VIEWPOINT

The role of gap junctions in the arrhythmias of ischemia and infarction

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Introduction

Gap junction remodeling (changes in function, quantity, and location) likely contributes to arrhythmias in ischemia and infarction by altering conduction, refractoriness, and automaticity,[1,2] therefore offering a novel target for antiarrhythmic therapy. However, this approach has many complexities and challenges.

Mechanisms of arrhythmias in ischemia and infarction; role of gap junctions

Ventricular arrhythmias caused by ischemia and infarction are subdivided into phases based on the duration of ischemia.[2] Each phase has a different arrhythmogenic substrate.[1,2] The nature of gap junction remodeling and its arrhythmogenic role in each phase differs.

Acute ischemic arrhythmias

Acute phase of ischemia refers to events occurring within the first 2 to 4 hours after sudden onset of coronary occlusion.[2]

First 10 to 15 minutes (phase 1a arrhythmias)

The loss of K^+ and subsequent Ca^{2+} overload that occur within minutes lead to partial membrane potential depolarization, decreased action potential amplitude, and velocity of depolarization and postrepolarization refractoriness,[2,3] and are associated with later changes in gap junction properties described below.

During the initial 15 minutes of ischemia, resistance through intracellular pathways from cell to cell, reflecting mainly gap junction conductance, remains unchanged. Increased myocardial resistivity results from collapse of the vascular bed and osmotic cell swelling, reducing extracellular space.[2,3] The precipitous slowing and heterogeneity of conduction and block causing polymorphic reentrant arrhythmias results principally from changes in the membrane potentials and extracellular resistance.[2]

At 15 to 45 minutes (phase 1b).

A marked decrease in gap junction conductance at around 15 minutes[3,4] is implicated in this second phase of arrhythmias resulting from a combination of factors that are a consequence of decreased oxygen availability. Potassium loss from cells and accumulation in extracellular space is associated with development of intracellular acidosis that closes gap junction channels.[2,3] The decrease in pH renders gap junctions more sensitive to effects of increasing intracellular calcium.[2,3] Accumulation of lysophosphoglycerides, arachidonic acid, and other substances reduce gap junctional conductance.[3] The presence of catecholamines may decrease conductance in the presence of calcium overload. Gap junction uncoupling is greater intramurally than in border zone regions, where some recovery of the severely depressed transmembrane potentials may occur.[2,4]

Increased intercellular resistance resulting from decreased gap junction conductance is accompanied by focal separation of intercalated disc membranes and reduction in gap junction surface density.[1] This is related to reduction of connexin (Cx) 43 quantity accompanied by appearance of Cx43 on lateral sarcolemmal membranes (lateralization),[5] where it is not normally located. Lateralized Cx43 likely represents protein that is not functional junctions and is part of the process of removal of gap junctions from intercalated disks triggered by decreased intracellular pH.[5] Changes in phosphorylation of Cx43 impacts both functional and structural remodeling. Reduced phosphorylation at some sites on the Cx43 molecule contributes to decreased Cx43 protein and lateralization (S325, S328, and S330), and a decrease in gap junction conductance (S364/365, S297, and S306). In contrast, S368 becomes phosphorylated through activation of protein kinase C (PKC), also decreasing conductance.[6]

As a consequence of these changes, conduction velocity in intramural regions falls steeply and inhomogeneously, creating an environment suitable for reentry.[2] Gap junction uncoupling might also expose heterogeneities in cellular

KEYWORDS Gap junctions; Remodeling; Antiarrhythmic drugs; Ischemia
ABBREVIATIONS Cx = connexin; **PKC** = protein kinase C (Heart Rhythm 2012;9:308–311)

N.S.P. is supported by the British Heart Foundation (RG/10/11/28457), Medical Research Council, and the NIHR Biomedical Research Center Program. **Address reprint requests and correspondence:** Dr. Andrew L Wit, Department of Pharmacology, Columbia University, 630 West 168th Street, New York, NY 10032. E-mail address: alw4@columbia.edu.

1547-5271/$ -see front matter doi:10.1016/j.hrthm.2011.09.056

repolarization that can contribute to slow conduction and block of premature beats leading to reentry.

Ischemia induced depression of action potentials, gap junction coupling, and conduction in border zones of surviving myocardium subjected to less intense ischemia than dying intramural regions may not be sufficient to provide a reentrant substrate.[2,4] A novel hypothesis proposes that the combination of slow conduction, block, and reentry may still occur in border zones because of the electrotonic current sink through gap junctional connections with the large mass of the highly ischemic region with depressed membrane potentials.[4]

Injury currents flow between normal and ischemic myocardium at ischemic borders as tissue resistance increases because of partial gap junction uncoupling and triggers premature beats by either reexcitation of cells or increasing diastolic depolarization.[2] Injury current and propagation wane when complete uncoupling occurs.

