

# I. Pathology of pulmonary arterial hypertension

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Rubin M. Tuder, M. D.

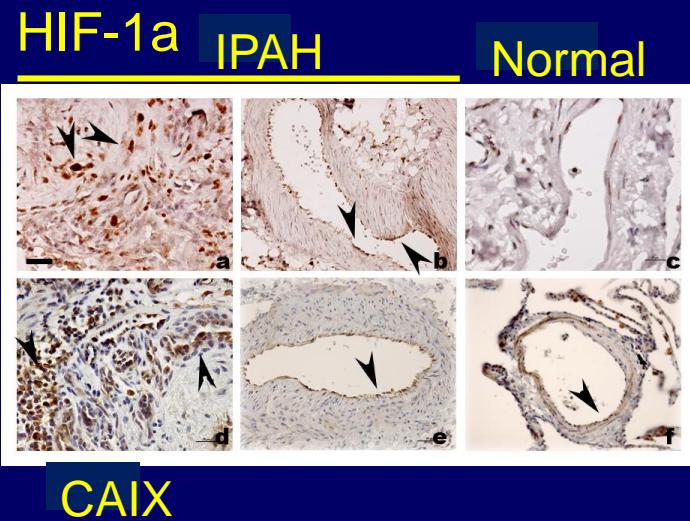
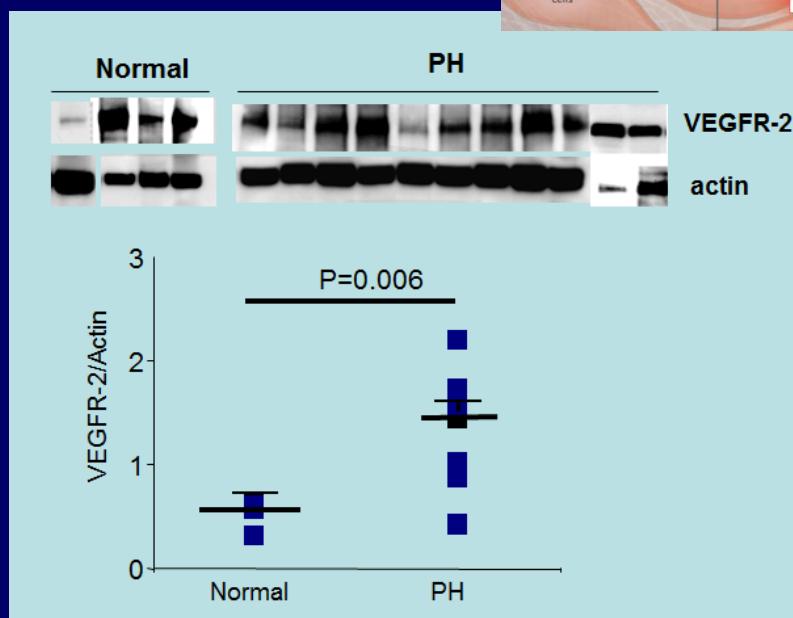
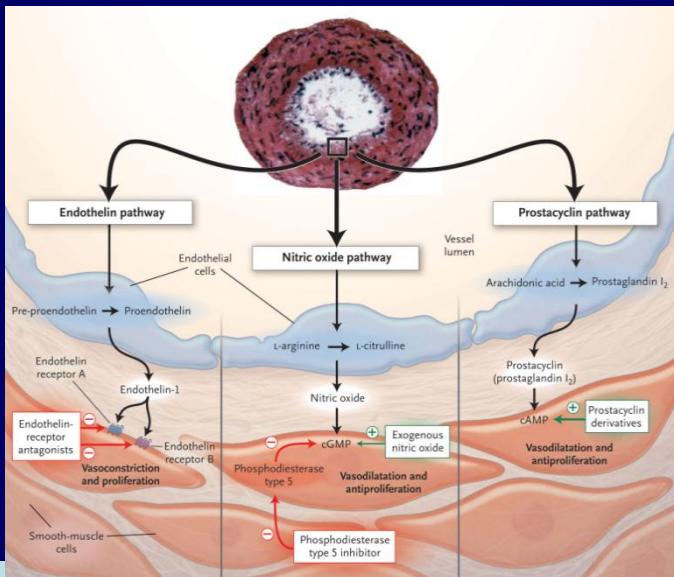
Program in Translational Lung Research

Division of Pulmonary Sciences and Critical Care  
Medicine, Department of Medicine

University of Colorado, School of Medicine

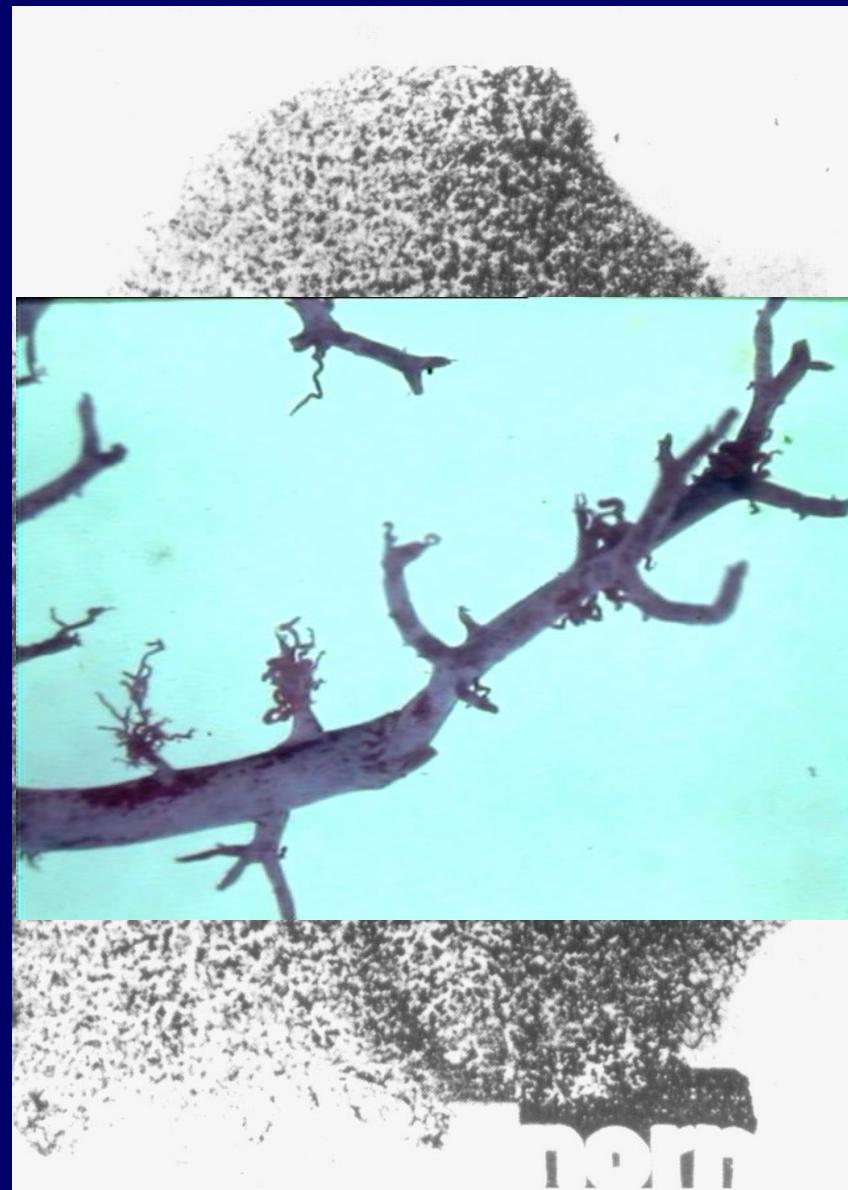
PVRI

# Pulmonary vascular pathology: importance



# Where do pulmonary vascular lesions occur?

- Number of pulmonary Arteries (17 orders)  
 $10^8$
- Elastic (orders 17-10):  
3,000
- Muscular (orders 9-5):  
800,000
- Precapillary (orders 4-1;  
25 um):  
70 million



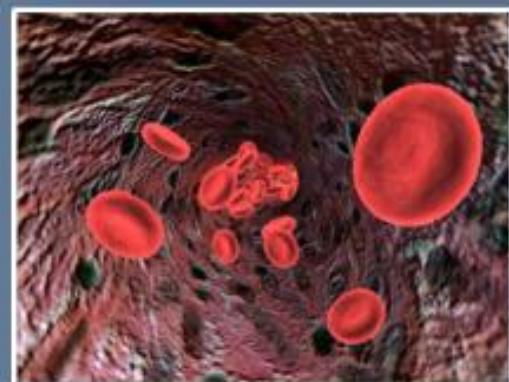
# Advancing our understanding of pulmonary vascular pathology: going back to basics

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<b>Publications- First Author and year</b>	Wagenvoort 1980	Bjornsson 1985	Pietra 1989
<b># of Centers / Countries</b>	- / 7	1 / 1	32 / 1
<b># of Patients and Demographics</b>	N = 63 - 8 wks - 63 yrs	N = 80 1:1.6 M:F 2 - 71 yrs	N = 58 1: 1.5 M:F -
<b>Referral Diagnosis</b>	CHD	PPH	PPH
<b>Diagnostic Criteria</b>	-	RHC (69)	RHC
<b>Clinical Parameters</b>	-	mPAP	-
<b>Medications</b>	-	-	-
<b>Tissue Source</b>	biopsy	autopsy, biopsy	autopsy, biopsy, pneumonectomy
<b>Controls</b>	-	-	-
<b>Sampling</b>	-	-	-
<b>Blocks/case</b>	-	1-13 (mean 5)	-
<b>Tissue Source</b>	biopsy	autopsy, biopsy	autopsy, biopsy, pneumonectomy
<b>Controls</b>	-	-	-
<b>Sampling</b>	-	-	-
<b>Blocks/case</b>	-	1-13 (mean 5)	-

# THE CARDIOVASCULAR MEDICAL RESEARCH AND EDUCATION FUND



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## The Cardiovascular Medical Research and Education Fund

