Do genetics help to better understand the underlying mechanisms of atrial fibrillation?

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Interaction of the minK (KCNE1) protein with the pore-forming K⁺ channel subunits KvLQT1 (KCNQ1) and HERG (KCNH2) enhances activity of the slow (Iₖₛ) and rapid (Iₖᵢ) component, respectively, of delayed rectifier potassium current. If KvLQT1 is co-expressed with minK 38G instead of minK S38, the amplitude of Iₖₛ is reduced without alterations in current kinetics. Provided that native atrial channels containing minK 38G behave similarly, the presence of the minK 38G variant will prolong the action potential (AP). Prolongation of atrial AP in patients with long QT syndrome is associated with higher incidence of polymorphic atrial tachyarrhythmias. In analogy, the presence of minK 38G could predispose to the initiation of AF. In contrast, protein levels of minK are low in patients with chronic AF, and mice that lack minK protein develop spontaneous episodes of AF associated with high Iₖₛ amplitudes and short atrial AP. Possible explanations for these apparently contradictory findings are unconcealed differences between heterologous expression systems and native atrial myocytes, accumulation of abnormal Iₖₛ current at high atrial rates, or interaction of KvLQT1 with other accessory subunits in native cells. Ion channels and their subunits are generally accepted to be organized as macromolecular complexes including regulatory proteins. Hence, by assembling with additional proteins, minK may influence function of large molecular complexes and genetically determined variant of the subunit could produce an arrhythmogenic substrate that promotes the initiation of AF. Thus, the minK-associated alterations in atrial function are complex and may predispose to NVAF even via mechanisms unrelated to Iₖₛ function.

NO modulates cardiac function by nitrosylation of target proteins and by increasing cyclic guanosine monophosphate production, which in turn enhances activation of L-type Ca²⁺ channels. Conversely, reduced NO production may result in less Ca²⁺ influx via L-type Ca²⁺ channels and hence the shortening of atrial AP. In the presence of the eNOS -786C allele, eNOS promoter activity is halved leading to low eNOS expression and reduced cellular NO production. Short AP due to low NO level could contribute to the associated predisposition for NV-AF in conjunction with minK 38G allele. In pigs, development of AF is in fact associated with decreased eNOS activity.

As part of the ryanodine receptor Ca²⁺ channel (RYR2) complex, eNOS modulates intracellular Ca²⁺ concentration, because NO decreases the open probability of RYR2 via
channel nitrosylation. In patients with AF, RYR2 become ‘leaky’, which is consistent with low NO production and RYR2 Ca$^{2+}$ release unopposed by nitrosylation. Diastolic Ca$^{2+}$ leak from RYR2 induces late after-depolarizations that trigger AF. In support of this hypothesis eNOS-deficient mice exhibit increased susceptibility to triggered activity mediated by late after-depolarizations. Finally, reduced NO release into the coronary circulation of eNOS allele carriers promotes severe coronary spasm. As coronary artery disease is a significant risk factor for AF and acute atrial ischaemia triggers AF in dogs, episodes of acute ischaemia may contribute to predisposing eNOS allele carriers to AF.

Although the study of Fatini et al. do not address the cellular mechanisms of increased susceptibility to NVAF in minK 38G and eNOS – 786C allele carriers, they provide strong evidence that genetic variants in these regulator proteins may promote the induction of NVAF. Currently, our understanding of the causative mechanisms of AF is incomplete. The identification of susceptibility genes for AF induction may help to identify subjects at risk for AF development.

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