Electrical Remodeling in Heart Failure

Cardiac resynchronization therapy (CRT) improves heart failure (HF) symptoms, ventricular performance, and myocardial efficiency. Gordon F. Tomaselli, MD, Johns Hopkins University, Baltimore, Maryland, USA, studied the effect of CRT on cardiac remodeling in HF using a canine model of HF with 3 to 4 weeks of 240 bpm right ventricular pacing and left-ventricular diastolic end pressure (LVEDP) of 30 to 45 mm Hg. Electrical changes included prolonged action potential duration, a hallmark of HF, and increased difference between the longest and shortest action potentials at slower rates.

Dogs with left bundle ablation (QRS >120 ms) were paced at 200 bpm for 3 weeks. One group continued at the same rate as a model of dyssynchronous HF (DHF). Another group underwent biventricular pacing at 200 bpm as a model of resynchronized HF (CRT). Left ventricular ejection fraction was significantly decreased in both groups but modestly more in DHF dogs. Other changes included reduced apoptosis and regional heterogeneity of stress protein expression in CRT animals. In decompensated HF (DHF) dogs, action potentials were prolonged, particularly in the lateral wall. CRT shortened these, decreasing the regional heterogeneity of action potential duration over a range of pacing cyclings, suggesting an antiarrhythmic effect.

Potassium currents downregulated in HF are improved by CRT except for transient outward potassium current. An abnormality of the depolarizing sodium current in DHF was partially corrected by CRT. Reduced depolarizing currents and increased repolarizing currents both constitute shortening of action potential duration in CRT with homogenization of repolarization. In DHF, calcium currents in lateral wall cells were dramatically reduced. CRT increased the peak calcium current in lateral but not anterior cells, resulting in increased calcium flux in lateral myocytes. In DHF, the lateral wall calcium transient was profoundly downregulated but almost completely restored by CRT. CRT has dramatic molecular and cellular effects on heart function, particularly in the lateral wall of dyssynchronously contracting failing ventricles. Early afterdepolarizations were common in DHF and reduced by CRT.

Beta-adrenergic signaling is completely deranged in HF. CRT restores isoproterenol responsiveness of contraction and augmentation of the calcium transient, largely improving beta-adrenergic signaling.

Genes in the oxidative phosphorylation pathway are downregulated in HF. Transcriptional profiling of 44,000 genes in the canine model showed that heterogeneity of gene expression between the anterior and lateral walls of the LV is dramatically downregulated in CRT versus DHF. There are profound changes in mitochondrial gene and protein expression as well as function in DHF. CRT corrects changes in gene and protein expression prominently in the electron transport chain and other energy producing pathways.

Remodeling of active membrane properties, network properties, and metabolism increase the risk of sudden cardiac death in HF patients. HF is associated with genetically driven remodeling of structure and function. Dr. Tomaselli concluded that CRT has the capacity to partially reverse cellular structural, electrical, and metabolic remodeling; such changes may improve both the contractile and electrical phenotypes in DHF.

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