### Announcements:

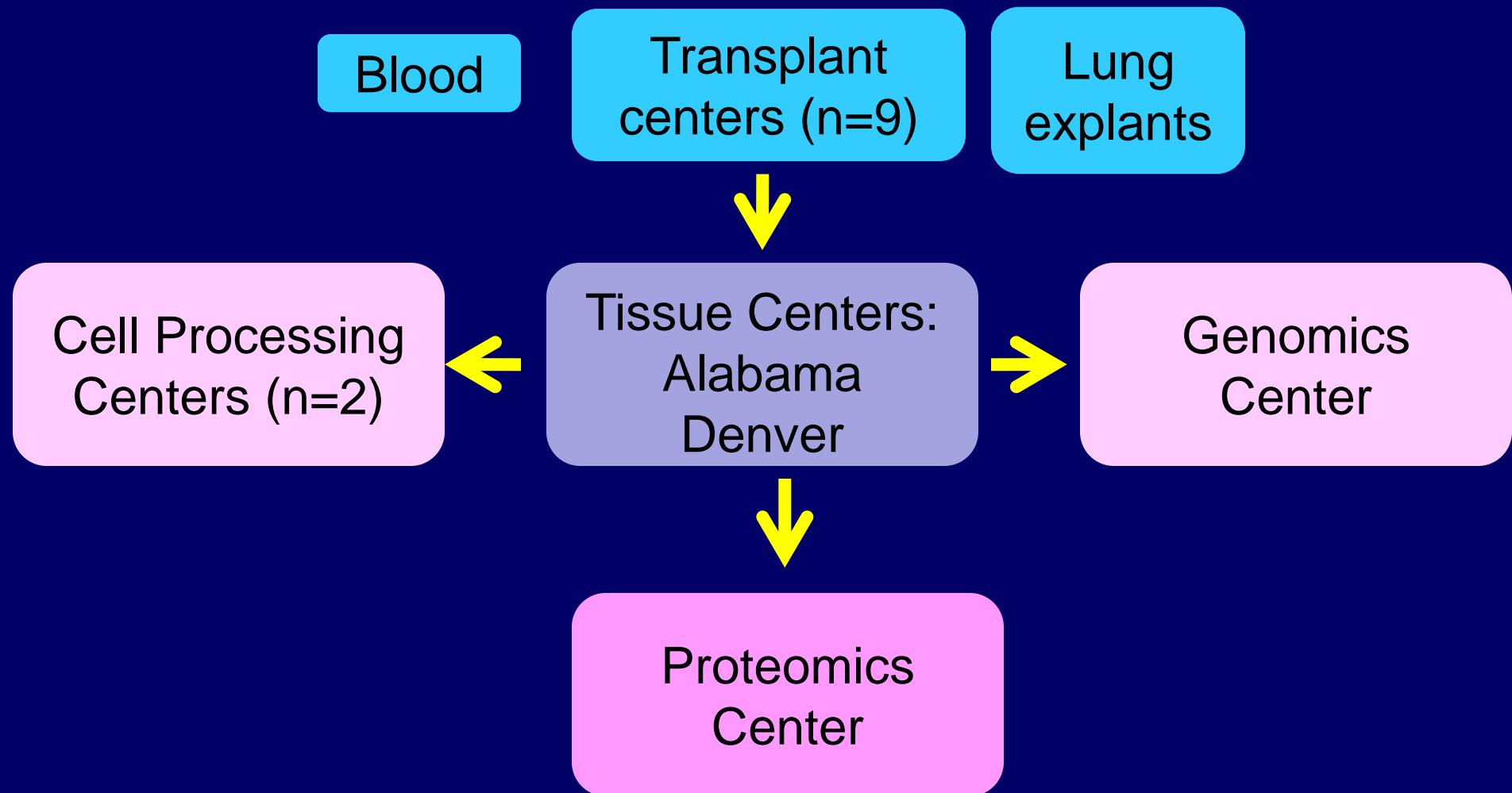
During 2010, in recognition of

### Focus on IPAH (PPH) Medical Research

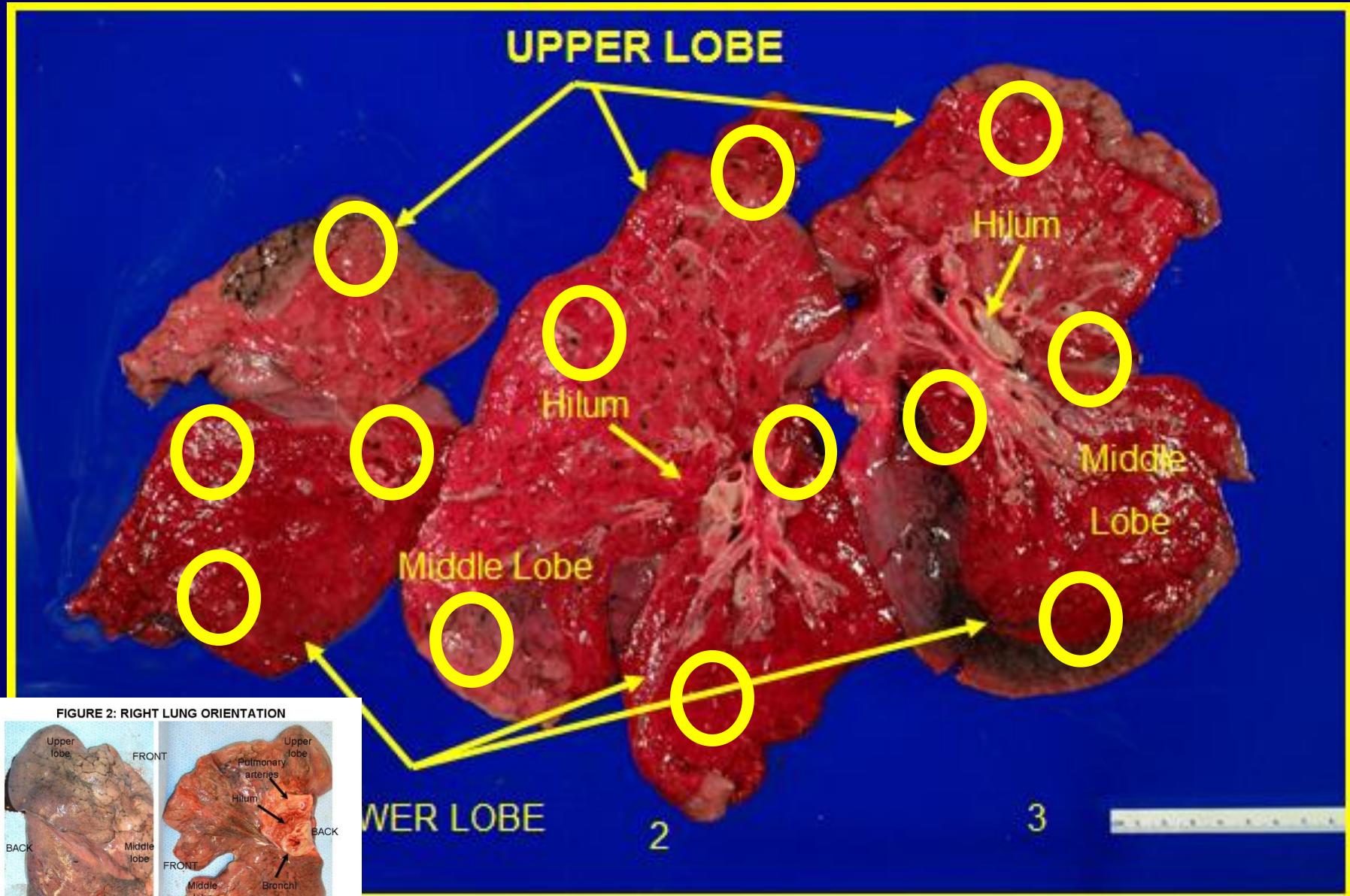
### News:

