I. Pathology of pulmonary arterial hypertension

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PVRI

European Cardiology Society, Nice, 2012
Pulmonary Hypertension: Future expectations
Pulmonary vascular pathology: importance

- Normal
- IPAH
- RCC: +ctl
- CAIX
- HIF-1α

VEGFR-2/Actin

- Normal
- PH

P = 0.006

CAIX

HIF-1α

IPAH

Normal
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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<thead>
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<tbody>
<tr>
<td># of Centers / Countries</td>
<td>- / 7</td>
<td>1 / 1</td>
<td>32 / 1</td>
</tr>
<tr>
<td># of Patients and Demographics</td>
<td>N = 63, 8 wks - 63 yrs</td>
<td>N = 80, 1:1.6 M:F, 2 - 71 yrs</td>
<td>N = 58, 1:1.5 M:F, -</td>
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<tr>
<td>Referral Diagnosis</td>
<td>CHD</td>
<td>PPH</td>
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<tr>
<td>Diagnostic Criteria</td>
<td>-</td>
<td>RHC (69)</td>
<td>RHC</td>
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<tr>
<td>Clinical Parameters</td>
<td>-</td>
<td>mPAP</td>
<td>-</td>
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<tr>
<td>Medications</td>
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<td>-</td>
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<tr>
<td>Tissue Source</td>
<td>biopsy</td>
<td>autopsy, biopsy</td>
<td>autopsy, biopsy, pneumonectomy</td>
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<td>Controls</td>
<td>-</td>
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<tr>
<td>Sampling</td>
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<td>Blocks/case</td>
<td>-</td>
<td>1-13 (mean 5)</td>
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Pulmonary hypertension breakthrough initiative (PHBI): 2006

Blood

Transplant centers (n=9)

Lung explants

Cell Processing Centers (n=2)

Tissue Centers: Alabama Denver

Genomics Center

Proteomics Center
Lung accrual: 2006-2011

Control

Gender

PAH

Clinical Dx at enrollment

IPAH

Drug

CVD

VOD

CHD

FPAH

Stacher et al., AJRCCM, 2012
Demographics and Hemodynamics

A

Males
Females

B

C

mPAP (mmHg)
PVR (Wood Units)

Stacher et al., AJRCCM, 2012
Vascular Quantification Method

- Step 1: a-SMA external layer
- Step 2: a-SMA internal layer
- Step 3: TM internal layer
- \( R = \sqrt{\frac{A}{\pi}} \)
Morphometric parameters: control vs. PAH

A

Intima Fractional Thickness

Control
N = 22
PAH
62

- ****

B

Media Fractional Thickness

Control
N = 22
PAH
62

- *

C

Adventitia Fractional Thickness

Control
N = 22
PAH
62

D

V_{(intima + media)/septa}

Control
N = 22
PAH
62

- ****

Stacher et al., AJRCCM, 2012
Morphometric parameters: control vs. PAH

![Image of histological section with arrows indicating areas of interest.]

Graphs showing:

A. Number of specimens vs. Total Wall Fractional Thickness
B. Number of specimens vs. Intima Fractional Thickness
C. Number of specimens vs. Media Fractional Thickness

Control vs. PAH

Stacher et al., AJRCCM, 2012
Morphometric parameters and pathological PAH subphenotypes: plx lesions

Stacher et al., AJRCCM, 2012
Variability of pulmonary vascular lesions

Stacher et al., AJRCCM, 2012
Plexiform lesions

Stacher et al., AJRCCM, 2012
Histopathological patterns

IPAH-

IPAH, FPAH, HIV
Schisto, Liver Dx

APAH-

CVD: Scleroderma,
Lupus.

VOD-


PAH patterns and lung hemodynamics

Stacher et al., AJRCCM, 2012
Pathological patterns and pulmonary vascular remodeling

Stacher et al., AJRCCM, 2012
BMPRII: worse pulmonary vascular remodeling

Stacher et al., AJRCCM, 2012
Impact of perivascular inflammation

Stacher et al., AJRCCM, 2012
Impact of treatments on pulmonary vascular lesions

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

Stacher et al., AJRCCM, 2012
Limitations

Population

- Transplant centers (n=9)
- Lung explants

Stereology: avoid biases (not reporting true data)

Sampling

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

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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.).

CMREF