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EDITORIAL

Channelopathies, cardiac hypertrophy, and the theory of light

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This editorial refers to 'A common co-morbidity modulates disease expression and treatment efficacy in inherited cardiac sodium channelopathy'†, by M.R. Rivaud *et al.*, on page 2898.

In the late 1600s, a memorable debate on the nature of light occurred between Sir Isaac Newton and the gifted Dutch physicist Christiaan Huygens. Newton held the theory that light is composed of tiny particles, whereas Huygens believed it to consist of energy waves. Both the wave theory and particle theory found important experimental support, but failed to explain every aspect of the behaviour of light. It was only in 1905 that Albert Einstein put an end to the dispute by suggesting that light is composed of tiny particles called photons, each provided with finite quantities of energy, thus crediting both theories with being simultaneously right. Quantum mechanics ultimately produced proof of the dual nature of light, presented to the modern eye as an inseparable mix of matter and energy.[1] Recent clinical and experimental evidence suggests that a dual nature also exists for genetic heart disease, although electrical and structural abnormalities are presented as mutually exclusive by existing guidelines and classifications, based on a rigid distinction between channelopathies and cardiomyopathies ('waves' vs. 'matter'). While such a distinction may be useful in order to characterize phenotypic paradigms in clinical practice, it is increasingly clear that structural abnormalities of the heart are part of ion channel disorders as much as ion channel dysfunction belongs to the extended phenotype of cardiomyopathies.

Sodium channelopathies are rare monogenic disorders caused by mutations in the cardiac sodium channel encoded by the *SCN5A* gene, comprising Brugada syndrome, long-QT type 3 (LQT3), and familial conduction abnormalities, all linked with an increased risk of sudden cardiac death (SCD), albeit with variable penetrance and severity. In this issue of the journal, Rivaud *et al.*[2] show that hypertension causing secondary cardiac hypertrophy is associated with increased risk of tachyarrhythmias and SCD in middle-aged patients carrying a Dutch *SCN5A* founder mutation (*SCN5A*-1795insD). The same arrhythmic propensity was observed in a transgenic mouse line carrying the homologous mutation, in which severe cardiac hypertrophy was induced by transverse aortic constriction. The authors went on to demonstrate that therapeutic interventions blocking the main mechanisms of hypertrophic remodelling in the mouse model were able to prevent arrhythmic propensity. Such a result was obtained by two different and independent approaches, i.e. prevention of the pro-hypertrophic response by inhibition of the calcineurin/NFAT pathway and treatment with ranolazine, a specific inhibitor of late sodium current (I_{NaL}). Of note, I_{NaL} is primarily increased by several *SCN5A* mutations, including the 1795insD variant, contributing to prolonged repolarization. Ranolazine normalized I_{NaL} in mutant mice subjected to transaortic constriction, although it did not prevent the development of hypertrophy.[2] This result highlights the central role of increased I_{NaL} in modulating the risk of arrhythmias in sodium channelopathies, suggesting novel treatment opportunities. The broader, most clinically relevant implication of the study by Rivaud *et al.*, however, is that superimposed structural damage by common environmental *noxa* to a primary 'electrical' disease leads to harmful synergies and a substantial increase in risk (*Take home figure*, left panel). In the clinic, this concept translates to the fact that patients with sodium channelopathies should be aggressively monitored and treated for causes of hypertrophic remodelling such as hypertension. Implications for research are even broader: cardiologists should look for other paradigms of matter–energy interaction in genetic disease.

