

# Ion current alterations in myocardial hypertrophy

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Myocardial hypertrophy has long been associated with an increased risk for sudden cardiac death<sup>1</sup>. Cardiac rhythm disturbances are considered an important mechanism contributing to the high mortality and sudden death in patients with left ventricular hypertrophy. The increased risk of sudden cardiac death in patients with left ventricular hypertrophy and heart failure is the result of remodeling that occurs in both the myocyte and interstitial compartments of the heart. Two alterations have been consistently reported to occur at a cellular level<sup>2</sup>. First, a prolongation of action potential is observed<sup>3</sup>, due to a reduced expression of repolarizing potassium currents<sup>4</sup>. Second, the expression of the pacemaker current  $I_f$ , which may be a source of increased automaticity<sup>5</sup>. Animal models of cardiac hypertrophy may be helpful for the understanding of events occurring in the diseased human heart. In fact, similar electrical abnormalities characterize the diseased ventricle of hypertensive rats and patients undergoing cardiac transplantation<sup>2</sup>. In rat and human ventricular cardiomyocytes,  $I_f$  activation occurs at voltages near the physiological resting potential<sup>5,6</sup>, and might contribute to arrhythmogenesis, especially in the presence of an increased adrenergic activity. In fact,  $\beta$ -adrenergic stimulation is able to positively modulate  $I_f$ <sup>7,8</sup>. As in rats<sup>6,9,10</sup>, also in humans  $I_f$  density is related to cardiac disease, being significantly higher in cardiomyopathy than in controls<sup>11</sup>. Interestingly enough,  $I_f$  activation occurs at less negative potentials in diseased than in undiseased hearts, possibly because of a different balance of channel isoforms<sup>12</sup>.

$I_f$  overexpression likely represents an example of a general phenomenon, i.e. cell reentry into a fetal program<sup>13</sup>. Indeed,  $I_f$

density is higher in neonatal rat ventricular cardiomyocytes and progressively decreases during post-natal growth<sup>14</sup>. Switching on/off the gene(s) encoding for the  $I_f$  may depend on several neurochemical or physical factors (e.g., angiotensin II)<sup>15</sup>, acting during physiological growth or pathological hypertrophy. Understanding the role of these factors and their relationship may help to get deeper insight into the mechanisms promoting the electrophysiological remodeling of the hypertrophied myocardium, to assess the influence of genetics and environment on disease expression, and to promote the development of novel therapeutics.

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