EDITORIAL

Does Remodeling of Gap Junctions and Connexin Expression Contribute to Arrhythmogenesis?
– Study in an Immobilization Rat Model –

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In the heart, gap junctions (GJs) mediate electrical coupling between cardiac myocytes, forming the cell-to-cell pathways for orderly spread of the wave of electrical excitation.[1] Connexin-43 (Cx43) is the primary component of cardiomyocyte GJs, which regulate intercellular coupling, conduction velocity, and anisotropy. In patients with myocardial infarction, cardiac hypertrophy, and heart failure, Cx43 undergoes remodeling (reduction or redistribution), and this mechanism appears to underlie arrhythmogenesis in ischemia and heart failure.[2,3]

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Extreme excitement or struggling against forced restraint (immobilization: IMO) occasionally results in sudden death,[4] but the mechanism of this and its connection to Cx43 remain unknown. IMO is a model of the cardiovascular response to emotional stress and recently, Unuma et al[5] investigated whether Cx43 distribution or GJ function during restraint is involved in sudden arrhythmic death in rats and they reported that IMO induced translocation of Cx43 to GJs. However, the involvement of adrenoreceptors[6] in the Cx43 translocation remains elusive.

In this issue of the Journal,[7] male Sprague-Dawley rats underwent IMO and the ventricular distribution of Cx43 was examined by Western blotting. IMO induced translocation of Cx43 to the GJ-enriched membrane fraction, with a peak at 60 min. The IMO-induced Cx43 translocation was inhibited by pretreatment with the α_1-adrenoceptor blockers, prazosin and bunazosin, but not with the β_1-blocker, metoprolol, or the β_{1+2}-blocker, propranolol. There was no translocation of hypoxia inducible factor-1α, and the distribution of Cx43 was different from that in ischemia.[8] Unuma et al concluded that translocation of Cx43 to the GJ-enriched fraction occurs via the α_1-adrenoceptor pathway independently of ischemia.[7]

The results provided by Unuma et al[7] are the first demonstration of α-adrenoreceptor-dependent Cx43 translocation to GJs in IMO rats. Other signaling molecules have been also studied in Cx43 upregulation. In cardiomyocytes, ERK, p38 MAP kinase, JNK, and *c-fos* are involved positively in Cx43 upregulation by the α-adrenoreceptor stimulant phenylephrine.[9]

Abnormalities of the action potential play a central part in the genesis of arrhythmia, but it is now recognized that GJs and their component connexins also play an important role.[1–3] In the present study by Unuma et al,[7] premature ventricular contractions (PVCs) were increased during 0–60 min of IMO. The heterogeneity of GJ distribution, combined with reduced Cx43 levels, appears to create an arrhythmogenic substrate at lower levels of overall GJ reduction than is predicted in theoretical models. In cardiac-restricted knock-out mice, a 59% reduction in Cx43 did not alter propagation velocity or susceptibility to arrhythmia, but when the Cx43 reduction reached 18% of control levels and appeared heterogeneous, propagation velocity was slowed by 50% and lethal ventricular arrhythmias were induced in 80% of the animals.[10] Combined effects of reduced Cx43 and other factors, such as those related to acute ischemia, may also alter the threshold at which the arrhythmic substrate is created; a halving of the Cx43 level in transgenic mice was sufficient to increase the incidence, frequency and duration of ventricular tachycardias when the heart was subjected to ischemia.[11]

In Unuma et al's paper,[7] β-blockers but not α-blockers inhibited PVCs and the ventricular tachycardia/fibrillation induced by IMO. They also show that α_1-adrenoreceptor blockers reduced the Cx43 level in GJs, the Cx43 immunofluorescence at intercalated discs, and GJ intercellular communication (GJIC), but not to less than the basal level. The authors speculate that a reduction in GJIC to a subnormal level and a ventricular conduction delay are required for the induction of ventricular tachycardia/fibrillation. On the other hand, catecholamines promote spontaneous calcium ion release or leakage from the sarcoplasmic reticulum, thereby triggering delayed afterdepolarization and triggered activity,[12] which may underlie ventricular tachycardia/fibrillation in heart diseases.[13] The increase in catecholamines in IMO[7] supports the hypothesis that IMO induces ventricular tachycardia/fibrillation when such non-GJ arrhythmic substrates emerge under subnormal GJ coupling. Beta-adrenoreceptor blockers have been acknowledged as the pharmacologic agents that reduce the incidence of sudden cardiac death and arrhythmias in patients with cardiac diseases. The findings presented by Unuma et al[7] may support the hypothesis of the anti-arrhythmic effects of β-adrenoreceptor blockers, possibly through suppression of non-GJ substrates.

Finally, there are other important issues about the remodeling of GJs, such as its role in atrial arrhythmias and the Purkinje/working ventricular myocyte connection.[2] Further-

more, the GJ has important roles in the intercellular transport of biologically active substances.[14] Further work is required to answer these questions.

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