In patients and animal models with Brugada syndrome, loss-of-function *SCN5A* mutations are associated with myocardial fibrosis, ventricular dilatation, and reduced contractility.[3] Structural changes are more pronounced in the right ventricular outflow tract but can also be observed in the left ventricle, and the degree of fibrosis and cardiomyocyte damage appears to correlate with arrhythmic risk.[4] Mechanisms linking *SCN5A* mutations to myocardial dysfunction and damage in Brugada syndrome include abnormalities of Ca^{2+} cycling resulting from Na^{+} current reduction[5] and disruption of cell to cell interactions due to abnormal Na^{+} channel localization, resembling those seen in arrhythmogenic cardiomyopathy (AC).[6] Gain-of-function *SCN5A* mutations, linked with LQT3 syndrome, are also

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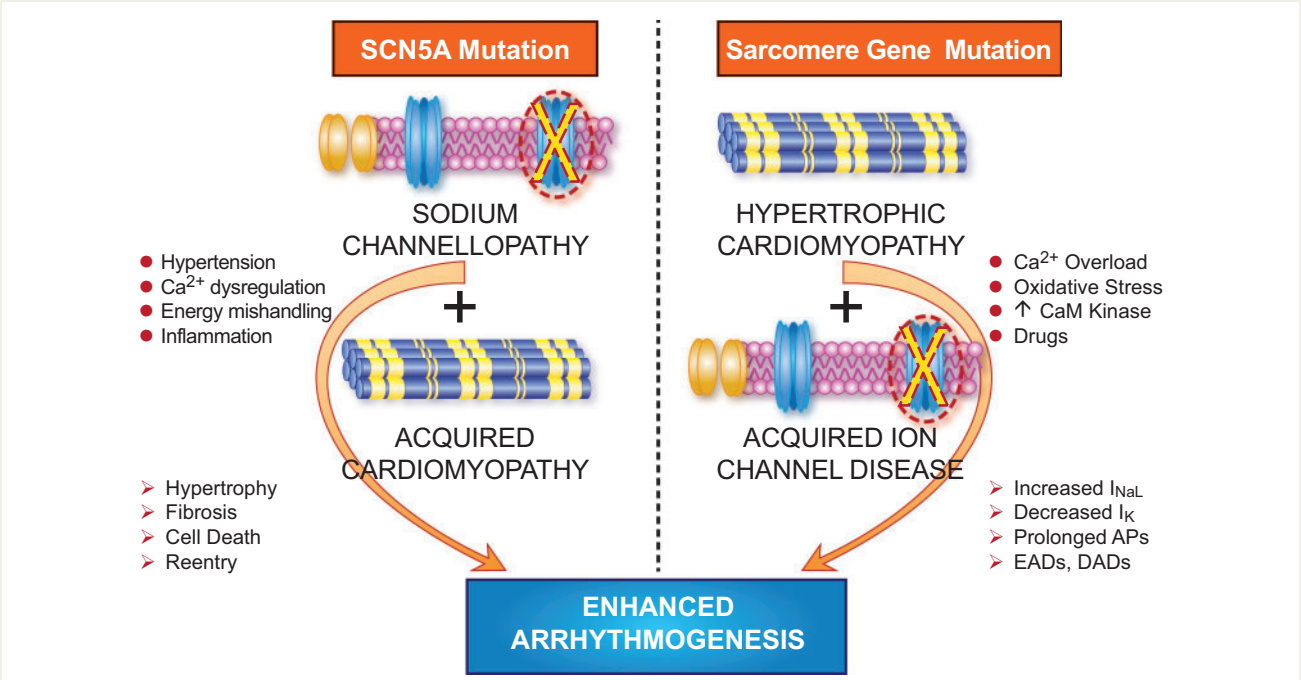

Take home figure

associated with myocardial damage and contractile abnormalities in patients and animal models;[7] this is thought to represent a direct consequence of the decreased channel inactivation kinetics triggering intracellular Ca^{2+} overload via altered Na^{+}/Ca^{2+} exchanger (NCX) function.[8] Notably, sustained cardiomyocyte Ca^{2+} overload is linked with diastolic dysfunction, hypertrophic cell signalling, and fibrotic remodelling, due to increased activation of calmodulin kinase type II (CaMKII). Because the *SCN5A*-1795insD mutation described by Rivaud *et al*. has both loss- and gain-of-function features, the two above-mentioned pathways of myocardial dysfunction/damage are likely to co-exist in this model.

