Pulmonary Hypertension in COPD----The Vascular Story

Airway Vista
Seoul, March 25-26,2017
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Clinical Profile and Underdiagnosis of Pulmonary Hypertension in US Veteran Patients

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Background—Pulmonary hypertension (PH) is a key contributor to cardiovascular morbidity and early mortality; however, reports are lacking on the epidemiology of PH in at-risk patient populations.

Methods and Results—The echocardiography registries from 2 major Veterans Affairs hospitals were accessed to identify patients with at least moderate PH, defined here as a pulmonary artery systolic pressure ≥60 mmHg detected echocardiographically. From a total of 10,471 individual patient transthoracic echocardiograms, we identified moderate or severe PH in 340 patients (332 men; mean, 77 years; mean pulmonary artery systolic pressure, 69.4±10.5 mmHg), of which PH was listed as a diagnosis in the medical record for only 59 (17.3%). At a mean of 832 days (0–4817 days) following echocardiography diagnosing PH, 150 (44.1%) patients were deceased. PH was present without substantial left heart remodeling: the mean left ventricular ejection fraction was 0.50±0.16, left ventricular end-diastolic dimension was 5.0±0.9 cm, and left atrial dimension was 4.4±0.7 cm. Cardiac catheterization (n=122, 36%) demonstrated a mean pulmonary artery pressure of 40.5±11.4 mmHg, pulmonary capillary wedge pressure of 22.6±8.9 mmHg, and pulmonary vascular resistance of 4.6±2.9 Wood units. Diagnostic strategies for PH were variable and often incomplete; for example, only 16% of appropriate patients were assessed with a nuclear ventilation/perfusion scan for thromboembolic causes of PH.

Why we need to know and tell the COPD vascular story

Prevalence and characteristics of three clinical phenotypes of chronic obstructive pulmonary disease (COPD).


Abstract

AIM: To determine the prevalence and analyze the most relevant clinical characteristics of three clinical phenotypes of COPD: emphysema (type 1), chronic bronchitis (type 2) or COPD-asthma (type 3).

An official American Thoracic Society/European Respiratory Society statement: research questions in COPD


European Respiratory Journal 2015 45: 879-905; DOI: 10.1183/09031936.00009015
Current Controversies in the Pharmacological Treatment of Chronic Obstructive Pulmonary Disease.

Singh D¹, Roche N², Halpin D³, Agusti A⁴, Wedzicha JA⁵, Martinez FJ⁶,⁷.

Abstract
Clinical phenotyping is currently used to guide pharmacological treatment decisions in chronic obstructive pulmonary disease (COPD), a personalized approach to care. Precision medicine integrates biological (endotype) and clinical (phenotype) information for a more individualized approach to pharmacotherapy, to maximize the benefit versus risk ratio. Biomarkers can be used to identify endotypes. To evolve toward precision medicine in COPD, the most appropriate biomarkers and clinical characteristics that reliably predict treatment responses need to be identified. FEV₁ is a marker of COPD severity and has historically been used to guide pharmacotherapy choices. However, we now understand that the trajectory of FEV₁ change, as an indicator of disease activity, is more important than a single FEV₁ measurement. There is a need to develop biomarkers of disease activity to enable a more targeted and individualized approach to pharmacotherapy. Recent clinical trials testing commonly used COPD treatments have provided new information that is likely to influence pharmacological treatment decisions both at initial presentation and at follow up. In this Perspective, we consider the impact of recent clinical trials on current COPD treatment recommendations. We also focus on the movement toward precision medicine and propose how this field needs to evolve in terms of using clinical characteristics and biomarkers to identify the most appropriate patients for a given pharmacological treatment.
Within the Group of Obstructive Lung Diseases

• There are several COPD phenotypes
• There is an association of COPD/emphysema with pulmonary hypertension and there is a subgroup of patients that manifest emphysema +interstitial fibrosis +PH
• There are 2 components to consider: the lung vessels --and Cor Pulmonale

• Hypothesis: cigarette smoke is toxic to all lung cells—including endothelial cells.
Airway disease  
fibrosis  
Muscularized arterioles  
Vessel loss  

COPD/emphysema: all compartments of the lung are involved  

In situ thrombosis  
thromboembolism
The spectrum of pulmonary vascular involvement within the group of COPD patients

• There are some patients that have no resting PH, but exercise-induced PH, but there are COPD patients that have severe PAH and even have plexiform lesions.

