Current Perspectives

Myocardial Architecture and Ventricular Arrhythmogenesis

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Conduction of the cardiac impulse is dependent on both the active membrane properties of cardiac cells (generating the action potential) and the passive properties determined by architectural features of the myocardium. The influence of tissue architecture on conduction is determined principally by the size, shape, and packing of individual myocytes and by the quantity, three-dimensional distribution, and physiological behavior of the specialized intercellular junctions responsible for impulse propagation from cell to cell, the gap junctions. It has long been recognized that abnormalities in conduction of the cardiac impulse are an important cause of arrhythmias in that they alter the relationships between conduction velocity, path length, and recovery of excitability (the determinants of reentrant excitation). However, it was not until more recently that myocardial architecture was considered important in determining patterns of activation and conduction velocity and some of the evidence for this forms the basis of this review.

Electrophysiological Architecture of Ventricular Myocardium: From Muscle to Molecule

Myocardial Syncytium: Anisotropy of Structure and Function

The early observation that conduction properties in myocardium were different in different directions, with more rapid conduction in the direction parallel to the myocardial fiber axis than in the transverse direction (the definition of the anisotropic conduction characteristic of heart muscle [Figure 1]), is attributable principally to the lower resistivity of myocardium in the longitudinal than the transverse direction. Gap-junctional channels create continuity between the cytoplasmic compartments of abutting myocytes but act as resistive discontinuities to the cytoplasmic current flow between the intracellular compartments of the cells (the "intracellular" conduction pathway). Longitudinal resistivity is lower than transverse because this intracellular pathway encounters fewer cell boundaries per unit distance in the longitudinal than the transverse direction. In normal ventricular myocardium, conduction in the direction parallel to the long axis of the myocardial fiber bundles is approximately three times more rapid than in the transverse direction, and the anisotropy is considered to be uniform because it is characterized by an advancing wave front that is "smooth," and because measured conduction velocity changes monotonically on moving from fast (longitudinal) to slow (transverse) axes. Although not a universal finding, directional differences in conduction velocity may be accompanied by differences in the action potential (Figure 1) and in the extracellular unipolar wave form.

Tissue Structure: The Topology of Myocyte Packing and Interaction

In normal adult ventricular myocardium, gap junctions are confined almost exclusively to the intercalated disks (Figure 2), the sites of mechanical, metabolic, and electrical cellular coupling that facilitate coordinated interaction of the cells. In ventricular myocardium, large intercalated disks exist at the ends of the myocytes, with smaller disks along the length of the cell (Figure 2). In mature human ventricular myocardium, the cells have an average of 11.6 intercalated disks (Figure 3). In canine ventricular (subendocardial) myocardium, each ventricular muscle cell is connected to ~11 to 12 other muscle cells. The distribution of intercalated disks dictates that gap-junctional connections therein occur between both the ends of cells and the sides of cells; in canine ventricular myocardium, cells are connected either side to side (29%), end to end (34%), or in a combination, such that approximately half of all connections are side to side and half are end to end. Therefore, with respect to gap-junctional coupling in ventricular myocardium, activation wave fronts may conduct readily between adjacent cells in the longitudinal or transverse directions. However, the resistivity of gap-junctional membrane, although several orders of magnitude lower than non-gap-junctional plasma membrane, is several orders of magnitude higher than the cytoplasmic intracellular resistivity. The result is that a wave front will encounter more gap junctions in the transverse direction than over an equivalent distance in the longitudinal direction, resulting in a greater resistance and slower conduction transversely than longitudinally.

The ratio of cell length to width measured in isolated canine ventricular myocytes is ~6:1. However, the irregular shape of the myocytes and the distribution of the side-to-side and end-to-end connections in whole tissue result in the effective length-to-width ratio, defined by the number of cell borders traversed per unit distance along straight lines parallel and perpendicular to the cell long axis, being only

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3.4:1. This ratio approximately equals the ratio of anisotropy of conduction as measured in ventricular myocardium and illustrates the importance of considering both the distribution of gap-junctional connections and the myocyte packing geometry in correlating architecture with conduction properties.

