Effects of aging in mouse heart expressing constitutively active α1B-adrenergic receptors

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Cardiac-directed overexpression of wild-type α1B-adrenergic receptor (AR) (26-43 fold) results in dilated cardiomyopathy and premature death at 9 months (mo) of age and suppression of α1-AR signalling. To investigate whether this heart failure phenotype is due to chronic activation of the α1B-ARs, transgenic mice[1] expressing constitutively active α1B-AR by 2-fold in the heart (TG) and their non-transgenic (NTG) littermates were non-invasively studied in anaesthetised mice (7.5 ketamine, 1.5 xylazine and 0.09mg atropine/100g) at 6, 9, 12 and 15 mo of age using M-mode and Doppler echocardiography. Fractional shortening (FS) was significantly increased in TG versus NTG mice (Table). Notably, the ratio of left ventricular (LV) early and atrial filling flow velocities (E/A) was reduced and the deceleration time (DT) of the E-wave was prolonged in TG mice. This LV diastolic dysfunction was evident at 6 mo of age and persisted at the advanced ages. LV mass, estimated via echocardiography and normalised for body mass (LVM/BM), was not significantly different between TG and NTG mice, a finding that was verified at autopsy. Catheterisation experiments performed in anaesthetised mice (10 ketamine, 2 xylazine and 0.12mg atropine/100g) at 15 mo revealed unchanged LV contractility at baseline and blunted responses to α-agonist stimulation for heart rate and –dP/dt in TGs. In summary, unlike cardiac overexpression of wild-type α1B-ARs, expression of constitutively active α1B-AR does not impart detrimental effects leading to premature death.

Group	E/A ratio	DT (ms)	FS (%)	LVM/BM (mg/g)
NTG 6mo	2.11 ± 0.11	32 ± 1	35 ± 1	3.3 ± 0.1
15mo	1.82 ± 0.11	30 ± 1	34 ± 1	3.0 ± 0.1
TG 6mo	1.31 ± 0.06*	48 ± 2*	44 ± 2*	3.6 ± 0.1
15mo	1.37 ± 0.06*	39 ± 1*	38 ± 1*	3.3 ± 0.1

* $p<0.05$ versus age-matched NTG group

(1) Milano et al: PNAS 1994;91:10109-13