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Neuregulin-1 (NRG1)-effects on systolic and diastolic function in experimental early childhood RV pressure overload

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Introduction:
Pressure load (PL) is the main cause of right ventricular failure (RVF). Functionally, RVF is characterized by progressive diastolic dysfunction. Neuregulin-1, a stimulator of cellular proliferation signaling, has been shown to improve survival in experimental models of PL-induced RVF. Whereas biomolecular data on the cardiac effects of NRG1 are accumulating, the functional effects on ventricular hemodynamics (under persisting pressure load) are unknown. We characterized the effects of NRG1 on systolic and diastolic RV function in an experimental model of early childhood (fixed) RV PL.

Methods:
Rat pups (aged 21 days, weighing 30-40 grams) were subjected to pulmonary artery banding (PAB, n=35) or sham surgery (n=18). NRG1 (n=19) or vehicle (VEH, n=16) was injected intraperitoneally from day 3 until day 14 post-surgery. Rats were evaluated daily for clinical symptoms of RVF (e.g. inactivity, cachexia, dyspnea, pleural effusion/ascites). 14 and 28 days post-surgery echocardiography and RV pressure-volume analysis were performed in subsets of the groups.

Results:
PAB induced severe PL (all data in table 1). Survival was 100% and merely at day 28 1 rat (in the VEH group) displayed signs of clinical RV failure. In this pre-failure situation we saw that NRG1 substantially improved cardiac output in the PL group on both time points, without increasing contractility (endsystolic elastance). In contrast, diastolic function showed a trend (p=0.09 at 14 days) to be improved in the NRG1 groups than in the VEH groups (lower enddiastolic elastance indicates less myocardial stiffness). Also, tau (the phase of active ventricular relaxation) was longer in NRG1 than in VEH at 14 days.

Conclusion:
In experimental early childhood RV pressure load, NRG1 improves cardiac output independent of contractility, while preserving diastolic function. This challenges the paradigm of contractility-afterload coupling.

Table 1; all data ± SEM	14 days		28 days	
*= p<0.05 vs VEH	VEH	NRG1	VEH	NRG1
RV systolic pressure (mmHg)	58±5	62±5	94±7	78±10
RV output index (mL/min/g)	0.50±0.05	0.72±0.08*	0.32±0.02	0.50±0.05*
End systolic elastance (mmHg/mL)	170±30	110±20	300±40	220±20
End diastolic elastance (mmHg/mL)	22±5	13±2	54±11	47±11
Tau indexed (ms/ms)	99±3	112±5*	108±8	105±4