Arrhythmogenesis and Ventricular Dysfunction After Myocardial Infarction
Is Anomalous Cellular Coupling the Elusive Link?

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Major advances in cardiovascular therapeutics generally have resulted from elucidation of pathogenetic mechanisms. For example, delineation of the role of thrombosis as the proximate cause of acute transmural myocardial infarction was seminal in the evolution of coronary thrombolysis as primary treatment.1 Similarly, recognition of the importance of afterload as a determinant of ventricular performance led ultimately to the extensive use of vasodilators in modern treatment of congestive heart failure.2

An association between impairment in left ventricular pump function and the extent of antecedent myocardial infarction was delineated soon after the dynamic nature of infarction and the dependence of its evolution on an imbalance between myocardial oxygen requirements and myocardial oxygen supply had been established.3 Ventricular tachycardia, which may occur more frequently when pump dysfunction is present, can precipitate derangements leading to cardiac death including hemodynamic impairment, augmentation of myocardial oxygen requirements, and impaired coronary perfusion secondary to hypotension and elevation of left ventricular diastolic pressure. Ventricular tachycardia may be presaged by distinct electrophysiological alterations such as late potentials.4 However, these important associations do not fully clarify the basis for the strength of the association between impairment of ventricular function and sudden cardiac death. Several factors may be involved, including heightened sympathetic neural activation and extensive regional conduction delay and block predisposing to reentrant ventricular tachycardias, as well as numerous other phenomena. In fact, multiple etiologies may apply even in a single instance, including alterations of membrane ion channels, fluctuations in global and regional autonomic function, and G protein–mediated effects among others.

The Nature of Arrhythmias Associated With Ischemic Heart Disease

Acute myocardial ischemia, potentially leading to infarction, can give rise to malignant, often lethal ventricular arrhythmias.5 Electrophysiological mechanisms involved include triggered activity, intramural reentry, and, rarely, increased automaticity.6 Myocardial deprivation of oxygen per se does not appear to be solely responsible. Altered local concentrations of hydrogen and potassium ions, amphipathic lipid metabolites that can impair sarcolemmal function, and catecholamines may contribute.6,7

Ventricular arrhythmia late after myocardial infarction could simply be a manifestation of acute, recurrent ischemia in hearts of patients with severe and progressive coronary artery disease. The salutary effects of β-adrenergic–blocking agents on survival despite the lack of conventionally recognizable antiarrhythmic effects8 and the deleterious effects on survival of class Ic antiarrhythmic agents despite suppression of premature ventricular contractions (PVCs)9 are consistent with this possibility. It is, of course, possible that the protective effects of β-adrenergic–blocking agents reflect their direct and indirect effects on sarcolemmal function.

Alternatively, the occurrence of severe ventricular arrhythmia late after myocardial infarction may be a reflection of an anatomic substrate predisposing to or potentiating arrhythmia.10 Inducibility of ventricular tachycardia by programmed electrical stimulation, the presence of late potentials on signal-averaged ECGs, and “triggering” of ventricular tachycardia or ventricular fibrillation by appropriately timed spontaneously occurring PVCs are consistent with this possibility. Unfortunately, however, specific electrophysiological consequences of responsible putative structural derangements have not yet been fully delineated.

The improved survival of patients with impaired left ventricular function treated with angiotensin converting enzyme (ACE) inhibitors late after infarction11 and their apparent salutary effects on ventricular remodeling support the possibility that altered tissue structure and cardiac dysfunction are linked, perhaps accounting for the concomitant amelioration of ventricular hypertrophy, cardiac dilatation, and mortality. However, available observations are consistent also with the possibility that structural derangements within and around regions of infarction are, in fact, a missing link accounting for the close correlation between the extent of ventricular dysfunction and arrhythmogenicity late after infarction, manifest also by an increased risk of late sudden cardiac death.
Recent observations by others and in multidisciplinary work from our institution supported by the National Heart, Lung, and Blood Institute Specialized Center of Research (SCOR) in Coronary and Vascular Diseases have identified some morphological candidates accounting for links between late, malignant ventricular arrhythmias and extensive infarction, reflected by severe ventricular dysfunction. Despite their preliminary nature, these observations implicate attractive potential targets for improved detection of the risk of late, malignant arrhythmia and perhaps, ultimately, for improved prevention of sudden cardiac death.

