# GAP JUNCTIONS: ANOTHER MECHANISM FOR HETEROGENEITY OF REPOLARIZATION ACROSS VENTRICULAR WALL

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Intercalated discs are the sites of the membrane where cardiomyocytes connect. Adherens or desmosomes, and gap junctions are located in intercalated discs, and ensure the mechanical coupling, thus enabling cardiac electrical impulse to spread.

Arrhythmogenic right ventricular cardiomyopathy/ dysplasia (ARVC/D) is an entity that affects these structures, and consequently the mechanical coupling with electric organic defficiency, and a tendency to fatal arrhythmias occurrence (1). In boxer dogs, one of the animal models of ARVD, severe mechanical and electrical modifications were observed in cell-to-cell interaction, with a significant reduction in gap junctions density, a factor that promotes the appearance of malignant ventricular arrhythmias. This model may help in the advancement of our understanding of molecular basis, pathophysiology, and potential therapeutic approach in patients carriers of ARVC/D(2).

Gap junctions are electrical points of continuity between cardiac cells and between smooth muscle fibers. These structures are protein channels with low resistance, dodecameric (12 structures), constituted by hexagonal hemichannels, arranged around a central watery pore with a 9 to 11 nm diameter, and located in the sarcolemma of neighbor cells. This pore enables the passage of molecules of up to 1000 daltons, and provides access to the cytoplasm of the two neighbor cells.

A dodecameric structure of gap junctions, is composed by 2 hexagonal hemichannels that surround a central watery pore, which enables the passage of small molecules. These structures are made up by proteins called connexins(3).

Which are the functions of gap junctions?

- Enabling the electrical binding between two adjacent cells, thus AP spreads more easily from fiber to fiber;
- Cardiac gap junction channels are crucial for conducting electrical impulse between cardiomyocytes;
- Structurally, they may be constituted by connexin 40 (Cx40), connexin 43 (Cx43), and connexin 45 (Cx45). A fourth isoform, Cx37, expresses in the endothelium;
- Enabling a greater conduction velocity in the site where they are. Because they are located in the longitudinal direction of the fiber, conduction velocity is two to three times greater in the longitudinal direction than in the transversal direction (anisotropic conduction). This longitudinal arrangement of gap junctions explains why dromotropic disorders and blocks occur more frequently in the longitudinal direction;
- Providing a biochemical coupling by enabling cell-to-cell movement of small molecules such as high-energy phosphates (energetic support, growth control, and embryogenesis), e.g. ATP. These are small molecules that may go through, because gap junctions enable the passage of elements of up to 1000 daltons.
- Suppression of tumor genes (Cx43, Cx32, and Cx36);
- Adhesive function, independent from dromotropic properties.

The proteins that make up the gap junctions are known as connexins. The most abundant connexin is found in the heart, and is connexin 43, and to a lesser degree, connexin 40 (Cx40) and 45 (Cx45) (4).

In the ventricles, there is a large amount of connexin 43 and 45, and a very small amount of connexin 40. SA and AV nodes only have connexins 40 and 45, and in the atria, there is a large amount of three types, however, connexin 40 (Cx40) and the largest gap-junction protein in atrial muscle tissue. Cx40 expressed abnormally increases the vulnerability to occurrence of atrial

fibrillation, which is triggered by alteration in the genetic formation of thoracic veins (5).

Connexin 43 is the main decisive factor between the electrical properties of the cardiac muscle (6). Closure of gap junctions at the level of this connexin causes negative dromotropism.

Purkinje cells have a greater concentration of gap junctions in comparison to bundle cells, which explains why the septal fascicle of the His bundle left branch (AF) activates the left middle surface earlier than the anterior fascicle and posterior fascicle (PF). This Purkinje cell has very prominent and abundant gap junctions, with a rapid termino-terminal and side-to-side transmission. The termino-terminal one is mainly constituted by connexin 43.

The entities that hamper gap junction conduction have arrhythmogenic potential. On the contrary, drugs that open these structures could potentially be used as another management strategy for arrhythmias. Peptide ZP123 increases conductance in gap junctions, significantly decreasing their closure during acidosis. This property of decreasing intracellular binding in these conditions, shows the antiarrhythmic potential of the drug in conditions of acidosis.