A further level of complexity in the relationship between myocardial architecture and electrical propagation is the properties of the extracellular space. In the papillary muscles, connective tissue septa subdivide the myocardium into unit bundles composed of 2 to 30 cells surrounded by a connective tissue sheath. Within a unit bundle, cells are well coupled with multiple intercellular connections both longitudinally and transversely and are activated uniformly as an impulse propagates along the bundle. Adjacent unit bundles appear to be connected to each other in a lateral direction at intervals in the range of 100 to 150 mm. Assuming that this apparent septation influences the degree of side-to-side coupling, it would be expected to contribute further to the anisotropy of conduction, but the relevance of this observation to other regions of ventricular myocardium is largely unknown.

Cellular Coupling: Gap-Junctional Organization

Gap junctions are specialized regions of the intercalated disk (for reviews, see References 1, 11, 16, and 17) in which integral proteins, connexins (Figure 4), exist in hexameric units called connexons, each of which possesses a 1.5- to 2-nm central pore. The connexons in the abutting myocyte membranes (Figure 4) align, and the pair forms a complete channel linking the cytoplasmic compartments, providing a relatively low-resistance pathway for the passage of ions and small molecules (up to ~1 kD) and for electrical propagation.

A variety of microscopy techniques have revealed gap junctions as ovoid or irregular clusters of channels, measuring up to >2 μm in diameter and containing up to several thousand connexons. The intercalate (longitudinally oriented) regions of the intercalated disk in ventricular myocardium contain large gap junctions, with smaller gap junctions interspersed among the anchoring junctions in the plicate regions (Figure 2).

Within each gap-junctional region of membrane, the connexons are clustered in multiple small hexagonal arrays with channel-free aisles of membrane separating each. The results of modeling gap junctions suggest that this channel arrangement increases the conductance of a gap junction compared with a denser mass of an equal number of channels. Furthermore, particularly large gap junctions have been observed at the periphery of intercalated disks in ventricular myocardium (Figures 2C and 3). The position of these large peripheral junctions directly in the path of the depolarizing action potential as it passes along the lateral sarcolemma of abutting myocytes is thought to enhance longitudinal conduction velocity and the degree of anisotropy of propagation. Although this remains unproven, this ultrastructural architecture is therefore likely to influence electrical conduction through myocardium.

Molecular Basis for Gap-Junctional Coupling: The Connexins

The connexins are a family of proteins present in many tissues throughout the animal kingdom and possessing various degrees of molecular homology and similarity of topology within the cell membrane (Figure 4B). The domains of the connexin molecule that lie on the cytoplasmic side of the membrane are the regions of greatest difference in sequence and length between the connexin species and appear to be the main determinants of the differences in biophysical properties between gap junctions composed of the different connexins. In the mammalian heart, a connexin composed of 342 amino acid residues with a molecular weight of 43 000 (so-called connexin43) is the most abundant connxin, but connexin40 (also abundant in the atria, specialized conducting tissues, and subendocardial ventricular myocardium) and connexin45 are the other connexins expressed by cardiac myocytes.
Gap-junctional channels can exist in open or closed states. The proportion of channels that are in an open state and the permeability and conductance of each channel are determined by the physiological properties of the connexin isoform composing the channel and have an important influence on the gap-junctional conductance. The conductance of a single connexin43 channel in its main conductance state is on the order of 40 to 60 pS, but the physiological and potential pathophysiological significance of two other minor conductance states remains to be determined. The main unitary conductance of connexin40 is 150 to 200 pS, a value higher than that of connexin43 and possibly contributing to the high conduction velocity of the His-Purkinje tissue, in which there is abundant connexin40. Connexin45 has low values for unitary conductance (36 pS, 22 pS). To add to the complexity of the molecular architecture of myocardial conduction, it has become apparent that connexons, at least in vitro, may be composed of a single connexin species (homomeric) or several connexin species (heteromeric), and a gap-junctional channel may be made up of two connexons that are identical
The turnover of connexins under certain physiological and pathophysiological conditions.

