CLINICAL PERSPECTIVES

Physiological *versus* pathological cardiac electrical remodelling: potential basis and relevance to clinical management

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Cardiac hypertrophy is an adaptive response to haemodynamic stress. Pressure and/or volume overload in hypertension, myocardial infarction (MI) and valvular heart disease are pathological stresses that lead to left-ventricular (LV) dilatation and/or wall thickening. While in the short term compensatory mechanisms maintain cardiac output, sustained hypertrophic responses can lead to maladaptive remodelling, predisposing to cardiac arrhythmias and heart failure.

Physical exercise and pregnancy are examples of physiological stress. The nature of the exercise determines the balance between dilatation and increased wall thickness, producing so-called physiological hypertrophy. Although similar degrees of LV hypertrophy are achieved in pathological and physiological hypertrophy, physiological hypertrophy generally fails to produce adverse consequences like ventricular arrhythmias (Viitasalo *et al.* 1982; Biffi *et al.* 2008).

So, what makes the consequences of physiological remodelling different from those of pathological remodelling?

Mechanisms of stress-related cardiac remodelling

Stress alters cardiac gene expression, remodelling the structural, functional and electrophysiological properties of the heart (Nattel *et al.* 2010). Remodelling affects cardiomyocytes, interstitial matrix, fibroblasts and the coronary vasculature, but the molecular and cellular events underlying decompensation are poorly understood (Armoundas *et al.* 2001).

Heart failure is associated with upregulation of myocardial fetal and stretched-response genes (Butter *et al.* 2008), and numerous targets and regulators controlling hypertrophy, including phosphoinositol-3-kinase (PI3K), calcineurin, microRNAs and gene mutations are recognized (Rohini *et al.* 2010). Alterations in ion channels, connexins and ion transporters lead to arrhythmogenesis (Nattel *et al.* 2010; Roden & Kupershmidt, 1999). The characteristic changes in cells and tissues from failing hearts are action potential (AP) duration (APD) prolongation and conduction slowing (Aiba & Tomaselli, 2010). APD prolongation results principally from K^+ current downregulation and typically leads to arrhythmias by inducing afterdepolarizations (Nattel *et al.* 2007). Heart failure also profoundly dysregulates Ca^{2+}-handling genes and proteins, increasing Na^+/Ca^{2+} exchange, decreasing sarcoplasmic reticulum Ca^{2+}-ATPase and impairing Ca^{2+}-release channel (RyR2a) function (Nattel *et al.* 2007). The mechanisms underlying ion channel remodelling in physiological hypertrophy are much less well understood. Regional differences in K^+ current adaptation have been suggested (Stones *et al.* 2009).

In this issue of *The Journal of Physiology*, Yang *et al.* (2010) investigate the ionic remodelling caused by physiological hypertrophy in two mouse models. They show that mice subjected to a swimming programme develop significant ionic remodelling. With the hypertrophic process almost all currents increase substantially in amplitude, but because of parallel increases in cell size current density, the primary factor controlling transmembrane voltage (Nattel, 2008), is unaltered or moderately increased. Because relatively similar increases occur in repolarizing K^+ currents and depolarizing Ca^{2+} current, repolarization indices remain unchanged. Similar results occur in a transgenic model of physiological hypertrophy, constitutively-active PI3K-p110a overexpression.

Different cardiac PI3K isoforms have distinct roles (Damilano *et al.* 2010). PI3K mediates cardiac hypertrophy, both in physiological (through PI3Kα, e.g. in exercise training) and pathological (through PI3Kγ, e.g. in pressure overload) conditions. Physiological hypertrophy is mediated primarily by the insulin-like growth factor-1 pathway, coupled with PI3Kα, and is triggered by tyrosine-kinase receptors. PI3Kα protects from fetal gene re-expression. PI3Kα inhibits apoptotic cell death by activating Akt (Dhanasekaran *et al.* 2008), which also suppresses pathological signalling cascades (Owen *et al.* 2009). The results of Yang *et al.* nicely link the cardioprotective effect of PI3Kα to physiological ion current remodelling. In contrast, G protein-coupled receptor (GPCR) stimulation by angiotensin II, endothelin-1 and catecholamines activates PI3Kγ, leading to pathological hypertrophy (Owen *et al.* 2009).

Clinical relevance of understanding electrical remodelling in physiological hypertrophy

Sudden arrhythmic death is a major cause of mortality in patients with heart failure, and repolarization abnormalities are an important predictor (Galinier *et al.* 1998). The observations of Yang *et al.* agree with the lack of repolarization changes in healthy individuals subjected to light exercise (Rajappan *et al.* 2003). Correspondingly, ventricular arrhythmias are not related to LV hypertrophy in athletes (Biffi *et al.* 2008).

The benign properties of physiological ion channel remodelling raise the attractive possibility of counteracting pathological electrophysiological adaptation and decreasing arrhythmia risk in heart disease patients by means of exercise training. Lachance *et al.* (2009) demonstrated a lower sudden-death rate in rats with heart failure and LV hypertrophy who were submitted to treadmill training. In rats with previous MI, normalization of APD abnormalities by exercise training has been reported (Zhang *et al.* 2001), although this is not a uniform finding (Bito *et al.* 2010). Exercise training can favourably alter signalling pathways involved in adverse cardiac remodelling (Guasch *et al.* 2010), and repolarization abnormalities in heart failure patients are improved by aerobic exercise training (Ali *et al.* 1999).

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Knowledge of the pathways involved in physiological *versus* pathological remodelling may help in designing innovative therapeutic paradigms. Activation of the PI3Kα system, demonstrated by Yang *et al.* to be central to the balanced electrical remodelling seen with physiological hypertrophy, could be an interesting strategy for preventing the pathological electrical remodelling that leads to sudden death in heart disease patients. Possible approaches could run from the simplest physiological methods (e.g. exercise training) to small-molecule activators or even gene-therapy techniques. Further comparisons between signalling pathways in pathological *versus* physiological remodelling may provide indications of additional promising molecular targets for sudden-death prevention.

Yang *et al.* carefully studied remodelling of ionic currents and APs by exercise training. However, arrhythmogenesis is determined not only by cardiomyocyte cellular electrophysiology, but also by additional factors such as cardiac structure (Burstein & Nattel, 2008; Saffitz *et al.* 2010) and autonomic tone (Chen *et al.* 2007). These factors may also be influenced by exercise training, and in some circumstances may not have totally benign consequences. Right-ventricular structural remodelling may contribute to an increased incidence of ventricular arrhythmias in trained endurance athletes (Benito *et al.* 2010). While protecting from ventricular arrhythmias in ischaemic myocardium (Tsutsumi *et al.* 2008), exercise-induced autonomic-tone changes may contribute to the well-recognized occurrence of atrial fibrillation in otherwise-healthy endurance athletes (Benito *et al.* 2009).

Finally, it may not be accurate to assume that all forms of 'physiological remodelling' are necessarily equivalent. The type and intensity of exercise training may be of critical importance for ion-channel remodelling. Swimming and treadmill training induce differential responses in rats, with swimming causing a greater resting bradycardia and increased cardiac-tissue adrenaline and noradrenaline concentrations compared to running (Geenen *et al.* 1988). Unlike the paradigm studied by Yang *et al.*, high-intensity exercise training can produce QT-interval prolongation reflecting ventricular repolarization delays (Sharma *et al.* 1999).

In conclusion, the elegant study by Yang *et al.* provides important and clinically relevant information about the electrophysiological changes and cell-signalling events induced by physiological remodelling. At the same time their work raises thought-provoking questions that will need to be addressed in future research.

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