The CMREF has approved a grant for

# Pulmonary hypertension breakthrough initiative (PHBI): 2006



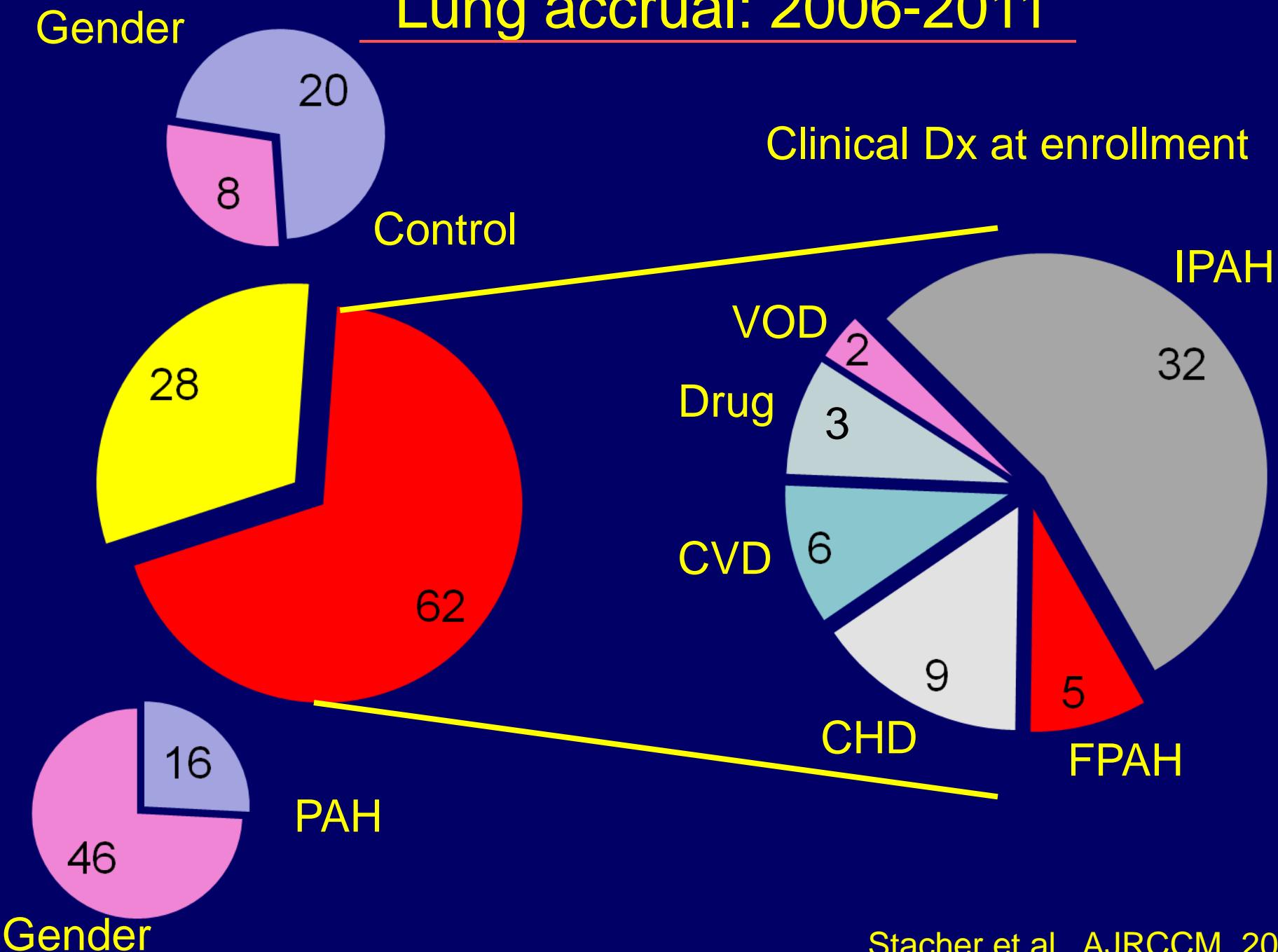
# Lung processing: sampling



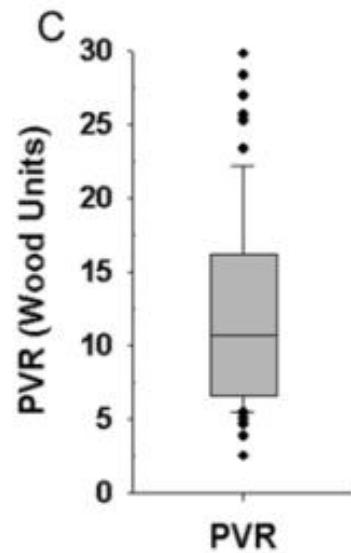
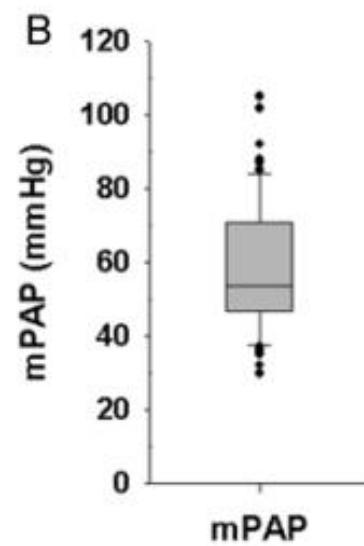
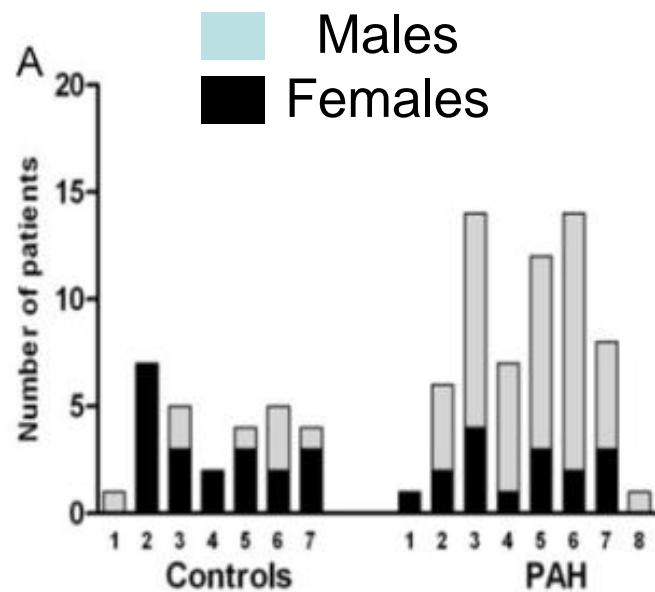
MACRO VIEW OF RIGHT LUNG SLICES

This is the same right lung with its lateral (left) and medial (right) views, obtained by turning the lung 180 degrees.

# Lung accrual: 2006-2011

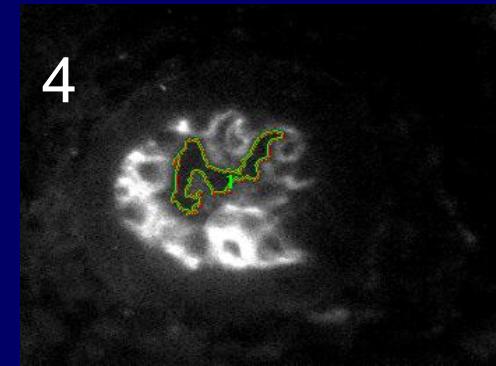
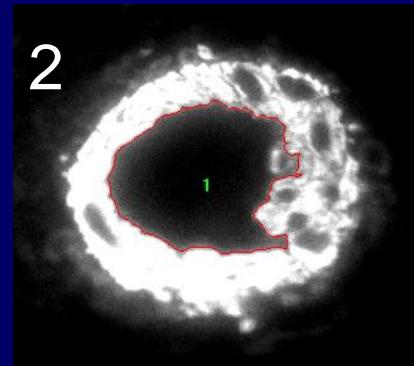
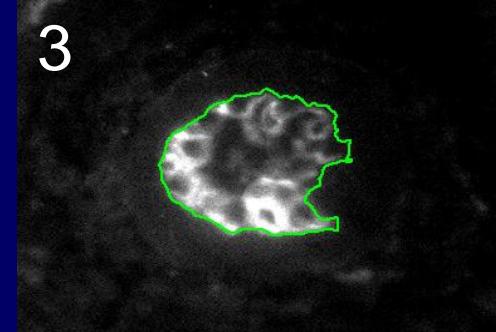
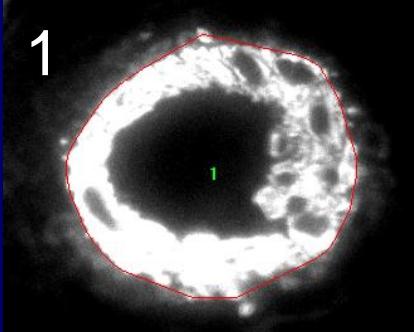
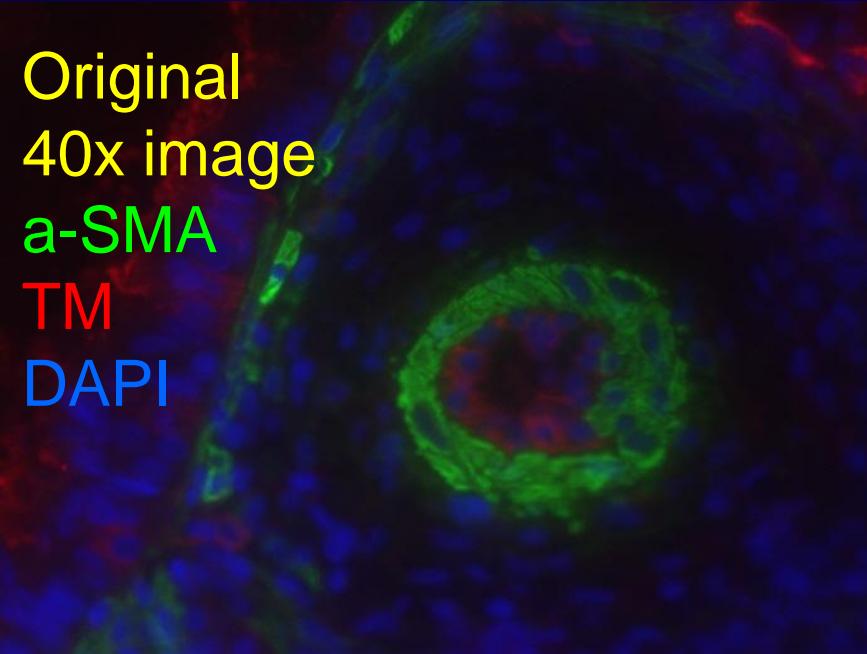


# Demographics and Hemodynamics

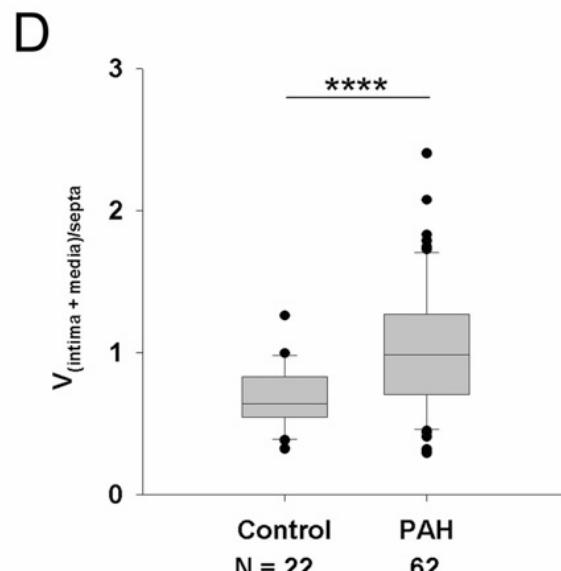
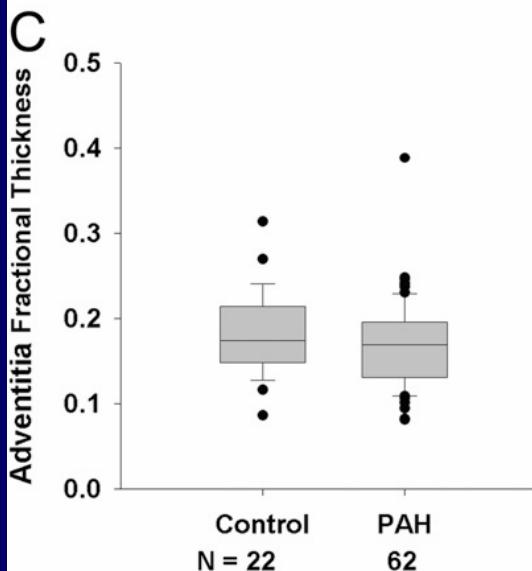
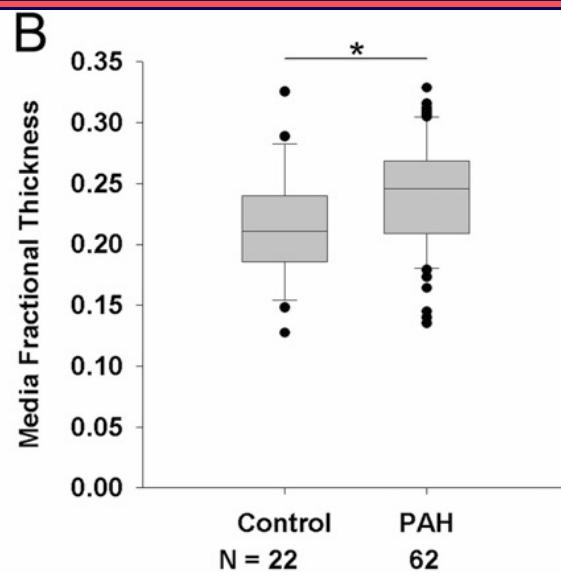
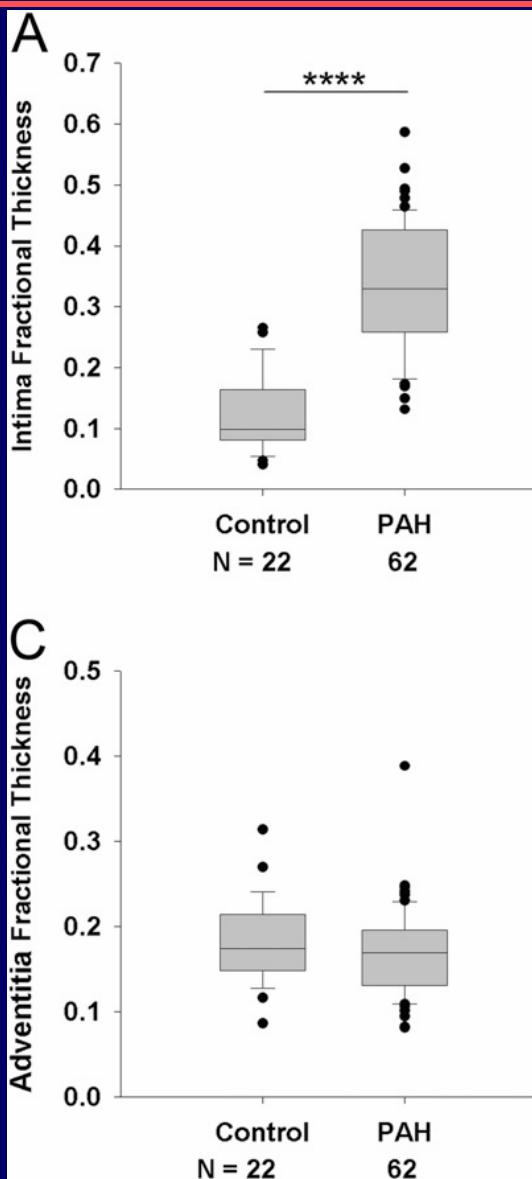
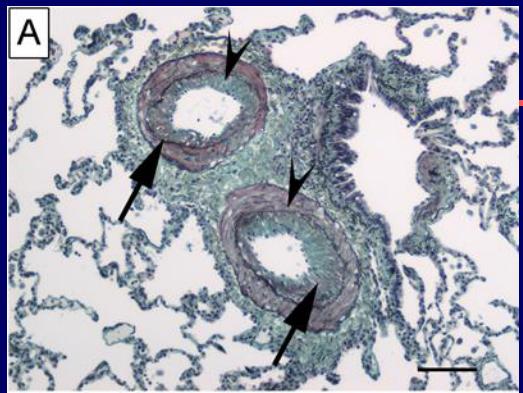