• Benjamin Burrows classic paper.
Figure 1. Relation of PAP and CI.
The crosses (+) indicate patients with arterial oxyhemoglobin saturation of less than 80 per cent. Resting and exercise values are connected by solid lines.
Years later...

Portillo K. et al, 2015: Resting and exercise induced PH
Quantitative maps of pulmonary blood flow of participants with varying COPD severities and a participant without COPD.
Reduction in lung blood flow

Due to reduced number of vessels (decrease in vascular surface area is reflected in a decrease in the DLCO)

Leads to an increase in the resistance to blood flow, PVR.
A. The pleura, highlighted by arrows, is mildly thickened and shows patchy lymphocyte clusters (star). Small vessel within the pleura are congested, filled with red blood cells. Although much of the septa are destroyed by emphysematous changes, the parenchymal small vessels (block arrows) stand out in stark relief to the airspaces. In contrast, small airways appear decreased in number.

B. This is an image from the same patient in which the small pulmonary arteries show medial hypertrophy; the arteries are unaccompanied by small airways. Marked emphysematous changes, characterized by enlarged airspaces (asterisk), are evident. There is congestion of the pleural vessels, highlighted by the intraluminal red blood cells.
Images, courtesy of Carlyne Cool, Denver
Figure 2. Photomicrographs of pulmonary muscular arteries from patients with COPD immunostained with monoclonal antibody against CD8. Positive cells (brown) were located in the adventitia of both arteries close to bronchioles (panel A) and arteries distant from bronchioles (panel B). (Br = bronchiolar lumen; Art = arterial lumen). Original magnification: ×200.
Carlsen J et al., J Heart and Lung Transplant 2013

- n=247 (100%)
  - Lung transplant recipients
  - PCWP ≤15mmHg

- PH
  - n=93 (37.7%)
  - (mPAP ≥25mmHg)

- Non-PH
  - n=154 (62.3%)
  - (mPAP <25mmHg)

- Mild to moderate PH
  - n=83 (33.6%)
  - (mPAP 25-34mmHg)

- Severe PH
  - n=10 (4.1%)
  - (mPAP ≥35mmHg)

- IPAH
  - Control group (n=18)

- 30 Lung specimens evaluated
- 30 Lung specimens evaluated
- 10 Lung specimens evaluated
- 18 Lung specimens evaluated
Prevalence and Localization of Pulmonary Embolism in Unexplained Acute Exacerbations of COPD: A Systematic Review and Meta-analysis

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Results The systematic search resulted in 1,650 records. The main reports of 22 articles were reviewed, and 7 studies were included. The pooled prevalence of PE in unexplained AE-COPD was 16.1% (95% CI, 8.3%-25.8%) in a total of 880 patients. Sixty-eight percent of the emboli found were located in the main pulmonary arteries, lobar arteries, or interlobar arteries. Mortality and length of hospital admission seemed to be increased in patients with unexplained AE-COPD and PE. Pleuritic chest pain and cardiac failure were more frequently reported in patients with unexplained AE-COPD and PE. In contrast, signs of respiratory tract infection was less frequently related to PE.

