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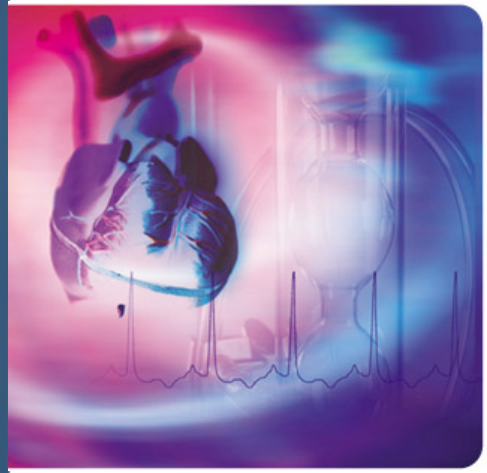
Longitudinal Analysis Supports Reproducibility of Treatment with Sildenafil in the Semaxanib/Hypoxia Rat Model of Pulmonary Arterial Hypertension



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American Heart Association 2022; P2624

DISCLOSURES

No relevant financial relationships exist for any authors.

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OBJECTIVE

The objective of this study was to assess the longitudinal stability and reproducibility of hypoxia/SU5416-induced pulmonary arterial hypertension (PAH) in male Sprague Dawley rats as well as to evaluate the response to sildenafil in this PAH rodent model.

INTRODUCTION

- PAH is characterized by a narrowing of the pulmonary arteries, leading to increased pulmonary vascular resistance, subsequent right heart hypertrophy and right ventricular failure[1].
- Rats develop PAH after exposure to the VEGF antagonist semaxanib (SU5416) concurrent with hypoxia exposure.
- In rodent models, PAH presents as an increase in pulmonary artery pressure (PAP), histological changes to the small pulmonary arterioles and right ventricular hypertrophy.
- Sildenafil, a phosphodiesterase-5 (PDE5) inhibitor, is approved for the treatment of PAH[2] and is commonly used as a positive control in assessing the effectiveness of test compounds in PAH studies.

([1]Maarman et al 2013, Colvin and Yeager 2014; [2] Parikh et al 2019)

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METHODS

- Data were pooled from 36 discrete rat PAH studies conducted from 2013-2021
- Male Sprague-Dawley rats were subcutaneously administered SU5416 (20 mg/kg or 200 mg/kg) on Day 1 and subsequently placed in a low oxygen environment (appx 13% O_2) for 28 days.
- Prevention studies (n = 18) were defined as studies that were terminated following 28 days of hypoxia, with dosing beginning within 1-2 days of study start.
- Intervention studies (n = 18) were defined as studies that may have added a protocol-defined normoxia period following the 28-days in hypoxia. Normoxia ranged from 0-28 days following hypoxia, with dosing beginning ≥ 7 days from study start.
- Sildenafil (60 mg/kg/day) was orally administered BID at protocol-specified timepoints.

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METHODS

- On the appropriate study day, rats were anesthetized via an IP injection of ketamine/xylazine and placed on a heating pad to maintain body temperature. Once consciousness was lost, both a Millar catheter and a fluid-filled catheter were placed to measure arterial blood pressure and pulmonary arterial pressure, respectively.
- Hemodynamic measurements were continuously monitored with ADI LabChart (Colorado Springs, CO) or Notocord HEM (Croissy sur Seine, France) data capture systems.
    - Post-equilibration average values were taken from a 10−15 second block of consecutive cardiac cycles uninterrupted by interference of ectopic beats during the fifteenth minute of the monitoring period for analysis.
    - Values from individual animals were pooled for analysis.
- Following hemodynamic data acquisition, animals were euthanized; hearts and lungs were harvested, rinsed with saline and weighed.

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RESULTS: LONGITUDINAL DATA for ANIMAL NUMBERS and SURVIVAL RATE

Animal Numbers and Survival Rates Based on Available sPAP Data								
	Prevention Studies				Intervention Studies			
	No. Animals		Survival Rate (%)		No. Animals		Survival Rate (%)	
Year	PVC	Sildenafil	PVC	Sildenafil	PVC	Sildenafil	PVC	Sildenafil
2013	20	10	96%	100%	16	16	90%	85%
2014	6	10	70%	100%	7	9	75%	83%
2016	30	22	97%	100%	16	30	90%	100%
2017	29	38	100%	100%	24	31	89%	97%
2018	43	36	100%	100%	12	11	100%	100%
2019	30	18	98%	90%	30	26	84%	100%
2020	32	31	93%	100%	29	29	97%	88%
2021	NA	NA	NA	NA	26	38	71%	97%
Mean	**NA**	**NA**	**96%**	**99%**	**NA**	**NA**	**87%**	**95%**
Sum Total	**190**	**165**	**NA**	**NA**	**160**	**190**	**NA**	**NA**

NA, not applicable; No, number; PVC, PAH vehicle control.

