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Pulmonary Vascular Remodeling in Pulmonary Hypertension

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Abstract

Pulmonary vascular remodeling is the key structural alteration in pulmonary hypertension. This process involves changes in intima, media, and adventitia, often with the interplay of inflammatory cells. We review the pathology of these changes and highlight some of the pathogenetic mechanisms that underlie the remodeling process.

Keywords

Pulmonary hypertension; pulmonary remodeling; endothelial cells; smooth muscle cells; lung

Pulmonary hypertension (PH) refers to hemodynamic alterations of the pulmonary circulation in which the pulmonary artery pressures are in excess of 25 mm Hg – largely the result of the ground breaking introduction of pulmonary catheterization in the late 40's in the past century (Fishman 1997). In this setting, the pulmonary arteries and veins undergo several structural alterations that have been recognized as *pulmonary vascular remodeling*. These structural alterations, though similar when recognized (and quantified) in pathological specimens, are likely heterogeneous molecularly. Pulmonary vascular remodeling is the result, and, likely, contributes to increased pulmonary vascular pressures by increasing pulmonary vascular resistance.

The pathology of PH has been summarized in all five international meetings held thus far, which primarily targeted at how to classify the disease, to direct treatment, and diagnostic algorithms. The pulmonary vascular pathology most strongly influenced the first international PH conference in 1973, reflecting the contributions of several outstanding pathologists dedicated to studying the disease, like Wagenvoort, Reid, Edwards, and Heath (Heath and Wagenvoort 1975). The conferences that followed (Evian, France in 1998 (Haworth et al. 1998), Venice, Italy, in 2003 (Pietra et al. 2004), Dana Point, USA in 2008, and Nice, France in 2013 (Simonneau et al. 2004, Simonneau et al. 2013), while recognizing the relevance of the pathology of pulmonary vascular remodeling, largely restricted its description as means to a better understanding of the pathobiology of the disease (Tuder et al. 2013a). The present classification, formulated in Nice, France (Simonneau et al. 2013), is widely used to guide investigators in the field.0020

In prior reviews (Tuder and Erzurum 2009), we chose to segment pulmonary hypertension in regards to the levels of pulmonary artery pressures; mild to moderate, when in between 25 to 45 mmHg and severe, when in excess of 45-50 mmHg. We acknowledge that this

categorization is largely arbitrary, but, in our experience, it underscores that severe disease shares some distinct structural alterations of hypertensive pulmonary arteries, many of which are irreversible. This two-level characterization of PH reflects with reasonable accuracy the overall impact of PH on the right ventricle – right ventricular failure is ultimately the trigger of a patient's demise and physiological impairment.

But to fully appreciate the clinical and research importance of pulmonary vascular remodeling, it is imperative to examine the intricate relationship between normal pulmonary arterial physiology and macro and micro anatomy. In a recent review, we summarized several important insights on the normal pulmonary vascular structure, bringing to light anatomical and structural insights (which are now more than 50 years old) with a handful of three dimensional casting studies in animals and (some) humans (Tuder et al. 2013b). A single right ventricular beat normally propels approximately 500 ml of stroke blood volume into the pulmonary arterial system, with approximately 140 ml of blood in 277 billion capillaries (or about 10^11), occupying the equivalent of a tennis court size pulmonary gas exchange area. This extensive capillary network is supplied by 10^8 pulmonary vascular segments with 15-40 μm in diameter. A key characteristic of the loss of a well-defined pulmonary vascular media composed by smooth muscle cells in arteries smaller than 70 μm in diameter: this structural characteristic may be teleologically critical to the requirement to be perfused at low pressures, a distinguishing feature of the pulmonary circulation vis-à-vis the systemic circulation.

Given the critical need to have a low capillary perfusion pressures for optimal gas exchange, one can envision the need for pulmonary vascular remodeling as means to dissipate (more) proximally (than the capillary bed) high pulmonary pressures. Where are these high pressures generated in an acutely hypoxic normal lung, such as during acute hypoxia (fraction of inspired O2 in air of less than 13%)? The property of hypoxic pulmonary vasoconstriction (HPV) resides in specialized pulmonary smooth muscle cells (McMurtry et al. 1976), which can depolarize under alveolar hypoxia and have a surge of intracytoplasmic calcium (Sylvester et al. 2012). HPV appears to occur in arteries as large as 1.2 mm in the dog; subsequent studies outlined that HPV would occur in arteries of less than 50 μm in diameter (in the dog) and approximately 80 μm in the sheep (Sylvester et al. 2012). Interestingly, this wide range of arterial diameters includes those arterial segments that undergo pulmonary vascular remodeling in PH. It is therefore possible that the combined effects of excessive vasoconstriction and of cell autonomous growth (combined with lack of cell death) may ultimately account to the structural alterations of the pulmonary circulation in PH (Tuder et al. 2013b).