At 12 to 96 hours (delayed phase)

After the acute phase subsides, the frequency of ventricular beats gradually increases again.[2] Whether or not gap junction remodeling in the endocardial border (Purkinje) zone where these arrhythmias arise is a factor in the development of the automaticity, and triggered activity causing these arrhythmias is not known.[2]

Subacute and chronic ventricular arrhythmias

Over several weeks during healing and scar formation, gap junctions disappear from necrotic regions.[1] Survival of myocytes adjacent to scar leads to formation of border zones.[1,2] Reentry in border zones or myocyte bundles traversing the scar is the principal mechanism of ventricular arrhythmias, but the electrophysiology of reentry is different from acute arrhythmias.[1-3] Action potentials of surviving border zone myocytes revert toward normal over several weeks. Slow conduction and conduction block necessary for reentry can no longer be attributed to sarcolemmal membrane properties.[2] Neither can the conduction block be attributed entirely to scar, because a component of the block is functional.[1,2,7] Conduction slowing and block are dependent on structural reorganization of both surviving myocardial bundles and the gap junctions.

Even before significant fibrosis occurs, there is continued and progressive lateralization and reduction of Cx43 reflecting a decrease in functional gap junctional connections.[1,5,6] Regions of lateralization adjacent to more normal regions of gap junction distribution have poor gap junctional coupling leading to formation of lines of conduction block in reentrant circuits in healing infarcts[1,2] (Figure 1). The reason for preferential localization of block at these sites is not known. With healing fibrosis may extend from the scar that is replacing necrotic regions, into viable border zones, physically disrupting and decreasing the total number of cell-to-cell contacts with side-to-side connections selectively affected by increased interstitial collagen, enhancing nonuniform anisotropy.[1,2] The disruption of gap junction

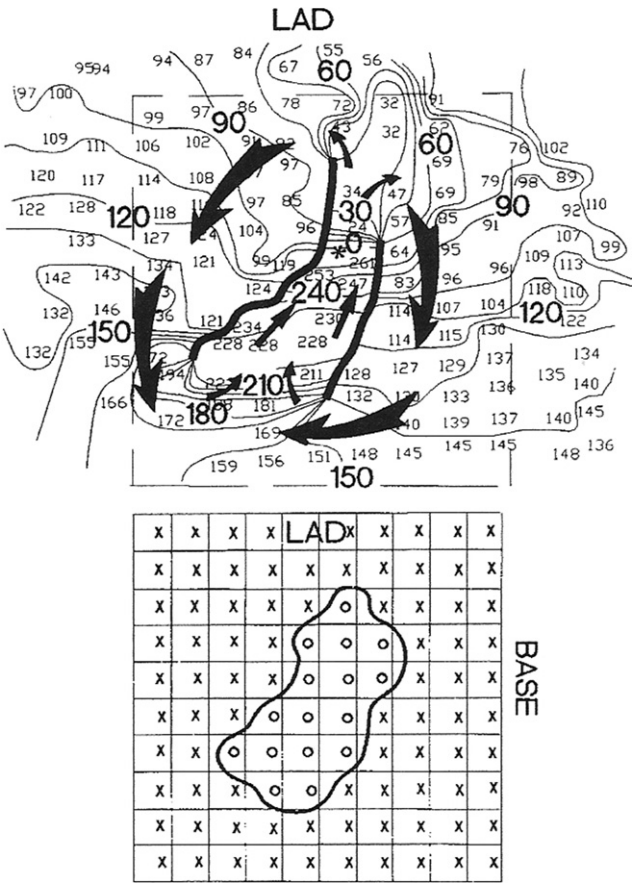

Figure 1 **Top:** Map of reentrant circuit during ventricular tachycardia in epicardial border zone of 4-day-old canine infarct. Activation times (ms, small numbers) and lines of isochronal activation at 10-ms intervals (larger numbers) are shown. Thick black lines show lines of functional block. Arrows point out reentrant activation pattern. **Bottom:** Distribution of gap junction remodeling (o = remodeling in reentrant circuit) in the same square of epicardial border zone. Area of gap junction remodeling coincides with common central pathway of reentrant circuit and lines of functional block. Reproduced with permission from Peters NS, Severs NJ, Coromilas J, Wit AL. Disturbed connexin43 gap junction distribution correlates with the location of reentrant circuits in the epicardial border zone of healing canine infarcts that cause ventricular tachycardia. Circ 1997;95:988–996.

connections by fibrosis is likely a major cause of fractionated electrograms that are characteristic of the arrhythmogenic substrate.[1,2]

In healed infarct border zones and myofiber bundles traversing scar, few gap junctions remain in discrete intercalated disks after many months postcoronary occlusion. The normal organization of gap junctions as a prominent ring enclosing small spots (gap junctional plaques) may not be discernible in remaining discs.[1] Lateralized Cx43 is still present and distributed in a disorderly fashion over the myocyte surface (Figure 2).[1] Lateralization seems to be part of the continuing process for destruction of gap junctions. There is little evidence that lateralized Cx43 at this time forms functional gap junctions. The decrease in gap junctions is likely to be of sufficient magnitude to cause severe depression of conduction and block underlying ventricular tachycardia and fibrillation.[1,2] The lines of block created by