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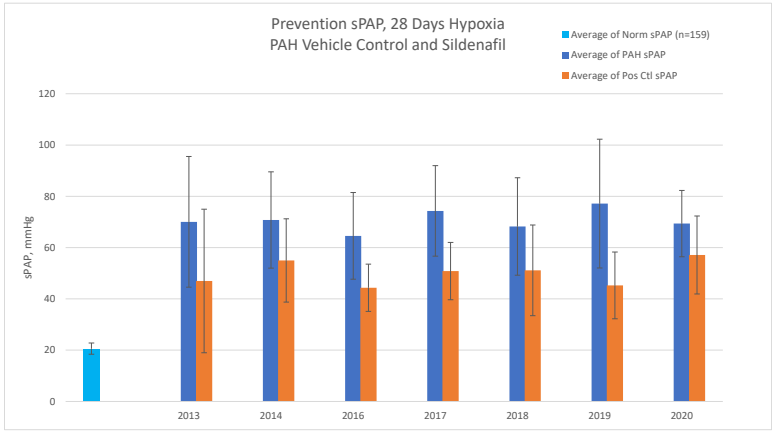
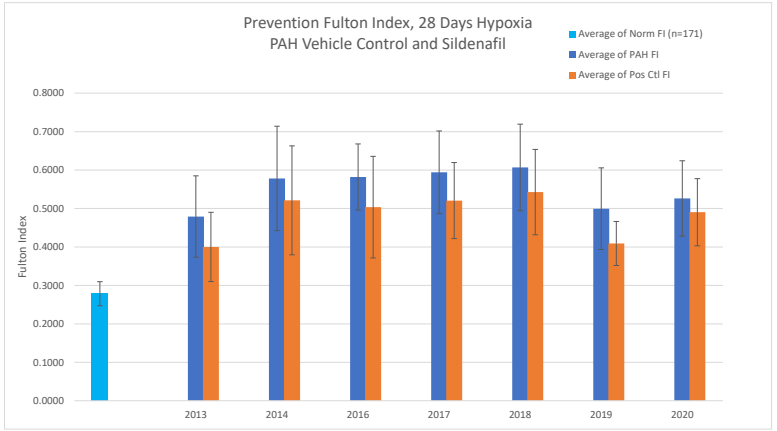
RESULTS: PREVENTION STUDIES





- In Prevention Studies, systolic pulmonary arterial pressure (sPAP) and Fulton Index (FI) increased in PAH vehicle control animals as compared to normoxia control animals while sildenafil reduced the magnitude of both sPAP and FI as compared to PAH vehicle control animals
- Effects were consistent over the 7- or 8-year period.

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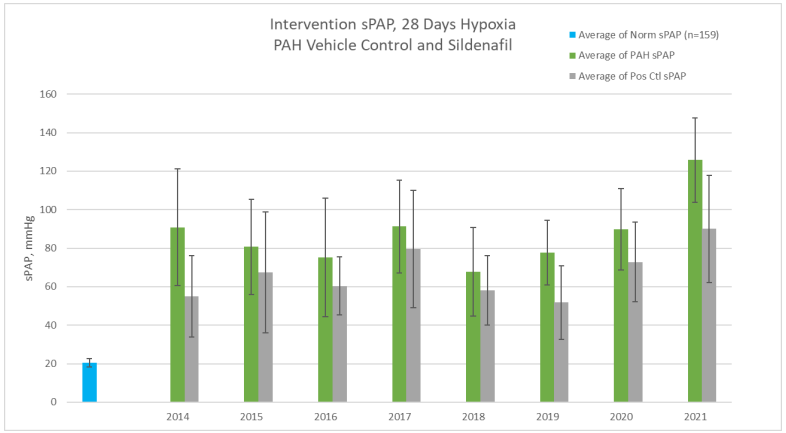
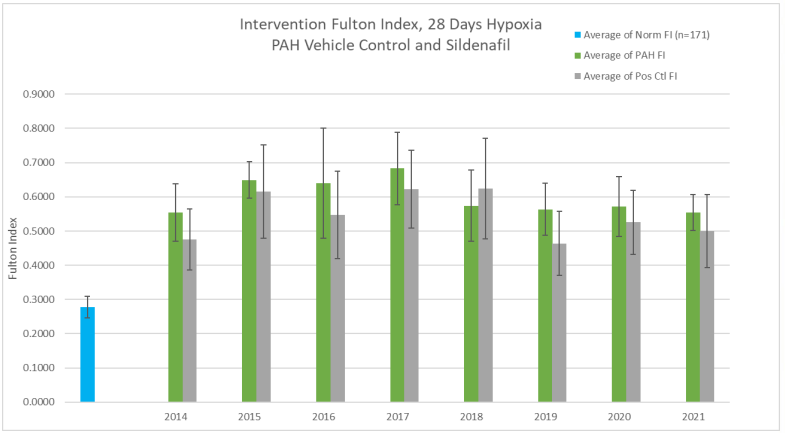
RESULTS: INTERVENTION STUDIES