Chronic exposure to hypoxia (usually modeled by exposing animals at a FiO2 of 50% or 8900 m) causes hypoxic PH. Due to HPV and/or superimposed release of growth factors, pulmonary arteries undergo excessive muscularization, with a predominance of media remodeling, with no or minimal intima remodeling. While there is debate over how the pulmonary artery remodels under chronic hypoxia, it is a valuable disease related process as it may relate to PH in association with hypoxic states, like high altitude and chronic obstructive pulmonary disease. However, hypoxic PH is largely of mild to moderate severity (see above).

In the review, we describe the spectrum of pulmonary vascular remodeling in PH, particularly of the group 1 disease, also named as pulmonary arterial hypertension (PAH) (Simonneau et al. 2013); moreover, we also extend these insights into (some) small animal models. We briefly outline approaches to quantify key structural/morphological alterations and the potential impact of these features (also referred as pulmonary vascular lesions (Pietra et al. 2004)) in disease pathogenesis and pulmonary arterial pressures. This discussion is framed in macroscopic and microscopic pulmonary vascular compartments of intima lined by endothelial cells, media composed largely by smooth muscle cells, and adventitia populated by fibroblasts and, in PH, by inflammatory cells. The readers are encouraged to complement the present reading with comprehensive reviews on pathobiology of PH (Archer et al. 2010, Schermuly et al. 2011, Tuder et al. 2013a).

Pulmonary vascular remodeling in PH

A. Intima remodeling (Figure 1)

The intima represents an endothelial cell-thick interface between the muscular media and the flowing blood. In the pulmonary circulation, the intima provides a vast surface area of unobstructed flow, therefore contributing to relatively low perfusion pressures, which is the trademark of the pulmonary circulation. In fact, the combined intima surface area of pulmonary arteries in the range of 20-30 μm in diameter is of 2-3 logs that of more proximal pulmonary arterial segments (Tuder et al. 2013b).

The extent that the intima is compromised in PH is unknown. In a recent study, we demonstrated that, based on cross sections of pulmonary arteries, normal intima represented approximately 10% on the overall thickness; these findings are in line with prior studies of the pathology of idiopathic pulmonary arterial hypertension (IPAH), the paradigmatic example of severe PH (Chazova et al. 1995); in severe disease, lungs with PAH showed an approximately 3-fold increase in intima fractional thickness (Stacher et al. 2012). Of note, this thickened intima would result in an approximately 1.5^4 (40-fold) increase in pulmonary vascular resistance. Interestingly, using the parameter of volume density with alveolar septa as reference, there is a doubling of PAH vs. control intima, overall within the range seen with another quantitative approach, of the measurement of intima fractional thickness (Stacher et al. 2012).

Interestingly, approximately 25% of lungs with PAH had intima thickening that overlapped the values seen in controls (normal lungs) (Stacher et al. 2012). As noted below, the overlap between media and adventitia fractional thickness between control and PAH pulmonary arteries was more pronounced than that seen with the intima.

The types of intima thickening are varied. They can be briefly summarized as based on the predominance of collagen and mucin, fibroblastic-like cells, or endothelial cells (Figure 1E). Endothelial-like cells, when proliferated in a disorganized fashion, form plexiform lesions (Figures 1B and D) (Tuder and Zaiman 2004). These are glomeruloid-like lesions, with variable formation of incipient blood vessels. Our prior studies demonstrated expression of markers of angiogenesis in these lesions (Tuder et al. 2001), including vascular endothelial growth factor (VEGF), VEGF receptors, and hypoxia inducible factor (HIF)-1α. Though its

pathogenesis remains unclear, it is often seen in severe group 1 PAH and in group 2 with PH associated with congenital heart malformations. Plexiform lesions are characteristic of IPAH morphology; moreover, they can be found in a significant number of cases of associated PAH (APAH, usually in the setting of collagen vascular diseases) (Stacher et al. 2012). Our data indicated that plexiform lesions were detected in 90% of lungs with PAH. There is a large variation of plexiform lesion profiles in a given lung and among PAH lungs; though it is tempting to speculate that plexiform lesions are the forerunners of occlusive intima lesions, no such correlation has been observed (Stacher et al. 2012).