A Working Hypothesis

We believe that malignant ventricular arrhythmias late after infarction depend in part on characteristic derangements in the three-dimensional structure of myocardium evolving well after the acute event. Derangements implicated include alterations in the number, size, and three-dimensional distribution of gap junctions both within and adjacent to zones of infarction. These structures, i.e., gap junctions, serve to electrically couple cardiac myocytes to each other. Altered genetic expression of specific gap junction proteins may occur in many regions of diseased ventricles and contribute to the electrophysiological abnormalities underlying arrhythmogenicity. Because the structural changes identified to date account for a disproportional augmentation of resistivity in the transverse direction, increased anisotropy, and therefore increased predisposition to reentrant arrhythmias, their potential contribution to malignant arrhythmia and sudden cardiac death is considerable.

Myocardial Gap Junctions

Because cardiac muscle is composed of discrete myocytes, electrical activation of the entire heart depends on rapid and highly regulated dispersion of current from one cell to another. Transfer of current occurs at gap junctions, specialized regions of densely packed intramembranous particles that traverse the membranes of adjacent cells and join in the extracellular gap to form an aqueous pore, thereby providing continuity of the cytoplasm of coupled cells \(^{12,13}\) (Figure 1). Rapid transfer of current required for efficient activation of the mammalian heart is facilitated by unusually large gap junctions located within the intercalated disk regions. The close proximity of gap junctions to adhesive elements of the disks minimizes shear stresses that the junctions would otherwise encounter throughout the cardiac mechanical cycle. Although intercalated disks and gap junctions are concentrated at the ends of cardiac myocytes, some exist at sites all along cell bodies.\(^ {14}\) Thus, cardiac myocytes are connected to one another in complex overlapping patterns of side-to-side and end-to-end apposition.\(^ {15}\)

A typical canine ventricular myocyte has approximately 100 gap junctions on its surface and is connected at disks and junctions to an average of 11.3 other myocytes.\(^ {14,15}\) As a consequence of the elongated shape of the cells and their complex interconnections at gap junctions, activation wave fronts moving through a uniform sheet of myocardium in a direction transverse to the long cell axis cross many intercellular junctions and therefore are propagated at only one third of the conduction velocity typical of wave fronts traveling equal distances in a direction parallel to the longitudinal fiber axis. In fact, myocyte size and shape, the three-dimensional packing geometry of myocytes in the ventricle, and the number and distribution of myocyte gap junctions are key structural determinants of anisotropic conduction in normal myocardium.

Connexin Family of Gap Junction Channel Proteins

Gap junctions are distributed widely in parenchymal and interstitial cells of most tissues.\(^ {16}\) The protein subunits constituting their channels, connexins, are encoded by members of a gene family.\(^ {16}\) The connexins characterized to date have four membrane-spanning domains and two extracellular loops with highly conserved sequences (Figure 2). However, the intracellular cytoplasmic domains of specific connexins exhibit characteristic primary sequences that are distinctive.\(^ {16}\) These cytoplasmic domains are likely to interact with intracellular regulators of channel conductance, thereby strongly influencing the physiological properties of gap junctional channels and modulating cell coupling.

Although until recently only one gap junction protein had been recognized in cardiac myocytes, three distinct connexins have been found in chick heart,\(^ {17}\) and three homologous gap junction proteins have been identified in mammalian heart myocyte gap junctions.\(^ {18}\) Results of electrophysiological studies in gap junction–deficient cell lines transfected with one of the three individual chick cardiac gap junction protein genes have demonstrated that each connexin forms channels with distinctive unitary conductances and distinctive sensitivities to transjunctional voltage.\(^ {16}\) Thus, the homologous individual mammalian cardiac connexins are likely to exhibit distinctive electrophysiological properties as well.

Structural Alterations Contributing to Arrhythmias Dependent on Reentry

Despite the longstanding implication of active membrane properties as pathogenetic determinants of ar-

\[\text{FIGURE 1. A model of the structure of a gap junction based on results of x-ray diffraction studies of Makowski et al.}^{27}\]

Individual units of current transfer called connexins are composed of paired hexamers that traverse the membranes of individual cells and meet in the extracellular gap to form aqueous pores and direct continuity of the cytoplasm of connected cells.
rhythmias induced by ischemia acutely, changes in passive myocardial resistivity are likely to play a critical role in the pathogenesis of lethal reentrant arrhythmias in patients with healed myocardial infarcts. In patients undergoing surgical interruption of pathways responsible for recurrent ventricular tachycardia, we have shown that reentry is dependent on slow conduction occurring typically in patchy fibrotic regions bordering healed infarcts. Although propagation of wave fronts through such regions is markedly abnormal, resting membrane potentials and action potential upstroke velocities in individual myocytes are typically normal or essentially normal. Thus, the marked decreases in conduction velocity and conduction block, particularly evident in response to premature stimuli, may be attributable primarily to altered myocyte interconnections.