Two possible mechanisms for changes in conductance of gap junctions are (1) the relatively rapid changes in the proportion of channels in the open state, a reduction in which occurs with metabolic alterations such as high intracellular calcium concentrations or low pH, changes in connexin phosphorylation, and increased transjunctional voltage; and (2) the slower mechanism of alteration in connexin expression, affecting the total number of channels or the relative proportions of the connexins expressed therein. The turnover of connexins within gap junctions is potentially a highly dynamic and flexible process, and observed connexin half-lives on the order of 3 hours indicate that although relatively slow compared with changes in gating of channels, altered turnover has the potential to change quantities of expressed connexins under certain physiological and pathophysiological conditions.

**Arrhythmogenic Changes in the Electrophysiological Architecture of Ventricular Myocardium in the Ischemic Heart**

Nonuniform Anisotropy

Although the definition of uniform anisotropy is an advancing anisotropic wave front that is smooth in all directions, this definition is based on the characteristics of activation at a macroscopic level, where the spatial resolution encompasses numerous myocardial cells and bundles, and therefore it describes the behavior of the myocardial “syncytium.” Because of the irregularities in cell geometry and irregular distribution of the gap junctions of normal ventricle, activation at a microscopic level measured with a spatial resolution comparable to individual cells is, in fact, quite irregular. Nonuniformities at a microscopic scale have been studied in a tissue culture preparation of neonatal myocytes in which optical dyes permitted the construction of high-resolution excitation maps. Although these preparations are not representative of the architecture of the three-dimensional, mechanically loaded myocardium of the adult heart, these studies have, for the first time, allowed detailed study of the anatomy of propagation at the microscopic level. Enhanced nonuniformity of conduction and conduction block were most evident in the transverse direction, particularly at sites of inhomogeneous gap-junctional distribution, intercellular clefts, and nonmyocyte cells. Although present in normal myocardium, such discontinuities studied in modeled diseased myocardium assume an arrhythmogenic pathophysiological role.

Change in the characteristics of anisotropic propagation at the macroscopic scale from uniform to nonuniform strongly predisposes to reentrant arrhythmias. This association was first described in the atrium, in which predominant disruption of the smooth transverse pattern of conduction characteristic of uniform anisotropy results in a markedly irregular sequence or “zigzag conduction,” producing the fractionated extracellular electrograms characteristic of nonuniform anisotropic conduction. The nonuniformity of anisotropic conduction in atrial myocardium so described was interpreted as resulting from disruption to the lateral gap-junctional connections by the formation of connective tissue septae during aging, while longitudinal coupling by gap junctions was maintained.

Chronic ventricular myocardial ischemia and hypertrophy have been shown to cause alterations in gap-junctional organization and connexin expression, regardless of any associated changes in extracellular connective tissue. Disruption of the patterns of impulse propagation under these pathological conditions would therefore be expected even in the absence of extracellular architectural changes. This is supported by the observations that sites of inhomogeneity of gap-junctional distribution in ventricular myocardial tissue culture studies represent sites for nonuniform transverse propagation and block of conduction and that a reduction in connexin43 expression is associated with a substantial slowing of ventricular myocardial conduction velocity.

**Effects of Ischemia**

**Acute Ischemia**

Within the first hour after the onset of severe ischemia, although alterations in membrane ionic channel function contribute to the slowing of conduction and vulnerability to reentrant excitation, changes in the gap-junctional function are central to the very slow conduction characteristic of acutely ischemic myocardium. Gap-junctional resistivity increases substantially in severely ischemic and hypoxic myocardium after 15 to 30 minutes, in association with morphological changes of gap junctions (reviewed in Reference 40), particularly with respect to the arrangement and
density of packing of the junctional channels.\textsuperscript{24,40} The quantity of gap-junctional membrane remains unchanged during this early stage of uncoupling,\textsuperscript{9} but more extensive uncoupling after 60 minutes of hypoxia is accompanied by a 45% reduction in gap-junctional membrane. This phase of cellular uncoupling coincides with the onset of irreversible damage,\textsuperscript{39} and because transverse propagation occurs over many more gap-junctional connections than longitudinal conduction, irregular slowing of conduction, particularly in the transverse direction, would be expected.\textsuperscript{1-3,34}