Obliterative concentric lesions are characterized by an onion-skin arrangement of endothelial- and/or smooth muscle cells (Figure 1D). These lesions appear to be completely restricted to the pulmonary vascular lumen. Both plexiform and concentric lesions have been linked to IPAH (Heath and Edwards 1958); we confirmed the geographical association of concentric and plexiform lesion, with the former being present proximally to plexiform lesions, based on three-dimensional reconstruction studies (Cool et al. 1999).

Additional intima lesions consist of lesions characterized by being paucicellular, with increase in connective tissue, including extracellular matrix. Many appear to contain excessive amounts of mucopolysaccharides. How these lesions develop and their overall fate remain unclear; they have been probably referenced as intima fibrosis in prior pathological descriptions of PH.

Interestingly, the intima fractional thickness, a measure of the extent of pulmonary artery intima contribution to the overall diameter, was significantly higher in IPAH pulmonary arteries when compared with APAH. Moreover, this index was also higher in lung of patients with documented mutations in bone morphogenetic protein receptor 2 (BMPR2) when compared with those with no identifiable mutations (Stacher et al. 2012). These novel findings appear to correlate with the clinical findings of more severe disease in patients with BMPR2 mutations and PAH.

B. Media remodeling

The media, composed predominantly of smooth muscle cells, has been the focus of prior pathological descriptions and pathophysiological studies in PH. Likely due to the properties of mediating HPV and the prominence of media remodeling in PH due to chronic hypoxia, PAH has been largely focused on studies targeting the media smooth muscle cell.

Prior studies delineated that normal media thickness corresponds to approximately 5% (or less) of the overall pulmonary artery diameter (Chazova et al. 1995). Our data indicate that, control lungs, largely obtained from accidental deaths of younger adults, exhibit media fractional thickness was approximately 20% (Stacher et al. 2012). The increase in PAH was approximately of 20% over that of control lungs. Remarkably, we found a significant overlap of media fractional thickness between 60% of PAH patients' lungs with control values (Stacher et al. 2012). These findings are of interest; they may reflect true differences between control population or sampling differences that may justify the observed differences. Moreover, if indeed there is a significant degree of shared medial pulmonary

artery thickness between control lungs and those with severe PAH, then functional alterations become critical to explain how media remodeling contributes to the disease.

Of interest, the parameter of combined intima and media thickness correlated significantly with pulmonary artery pressures and pulmonary resistance. These findings might appear predictable, as with increased pulmonary artery pressures and pulmonary vascular resistance, there is an associated heightened media (and intima) remodeling (notwithstanding the degree of overlap with media thickness with control lungs). On the other hand, this finding also supports that the combined remodeling of both the intima and the media plays a role in the pathogenesis of pulmonary hypertension.

C. Adventitia remodeling

The remodeling of adventitia was one of the most prominent findings reported in an autopsy series of 19 patients with IPAH (Chazova et al. 1995). This study reported an increase in adventitia thickness of approximately 2- to 4-fold in IPAH lungs vs. controls. Similar prominent adventitia remodeling was noted in cows with Brisket's disease (enhanced susceptibility to severe PH and right ventricular failure due to grazing in high altitude) (Newman et al. 2011) and cows exposed to chronic hypoxia (simulated altitude of 17000 ft, i.e., fraction of inspired oxygen (FiO2) of 10%) (Davie et al. 2006)

Our data however did not indicate that remodeled pulmonary arteries had more advanced adventitia remodeling than controls (with 98% of patients with PAH overlapping with controls) (Stacher et al. 2012). However, it is conceivable that methodological limitations hamper how best measure adventitia remodeling. The precise boundaries of the adventitia impose a challenge for precise demarcation (at least in the human lung), and therefore introduces significant pitfalls for analyses; adventitia is largely composed of a connective tissue sheath that surrounds airways and pulmonary arteries. It contains lymphatic vessels and is the conduit of inflammation, either targeted at airways (like in bronchiolitis or asthma) or pulmonary arteries (like in pulmonary hypertension).

Notwithstanding the difficulties in analyzing the extent of adventitia remodeling in PH, there is substantial evidence that the adventitia may play key roles as an inflammatory cell signaling hub (Pugliese et al. 2015, Stenmark et al. 2015). It acts as a signaling hub, holding feedforward interactions between resident fibroblasts and incoming macrophages. Moreover, the adventitia may act as a reservoir for bone marrow derived progenitors, which may directly or indirectly stimulate pulmonary vascular remodeling (Majka et al. 2008).

