissue. Some animals then underwent adenoviral gene transfer in which the Cx43 gene was targeted to the infarct border-zone region by selective delivery via the infarct artery. Others received a control virus containing beta-galactosidase to independently identify the region of gene transfer but without any expected effect on Cx43 expression. A third group received no virus. A week later, animals receiving the Cx43 gene showed less electrogram fractionation and faster conduction velocity in the infarct border zone. Only 4 of 10 receiving the Cx43 construct were inducible for VT, whereas all of the controls remained inducible after gene transfer. The border-zone region contained a 2-fold greater amount of Cx43 but with similar proportions of phosphorylated Cx43 and Cx43 localized to cell-cell junctions (both of which relate in complex ways to channel function). The diminished electrical fractionation suggests that enhanced expression of Cx43 partially reversed microscopic heterogeneity in excitation, producing a more uniform propagation pattern that, at the scale of mapping used in this study, would be manifest as an increase in velocity. Greener et al. (23) conclude that increased expression of Cx43 in healed infarct border zones is sufficient to reduce arrhythmia susceptibility, and they suggest further that targeted Cx43 gene transfer might be a viable future therapy in patients with post–infarction VT.

A skeptic might ask where the significant advance in this work lies. Although the investigators have pioneered the development of gene transfer methods, they used an existing approach in the present study (24). They have also previously demonstrated that connexin gene transfer improves conduction velocity and prevents atrial fibrillation in a model involving Yorkshire pigs (25). And, as observed in this editorial comment, we have had more than 3 decades of research linking reduced cell-cell coupling and connexin expression to the development of fractionated electrograms, conduction slowing, and VT in the post-infarction setting. Taken together, this might lead one to suggest that the conceptual advance in the present study is modest.

Nevertheless, the study by Greener et al. (23) is significant for several reasons. First, it is probably the most direct proof to date that augmenting Cx43 expression in the healed infarct border zone is sufficient to reduce arrhythmogenesis in a large animal model that is far more pertinent to human disease than similar models in mice. Second, it establishes potential clinical efficacy and provides a compelling rationale for future therapeutics advances. As noted by the investigators, questions remain about the durability of the effect and the possibility of creating new slow conduction pathways which could have a deleterious effect. Such questions can be answered only by additional work and depend on further advances in gene transfer technology, but we now have a model and a method with which to move forward. Third, the approach taken by Greener et al. (23) appears to avoid potential risks and unintended consequences inherent in other antiarrhythmic strategies, such as manipulating repolarization or using pharmacological agents to maintain opening of gap junction channels. The former strategy can increase the risk for arrhythmogenicity, whereas the latter is designed to counteract the presumably adaptive responses of gap junction channels in response to injury or stress (26). Potential clinical applications of so-called antiarrhythmic peptides or other compounds designed to keep gap junction channels open run the risk of increasing infarct size by allowing unimpeded junctional spread of injurious metabolites of ischemia. In contrast, Greener et al. (23) provide at least some evidence that although their approach increases Cx43 expression, the resultant channels presumably respond normally to environmental cues and would close appropriately in response to acute ischemia. Whether this might still lead to adverse outcomes remains to be seen, but this approach would appear to be more physiological and therefore potentially safer than the alternatives.

Finally, the impressive technical success of this work and the resultant triumph of the reductionist approach should not obscure our growing appreciation of the remarkably complex interrelatedness of the individual components in living systems. The importance of a systems-based approaches in cardiovascular therapeutics, so eloquently articulated by Loscalzo (27), reminds us that “disease and pharmacology, like life itself, are much more complicated than reductionist simplicity could ever allow, and failing to acknowledge this complexity is an increasingly perilous proposition.” No one would suggest that augmenting Cx43 expression in the healed infarct border zone is the ultimate solution to the problem of post–myocardial infarction arrhythmias. Rather, we must continue to strive toward a deeper understanding of arrhythmia mechanisms, although in the end, phenotypic screening may be the most efficient path to identification of truly effective antiarrhythmic therapies.

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