The relative proportions of viable cardiac myocytes and interstitial collagen in border regions of healed infarcts and the extent to which myocyte orientation and packing density are deranged very markedly. In one pattern observed commonly, multiple layers of uniformly oriented myocytes are separated by interspersed bundles of collagen running parallel to the long axis of the myocytes (Figure 3). This arrangement appears consistently in regions identified by electrophysiological mapping to exhibit slow conduction and complex fractionated electrograms, particularly in response to premature stimuli sufficient to elicit ventricular tachycardia.

Quantitative assessment of intercellular connections in regions with this “anatomic substrate” in zones bordering healed infarcts in canine hearts indicates how the structural alterations may produce electrophysiological derangements leading to reentrant arrhythmias.

The peri-infarct myocytes separated by interspersed bundles of collagen have been shown by ultrastructural morphometry to be connected to one another by fewer and shorter gap junctions than those seen typically with normal cells. Accordingly, the average number of cells connected to an individual myocyte is reduced markedly with a reduction in intercellular connections that is distributed anisotropically. The junctions connecting cells in a side-to-side configuration are the ones most frequently and most severely disrupted.

The anticipated pathophysiological consequences of such structural alterations are confirmed by observations in hearts of laboratory animals and patients. With normal sinus rhythm, wave front velocity through border zone regions often is essentially normal, particularly when the wave fronts are moving in a direction parallel to the longitudinal axis of the myocytes. Longitudinal propagation occurs rapidly because end-to-end connections are relatively well preserved. However, as ventricular tachycardia is induced, wave fronts typically propagate through the same regions in a direction transverse to the longitudinal axis of the myocytes. Propagation in the transverse direction is impaired because the side-to-side connections are so markedly disrupted. Accordingly, propagation transverse to the longitudinal fiber axis is the dominant direction in which conduction block is exhibited, a critical factor in the initiation of a reentrant circuit.
Thus, increased anisotropy and the resultant complexity of pathways of propagation of transversely oriented wave fronts are likely to account for slow, heterogeneous conduction, fractionated electrograms, and late potentials commonly seen in border zones of infarcts.

Implications of the Working Hypothesis

If, in fact, the altered number, size, and three-dimensional distribution of gap junctions within or around infarct regions are linked to the extent of injury sustained after infarction and both these structural derangements and the severity of ventricular dysfunction are consequences of the magnitude and extent of initial ischemic injury, the association between late ventricular dysfunction and the incidence of late ventricular arrhythmia would be explained. Furthermore, identification of patients at high risk for sudden cardiac death would be facilitated if means were developed to quantify the severity of structural derangements in gap junctions in individual patients with ventricular dysfunction. One approach that might prove effective, if the changes in gap junction structure are as generalized as preliminary data indicate them to be, includes endomyocardial biopsy in a small subset of patients to evaluate this hypothesis. In addition, delineation of the distribution of specific connexins with noninvasive modalities such as cardiac positron emission tomography and the use of specific gap junction ligands or labeled antibodies are approaches that could be applied to a larger number of patients if their discriminative power proves to be sufficient.

This working hypothesis has therapeutic implications as well. Prevention of disruption of gap junctions in infarct border regions and preservation of gap junction function by facilitation of ventricular remodeling at the ultrastructural level may be important therapeutic targets. Potential approaches include somatic gene transfer to modify ventricular remodeling and maintain normal spacial distributions of gap junction proteins, perhaps with gene transfer techniques used to diminish the synthesis of proteins that impair the function of gap junctions including individual connexins that do not facilitate but instead hinder cell coupling. An alternative approach may be to enhance synthesis of normal gap junction protein constituents in normal spatial distributions. Despite the speculative nature of such approaches in the prevention of sudden cardiac death, their ultimate promise may surpass that of nonspecific suppression of arrhythmias with agents that affect primarily active membrane properties and appear to be associated with unavoidable, potentially deleterious consequences in survivors of acute myocardial infarction.

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