**TARGETING CaMKII IN HEART FAILURE**

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There is growing body of evidence suggesting that CaMKII is an important sensor for the altered Ca2+handling in heart failure (HF). Excessive CaMKII activation causes dysfunction of excitation-contraction coupling by phosphorylating several important Ca2+ regulatory proteins in response to Ca2+ signals, including L-type Ca2+ channel (LTCC), ryanodine receptor, sarcoplasmic reticulum, Ca2+-ATPase (SERCA2a) and its regulatory protein phospholamban. Thus, CaMKII is proposed to be a therapeutic target for HF and HF-related ventricular arrhythmias. However, due to the ubiquitous distribution of CaMKII and lack of cardiac specific CaMKII inhibitor, the pharmacological CaMKII inhibition is actually not applicable. In addition, we have demonstrated that CaMKII knockout or in vivo injection with CaMKII inhibitor can significantly impair diastolic function in failing ventricle, although the contractility is improved. Thus, it is in need to explore an applicable approach for CaMKII inhibition which improves contractility without detrimental effect on relaxation. We have recently discovered an important mechanism that there is a dynamic molecular complex in ventricular myocytes composed of CaMKII and Ito channel protein Kv4.3. Kv4.3 binds to CaMKII at the CaM binding sites and prevents CaMKII from activation, whereas Kv4.3 dissociation from the complex releases the CaM binding sites and leads to a substantial CaMKII activation. This finding revealed that the CaMKII-Kv4.3 units are important intrinsic negative modulators for the delicate regulation of CaMKII activity in ventricular myocytes, implicating Kv4.3 down-regulation in excessive CaMKII activation in HF. Therefore, reestablishing Kv4.3 expression to inhibit the membrane-coupled CaMKII is likely an effective approach for HF treatment. Indeed, we found that reestablishing Kv4.3 expression in HF ventricle can reverse LTCC remodeling and improve systolic function, without deterioration of diastolic function, indicating Kv4.3 expression as an effective approach for HF treatment.