Editorial

Penetrance of monogenetic cardiac conduction diseases. A matter of conduction reserve?

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Loss-of-function mutations in the SCN5a gene coding for the human Nav1.5 cardiac sodium channel, which lead to decreased peak sodium current, are associated with cardiac conduction defects (CCD), progressive cardiac conduction disease [1] or Brugada syndrome [2]. However, despite the strong linkage of sodium channel mutations to the disease in probands, the same mutation is often found in non-affected family members. The study by Tan and coworkers in this issue describes a SCN5a mutation leading to a C-terminal truncation (L1821fs/10) that was found in a patient with sick sinus syndrome, CCD and ventricular tachycardia [3]. This particular mutation was shown to lead to an almost complete loss of channel function and thus to haploinsufficiency of the peak sodium current. Interestingly, the same mutation was found in 6 family members of which 2 had very mild symptoms and 4 were completely asymptomatic. In genetic terms, this mutation shows incomplete penetrance and variable expressivity.

Penetrance describes the extent to which the properties controlled by a gene, its phenotype, will be expressed. In case of high penetrance, the mutation or gene always leads to a certain phenotype. Conversely, if penetrance is low or incomplete, the mutation only sporadically leads to a detectable phenotype.

Variable expressivity refers to the range of signs and symptoms that can occur in different individuals with the same genetic condition.

Impulse conduction in the heart is determined by three factors: 1. cellular excitability (Nav1.5), 2. electrical coupling (connexin43 in the ventricle), and 3. cellular/tissue architecture (fibrosis, myocyte size and shape) [4,5]. The effect of haploinsufficiency of conduction parameters has been studied in several mouse models. Conflicting results have been published for haploinsufficiency of connexin43 (Cx43). Several studies reported increased QRS duration and reduced conduction velocities [6–8], while other studies showed no effect [9–11]. It is unknown what the underlying mechanisms are for the variable expressivity of Cx43 haploinsufficiency in mice. It is known, however, that ECG parameters are very different in different mouse strains and dependent on anaesthetics [12,13].

Studies using mouse models of loss-of-function mutations in SCN5a have shown that haploinsufficiency is associated with QRS prolongation and conduction slowing [14–17]. However, in both patients and mice haploinsufficient for SCN5a [1,16], there was a large overlap between carriers and non-carriers in QRS duration. During aging in both mice and men these differences became more pronounced [1,16]. The mechanism of this age-induced increase in penetrance was revealed from epicardial mapping experiments on young and old SCN5a−/− [17]. In young SCN5a−/− mice, ventricular epicardial conduction velocity was only moderately reduced in the right ventricle (<20% reduction) but not in the left. However, in old (12–17 months) SCN5a−/− mice, conduction velocity was severely reduced in both ventricles by 30–35% [17]. Histological analyses showed high levels of interstitial...
fibrosis and disturbed expression of Cx43 in old SCN5a−/− mice, even much higher than in age-matched controls [17]. These experiments from mice indicate that the heart has a conduction reserve. Conduction velocity can be maintained at near normal values when either excitability or cell–cell coupling is reduced [5,18]. Thus, conduction parameters of the heart might be affected up to a certain level without influencing impulse propagation or increasing vulnerability to tachyarrhythmias.

Conduction reserve may partly explain the differences in penetrance or expressivity in human monogenic conduction disorders. For Brugada syndrome, additional reduction of sodium current (e.g. flecainide administration) is frequently needed for proper identification of the disease [2,19]. In addition, the progressive nature of electrical abnormalities with age strongly suggests that cofactors for arrhythmogeneity develop in time [1,20]. This is evidenced by recent reports that have shown that sodium channel mutations may lead to structural remodelling (increased fibrosis), thereby exhausting conduction reserve and enhancing arrhythmogeneity [21,22].

An important finding was previously published by the group of Makielski showing that the human heart can express several common SCN5a polymorphisms in different splice variants (Q1077 and Q1077del) of which the current density is markedly different [23,24]. This indicates that within the normal population, the background sodium current density, and thus conduction reserve for sodium channel mutations, may vary, which can explain differences in penetrance or expressivity for SCN5a loss-of-function mutations. These polymorphisms were not present in the family presented in this issue [3], and the ratio of Q1077 and Q1077del mRNA, shown to be constant in the population (35%/65%, respectively) [23], is not known for this family.

References