**Chronic Ischemia**

Chronic myocardial ischemia is also associated with arrhythmogenesis that may involve alterations in intercellular coupling and anisotropy. Despite a normal pattern of gap-junctional distribution in a normal number of intercalated disks per myocyte and a normal mean density of packing of the constituent connexons, there is a 47% reduction in connexin43 gap-junctional membrane in chronically ischemic but noninfarcted human ventricular myocardium.\textsuperscript{8} Thus, although ultrastructural studies have suggested that gap-junctional surface area is reduced in the setting of ischemia persisting to the point of irreversible damage and infarction,\textsuperscript{29} this stage is, by definition, not reached in patients with recurrent or persistent ischemia without infarction. Nevertheless, a substantial reduction in connexin43 expression may be an architectural factor in the slowing and nonuniformity of conduction, with no need to invoke the gross alterations consequent on infarction and ensuing fibrosis as the explanation. This expectation is borne out by the observation that a similar halving of gap-junctional connexin43 content in ventricular myocardium from mice heterozygous for a connexin43 null mutation results in a 27% reduction in conduction velocity.\textsuperscript{37}

**Effects of Myocardial Infarction**

**Healing Phase**

In a canine model studied 4 days after left anterior descending coronary artery ligation, the demonstration of abnormal conduction in the healing infarct border-zone myocardium in the setting of normalizing action potential generation after the severe depression of the acute ischemia\textsuperscript{41} indicates that remodeling of the myocardium and of the coupling of its constituent myocytes is a likely cause of the observed conduction disturbances. The changing microscopic architecture of the surviving subepicardial myocardial fibers (Figure 5) of the canine infarct border zone has important time-dependent influences on impulse conduction that cause arrhythmias in the experimental model.\textsuperscript{42,43} The subepicardial fiber orientation, perpendicular to the left anterior descending coronary artery, forms an anisotropic structure that is maintained during the first week after coronary occlusion, when the fibers may remain tightly packed together or become partially separated by edema.\textsuperscript{44-46} Although the surviving myocytes in the border zone adjacent to necrotic cells have normal histological features, they have varying degrees of disruption of connexin43 gap junction distribution,\textsuperscript{45} similar to that described in healed human infarcts.\textsuperscript{35} In contrast with normal, the healing canine epicardial border zone reveals immunolabeled connexin43 distributed around the entire cell surface, with a large amount located along the lateral membrane (Figure 6). The disturbed gap-junctional pattern is most prominent immediately abutting the necrotic tissue and extends through the border zone toward the epicardial surface,\textsuperscript{42} where the subepicardial myocytes distant from the necrotic tissue almost universally show the normal, transversely oriented pattern describing the locations of the normal intercalated disks (Figure 6C). In thinner regions of the epicardial border zone, however, the layer of disturbed gap-junctional distribution extends throughout the entire thickness of the surviving epicardial border zone, all the way to the epicardial surface (full-thickness gap-junctional disarray) (Figure 6C).

These profound alterations in the organization of intercellular connections occur in the healing experimental canine epicardial border zone, which exhibits nonuniformity of anisotropic conduction, fractionated electrograms, and ready inducibility (in a proportion of the dogs) of reentrant circuits, producing stable monomorphic ventricular tachycardia (Figure 7), but no evidence of any fibrotic scarring.\textsuperscript{45-48} Reentrant circuits in these epicardial border zones are functional, in that they are not formed by fixed anatomic block to conduction but rather are induced by programmed stimulation when a sufficiently premature impulse encounters a refractory region and deviates around to form a complete circuit of continuous reentrant excitation dependent on the functional properties of

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**Figure 5.** Photomicrographs of parallel-oriented surviving muscle fibers in epicardial border zone of healing canine infarct (4 days old). In some regions, fibers are widely separated (A) and in others (B) more closely packed together. Reproduced from Reference 43 with permission.
the tissue. The mechanism for block may involve anisotropic properties of this region, with preferential longitudinal conduction block, or a prolonged refractory period at the site of block. In the canine model, these lines of block form in regions of very slow transverse propagation associated with the nonuniform anisotropic conduction characteristic of this area, resulting in a failure of transverse propagation during the tachycardia (Figure 7). Functional reentry so described is called anisotropic reentry. The lines of functional block and the slow activation around the ends of the lines of block that occurs transverse to the long axis of the fiber bundles must be stable if monomorphic tachycardia is to sustain but may cause nonsustained tachycardia or ventricular fibrillation if not stable.