# Vascular Quantification Method

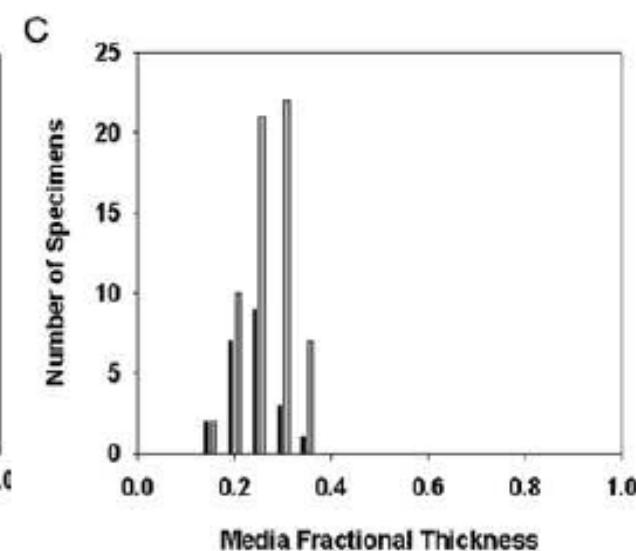
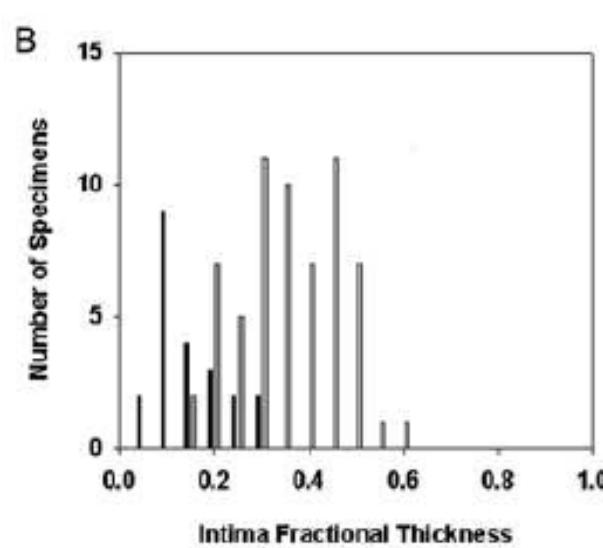
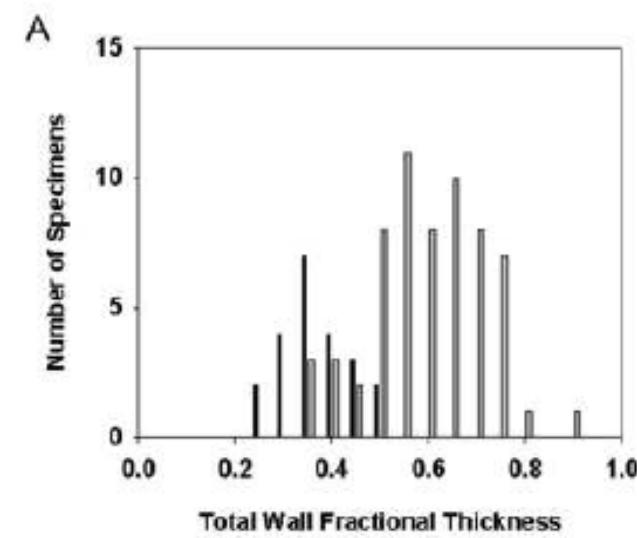
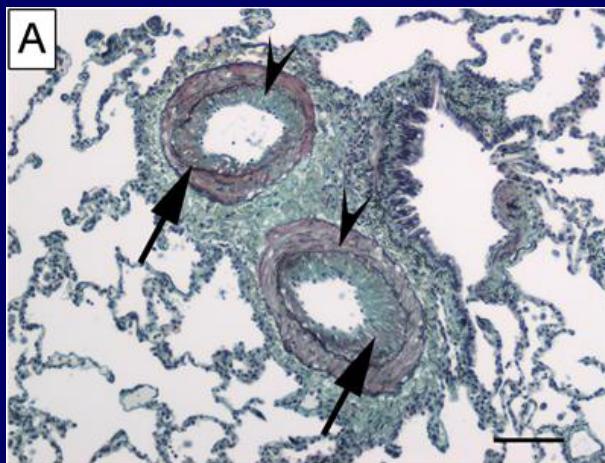
- Step 1: a-SMA external layer
- Step 2: a-SMA internal layer
- Step 3: TM internal layer
- $R = \sqrt{A/\pi}$



# Morphometric parameters: control vs. PAH



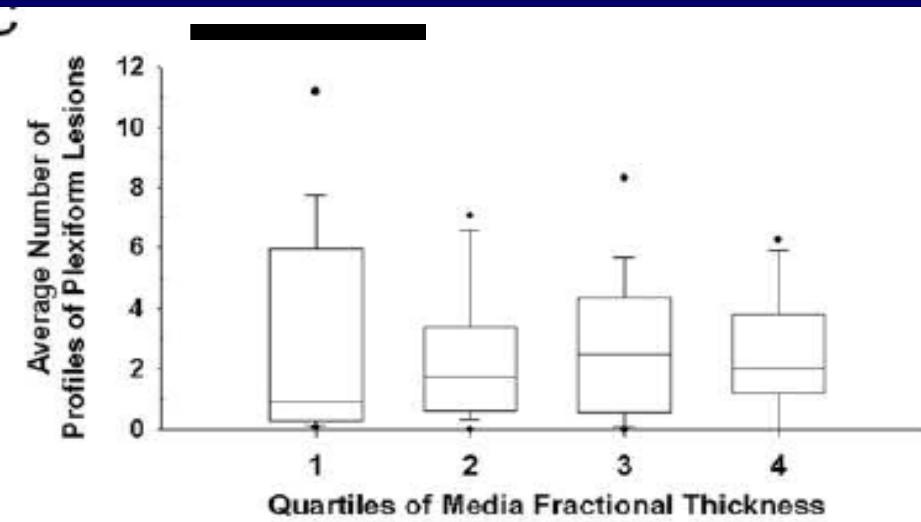
# Morphometric parameters: control vs. PAH



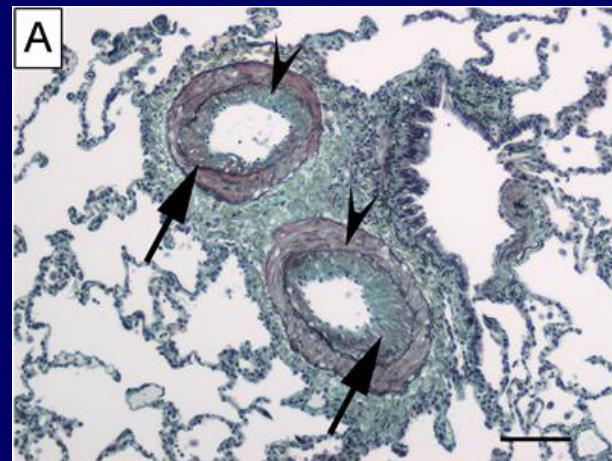
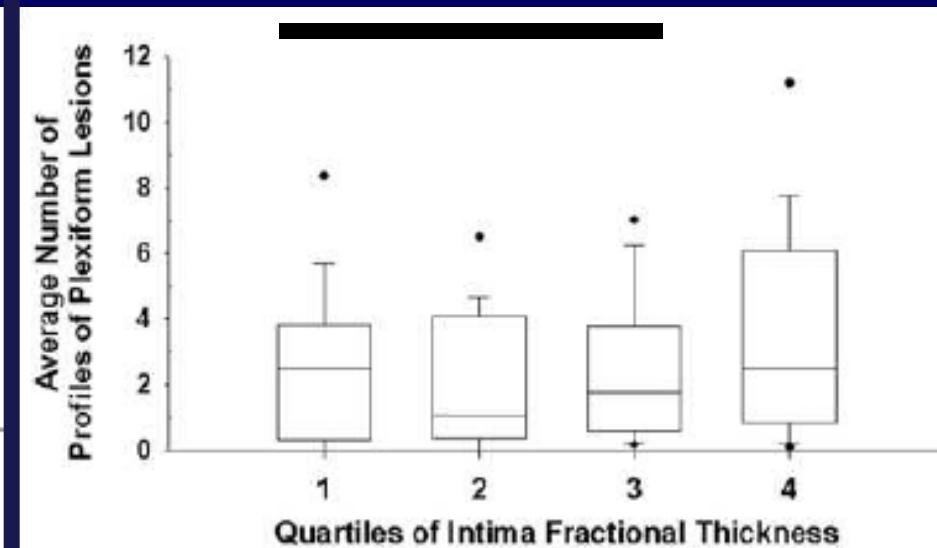
■ Control ■ PAH

