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Inhibition of calcineurin-signalling attenuates RV adaptation to pressure load in mice

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Introduction: Right ventricular (RV) failure is an important determinant of outcome in congenital heart disease and pulmonary hypertension. RV adaptation to pressure load is characterized by calcineurin-activation and pathological hypertrophy. We tested the effects of genetic blockade of calcineurin on RV adaptation to pressure load in mice.

Methods: Mice with cardiac-specific inducible upregulation of Modulatory Calcineurin-Interacting Protein (carMCIPtg), the inhibitor of calcineurin-activation, were injected with tamoxifen to induce the upregulation. Next, they were subjected to pulmonary artery banding (PAB) via a left lateral thoracotomy or sham-operated (Sham) and to cardiac MRI 4 weeks after surgery. Results were compared with the response of wild type mice (WT) to PAB.

Results: In carMCIPtg, activation of calcineurin in response to pressure load (PAB) was successfully blocked as shown by the lack of endogenous MCIP1 upregulation (all data in Table). Also, beta-MHC upregulation in response to PAB was blocked, but not alpha-MHC downregulation. CarMCIPtg had reduced RV hypertrophy in response to PAB as shown by lesser RV weight/body weight ratio. Moreover, RV dilatation in response to the pressure load, seen in the WT mice, was attenuated. However, the sham-operated α -MHC-MCIP mice also had RV dilatation, suggesting that calcineurin-signalling is required for normal RV homeostasis.

Conclusions: These results show that blocking calcineurin in the pressure loaded RV attenuates RV hypertrophy and dilatation, but induces RV dilatation in the unstressed RV. Hence, there is a delicate balance in calcineurin-signalling in the normal versus the pressure loaded RV. Intervention in this balance may be selectively beneficial in stressed RV's.

Table	carMCIPtg		Wild Type	
	Sham	PAB	Sham	PAB
Gene Expression (relative to reference gene)				
Endogenous MCIP1	1.0±0.3	0.9±0.3†	1.0±0.1	4.6±1.3*
Beta-MHC	1.0±0.3	1.3±0.6†	1.0±0.1	14.1±4.1*
Alpha-MHC	1.0±0.3	0.4±0.1*	1.0±0.2	0.4±0.1*
RV hypertrophy (RV weight/ body weight mg/g)				
	0.8±0.1	1.2±0.1*,†	0.9±0.2	1.6±0.1*
MRI derived RV volumes				
End-diastolic (µl)	65±9	58±5†	30±5	39±6*
End-systolic (µl)	32±6	31±4†	10±2	15±3*
Ejection Fraction (%)	52±3	47±3†	69±4	62±6
Cardiac output (µl/min/g)	333±41	351±28	362±69	355±25

N=4-6 per group, *p<0.05 vs. Sham, †p<0.05 vs. WT

Figure: typical examples of cine MRI slices

