A phosphodiesterase inhibitor promotes the premature development of adverse cardiac remodelling mediated by beta-adrenergic activation in hypertension

To the Editor: Cardiac dilatation is thought to contribute to pump dysfunction in heart failure. In hypertension, left ventricular hypertrophy (LVH) can progress from a concentric geometry to left ventricular (LV) dilatation. The mechanisms responsible for the transition from concentric LVH to cardiac dilatation in hypertension are uncertain. In human studies LVH is associated with an increased sympathetic activity to the myocardium, but not to other tissue beds.[1] Our group has therefore proposed that sympathetic over-activation in LVH could mediate the transition from concentric LVH to cardiac dilatation. Indeed, we have demonstrated that in spontaneously hypertensive rats (SHRs) with concentric LVH, daily administration of low doses of a beta-adrenoreceptor (β-AR) agonist promotes the development of marked cardiac dilatation.[2] However, β-AR-induced effects can be mediated by cyclic adenosine monophosphate (cAMP)-dependent and independent pathways.[3] To explore the role of β-AR-cAMP pathways in mediating the transition from concentric LVH to LV dilatation, we evaluated the effect of a phosphodiesterase inhibitor (PDEI), used either alone or with a β-AR agonist, on LV geometry and function in SHRs with concentric LVH.

Methods

Fourteen-month-old SHRs and Wistar Kyoto (WKY) control rats were used for this study. SHRs either received no therapy, a β-AR agonist (isoproterenol, daily as previously described[2]), a PDEI (pentoxifylline, 50 mg/kg/day in the drinking water), or both the β-AR agonist and the PDEI for 3 months. To ensure that the β-AR agonist was effective, additional SHRs were either left untreated or received the β-AR agonist for 5.5 months.

LV cavity size was assessed using three techniques. First, two-dimensional directed M-mode echocardiography was performed using a Sonos model 2500 Hewlett Packard echocardiograph with a 7.5 MHz transducer.[4] Second, LV end diastolic (LVED) dimensions were assessed using piezoelectric ultrasonic transducers placed across the short axis of the heart at controlled LVED pressures (LVEDP) in open-chest, ventilated rats.[2] Third, LV diastolic pressure-volume relations were constructed in isolated, perfused heart preparations and the volume intercept at a diastolic pressure of 0 mmHg (LV V_0) was determined.[2,4] To assess further the impact of the β-AR agonist and the PDEI on cardiac remodelling, myocardial collagen content was determined using hydroxyproline ((HPRO) determinations.[2,4]

Results

LV cavity dimensions were similar between WKY rats (data not shown) and untreated SHRs (Table I). Although the β-AR agonist was able to induce significant cardiac dilatation after 5.5 months of administration to SHRs (data not shown), 3 months of administration of the β-AR agonist to SHRs failed to induce LV dilatation (Table I). Further, although administration of the PDEI alone failed to modify LV parameters (data not shown), co-administration of the β-AR agonist and the PDEI to SHRs produced marked increases in LV cavity dimensions and myocardial collagen concentrations (Table I).

Table I. Effect of chronic administration of the phosphodiesterase inhibitor (PDEI), pentoxifylline, on left ventricular (LV) dimensions and myocardial collagen characteristics in spontaneously hypertensive rats (SHRs) (mean ± SEM)

	SHR groups		
Treatment	Placebo	β-AR agonist	β-AR agonist + PDEI
Sample size (*N*)	8	7	9
LVEDD (cm)	0.67 ± 0.02	0.65 ± 0.03	0.75 ± 0.03*
LVEDr† (cm)	0.25 ± 0.04	0.31 ± 0.04	0.37 ± 0.03*
LV V_0 (ml)	0.20 ± 0.01	0.22 ± 0.01	0.27 ± 0.01*
HPRO‡	5.6 ± 0.6	6.4 ± 0.9	8.5 ± 0.8*

*$p < 0.05$ versus placebo treated.
†At an LVED pressure of 2 mmHg.
‡In µg/mg dry LV.
β-AR = beta-adrenoreceptor; PDEI = phosphodiesterase inhibitor; LVEDD = left ventricular end diastolic diameter; LVEDr = left ventricular end diastolic radius; LV V_0 = volume intercept at a left ventricular diastolic pressure of 0 mmHg; HPRO = hydroxyproline.

Discussion

The main findings of this study are that a PDEI potentiates β-AR agonist-mediated LV dilatation in SHRs with concentric LVH. As PDEIs and β-AR agonists share a common cellular pathway, namely the β-AR-cAMP pathway, these data suggest that cAMP is an important mediator of the transition from concentric LVH to LV dilatation. The clinical implication of these findings is that pharmacological agents that increase the activity of this pathway could promote further dilatation in LVH in heart failure.

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1. Schlaich MP, Kaye DM, Lambert E, Sommerville M, Socratous F, Esler MD. Relations between cardiac sympathetic activity and hypertensive left ventricular hypertrophy. *Circulation* 2003; **108:** 560-565.
2. Badenhorst D, Veliotes D, Maseko M, *et al*. Beta-adrenergic activation initiates chamber dilatation in concentric hypertrophy. *Hypertension* 2003; **41:** 499-504.
3. Ma YC, Huang XY. Novel signaling pathway through the beta-adrenergic receptor. *Trends in Cardiovascular Medicine* 2002; **12:** 46-49.
4. Norton GR, Woodiwiss AJ, Gaasch WH, *et al*. Heart failure in pressure overload hypertrophy: the relative roles of ventricular remodeling and myocardial dysfunction. *J Am Coll Cardiol* 2002; **39:** 664-667.