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ANTI-REMODELING EFFECTS OF MTOR INHIBITION IN ESTABLISHED SEVERE HEART FAILURE

ACC Poster Contributions
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Session Title: Myocardial Function/Heart Failure -- Clinical Pharmacologicial Treatment
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Background: Pressure overload (POL) promotes LV remodeling which may progress to heart failure (HF). HF is characterized by neurohumoral activation which promotes sodium retention and activates pathways which may modulate mTOR signaling. We hypothesized that effects of mTOR inhibition (rapamycin, RAPA) on autophagy and LV remodeling may be altered in POL associated with HF.

Methods: Reduced ejection fraction (EF) at 3 wks post transverse aortic constriction (TAC) correlates with severe remodeling and HF (increased lung weight). Thus, male C57BL/6 mice underwent TAC and 3 wks later TAC mice were designated compensated (COMP, EF≥65%) or HF (EF<65%) by echo. Each group was treated with RAPA or vehicle for 6 wks. Autophagy (increased microtubule-associated protein light chain 3-II (LC3-II), marker of autophagosome formation) was assessed.

Results: In untreated mice, COMP had normal lung weight and less severe remodeling than HF. Compared to non-TAC, untreated COMP and HF had no change in LC3-II. RAPA (trough level = 11±7 ng/ml) ameliorated LV remodeling in both groups. LC3-II was higher in RAPA treated HF mice.

Variable (mean±SD)	Non-TAC	COMP	COMP+ RAPA	HF	HF+RAPA	p-ANOVA
n	9	7	9	13	13	
EF at end study, %	83±4	69±8 *†	74±6*	31±9*	61±1*‡	<0.001
LV:body weight, mg/g	3.12±0.35	5.06±1.52*†	3.93±0.81‡	7.49±1.19*	5.02±0.83*‡	<0.001
Lung:body weight, mg/g	5.87±0.78	6.93±1.45†	6.41±1.20	14.47±5.10*	9.04±3.39*‡	<0.001
End Systolic LV Pressure, mmHg	103±17	146±25*	138±26*	123±13	151±28*‡	0.004
LC3-II, arbitrary units relative to non-TAC	1.00±0.11	1.05±0.20	0.99±0.36	1.02±0.14	1.46±0.36*‡	0.003

*p<0.05 vs non-TAC; † p< 0.05 untreated COMP vs HF; ‡ p<0.05 RAPA treated vs respective untreated group (HF or COMP)

Conclusion: mTOR inhibition reversed LV remodeling in severe established HF and COMP hypertrophy. Increased autophagy was associated with the ameliorative effects of mTOR inhibition in HF. Autophagy stimulators may provide benefit in HF.