Editorial

Gap junction heterogeneity in reentrant ventricular tachycardia

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See article by Cabo et al. [18] (pages 241–249) in this issue.

The cells of all tissues are coupled by gap junctions, with the exception of blood and adult skeletal muscle cells. Gap junctions provide for homoeostasis and integrative function by mediating the exchange of ions and chemical second messenger molecules between adjacent cells. The electrical signaling provided by these specialized intercellular junctions is perhaps best understood in the heart, where their abundance serves to provide low electrical resistance pathways for current flow — ensuring fast and efficient transfer of the propagating cardiac action potential throughout the working myocardium. This role of the gap junction, or nexus as it was then called, was best demonstrated by Barr et al. [1] when they correlated the block of cardiac action potential propagation with disruption of the gap junction structure by extracellular hypertonic sucrose solutions [1]. Studies since the 1960s investigated the membrane structure of gap junctions, and the only structural changes noted were associated with irreversible uncoupling procedures [2–4]. These irreversible structural changes occurred after prolonged acidification or mechanical trauma and were first described as the “healing-over” phenomenon of the heart [5,6]. Gap junctions were otherwise still regarded as relatively static structures that changed their conformation only after severe pathological events such as a healing infarct or surgical repair.

Today we know this not to be the case. The channel function and molecular composition of cardiac gap junctions was elucidated in the mid-1980s, and the half-life of connexin43 (Cx43), the primary gap junction protein of the ventricular myocardium, has since been demonstrated to be on the order of hours, not days [7–9]. Cx43 protein content is reduced in various disease states such as chronic heart failure, hypertrophy, and dilated cardiomyopathy [10]. More important than the overall expression level of Cx43, and Cx40, in the myocardium is the spatial distribution of gap junctions. In healed infarct border zones, the number of cardiomyocytes connected by intercalated disc gap junctions is reduced by almost half, from 11.2 to 6.5 myocytes on average [11]. This long-term reduction in myocardial gap junctions occurs mostly in the transverse direction owing to a 75% reduction in lateral intercalated discs relative to a 22% reduction in the longitudinal direction. Epicardial mapping studies have identified the healing infarct border zone as the location of reentrant circuits responsible for inducible ventricular tachycardias [12]. Ischemia-induced gap junction uncoupling has been correlated with dephosphorylation and internalization of Cx43 [13]. Lateralization of Cx43 protein occurs during a variety of pathophysiological conditions, including hypertensive or obstructive ventricular hypertrophy and myocardial infarctions — especially in the healing infarct border zone [10,12,14,15]. How these short-term and long-term alterations in Cx43 content and distribution affect the induction and sustainability of cardiac arrhythmias is incompletely understood, but these studies reveal the complexity of gap junction regulatory mechanisms involved in the response.

Gap junction redistribution need not be global to affect cardiac function. In fact, heterogeneous loss of Cx43 produces more discontinuities in conduction velocity, spontaneous ectopic ventricular arrhythmias, and systolic dysfunction with less overall reductions in Cx43 protein content than if uniformly distributed [16,17]. While focal gap junction heterogeneities can trigger arrhythmias, it is hypothesized that sustained ventricular arrhythmias require more widespread reductions in gap junction uncoupling [17].
In this issue of *Cardiovascular Research*, Cabo et al. [18] demonstrate that cardiac gap junctions are redistributed within the “figure of eight” reentrant circuit in 5-day-old infarcted canine hearts with sustained ventricular tachycardia. This remodeling of Cx43-immunolabeled protein is heterogeneous, observed as an increased lateralization of Cx43 protein but restricted to myocytes from the central common pathway (CCP) of the reentrant circuit. No significant differences in longitudinal or lateral Cx43-containing gap junctions were observed in the outer reentrant pathway (OP) or within the normal (NZ) myocardium. This increased lateralization of Cx43 appears to preserve the transverse junctional conductance within the CCP and the anisotropy ratio of 1.6 found in the NZ myocardium. It is true, however, that longitudinal conduction velocity is reduced within the CCP, and transverse conduction velocities are reduced in both the CCP and OP regions compared to normal myocardium. The greater relative reduction in transverse conduction velocity within the OP results in an increased anisotropic ratio of 2.1. Of course, the effect on conduction velocity is not limited to changes in longitudinal and transverse junctional conductances since the sodium and calcium current densities are also reduced in both the CCP and OP cells [19]. The detection of Cx43 protein is also not necessarily indicative of functional gap junctions, since reduced gap junctional conductance and altered function has been observed in epicardial border zone cardiomyocytes without a concomitant reduction in Cx43 levels [20].

The results of this investigation suggest that focal heterogeneous redistribution of cardiac gap junctions can induce ventricular arrhythmias. The myocardium may also attempt to compensate for the loss of functional gap junctions in the transverse direction by increasing the lateralization of Cx43 protein within the CCP. The ultimate result is a partial preservation of function that perhaps helps to stabilize the reentrant circuit and sustain the ventricular tachycardia. This new line of evidence indicates an increasing role of heterogeneous cardiac gap junction remodeling in the maintenance, not just the development, of cardiac arrhythmias. The mechanisms involved in the cellular responses to ischemic injury, infarction, heart failure, and hypertrophy that bring about these alterations in Cx43 and Cx40 distribution and function remain to be fully elucidated.

References