Conclusions PE is frequently seen in unexplained AE-COPD. Two-thirds of emboli are found at locations that have a clear indication for anticoagulant treatment. These findings merit clinical attention. PE should receive increased awareness in patients with unexplained AE-COPD, especially when pleuritic chest pain and signs of cardiac failure are present, and no clear infectious origin can be identified.
Severely reduced diffusion capacity in idiopathic pulmonary arterial hypertension: patient characteristics and treatment responses

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Idiopathic and hereditary PAH
n=205

Exclusion:
- Age at diagnosis <18 years n=7
- No DLCO measurement n=15
- FEV1 or FVC <60% pred n=13
- Severe emphysema/fibrosis n=4

Inclusion
n=166

DLCO <45% pred
n=48

DLCO ≥45% pred
n=118

b) 12

Frequency %

10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105

DLCO % pred
A problem with stem cell-dependent repair?

Janssen WJ et al, COPD, 2014
Pathophysiology

\[ \text{mPAP} = [\text{CO} \times \text{PVR}] + \text{PAWP} \]

- Pulmonary vasoconstriction
- Vascular remodeling
- Polycythemia
- Destruction of vascular bed
- Compression of alveolar vessels

Hyperinflation

Auto-PEEP → ↓ pleural and juxtacardiac pressures

Figure 1
Scale free node (hub) model of COPD

- Dendritic cells
- Acrolein
- Elastase
- H2O2
- O2-
- Alpha 1 AT
- MPO
- CRP
- IL-6
- Fibrinogen
- TNF
- LTB4
- Abs
- T cells
- Myopathy
- Microvessel loss
- EC dysfunct.
- Clotting
- VEGF
Autoimmune Disease Fingerprints?

CD 20 - 40x

CD 8 - 40x

CD 20 - 100x

CD 8 - 100x
Cigarette smoke is toxic to mouse lung vessels

iNOS KO mice are protected

Parajuli N......Weissmann N. et al, AJRCCM 2014
Molecular pathobiology of cell death in smoking-induced emphysema
Deregulation of apoptosis mediators' p53 and bcl2 in lung tissue of COPD patients.

Siganaki M¹, Koutsopoulos AV, Neofytou E, Vlachaki E, Psarrou M, Soulitzis N, Pentilas N, Schiza S, Siafakas NM, Tzortzaki EG.
MicroRNA-199a-5p Is Associated With Hypoxia-Inducible Factor-1α Expression in Lungs From Patients With COPD

Shiro Mizuno, MD, PhD, Harm J. Bogaard, MD, PhD, Jose Gomez-Arroyo, MD, Aysar Alhussaini, MD, Donatas Kraskauskas, DVM, Carlyne D. Cool, MD, and Norbert F. Voelkel, MD
Endothelial p53 Deletion Improves Angiogenesis and Prevents Cardiac Fibrosis and Heart Failure Induced by Pressure Overload in Mice

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Background—Cardiac dysfunction developing in response to chronic pressure overload is associated with apoptotic cell death and myocardial vessel rarefaction. We examined whether deletion of tumor suppressor p53 in endothelial cells may prevent the transition from cardiac hypertrophy to heart failure.

Methods and Results—Mice with endothelial-specific deletion of p53 (End.p53-KO) were generated by crossing p53<sup>fl/fl</sup> mice with mice expressing Cre recombinase under control of an inducible Tie2 promoter. Cardiac hypertrophy was induced by transverse aortic constriction. Serial echocardiography measurements revealed improved cardiac function in End.p53-KO mice that also exhibited better survival. Cardiac hypertrophy was associated with increased p53 levels in End.p53-WT controls, whereas banded hearts of End.p53-KO mice exhibited lower numbers of apoptotic endothelial and non-endothelial cells and altered mRNA levels of genes regulating cell cycle progression (p21), apoptosis (Puma), or proliferation (Pcna). A higher cardiac capillary density and improved myocardial perfusion was observed, and pharmacological inhibition or genetic deletion of p53 also promoted endothelial sprouting in vitro and new vessel formation following hindlimb ischemia in vivo. Hearts of End.p53-KO mice exhibited markedly less fibrosis compared with End.p53-WT controls, and lower mRNA levels of p53-regulated genes involved in extracellular matrix production and turnover (eg, Bmp-7, Ctgf, or Pai-1), or of transcription factors involved in controlling mesenchymal differentiation were observed.