# Morphometric parameters and pathological PAH subphenotypes: plx lesions

Controls

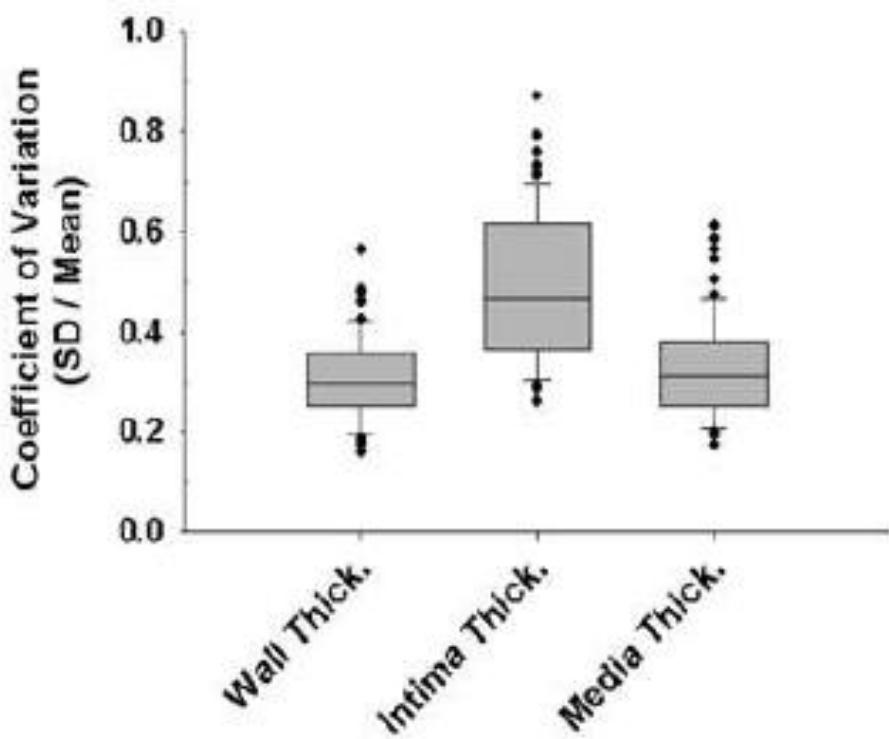


Controls

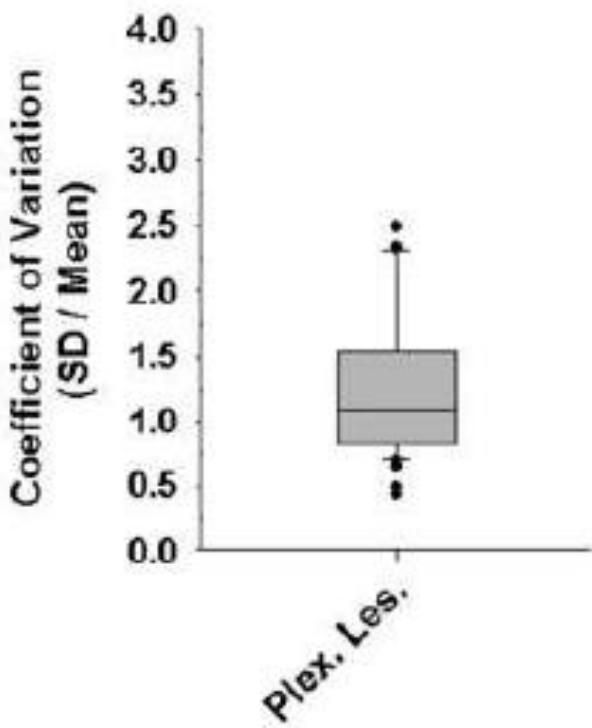


# Variability of pulmonary vascular lesions

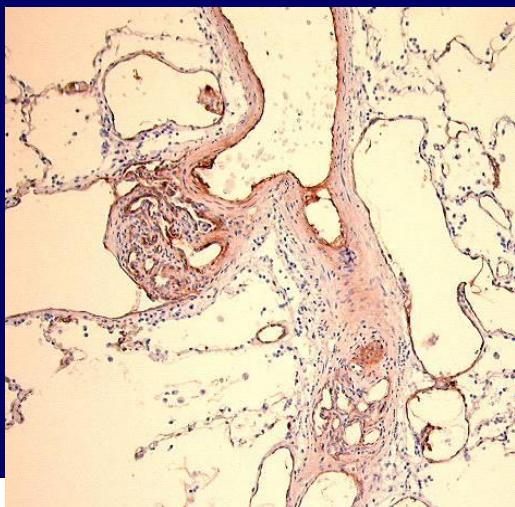
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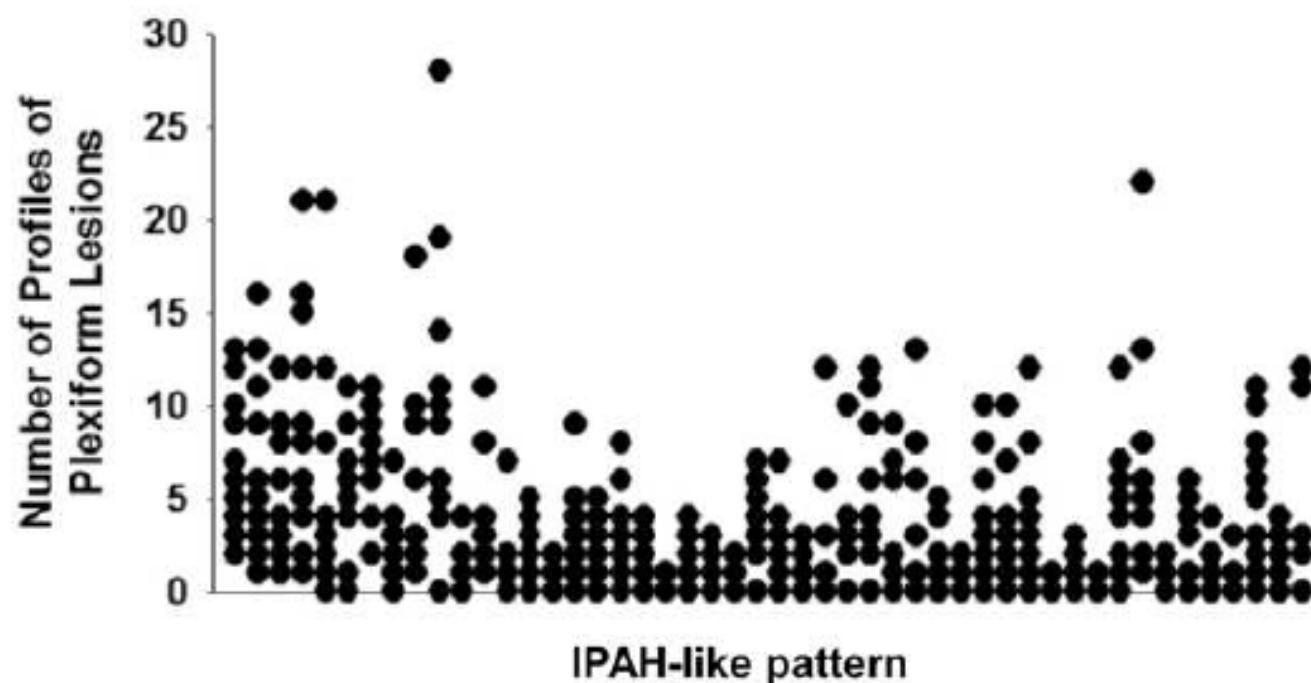
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# Plexiform lesions

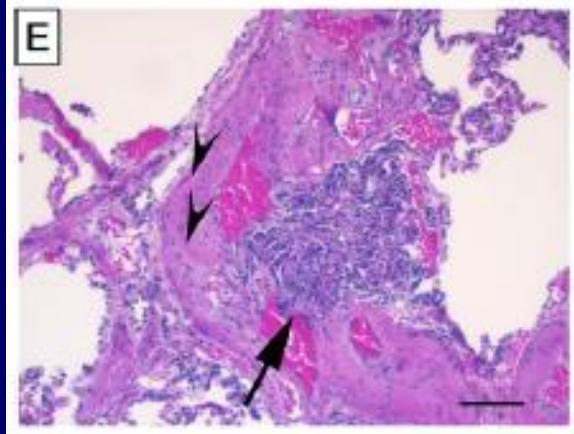
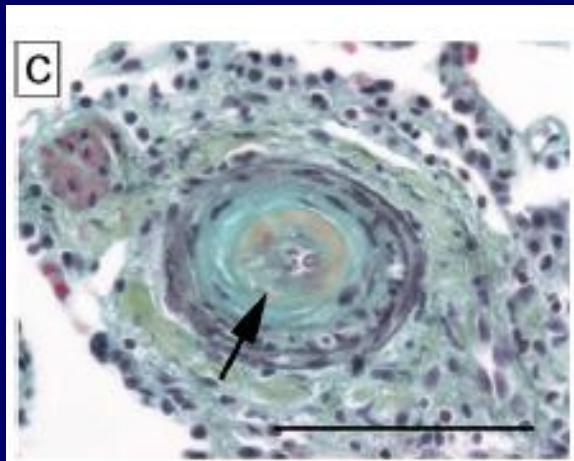


