Strengthening intercellular communication to prevent atrial fibrillation

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This editorial refers to ‘Connexin 43 gene therapy prevents persistent atrial fibrillation in a porcine model’ by O. Bikou et al., pp. 218–217, this issue.

Many complex pathophysiological mechanisms underlie atrial fibrillation (AF). The classical view of AF is of a trigger causing abnormal impulse formation and a substrate-supporting reentrant impulse conduction which combines to sustain the arrhythmia. Furthermore, time seems to be important in the development of the disease, such that short episodes of AF gradually prime the atria for longer lasting and eventually perpetuating episodes of AF. Multiple reentrant wavelets are suggested to underlie the persistent episodes, in which a short refractory period and slow conduction velocity unite to maintain the reentrant circuits. Additionally, a high-frequency firing source may cause AF via non-homogeneous spreading of the propagating wave front in a manner called fibrillatory conduction.

Irrespective of the suggested underlying mechanism, atrial structural, mechanical, and electrophysiological remodelling provide the bridge leading from short, isolated episodes of AF to a persistent and debilitating arrhythmia requiring intervention. Atrial dilatation, fibrosis, and alterations in the organization of the myocardial sarcomeres constitute the predominant structural changes. Downregulation of the L-type calcium current and an increased inward-rectifier current, I\textsubscript{K1}, underlie a shortening of atrial action potential duration. Rather than uniform up- or downregulation, there is heterogeneous remodelling that promotes and sustains inhomogeneous slow conduction and block. Nevertheless, changes in ion channel expression and function, which appear to follow a faster time course than AF, may not suffice to support multiple sustained reentry circuits. Gap-junctional remodelling correlates better, albeit not perfectly, with AF stability, thus suggesting that remodelling of connexins (Cx) might be involved in the pathogenesis of sustained AF.

The atria express Cx40 and Cx43, which can assemble into both homomeric and heteromeric gap junctions, make it difficult to predict the impact of connexin remodelling on AF. The conduction reserve in mice with a 50% reduction in Cx43 suggests that a substantial downregulation of gap-junctional proteins is required for a functional impact on conduction velocity. Protein quantity, cellular distribution, and phosphorylation status of the connexins will all influence the strength of the intracellular communication after the remodelling process. In samples from patients and from experimental animal models of AF, Cx40 has been reported to be both up- and downregulated as well as unaltered. Ultimately, it appears that inhomogeneous redistribution of Cx43 is the common finding associated with AF. Increased, decreased, but most often no change in the amount of Cx43 in AF is coupled with frequent observations of cellular lateralization of Cx43.

Bikou et al. report on their study of a porcine model of burst pacing-induced AF. They found reduced Cx43 levels in AF and used Cx43 overexpression to evaluate whether this was critical for the development of the arrhythmia. Cx43 overexpression was achieved by directly injecting adenovirus-encoding Cx43 into the atrial wall followed by electroporation, or electroporpermabilization, of the atria. This dual approach resulted in a restoration of total Cx43 protein to sinus rhythm control levels. Importantly, this intervention increased conduction velocity, primarily in the right atria, and prevented development of persistent AF.

Electroporation to boost infection rate after adenoviral administration is a novel and interesting approach for the experimental setting, but due to its invasiveness it is a long way from being clinically applicable. Adenovirus only has limited expression after a few weeks, but was used for its high infection rate of cardiomyocytes in this proof-of-concept study. The important finding of Bikou et al. is the prevention of persistent AF through preservation of sinus-rhythm levels of Cx43: maintaining conduction velocity presumably breaks the reentrant circuits perpetuating the arrhythmia, strengthening the hypothesis that short refractory periods and slow conduction velocities conspire to support AF. Will this lead to novel strategies for the treatment of AF? Flecainide and similar sodium channel blockers are currently the most frequently used pharmacological approaches. Their mechanism of AF conversion is a paradoxical slowing of conduction with negligible prolongation of the atrial refractory period. Thus, both increased and decreased conduction velocities are able to break the reentrant circuits and stop the propagating arrhythmia. Slowing of the AF conduction extends the duration of the excitable period, thereby increasing the likelihood of restoration of sinus rhythm. Improving conduction, on the other hand, increases the probability of the wave front reaching refractory areas, bringing the reentrant circuit to an end.
Several follow-up studies will be required for a better understanding of the optimal antiarrhythmic treatment of AF. The proposed strategy needs to be confirmed in other experimental models of AF, including those without prominent Cx43 downregulation. Can Cx43 upregulation intervene in established AF to restore sinus rhythm, or is the concept limited to prevention of the arrhythmia? The authors found no change in protein expression of Cx40 and Cx45; however, a more detailed description of the molecular and functional aspects of gap-junctional remodelling secondary to Cx43 overexpression is essential. In particular, it will be interesting to determine the cellular localization and phosphorylation status of Cx43 in the transfected atrial cardiomyocytes. Nevertheless, the present study provides renewed optimism to the future of the novel pharmacological enhancers of cellular communication.10

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References