Conclusions—Our analyses reveal that accumulation of p53 in endothelial cells contributes to blood vessel rarefaction and fibrosis during chronic cardiac pressure overload and suggest that endothelial cells may be a therapeutic target for preserving cardiac function during hypertrophy. *(J Am Heart Assoc. 2015;00:e001770 doi: 10.1161/JAHA.115.001770)*

Key Words: angiogenesis • endothelium • fibrosis • heart failure • p53
Lung tissue protein analysis in COPD
Inhibition of histone deacetylase causes emphysema.

Mizuno S¹, Yasuo M, Bogaard HJ, Kraskauskas D, Natarajan R, Voelkel NF.
Vessel loss

- cigarette smoke
  - miRNA
  - HDAC 2
  - p53
    - HIF 1alpha
      - VEGF
p53 signaling pathway polymorphisms associated with emphysematous changes in COPD patients.

Mizuno S¹, Ishizaki T², Kadowaki M³, Akai M⁴, Shiozaki K⁴, Iguchi M², Oikawa T², Nakagawa K², Osanai K², Toga H², Gomez-Arroyo J⁵, Kraskauskas D⁵, Cool CD⁶, Bogaard HJ⁷, Voelkel NF⁵.

Abstract

BACKGROUND: The p53 signaling pathway may be important for the pathogenesis of emphysematous changes in the lungs of smokers. Polymorphism of p53 at codon 72 is known to affect apoptotic effector proteins, and the polymorphism of mouse double minute 2 homolog (MDM2) SNP309 is known to increase MDM2 expression. The aim of this study was to assess polymorphisms of the p53 and MDM2 genes in smokers and confirm the role of SNPs in these genes in the pathogenesis of pulmonary emphysema.

METHODS: 365 patients with a smoking history were included in this study, and the polymorphisms of p53 and MDM2 genes were identified. The degree of pulmonary emphysema was determined by computed tomography scanning. SNPs, MDM2 mRNA and p53 protein levels were assessed in human lung tissues from smokers. Plasmids encoding p53 and MDM2 SNPs were used to transfect human lung fibroblasts (HLFs) with or without cigarette smoke extract (CSE), and effect on cell proliferation and MDM2 promoter activity were measured.

RESULTS: The polymorphisms of p53 and MDM2 genes were associated with emphysematous changes in the lung, and were also associated with p53 protein and MDM2 mRNA expression in the lung tissue samples. Transfection with a p53 gene-coding plasmid regulated HLFs proliferation, and the analysis of P2 promoter activity in MDM2 SNP309-coding HLFs showed the promoter activity was altered by CSE.

CONCLUSIONS: Our data demonstrate that p53 and MDM2 gene polymorphisms are associated with apoptotic signaling and smoking-related emphysematous changes in the lungs from smokers.
This graph emphasises the importance of RV function, over PVR.
Remodeling of rat pulmonary artery induced by chronic smoking exposure.

Zhao L¹, Wang J¹, Wang L¹, Liang YT¹, Chen YQ¹, Lu WJ¹, Zhou WL¹.
Activation of renin-angiotensin-aldosterone system (RAAS) in the lung of smoking-induced pulmonary arterial hypertension (PAH) rats.

Yuan YM¹, Luo L², Guo Z³, Yang M², Ye RS⁴, Luo C².

After six months of cigarette exposure the RVSP of rats significantly increased (Figure 1); losartan can significantly reduce the increased RVSP caused by smoking, suggesting that losartan may relieve chronic smoking-induced PAH.

Figure 1. Smoking-induced increased right ventricular systolic pressure in rats. Y-axis: RVSP level (mmHg).
Modulators of right ventricular apoptosis and contractility in a rat model of pulmonary hypertension.