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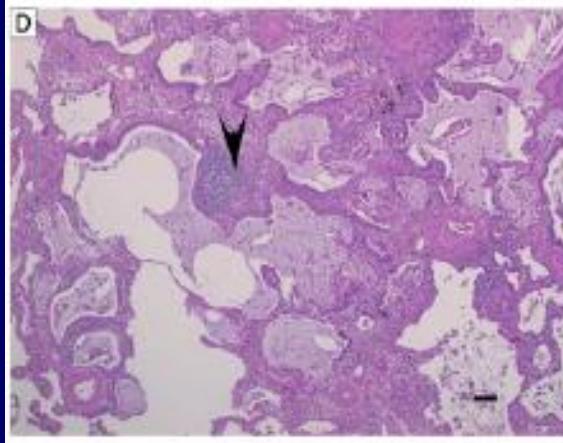
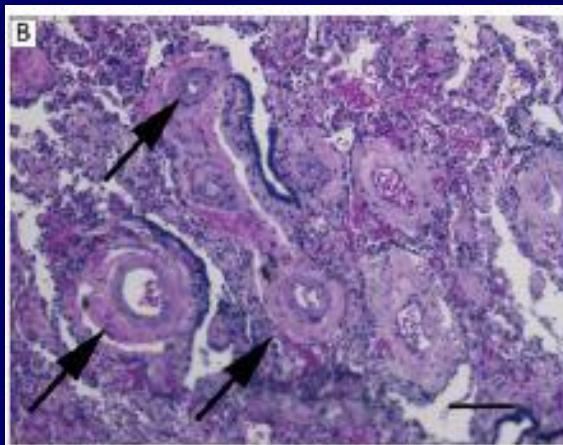
# Histopathological patterns

IPAH-



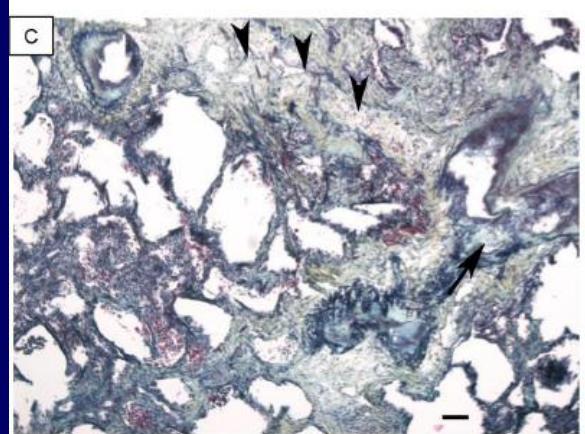
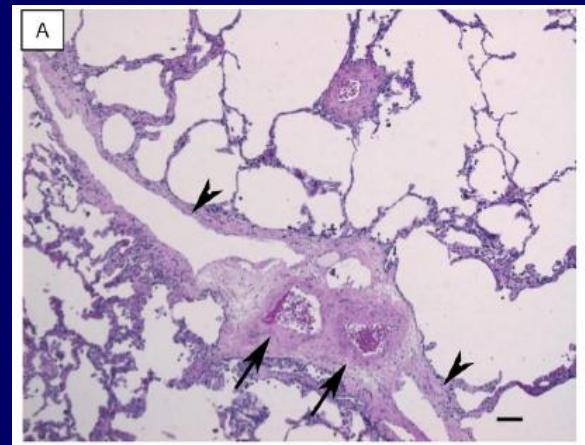
IPAH, FPAH, HIV  
Schisto, Liver Dx

APAH-

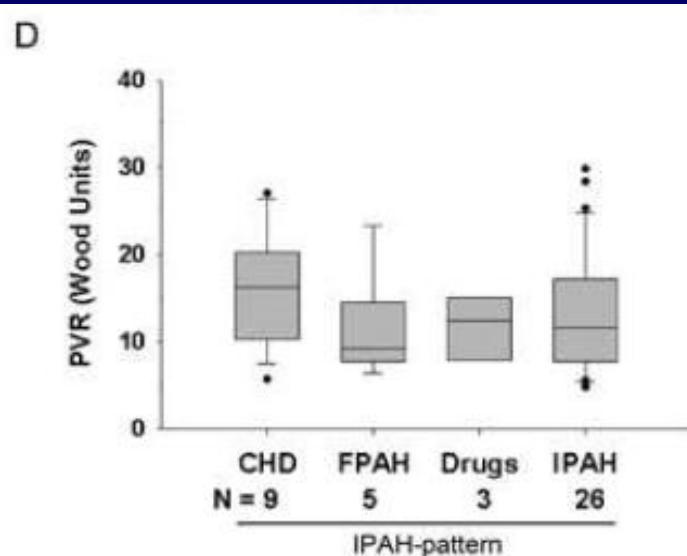
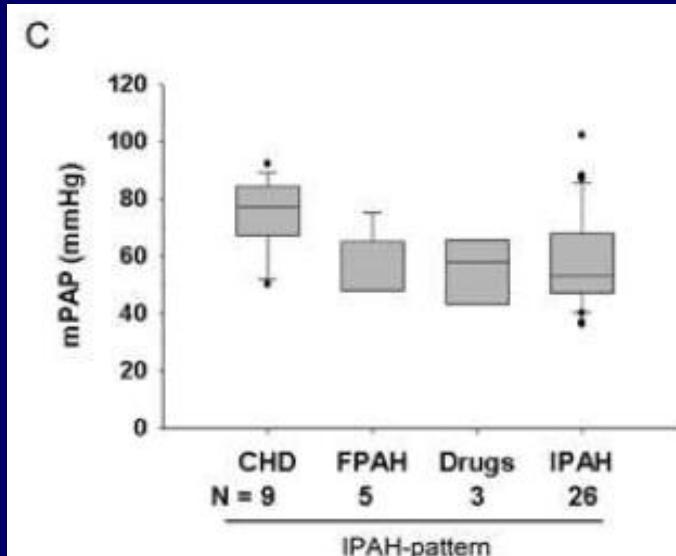
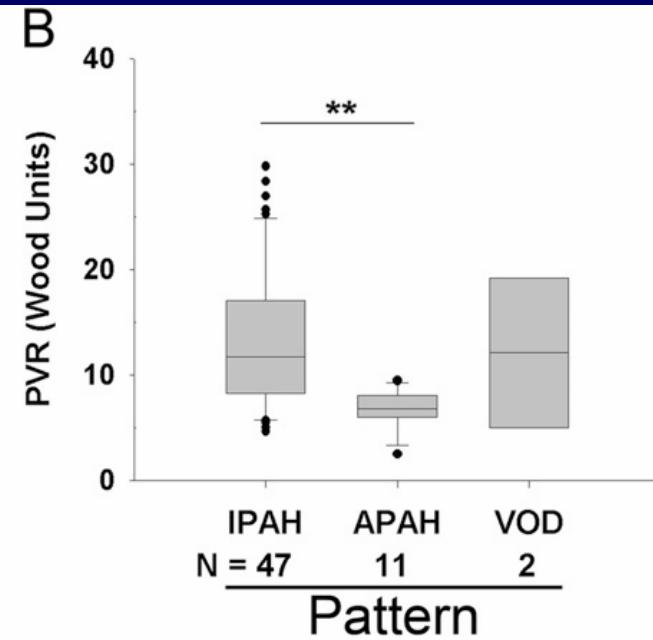
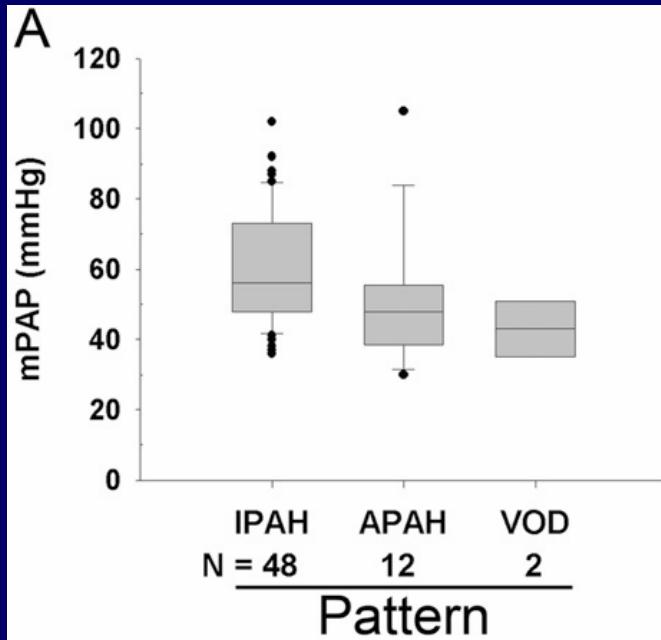


CVD: Scleroderma,  
Lupus.

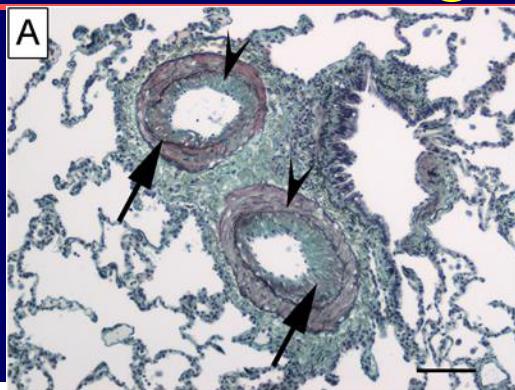
VOD-



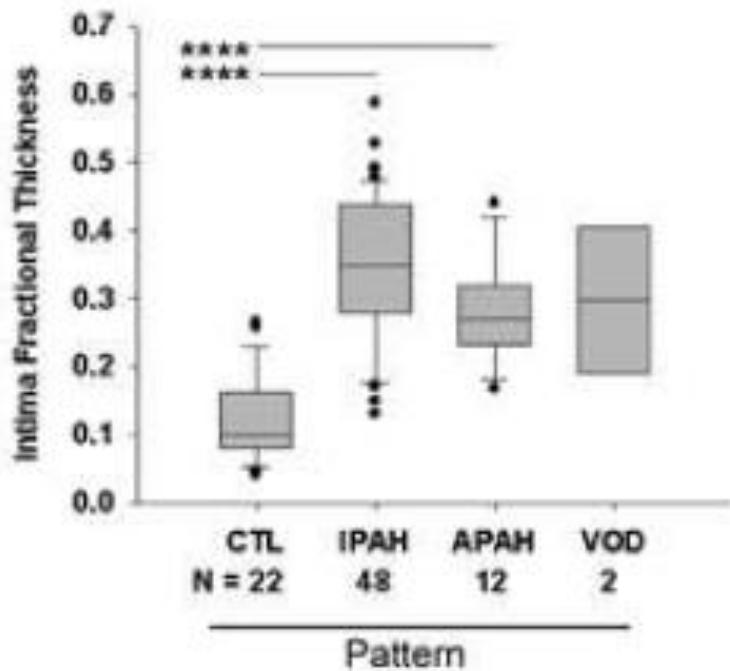
# PAH patterns and lung hemodynamics



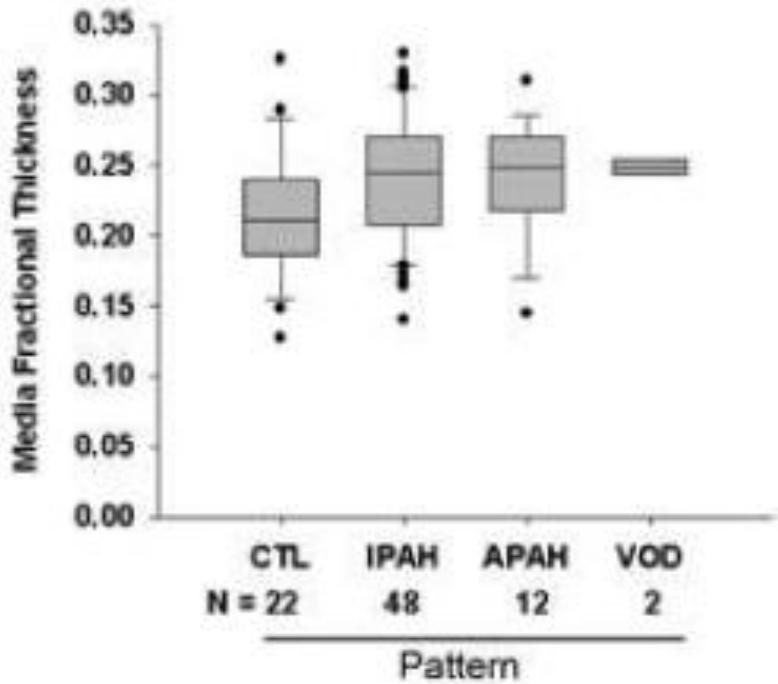
# Pathological patterns and pulmonary vascular remodeling