Although the mechanisms for the formation of the stable functional lines of block in canine anisotropic reentrant circuits 4 days after infarction remain uncertain, there is a relationship between their location and the microscopic anatomy of these regions. A stable reentrant circuit causing sustained, monomorphic ventricular tachycardia appears to occur only if the altered distribution of connexin43 extends throughout the full thickness of a region of the infarct border zone, and this region defines the location and dimensions of the lines of functional block and of the central common pathway between them (Figure 7). Boundaries between the region of full-thickness abnormalities and adjacent regions that have abnormal connexin43 distribution extending only partway through the epicardial border zone are the locations of the functional lines of block in the reentrant circuits. The mechanism by which the change in gap-junctional distribution influences the location and characteristics of the reentrant circuit has yet to be determined. It is possible that the interface between areas with disturbed junctional distribution in their most superficial layer and the surrounding normal distribution may represent a line of particularly vulnerable transverse conduction (Figure 8). The metabolic disturbances of ischemic tissue and the possibility of either alterations in channel conductance or the relative expression of the different connexins may also contribute to changes in coupling characteristics in the infarct zone.

Healed Phase
Remodeling of experimental and human infarct structure continues as the infarct heals, leading to further changes with time. Although a human infarct may be described as transmural, there may be surviving subepicardial muscle supporting reentry, as in the canine infarct model, and surviving muscle and Purkinje fibers on the subendocardial surface. The reentrant pathway in most clinical reentrant circuits causing ventricular tachycardia principally involves this surviving subendocardial tissue, but deeper myocardial and epicardial involvement may be critical to maintaining the circuit.

The deposition of the connective tissue scar distorts the normal relationship of the surviving myocardial fiber bundles. In some regions myocardial fibers become markedly separated from each other along their length. In the myocardium associated with healed canine infarcts, there is a concomitant reduction in the number of cells to which each myocyte is connected, from 11.2 to 6.5, associated with a greater reduction of predominately side-to-side cell interconnections (by 75%) than end-to-end (22%), with smaller and fewer gap junctions. In the border zone of healed human infarcts, altered connexin43 gap junction distribution occurs in surviving myocytes up to 700 μm from the interface with the fibrotic infarcted tissue (Figure 9). Within this border zone region, comparatively few labeled gap junctions are organized into discrete, transversely oriented intercalated disks, and many are spread longitudinally over the cell surface, apparently similar to the disturbance in the canine epicardial border zone 4 days after infarction. This gap junction reorganization, possibly due to a redistribution of the preexisting population of junctions, is most evident in

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**Figure 6.** Confocal micrographs of connexin43-labeled canine epicardial (epi) border zone myocardium 4 days after left anterior descending coronary artery ligation. A, Necrotic infarct (inf) is free of label, but surviving myocytes abutting infarct show grossly abnormal connexin43 gap junction distribution with label distributed all around cell borders. B, Transmural section showing order, predominantly transversely oriented arrays of label abutting epicardium at top of micrograph, contrasting with abnormal longitudinal arrays in myocytes abutting label-free infarct beneath. Note frequently observed absence of label along border of myocytes immediately abutting infarct. Bar=10 μm. C, Schematic of connexin43-immunolabeled epicardial border zone of 4-day-old canine infarct showing distinction between partial-thickness (left) and full-thickness (right) disturbance of connexin43 gap-junctional distribution (gj disarray). Reproduced from Reference 42 with permission.
healed non–Q-wave myocardial infarction, in which the demarcation between scar and myocardium is least discrete. In accordance with confocal light micrographs indicating that most of this label is situated at the cell surface (ie, at or within the cell membrane), electron microscopic examination confirms the presence of morphologically recognizable gap junctions within the plasma membranes of abutting infarct border zone myocytes. Some of these junctions are apparently isolated and distant from any of the other components, such as the anchoring junctions, of the intercalated disk. In addition, a small proportion of junctional contacts are entirely disrupted and internalized.

