Ion current alterations in myocardial hypertrophy

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Myocardial hypertrophy has long been associated with an increased risk for sudden cardiac death[1]. 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[2]. First, a prolongation of action potential is observed[3], due to a reduced expression of repolarizing potassium currents[4]. Second, the expression of the pacemaker current I_f, which may be a source of increased automaticity[5]. 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[2]. In rat and human ventricular cardiomyocytes, I_f activation occurs at voltages near the physiological resting potential[5,6], and might contribute to arrhythmogenesis, especially in the presence of an increased adrenergic activity. In fact, β-adrenergic stimulation is able to positively modulate I_f[7,8]. As in rats[6,9,10], also in humans I_f density is related to cardiac disease, being significantly higher in cardiomyopathy than in controls[11]. 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[12].

I_f overexpression likely represents an example of a general phenomenon, i.e. cell reentry into a fetal program[13]. Indeed, I_f density is higher in neonatal rat ventricular cardiomyocytes and progressively decreases during post-natal growth[14]. Switching on/off the gene(s) encoding for the I_f may depend on several neurochemical or physical factors (e.g., angiotensin II)[15], 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.

References

1. Messerli FH. Hypertension and sudden cardiac death. Am J Hypertens 1999; 12 (Part 3): 181S-188S.
2. Tomaselli G, Marban E. Electrophysiological remodeling in hypertrophy and heart failure. Cardiovasc Res 1999; 42: 270-83.
3. Beuckelmann DJ, Nabauer M, Erdmann E. Alterations of K^+ currents in isolated human ventricular myocytes from patients with terminal heart failure. Circ Res 1993; 73: 379-85.
4. Kaab S, Dixon J, Duc J, et al. Molecular basis of transient outward potassium current downregulation in human heart failure: a decrease in Kv4.3 mRNA correlates with a reduction in current density. Circulation 1998; 98: 1383-93.
5. Cerbai E, Pino R, Porciatti F, et al. Characterization of the hyperpolarization-activated current, I_f, in ventricular myocytes from human failing heart. Circulation 1997; 95: 568-71.
6. Cerbai E, Barbieri M, Mugelli A. Occurrence and properties of the hyperpolarization-activated current I_f in ventricular myocytes from normotensive and hypertensive rats during aging. Circulation 1996; 94: 1674-81.
7. Cerbai E, Pino R, Rodriguez ML, Mugelli A.

Modulation of the pacemaker current I_f by β-adrenoceptor subtypes in ventricular myocytes isolated from hypertensive and normotensive rats. Cardiovasc Res 1999; 42: 121-9.
8. Sartiani L, Cerbai E, De Paoli P, et al. β_1, β_2 and β_3 adrenoceptor subtypes differently modulate the pacemaker current in human ventricular myocytes. (abstr) Circulation 1999; 100 (Suppl): I-488.
9. Cerbai E, Barbieri M, Mugelli A. Characterization of the hyperpolarization-activated current, I_f, in ventricular myocytes isolated from hypertensive rats. J Physiol (Lond) 1994; 481: 585-91.
10. Cerbai E, Barbieri M, Porciatti F, Mugelli A. Ionic channels in hypertrophy and heart failure: relevance for arrhythmogenesis. New Trends in Arrhythmias 1995; 11: 135-9.
11. Cerbai E, Sartiani L, De Paoli P, et al. The properties of the pacemaker current I_f in human ventricular myocytes are modulated by cardiac disease. J Mol Cell Cardiol 2001; 33: 441-8.
12. Ludwig A, Zong X, Hofmann F, Biel M. Structure and function of cardiac pacemaker channels. Cell Physiol Biochem 1999; 9: 179-86.
13. Swynghedauw B. Molecular mechanisms of myocardial remodeling. Physiol Rev 1999; 79: 215-62.
14. Cerbai E, Pino R, Sartiani L, Mugelli A. Influence of postnatal-development on I_f occurrence and properties in neonatal rat ventricular myocytes. Cardiovasc Res 1999; 42: 416-23.
15. Cerbai E, Crucitti A, Sartiani L, et al. Long-term treatment of spontaneously hypertensive rats with losartan and electrophysiological remodeling of cardiac myocytes. Cardiovasc Res 2000; 45: 388-96.