F

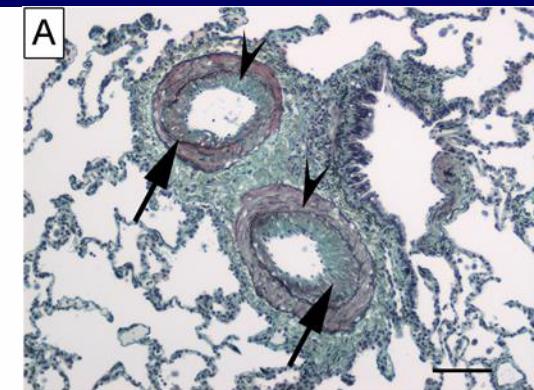
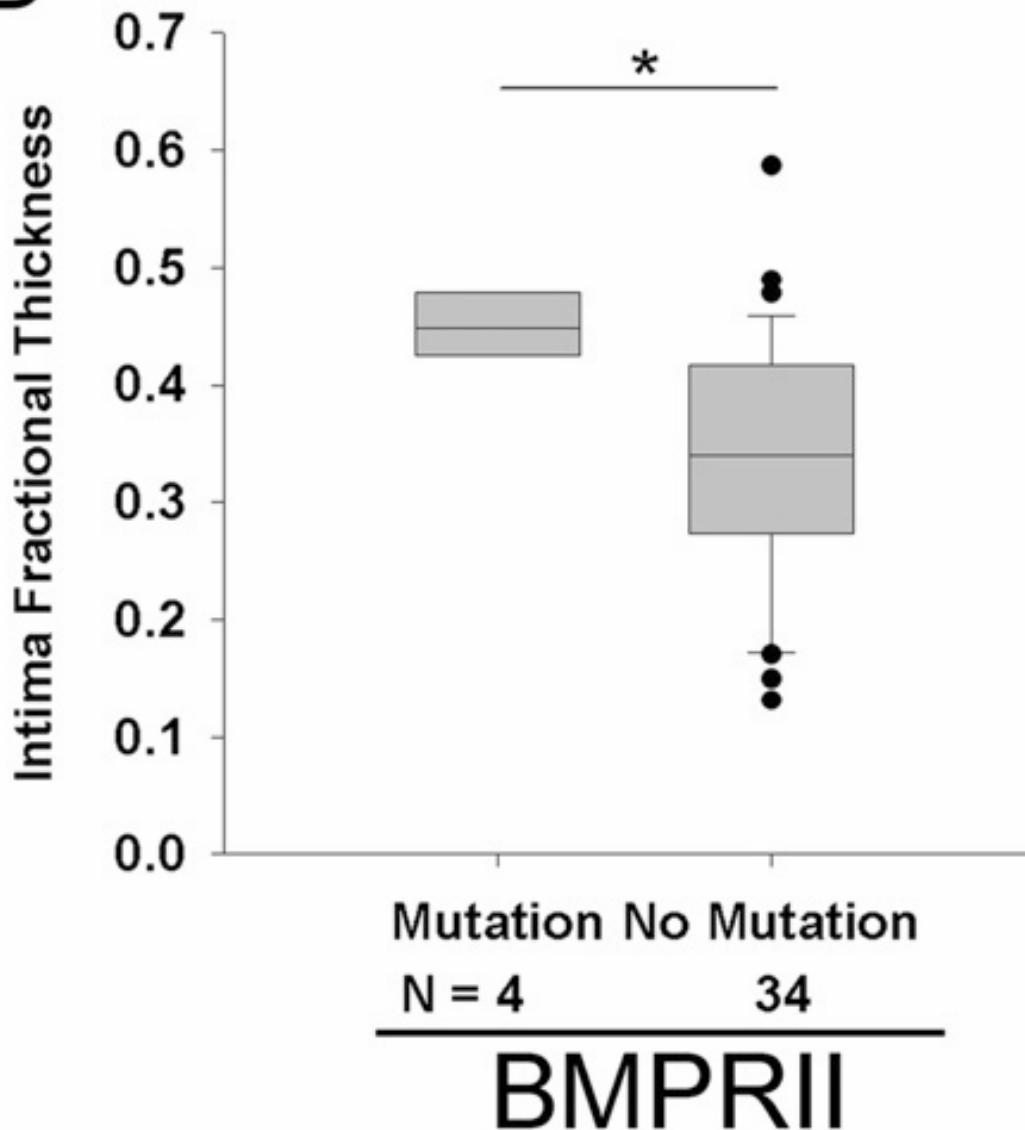


G

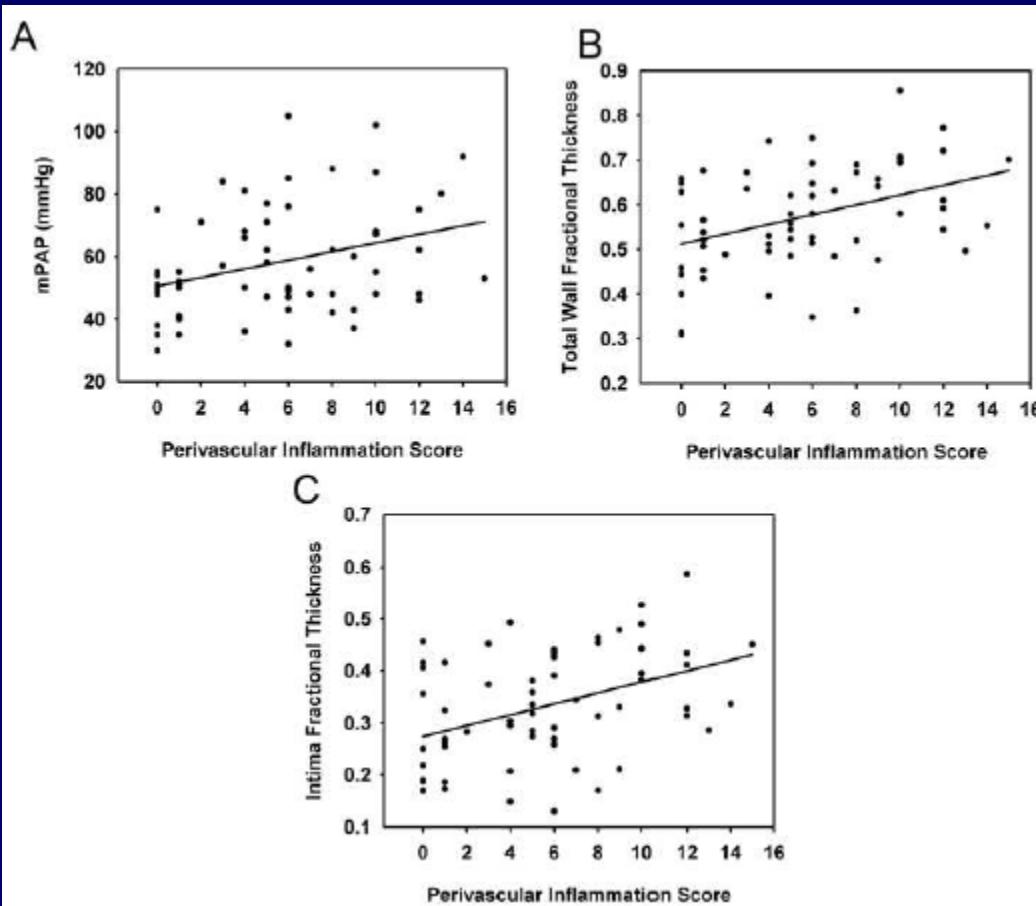
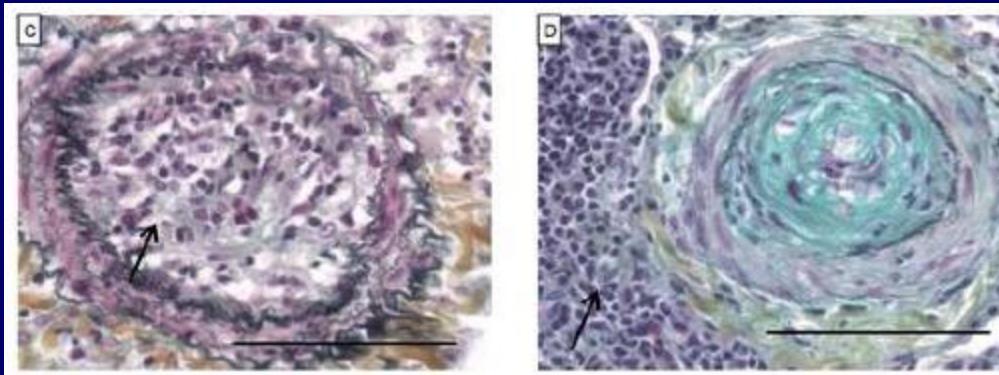


