Conductive Bridges in Cardiac Tissue
A Beneficial Role or an Arrhythmogenic Substrate?

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For many years, propagation of excitation in cardiac tissue was considered to occur in a homogeneous electrical syncytium. This view has permitted the application of concepts and quantitative relationships developed originally by Hodgkin and Huxley to describe action-potential propagation in the continuous structure of the nerve axon. The properties of action-potential conduction were associated with membrane properties alone, while effects of the myocardial architecture were, for the most part, ignored. The microscopic anatomical structure of the myocardium as an assembly of discrete cells separated by a periodic intercalated disk structure was established in the 1950s, followed in later years by the identification of gap junctions as specialized structures for electrical communication between cardiac cells. The pioneering work of Madison Spach and coworkers in the early 1980s directed attention to the effects of structural discontinuities on action-potential propagation in the heart. Spach’s experiments revealed electrical properties of cardiac tissue that could not be explained on the basis of the theory that describes conduction of excitation in a continuous medium (the so-called continuous cable theory). For example, the maximum rate of action-potential depolarization, \( (dV/dt)_{\text{max}} \), was observed to increase as propagation velocity decreased with wider angles of propagation relative to the myocardial fiber axis. This inverse relationship between \( (dV/dt)_{\text{max}} \) and velocity is in sharp contrast to the direct relation between these parameters, which is a hallmark of conduction in continuous structures. Thus, conduction in cardiac tissue is discontinuous and its properties are influenced profoundly by the myocardial architecture. The theory of discontinuous conduction predicts the experimentally observed differences from continuous conduction and provides a mechanistic explanation for these differences in terms of the interplay between membrane factors and structural factors during action-potential propagation.

In recent years, increasing attention has been given not only to the discontinuities of myocardial architecture, but also to inhomogeneities in its structure and their effects on cardiac electrical activity. Such inhomogeneities include regional differences of ion-channel expression and localization of ion channels to subcellular structures of the myocyte, and differences in the molecular structure of gap junctions in different cardiac tissues.

The article by Camelliti et al in this issue of Circulation Research draws attention to another form of structural heterogeneity, the presence of nonmyocytes in cardiac tissue, as a possible modulator of action-potential conduction in the heart. About half of the cells in the normal heart are noncardiomyocytes, with fibroblasts being the predominant cell type. Fibroblasts synthesize the scaffolding structure that supports cardiomyocytes. In aged, hypertrophied, or infarcted hearts, fibroblasts produce electrically insulating collagenous septa. Camelliti et al explore the possibility that fibroblasts form functional gap junctions and communicate electrically with other fibroblasts and with cardiomyocytes in native cardiac tissue. Using confocal laser-scanning microscopy and immunohistochemical techniques to study structure, and spread of Lucifer yellow dye to evaluate the functionality of intercellular coupling, they arrive at the following conclusions. (1) Fibroblasts express both Cx40 and Cx45 to form functional gap junctions. (2) Cx40 is found primarily in regions where fibroblasts are surrounded by other fibroblasts, while Cx45 is expressed mostly where fibroblasts intermingle with myocytes. (3) Gap junctions formed by Cx40 provide fibroblast-fibroblast coupling, while heterogeneous fibroblast-myocyte coupling is provided mostly by the Cx45 isoform. (4) Cx43 is not expressed in nodal tissue from the central region of the sinus node but provides myocyte-myocyte coupling in atrial fibers that protrude into this region. Importantly, the dye-spread studies suggest that fibroblasts can provide conductive pathways between myocytes that are not in direct contact, thus forming bridges for electrical communication.

The study of Camelliti et al suggests the possibility of electrical bridging by fibroblasts in native cardiac tissue. An earlier study by Gaudesius et al demonstrated such a phenomenon in a patterned cell culture, where strands of myocytes were bridged by chains of cardiac fibroblasts over various distances. Using multisite optical recording of the transmembrane voltage, action-potential propagation in this preparation was documented. Bridging of impulse propagation by fibroblast inserts was successful over distances up to 300 μm, with long propagation delays ranging from 1 to 68 ms introduced by the fibroblast discontinuities (the delay increased with the length of the fibroblast chain). The electrotonic nature of the transmission across the fibroblasts was supported by excluding mechanical stretch as a possible mechanism (replacement of fibroblasts by communication-deficient HeLa cells stopped conduction, while HeLa cells...
Propagation of excitation in cardiac tissue is determined by the balance between the availability of depolarizing charge (source) and the amount of charge required for successful propagation (sink). This relationship reflects complex interactions between membrane ionic currents that generate the depolarizing charge and structural properties of the tissue that determine the electric load on a depolarizing cell. Both membrane factors and structural factors can be affected by pathology. Inexcitable bridges constitute an electrical load that, under certain conditions, could tilt the balance in the negative direction, causing conduction failure. Excessive electrical loading can also draw depolarizing charge during the plateau phase of an action potential, leading to location-dependent shortening of action potential duration and arrhythmic excitability gradients ("dispersion of repolarization"). The long conduction delays across such bridges can support very slow conduction, which, together with large dispersion of repolarization, provides the substrate for reentrant arrhythmias. On the other hand, fibroblast bridges could have a beneficial effect by providing a mechanism for electrical communication and synchronization across inexcitable barriers in the heart. Such barriers are formed by collagenous septa and scars in fibrotic hearts in association with aging, myocardial infarction, and other forms of structural heart disease. It will be of great interest to establish whether fibroblast bridges form functional gap junctions with cardiomyocytes in such substrates, and if so, to understand their beneficial effects and arrhythmogenic potential in these settings.

The article by Camelliti et al. describes fibroblast networks in the sinoatrial node. As stated above, it will be of interest and of important clinical relevance to conduct similar studies in other regions of the heart. The sinoatrial node is a highly heterogeneous structure. Nodal cells rely on a multiplicity of ion channels for pacemaking, and these ion channels are expressed heterogeneously within the sinus node structure. An article by Vinogradova et al. also in this issue of Circulation Research, suggests that rhythmic calcium release also participates in the pacemaking function of sinoatrial nodal cells, an observation that further complicates structure-function relationships in the sinus node. In addition, the heterogeneous architecture of the sinoatrial node (heterogeneous distribution of gap junctions, branching of fibers) serves to optimize its electrical loading by the surrounding atrial tissue, thereby facilitating its ability to drive the heart. The work of Camelliti et al suggests that fibroblast bridges exist in the operational sinoatrial node. The role of such bridges is not known. One possibility is that they provide synchronization to this complex heterogeneous structure. Understanding of their functional importance and arrhythmic implications in the sinoatrial node and other tissues of the heart will require further extensive investigation.

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