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Acute Hypoxic Pulmonary Artery Responses in the WKY and BN Rodent Strains

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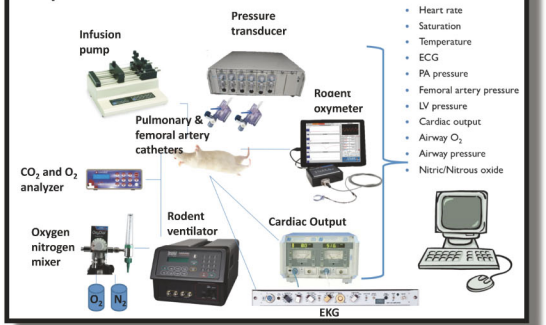
Background

- We previously showed that the acute hypoxic stimulus response could be determined in an intact sedated rodent model
- Aldashev et al. suggested that the acute hypoxic response could predict the development of pulmonary artery hypertension (1)
- Hypoxic stimulus response curve was compared for two rodent strains: Wistar Kyoto (WKY) and Brown Norway (BN) rats which differ significantly in their right ventricular hypertrophic response to chronic hypoxia (91% vs 84% increase in the right ventricular to left ventricular ratio respectively)
- We hypothesized that the BN would have a higher acute response predicting the higher chronic hypoxic response

Objectives

- Compare the hypoxic dose response curves in two rodent starins known to differ significantly in their right ventricular hypertrophic response to chronic hypoxia
- Determine whether the acute response could predict the chronic hypoxic effects in these two strains
- Identify potential genetic differences and design of future studies

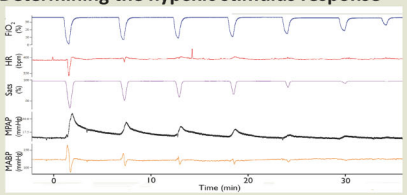
Setup



Methods

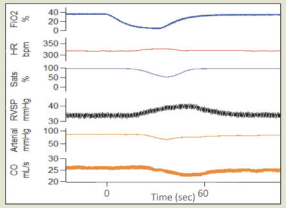
- Rodents were anesthetized and paralyzed to inhibit the hypoxic ventilatory response (urethane and vecuronium)
- Stimulus response curve was obtained in 8 BN rats and compared to our prior data in WKY rats

Determining the hypoxic stimulus response



- 30sec hypoxic challenges (40-0%)
- 5min rest between episodes
- Continuous hemodynamic monitoring
- PA response measured as % increase from baseline at each hypoxic challenge

Representative response to 8% FiO_2 for 30sec (WKY rat)

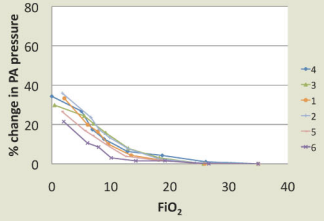


	Baseline	Response	% Change
HR bpm	313.0	315.8	*0.9%*
Sats %	97.2	53.4	
RVSP mmHg	34.0	41.1	*20.8%*
Arterial mmHg	91.0	74.3	*-18.4%*
CO mL/min	26.3	22.4	*-14.8%*
RVSP/CO	1.3	1.8	*+41%*

Results

WKY rats

	Baseline	Response to 2 weeks 12% FiO2	%
PAP	14.9±1.5		
FAP	94.8±4.6		
HR	387.9±20.2		
PVR	0.096±0.006	0.191±0.005	99%
RV/LV	0.267±0.018	0.51±0.033	91%

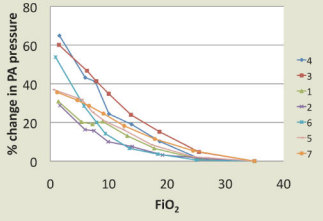


r^2=0.913

		Standard Error
Min	-0.8	1.4
Max	30.9	1.6
EC50	7.6	0.5
Hillslope	-2.6	0.5

BN rats

	Baseline	Response to 2 weeks 12% FiO2	%
PAP	15.3±1.4		
FAP	86.4±10.0		
HR	344.3±14		
PVR*	0.102±0.009	0.133±0.005	30%
RV/LV*	0.195±0.1	0.359±0.021	84%



r^2=0.756

		Standard Error
Min	-7.7	10.4
Max	45.5	4.5
EC50	10.9	2.9
Hillslope	-1.6	0.6

*Obtained from PhysGen (pga.mcw.edu)

Conclusion

- ***Contrary to the hypothesis generated from the existing literature, the BN rats are distinguished from the WKY rats by a trend toward a higher maximal response, with a relatively higher inflection point.***

Future Directions

- Effect of chronic hypoxia on the pulmonary artery acute dose response curve
- Effects of drugs on the dose response curve and the potential use of this response for pre-clinical testing

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References

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