# BMPRII: worse pulmonary vascular remodeling

D



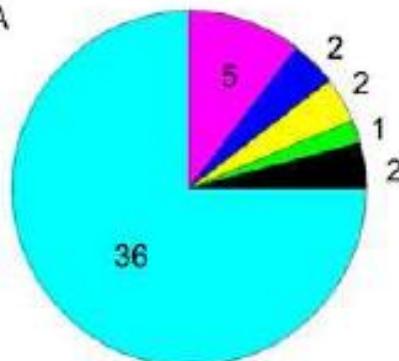
# Impact of perivascular inflammation



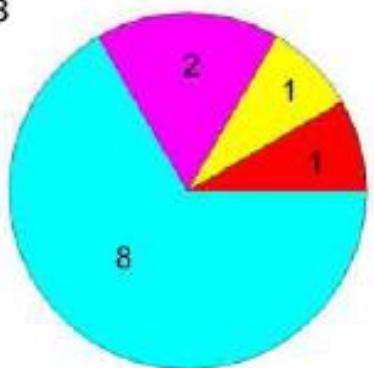
Stacher et al.,  
AJRCCM,  
2012

# Impact of treatments on pulmonary vascular lesions

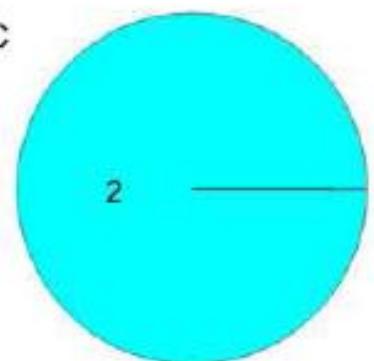
A



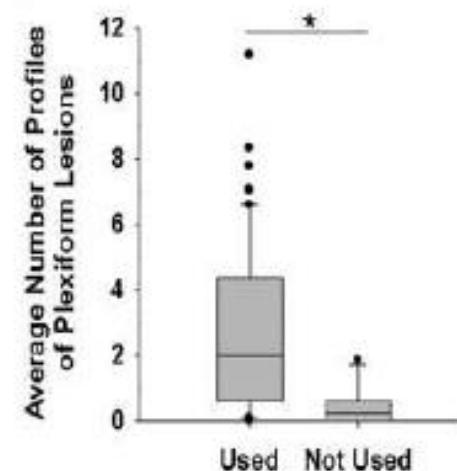
B



C



D

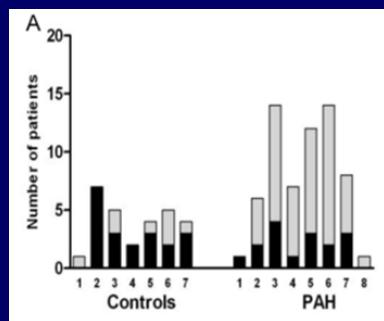


- ERA only
- PDE5i only
- Prostanoid only
- ERA + PDE5i
- ERA + Prostanoid
- Prostanoid + PDE5i
- ERA + PDE5i + Prostanoid

Lack of correlation:  
Yes/No: tx and  
vessel wall  
(intima, media)  
plexiform lesions

# Limitations

## Population

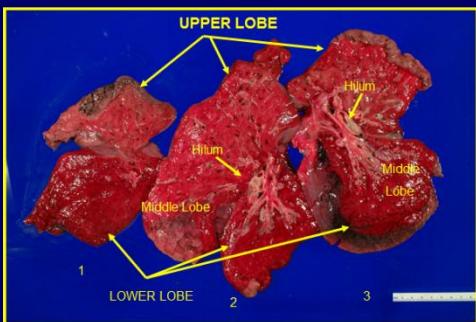
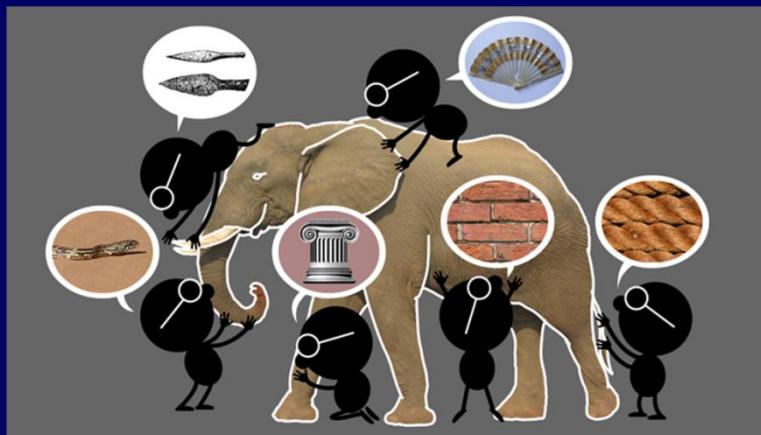


Transplant  
centers (n=9)

Lung  
explants

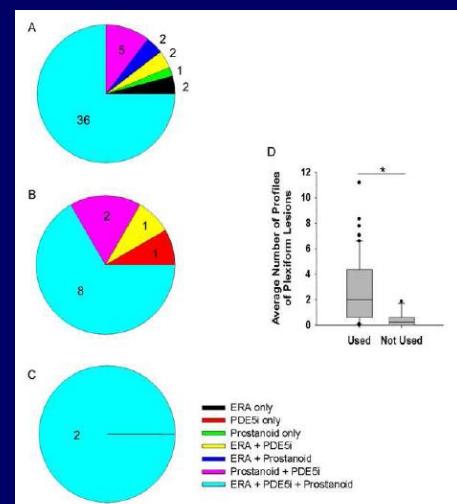
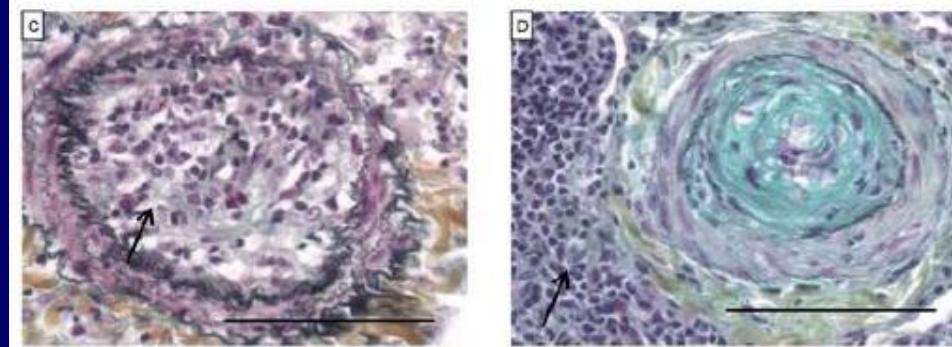
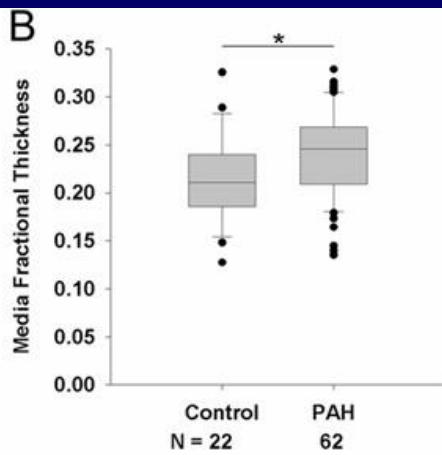
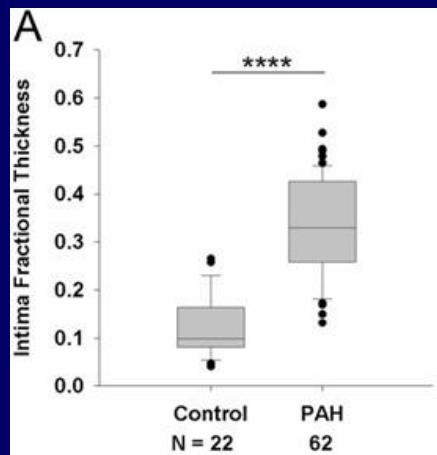
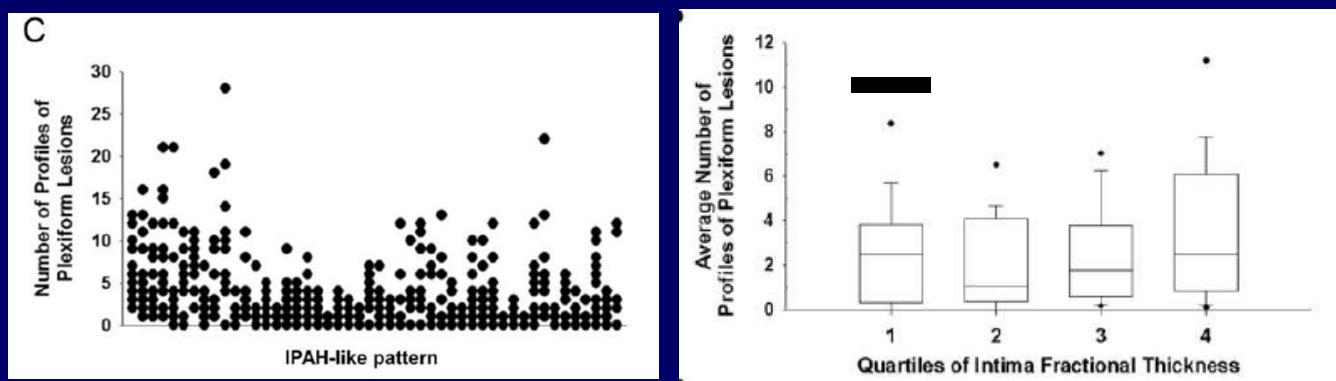
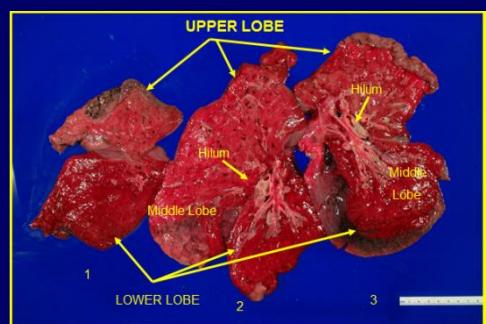


Stereology: avoid biases (not reporting true data)



- ❖ Random: equal chance of sampling
- ❖ Using the correct parameters and tools for analyses

# Summary



# Acknowledgments

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Univ. Colorado: Elvira Stacher (Univ. of Graz), Brian Graham, James Hunt, Aneta Gandjeva, Carlyne Cool, Steve Groshong

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Univ. Alabama: William Grizzle

## PHBI:

Transplant sites: Alleghene University of Medical Sciences (PI: Raymond L. Benza, M.D.); Baylor College of Medicine (George Noon, M.D.); Cleveland Clinic (PI: Serpil Erzurum, M.D.); Duke University (PI: Pang-Chieh Jerry Eu, M.D.); Stanford University-UCSF (PI:: Marlene Rabinovitch, M.D.); University of Alabama (PI: Keith Wille, M.D.; prior PI: Raymond L. Benza, M.D.); University of California, San Diego (PI: Patricia Thistlethwaite, M.D., Ph.D.); Vanderbilt University (Barbara Meyrick, Ph.D..