Zungu-Edmondson M¹, Shults NV¹, Wong CM¹, Suzuki YJ².

Abstract

AIMS: Right ventricular (RV) failure is the major cause of death among patients with pulmonary arterial hypertension (PAH). However, the mechanism of RV failure has not been defined.

METHODS AND RESULTS: This study examined mechanisms and consequences of RV myocyte apoptosis and fibrosis in response to PAH. Rats were injected with SU5416 (vascular endothelial growth factor inhibitor), followed by hypoxia for 3 weeks, and subsequently maintained in normoxia for 2, 5, or 14 weeks (5-, 8-, and 17-week time points after the SU5416 injection, respectively). RV systolic pressure (RVSP) was elevated to >70 mmHg at 5-week time point, and this pressure was sustained thereafter. Significant RV myocyte apoptosis and fibrosis were observed at 8- and 17-week time points. Apoptosis was associated with downregulated Bcl-xL (anti-apoptotic protein), downregulated GATA4 (transcriptional regulator of Bcl-xL), and upregulated p53 (negative regulator of GATA4 gene transcription). PAH-mediated RV apoptosis and fibrosis were attenuated in p53 knock-out rats. Despite the major loss of cardiomyocytes, RV contractility was enhanced, suggesting that the remaining myocytes can perform improved contractile functions.

Improved RV contractility is associated with the increased expression of contractile and sarcoplasmic reticulum Ca(2+) uptake proteins. In contrast, the expression of calsequestrin 2 (CSQ2) was downregulated. The siRNA knockdown of CSQ2 improved RV contractility and increased the expression of contractile and Ca(2+) uptake proteins.
The COPD/PH phenotype remains widely neglected and under-researched. PH in COPD patients is underdiagnosed. Cigarette smoke is endothelial cell & cardiotoxic.

Some of the molecular mechanisms triggering the pathobiology of smoking-related PH & RV dysfunction are emerging from experimental studies [VEGF, p53, HDAC..]; clinical (tissue) validation in COPD patients is largely lacking.
Speculation

The prevailing dominant emphasis on the airways (bronchial wall thickness and FEV1) is likely explained by the availability of an increasing number of inhaled drugs that target bronchial muscle tone and bronchial inflammation.

A therapeutic nihilism — “the PH in COPD can’t be treated” — contributes to the lack of interest in PH in COPD patients.
Outlook: Treatment of Pulmonary Hypertension in COPD patients

The therapeutic nihilism is not justified.
Thank you!

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Cigarette smoke

Inflammation → Proteolysis
Oxidative Stress

Apoptosis
Endothelial cells

Impaired clearance of apoptotic cells

Autoantigens

Immune responses
T and B lymphocytes

Autoantibodies

Vascular tree pruning
Alveolar destruction
EMPHYSEMA

Macrophages-LTB4

HDAC, HIF, VEGF

Fig. 1. Overall hypothesis
Inflammation in chronic airway diseases is COMPLEX
Asthma–COPD Overlap
Clinical Relevance of Genomic Signatures of Type 2 Inflammation in Chronic Obstructive Pulmonary Disease

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Sirt1 expression is associated with CD31 expression in blood cells from patients with chronic obstructive pulmonary disease.

Kato R\textsuperscript{1}, Mizuno S\textsuperscript{2}, Kadowaki M\textsuperscript{3}, Shiozaki K\textsuperscript{4}, Akai M\textsuperscript{4}, Nakagawa K\textsuperscript{1}, Oikawa T\textsuperscript{1}, Iguchi M\textsuperscript{1}, Osanai K\textsuperscript{1}, Ishizaki T\textsuperscript{1}, Voelkel NF\textsuperscript{5}, Toga H\textsuperscript{1}.

A strong positive correlation was seen between CD31 and Sirt1 mRNA (left), and a weak positive correlation was seen between CD31 mRNA and miR126-3p expressions (right).

CD 31 = PECAM, Sirt 1 = a HDAC, one target is p53