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Increased nitrosative/oxidative stress lowers myocardial protein kinase G activity in heart failure with preserved ejection fraction

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Background

Prominent features of myocardial remodeling in heart failure with preserved ejection fraction (HFPEF) are high cardiomyocyte resting tension ($F_{passive}$) [1-4] and cardiomyocyte hypertrophy [2]. In experimental models, both reacted favorably to raised protein kinase G (PKG) activity [4,5]. The present study assessed myocardial PKG activity, its downstream effects on cardiomyocyte $F_{passive}$ and cardiomyocyte diameter, and its upstream control by cyclic guanosine monophosphate (cGMP), nitrosative/oxidative stress, and brain natriuretic peptide (BNP). To discern altered control of myocardial remodeling by PKG, HFPEF was compared with aortic stenosis and HF with reduced EF (HFREF).

Results

Patients with HFPEF (n=36), AS (n=67), and HFREF (n=43) were free of coronary artery disease. More HFPEF patients were obese (P<0.05) or had diabetes mellitus (P<0.05). Left ventricular myocardial biopsies were procured transvascularly in HFPEF and HFREF and perioperatively in aortic stenosis. $F_{passive}$ was measured in cardiomyocytes before and after PKG administration. Myocardial homogenates were used for assessment of PKG activity, cGMP concentration, proBNP-108 expression, and nitrotyrosine expression, a measure of nitrosative/oxidative stress. Additional quantitative immunohistochemical analysis was performed for PKG activity and nitrotyrosine expression. Cardiomyocyte $F_{passive}$ was higher in HFPEF (7.6±0.4 kN/m^2) than in AS (3.4±0.2 kN/m^2; P<0.001) and in HFREF (5.1±0.2 kN/m^2; P<0.001). In-vitro administration of PKG acutely lowered cardiomyocyte stiffness in all groups with the largest decrement in $F_{passive}$ in DHF patients. PKG activity in myocardial tissue homogenates was significantly lower in HFPEF (5.11±0.62 pmol/min/mg) than in both AS (9.18±0.64 pmol/min/mg; P<0.01) and HFREF (11.51±2.0 pmol/min/mg; P<0.001). Immunohistochemical determination of myocardial PKG activity by pVASP/VASP ratio provided confirmatory evidence as it was also significantly lower in HFPEF (0.70±0.03) than in both AS (0.84±0.02; P<0.001) and HFREF (0.85±0.03; P<0.001). Lower PKG activity in HFPEF than in aortic stenosis or HFREF was associated with higher cardiomyocyte $F_{passive}$ (P<0.001) and related to lower cGMP concentration (P<0.001) and higher nitrosative/ oxidative stress (P<0.05). Reduced PKG activity and lower myocardial cGMP concentration in HFPEF did not result from altered myocardial sGC or PDE5A expression, which was similar in all groups nor from unequal BNP expression, which was comparable in HFPEF and AS. The downregulated cGMP-PKG signaling in HFPEF was therefore related to low myocardial nitric oxide bioavailability because of high nitrosative/oxidative stress.

Conclusion

Low myocardial PKG activity in HFPEF was associated with raised cardiomyocyte $F_{passive}$ and was related to increased myocardial nitrosative/oxidative stress. The latter was probably induced by the high prevalence in HFPEF of metabolic comorbidities. Correction of myocardial PKG activity could be a target for specific HFPEF treatment.

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