D. Perivascular inflammation

Given the prominence of pulmonary vascular remodeling, the component of inflammation remained largely on the side lines during the first more detailed descriptions of pulmonary vascular remodeling in PH (Bjornsson and Edwards 1985, Heath and Edwards 1958). However, there has been a growing interest in the findings, characterization, and functional studies regarding the role of inflammation in PH (Figure 1F).

The presence of macrophages and lymphocytes was highlighted in the early 90's (Tuder et al. 1994), suggesting that they may participate in the process of pulmonary vascular

remodeling. Mast cells were recognized as participants of the structural findings in PAH (Caslin et al. 1990), confirmed in more recent studies (Savai et al. 2012).

Only more recently, perivascular remodeling was semi-quantitatively assessed and shown to correlate with hemodynamic parameters in PAH (Stacher et al. 2012); despite attempts to use volume density with alveolar septa as reference tissue, a semi-quantitative grading ranging from 0 (absent) to 3 (abundant) was used to generate an inflammatory score. Of note, there was a correlation between perivascular inflammation score with intima+media fractional thickness and a strong correlational trend with pulmonary artery pressures.

These studies were followed by an effort to better characterize the types of inflammatory cells in PAH lungs (Savai et al. 2012). This study confirmed that CD68+ macrophages, CD14+ monocytes, and dendritic cells do accumulate in the adventitia of remodeled pulmonary arteries in IPAH. Increases in all T lymphocyte populations, while with a decreased number of FoxP3 cells were noted in IPAH lungs vs. controls.

However, inflammation involves more than just the presence of inflammatory cells around remodeled pulmonary arteries in PH. Cytokines and chemokines are clearly drivers and contributors to perivascular inflammation in PH. IL-1 was recognized as a mediator of monocrotaline-induced rodent PH in the 90's (Voelkel et al. 1994), which was supported by observations in samples of patients with PAH (Humbert et al. 1995). These early observations led to a large set of new data linking inflammation to the pathobiology of PAH (Dorfmuller et al. 2003, Hassoun et al. 2009, Soon et al. 2010), some of which with a strong correlation with severity of disease (notably interleukin (IL) 6, IL8, IL20, and IL12) (Soon et al. 2010). Schistosomiasis-induced PAH is perhaps the paradigmatic entity in which a parasite, S. mansoni, triggers a TH-2 dominant response (Graham et al. 2010) and pulmonary vascular lesions identical to those seen in idiopathic PAH. Experimentally, the TH-2 inflammation leads to increased transforming growth factor (TGF)-β1 (Kumar et al. 2015), which ultimately trigger pulmonary artery remodeling and PH. This process is largely dependent of thrombospondin-1 producing blood marrow monocytes (Kumar et al, unpublished). The aggregate of these data support, not only that inflammation is part of the pathology of PH, but it may indeed drive several of the key pulmonary vascular lesions characteristic of the disease.

E. Other pathological alterations present in PH

Old and recent clots are among the pathological alterations seen in PH lungs. They were reported in prior pathological assessments of the pulmonary circulation in PH (Palevsky et al. 1989), largely called thromboembolic primary pulmonary hypertension. However, this study reported significant thrombi in the group called “arteriopathy with plexiform lesions”. We confirmed these findings in our series, with 50% detection of clots in remodeled pulmonary arteries (Stacher et al. 2012); a large number of these patients (42%) were being anti-coagulated.

Although some unusual pathological findings can occur in lungs with PAH, including areas of alveolar exudates, granulomas, peribronchiolar inflammation. They are rather incidental and probably reflect underlying alternative diseases or exposures, unrelated to PH.

How to analyze pulmonary vascular remodeling in PH

Notwithstanding the important contributions made by detailed, largely qualitative, descriptions of pulmonary vascular remodeling in PH (in fact, mostly PAH) (Bjornsson and Edwards 1985, Chazova et al. 1995, Heath and Edwards 1958, Pietra et al. 1989, Wagenvoort and Wagenvoort 1970), a stringent quantitative assessment of the pathology of severe PH remains to be done. Most of these prior studies are biased (i.e., contain analytical errors) due to inappropriate random and systematic sampling and lack of assessment of key stereological parameters (such as assessments of surface area and length). As summarized in excellent reviews (Hsia et al. 2010, Hyde et al. 2006, Muhlfeld and Ochs 2013), these approaches require a priori experimental planning and design and knowledge of fundamentals of stereology applied to organ samples. In fact, many of the current concepts of stereology, while founded by the seminal work of Weibel and collaborators (Weibel and GOMEZ 1962), were developed in the last 2 decades and require proper knowledge and training. These have been largely absent in the approaches in the pulmonary vascular field.