Consistent with such observations, detailed measurements in isolated superfused preparations of the epicardial border zone from healed canine infarcts have shown that very slow conduction displaying nonuniformity of anisotropy occurs despite normal transmembrane potentials recorded at most sites. Rather than abnormalities in action potential generation, therefore, the slow and deranged activation appears to be dependent on the underlying derangement of cellular connections among and between disarrayed myocardial fiber bundles.

Figure 7. Activation map of stable reentrant circuit during sustained ventricular tachycardia in epicardial border zone of 4-day-old canine infarct (top). Activation times (ms, small numbers); lines of isochronal activation at 10-ms intervals (larger numbers). Thick black lines show lines of functional block. Arrows point out activation pattern. Bottom, Map of distribution of full-thickness disturbance of gap junction organization (o, full-thickness disturbance; x, partial-thickness disturbance) in same 6 × 6-cm square of epicardial border zone. Area of full-thickness gap junction disarray coincides approximately with common central pathway of reentrant circuit, and borders between full-thickness and partial-thickness gap-junctional array locate lines of functional block. Reproduced from Reference 42 with permission.

Figure 8. A, Diagram of how area of myocardium with enhanced anisotropy due to impaired transverse coupling (shaded area) may form common central pathway of a reentrant circuit and define lines of functional block at its longitudinal interface with surrounding myocardium. Curvature to transverse ends of area results in longitudinal wave front encountering “normal” tissue and propagating transversely, thus defining end (turning point) of line of functional block. Once transverse propagation extends lateral to longitudinal interface, propagation will then occur longitudinally (in opposite direction) through excitable tissue lateral to and previously protected from depolarization by lines of functional block. With curvature at other end of area of enhanced anisotropy, parallel wave fronts in outer pathways will, by same mechanism, start to propagate medially to coalesce, thus defining turning point at other end of line of functional block. B, Propagation around line of functional block.

Remodeling of the Electrophysiological Architecture: A General Feature of Myocardial Disease?

It has long been recognized that fibrosis plays an important role in the arrhythmogenic myocardial architecture promoting reentrant excitation, mediated largely by its effects on uncoupling of the constituent cardiac myocytes. It has also become apparent that gap-junctional coupling of myocardium, irrespective of fibrosis, is central to arrhythmogenic alterations to myocardial architecture. Because of the complex topology of the cellular interactions, it has until recently been difficult to generate experimental data linking gap-junctional coupling directly to conduction properties in whole myocardium, whether in health or in disease, but we have reviewed some of the recent studies showing that gap-junctional quantity and distribution, in conjunction with tissue structure, provides the basis for the observed nature of anisotropic conduction and arrhythmogenic alterations in disease, principally ischemic heart disease.

Disease-related alterations in connexin expression are not confined to the ischemic heart, however, with changes having been observed in hypertrophy, idiopathic dilated cardiomyopathy, and Chagas’ disease, all of which are strongly associated with ventricular arrhythmias. Altered expression
of connexins in the heart may therefore prove to be a general feature of arrhythmogenic myocardial remodeling in diverse myocardial diseases. The development of models for investigating the effects of overexpression and underexpression (or complete ablation) of connexins\(^55\) will provide a useful tool to investigate this further.

Myocardium has the potential for substantial remodeling of its gap-junctional network. The nature of the communication via these networks and how these act in concert with the disturbed electrophysiology of the individual cells to create the conditions for the initiation and maintenance of reentry have yet to be fully elucidated. What is clear, however, is that the relationship between the individual cells and the way in which they are electrically coupled has a central role in establishing the conditions for reentry.

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**References**

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