Gap junctions are properly developed in Purkinje cells and in cells with which bundle fibers bind, and ventricular myocardial cells; they are very prominent and abundant, with fast termino-terminal and side-to-side transmission. The first one is mainly made up by connexin 45.

Note: Purkinje cells usually make up groups of three, yielding an aspect of Y. This arrangement is the anatomical basis for the main mechanism of arrhythmias: anatomical reentry.

These cells are located in the His bundle, Purkinje branches and arborizations, with less density in the baseline region of the ventricles, and tip of papillary muscles. Additionally, they are observed in a low amount in the preferential pathways or interatrial bundles.

Substantial heterogeneity in ion channel density and expression exists in cells isolated from various regions of the heart. Cell-to-cell coupling in the intact heart, however, is expected to attenuate the functional expression of the ion channel heterogeneities. Due to limitations of conventional electrophysiological

recording techniques, the extent to which cellular electrical heterogeneities are functionally present in intact myocardium remains unknown. High-resolution optical mapping with voltage-sensitive dyes was used to measure transepicardial and transmural repolarization gradients in the Langendorff perfused guinea pig ventricle and the canine wedge preperation, respectively. Diversity of repolarization kinetics in the transepicardial direction modulated dispersion of repolarization in a biphasic fashion as premature coupling interval was shortened. Moreover, modulation of repolarization paralleled arrhythmia vulnerability in a predictable fashion. Transmural optical mapping revealed significant gradients of repolarization across the ventricular wall that were markedly increased in a surrogate model of LQTS.

Transmural gradients of repolarization in LQTS were associated with an enhanced susceptibility to TdP. Therefore, despite strong cell-to-cell coupling in the normal heart, heterogeneities in the ionic make-up of cells across the epicardial and transmural surfaces result in functional heterogeneities of repolarization leading to arrhythmias.

Electrophysiological (EP) heterogeneities between subepicardial and midmyocardial cells can form a substrate for reentrant ventricular arrhythmias. However, cell-to-cell coupling through gap junctions is expected to attenuate transmural heterogeneities between cell types spanning the ventricular wall. Because connexin43 (Cx43) is the principal ventricular gap junction protein, Gap junctions are critical to maintaining synchronized impulse propagation and repolarization. Heterogeneous expression of the principal ventricular gap junction protein connexin43 (Cx43) is associated with APD dispersion across the anterior ventricular wall. Little is known about Cx43 expression patterns and their disparate impact on regional electrophysiology throughout the heart. Strom et al. aimed to determine whether the anterior and posterior regions of the heart are electrophysiologically distinct. Multisegment, high-resolution optical mapping was performed in canine wedge preparations harvested separately from the anterior left ventricle (aLV; n = 8) and posterior left ventricle (pLV; n = 8). Transmural APD dispersion was significantly greater on the aLV than the pLV. Conduction velocity dispersion was also significantly higher across the aLV than the pLV. Carbenoxolone perfusion significantly enhanced APD and

conduction velocity dispersion on the aLV, but not the pLV and produced a 4.2-fold increase in susceptibility to inducible arrhythmias in the aLV. Confocal immunofluorescence microscopy revealed significantly greater transmural dispersion of Cx43 expression on the aLV compared with the pLV wall, suggesting that regional expression of Cx43 expression patterns may account for regional electrophysiological differences. Computer simulations affirmed that localized uncoupling at the epicardial-midmyocardial interface is sufficient to produce APD gradients observed on the aLV. These data demonstrate that the aLV and pLV differ importantly with respect to their electrophysiological properties and Cx43 expression patterns. Furthermore, local underexpression of Cx43 is closely associated with transmural electrophysiological heterogeneity on the aLV. Therefore, regional and transmural heterogeneous Cx43 expression patterns may be important mechanism underlying arrhythmia susceptibility, particularly in disease states where gap junction expression is altered (7).

Additionally, in heart failure, midmyocardial Cx43 expression is heterogeneously reduced. This is associated with increased transmural dispersion in refractoriness and conduction, and with increased arrhythmia inducibility(8).

Heterogeneous Cx43 expression is closely associated with functionally significant EP heterogeneities across the transmural wall. Therefore, Cx43 expression patterns can potentially contribute to arrhythmic substrates that are dependent on transmural electrophysiological heterogeneities (9).

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