- Similar to the Prevention Studies, sPAP and FI increased in PAH vehicle control animals as compared to normoxia control animals while sildenafil reduced the magnitude of both sPAP and FI as compared to PAH vehicle control animals
- Effects were consistent over the 7- or 8-year period.

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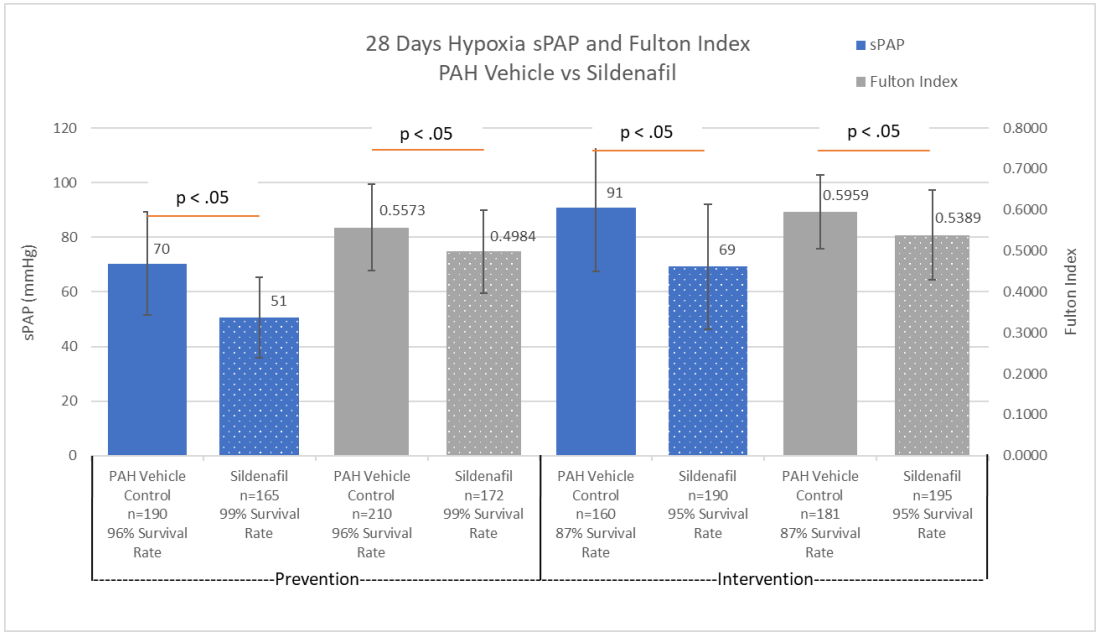
RESULTS: COMPARISON of DATA from PREVENTION and TREATMENT STUDIES



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CONCLUSION

- Mean survival rates were comparable among groups over the 8-year period.
- Sildenafil treatment elicited a statistically significant decrease in the development of pulmonary hypertension (sPAP) and right heart hypertrophy (FI) in both prevention and intervention studies.
- The effects of sildenafil on reduction of PAH were stable and of similar magnitude in both prevention and intervention studies over the analysis period.
- Overall, this longitudinal analysis indicates a reproducible and consistent effect of both the SU5416/Hypoxia PAH model and the use of sildenafil as a positive control.