Recently, we summarized the importance of stereological methods to properly assess parameters of pulmonary vascular remodeling (Tuder 2014). Unfortunately, most of the current endpoints, including percent fully, partially, and nonmuscularized small, medium, and large pulmonary arteries or percent occluded arteries provide an unclear picture of pulmonary vascular remodeling due to errors (or biases) in their assessment. The parameter of % media thickening, which in fact conveys the volume density of media in relation to the overall arterial wall, is limited by the need of almost perfect cross sections. In our prior work (Stacher et al. 2012), we used volume of media and intima in relation to the volume of alveolar septa. This approach allowed us to analyze pulmonary arteries independent of their orientation and of the degree of lung inflation; we relied on the evidence that, in PAH, there is no evidence of alveolar destruction with emphysema. However, this assessment was limited by the lack of uniform random sampling of the entire lung, i.e., the data pertained to fragments of lungs obtained from specific regions as per protocol design. We propose that assessment of pulmonary vascular remodeling follows stereological rules (Muhlfeld and Ochs 2013), which will allow better correlation with pulmonary hemodynamics. This approach will generate more robust and stringent data, allowing better correlation with similar parameters obtained with the human diseased samples. Moreover, it will provide better quality data regarding interventions that can attenuate or overcome specific components of pulmonary vascular remodeling in PH. These experimental advantages are particularly relevant to severe PAH, often modeled in rats that received the VEGF receptor blocker SU 5416 and exposed to chronic hypoxia (Taraseviciene-Stewart et al. 2001). This model shares intima remodeling with concentric and plexiform-like lesions (Abe et al. 2010) with human PAH.

Conclusions

There have been few attempts to properly quantify the pathological alterations in PAH lungs; this limitation also pertains to other forms of pulmonary hypertension, including the highly frequent Group 3, associated with interstitial lung disease and COPD. While the clinical advances in diagnosing and managing PAH do not require pathological support, updates in

the classification (including changes in subgrouping) often rely on the pathology to cluster similar forms of the disease. There still remains the challenge of appropriately conducting stereological studies in lung with PAH, which would require systematic random sampling (Tuder 2014).

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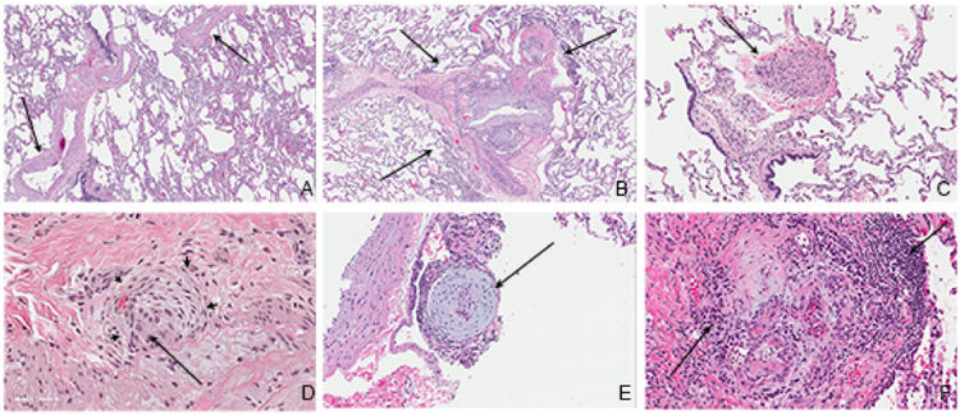

Figure 1.

A. Moderately thickened pulmonary arteries (arrows) in a normal lung, obtained as a potential graft.

B. Exuberant plexiform lesion (arrows) with whorls of endothelial cells with abnormally organized blood vessel lumina.

C. Pulmonary artery in PAH with marked intima obliteration (arrow).

D. Small cluster of endothelial cells, consistent with incipient plexiform lesion (arrow), surrounded by cells organized in concentric pattern (small arrows).

E. Pulmonary artery with cellular and mucoid intima thickening (arrow).

F. Marked inflammation around and within plexiform lesion (arrow).