If we take the opposite perspective of genetically determined cardiomyopathies, a specular paradigm can be proposed, based on the observation that 'acquired' Na^{+} channelopathies modulate arrhythmic risk (*Take home figure*, right panel). A functional Brugada-like phenotype is observed in patients and animal models carrying mutations in desmosome-related genes associated with AC, exhibiting reduced Na^{+} current and impaired electrical conduction.[6,9] These functional abnormalities often appear before the onset of the typical morphological features of AC and are caused by the loss of the interaction between mutated desmosome proteins and the Na^{+} channel complex.[10] Thus, secondary Na^{+} channel dysfunction might represent a critical trigger of ventricular arrhythmias in the early phase of AC preceding detectable structural remodelling.

An acquired LQT3-like phenotype, i.e. overexpression of I_{NaL}, is an even more common feature of myocardial disease, and has been described in nearly all experimental models of heart failure and cardiac hypertrophy. In ventricular cardiomyocytes from patients with advanced heart failure (including inherited dilated cardiomyopathy), a large component of Na^{+} current with very slow inactivation kinetics is commonly recorded.[11] Our group demonstrated a striking increase of I_{NaL} in cardiomyocytes from patients with hypertrophic cardiomyopathy (HCM) undergoing surgical myectomy.[12] As in primary LQT3, increased I_{NaL} in HCM prolongs the duration of ventricular action potential and reduces the repolarization reserve, increasing the risk of early afterdepolarizations. Moreover, secondary impairment of NCX-mediated Ca^{2+} extrusion leads to intracellular Ca^{2+} overload, spontaneous diastolic Ca^{2+} release from the sarcoplasmic reticulum, and delayed afterdepolarizations. Early and delayed afterdepolarizations are cellular triggers of arrhythmias, and may be responsible for the onset of propagated premature ventricular activations or even sustained triggered activity. Notably, cardiomyocytes from HCM patients with a history of non-sustained ventricular tachycardia had a greater expression of I_{NaL}, longer APs, and more frequent afterdepolarizations.[12]

The acquired, gain-of-function channelopathy seen in heart failure and HCM is the consequence of post-translational modifications of NaV1.5, the sodium Na^{+} channel encoded by *SCN5A*. These modifications may occur via different mechanisms, including oxidative stress and enhanced phosphorylation by CaMKII at specific sites of the channel complex.[13] The activity of CaMKII is constitutively increased in the hypertrophic heart, including HCM,[12] due to sustained cardiomyocyte Ca^{2+} overload. The latter is further aggravated by increased I_{NaL} and in turn increases CaMKII activity, leading to further phosphorylation of NaV1.5 and thus forming a vicious circle.[12] As in the case of AC, these modifications appear to occur early during disease development and probably precede the onset of overt structural abnormalities. Finally, the pro-arrhythmic effects of enhanced I_{NaL} are potentiated by other acquired electrical defects in HCM cardiomyocytes, including reduction of K^{+} currents, slower Ca^{2+} current

inactivation, and anomalous response to β-stimulation.[12,14] Of note, in a recent randomized trial enrolling symptomatic HCM patients, ranolazine significantly reduced the number of ventricular ectopies on 24 h Holter-ECG, compared with placebo.[15]

In conclusion, energy and matter travel together in genetic heart disease. It is naïve to believe that ion channel abnormalities and their cascade of complex molecular interactions will not interfere with myocardial structure and function, or vice versa. Original phenotypes are exposed to environmental perturbations brought on by lifestyle and co-morbidities, and are simultaneously modelled by a web of downstream consequences related to the primary defect, in a vortex of autoamplifying loops. Preventing left ventricular hypertrophy in channelopathies or treating secondary ion channel dysfunction in cardiomyopathies may be as important as treating the more obvious, pathognomonic phenotypes of each disease. This lesson should help promote cross-fertilization between different fields of expertise in genetic heart disease, develop more comprehensive and radical therapeutic approaches, and ultimately advance our understanding of universal health problems ranging from heart failure to hypertension. An exciting, but challenging perspective that may require some time: as Newton warns us, 'to explain all nature is too difficult a task for any one man or even for any one age.' 'Tis much better to do a little with certainty & leave the rest for others that come after you.'

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