Beneficial effects of paricalcitol on cardiac dysfunction and deleterious remodeling after established heart failure

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Chronic heart failure (HF) is a major health concern in aging societies. It is commonly accompanied by progression to maladaptive hypertrophy with cardiac dilation and diminished left ventricular (LV) ejection fraction (EF). Adverse cardiac remodeling is an important determinant of HF clinical outcomes and is linked to disease progression and poor prognosis. Ventricular remodeling involves cardiomyocyte hypertrophy, pro-fibrotic responses and down-regulation of K⁺ currents, which lead to altered electrotonic coupling between cells and prolonged QT intervals, increasing the risk of ventricular arrhythmias and sudden cardiac death. Furthermore, depressed cardiac function in HF is commonly associated with impairment of intracellular Ca²⁺ homeostasis. Paricalcitol (PC) is a synthetic vitamin D3 analog that acts as a selective activator of vitamin D receptor (VDR). There is clear evidence demonstrating cardioprotective properties associated with the VDR pathway. However, less information is available on the structural and functional cardiac effects of PC on established HF, and especially regarding its effects on electrophysiological or Ca²⁺-handling remodeling associated with HF. In the present study, we used a murine model of HF induced by pressure overload (transverse aortic constriction; TAC). Mice were divided into two experimental groups: sham and TAC-operated. Cardiac magnetic resonance image (CMRI) was performed 4 weeks after surgery and only TAC-operated animals with EF <60% were included in the study. Treatment with 300 ng/kg PC or vehicle was initiated 4 weeks after surgery over 5 consecutive weeks and CMRI was repeated 9 weeks after surgery. Animals were sacrificed and hearts were used for biochemical and histological studies. In some cases, hearts were retrograde perfused to isolate ventricular myocytes for electrophysiological and intracellular calcium imaging studies. CMRI analysis showed that LV end-diastolic and end-systolic volumes were increased 4 weeks after TAC relative to sham animals, indicating dilation of the LV, which was significantly greater 9 weeks after surgery. PC treatment for 5 weeks prevented the progression of both parameters and similar results were observed for EF. The progressive decline in EF from 4 to 9 weeks after TAC was prevented by PC treatment. This beneficial effect on cardiac dysfunction was related to prevention of intracellular Ca²⁺-mishandling remodeling by improving the amplitude of the intracellular calcium transients and preventing their slower time decay. Histological examination of hearts and the heart ratio weight/tibia length confirmed the presence of cardiac LV hypertrophy in the TAC group. Treatment with PC had antihypertrophic effects by attenuating calcineurin/NFAT signaling. Additionally, PC had antifibrotic effects linked to prevention of the expression of the profibrotic genes Serpine-1, Colla1 and Col3a1. Electrocardiographic recordings on mice 9 weeks after TAC showed long QT intervals when compared with sham groups, and this was mitigated by PC treatment. Finally, electrophysiological study of K⁺ currents (IK⁺) showed that the IK⁺ density was reduced in TAC mice with established HF after 9 weeks, and PC treatment prevented this reduction. Overall, these data suggest that PC treatment in established HF attenuates disease progression by preventing adverse cardiac remodeling at the cellular and molecular level.

Keywords: Chronic heart failure, cardiac hypertrophy, QT interval, paricalcitol, vitamin D receptor, Calcineurin/NFAT pathway, myocardial fibrosis, cardiac cellular electrophysiology, ventricular cardiomyocytes, K⁺ currents.

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