Pulmonary venous remodeling in COPD-pulmonary hypertension and idiopathic pulmonary arterial hypertension

Andersen, Kasper Hasseriis; Andersen, Claus Bøgelund; Gustafsson, Finn; Carlsen, Jørn

Published in:
Pulmonary Circulation

DOI:
10.1177/2045893217709762

Publication date:
2017

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (APA):
Andersen, K. H., Andersen, C. B., Gustafsson, F., & Carlsen, J. (2017). Pulmonary venous remodeling in COPD-pulmonary hypertension and idiopathic pulmonary arterial hypertension. Pulmonary Circulation, 7(2), 514-521. https://doi.org/10.1177/2045893217709762

Research Article

Pulmonary Circulation

Pulmonary venous remodeling in COPD-pulmonary hypertension and idiopathic pulmonary arterial hypertension

Kasper Hasseriis Andersen[1], Claus Bøgelund Andersen[2], Finn Gustafsson[1] and Jørn Carlsen[1]

[1]Department of Cardiology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [2]Department of Pathology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

Abstract

Pulmonary vascular arterial remodeling is an integral and well-understood component of pulmonary hypertension (PH). In contrast, morphological alterations of pulmonary veins in PH are scarcely described. Explanted lungs (n = 101) from transplant recipients with advanced chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary arterial hypertension (IPAH) were analyzed for venous vascular involvement according to a pre-specified, semi-quantitative grading scheme, which categorizes the intensity of venous remodeling in three groups of incremental severity: venous hypertensive (VH) grade 0 = characterized by an absence of venous vascular remodeling; VH grade 1 = defined by a dominance of either arterialization or intimal fibrosis; and VH grade 2 = a substantial composite of arterialization and intimal fibrosis. Patients were grouped according to clinical and hemodynamic characteristics in three groups: COPD non-PH, COPD-PH, and IPAH, respectively. Histological specimens were examined by a cardiovascular pathologist blinded to clinical and hemodynamic data. Pathological alterations of pulmonary veins were present in all hemodynamic groups, with the following incidences of VH grade 0/1/2: 34/66/0% in COPD non-PH; 19/71/10% in COPD-PH; and 11/61/28% in IPAH. In COPD, explorative correlation analysis of venous remodeling suggested a modest positive correlation with systolic and mean pulmonary artery pressure ($P = 0.032$, respectively) and an inverse modest correlation with diffusion capacity for carbon monoxide ($P = 0.027$). In addition, venous remodeling correlated positively with the degree of arterial remodeling ($P = 0.014$). In COPD-PH and IPAH, advanced forms of pulmonary venous remodeling are present, emphasizing that the disease is not exclusively restricted to arterial lesions. In addition, venous remodeling may be related to the hemodynamic severity, but more rigorous analysis is required to clearly define potential relationships.

Keywords

pulmonary vasculature, vascular changes, pulmonary hypertension, chronic obstructive pulmonary disease, idiopathic pulmonary arterial hypertension

Date received: 28 November 2016; accepted: 18 April 2017

Pulmonary Circulation 2017; 7(2) 514–521
DOI: 10.1177/2045893217709762

Pulmonary hypertension (PH) is a hemodynamic pathophysiological disorder involving the pulmonary circulation and the right ventricle. The pathogenesis of PH includes pulmonary arterial vascular remodeling, which is an integral and well described component caused by several complex cellular and molecular mechanisms.[1] Arterial remodeling affects all three layers of the arterial vasculature, thereby narrowing or obstructing the lumen and disrupting vascular compliance and distensability.[2] By contrast, limited information regarding the involvement of pulmonary veins exists. It is increasingly believed that venous abnormalities

Corresponding author:
Jørn Carlsen, Department of Cardiology 2141, Copenhagen University Hospital, Rigshospitalet, 9-Blegdamsvej, 2100 Copenhagen, Denmark.
Email: joern.carlsen@regionh.dk

may be relevant in many clinical PH phenotypes besides pulmonary veno-occlusive disease (PVOD).[3]

This retrospective study examined explanted lungs from transplant recipients with an emphasis on pulmonary venous vascular remodeling in PH secondary to chronic obstructive pulmonary disease (COPD-PH) and idiopathic pulmonary arterial hypertension (IPAH). Specifically, the study objectives were to identify, examine, and classify pulmonary venous lesions. Next, to relate venous vascular remodeling in advanced COPD to hemodynamic and pulmonary function variables in advanced COPD. Lastly, to describe a potential correlation between the severity of arterial and venous remodeling in advanced COPD.

Methods

This was a retrospective investigation of explanted lungs from transplant recipients diagnosed with advanced COPD and IPAH at Copenhagen University Hospital, Rigshospitalet, Denmark during 1991–2015. During this period, 361 advanced COPD patients underwent lung transplantation and parallel hemodynamic assessment by right-heart catheterization (RHC) as part of the transplantation work-up program. The analysis of explanted lungs in COPD was focused on hemodynamic distinction based on the presence or absence of PH designated by the mean pulmonary artery pressure (mPAP), as follows: (1) COPD non-PH, defined by mPAP < 25 mmHg; and (2) COPD-PH, defined by mPAP ≥ 25 mmHg and pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg. These groups were compared to patients with IPAH. Patients with COPD-PH and PAWP > 15 mmHg were excluded from analysis due to a possible post-capillary contribution. We randomly selected 35 of 196 COPD non-PH patients for inclusion. The COPD-PH group comprised 35 of 119 patients with mild–moderate COPD-PH (mPAP 25–34 mmHg) who were randomly selected, as well as 13 of 15 patients with severe COPD-PH (mPAP ≥ 35 mmHg; unavailable histological material in the remaining two patients) (Fig. 1). COPD patients were compared to 18 patients with IPAH. Clinical characteristics and description of pulmonary arterial remodeling related to the PH component in the advanced COPD cohort has previously been thoroughly described.[4,5] Transplant recipients met the criteria for lung transplantation in accordance with International Society for Heart and Lung Transplantation guidelines at the time of listing.[6]

Histological analysis of pulmonary veins

Explanted lungs were formalin-inflated overnight after the transplantation procedure before being extensively sampled and embedded in paraffin. Sections (two to three from each lobe) were stained with hematoxylin and eosin (H&E). In addition, some sections were stained with Masson's trichrome, Verhoeff or with combined Alcian, Orcein and Van Gieson stains for elastin. Sections were assessed by the same experienced pulmonary cardiovascular pathologist, who was blinded to clinical and hemodynamic data.[5]

Pulmonary veins were identified by their anatomical localization to distinguish them from pre-capillary vessels. Accordingly, veins were identified in the periphery of lung lobules in the interlobular septae and trabeculae, whereas smaller pulmonary venous branches were recognized by their position adjacent to, but not appositional to, bronchovascular bundles. Serial sections were used to track and confirm connection to the larger veins localized in the trabeculae. The study focused solely on the vascular changes observed in inter- and intra-lobular pulmonary veins.

A semi-quantitative grading scheme, which was pre-specified before analysis, was used to determine pulmonary venous hypertensive (VH) remodeling of increasing complexity (Table 1). The distinct groups are broadly characterized by: VH grade 0 = non-remodeled veins; VH grade 1 = predominance of either intimal fibrosis or

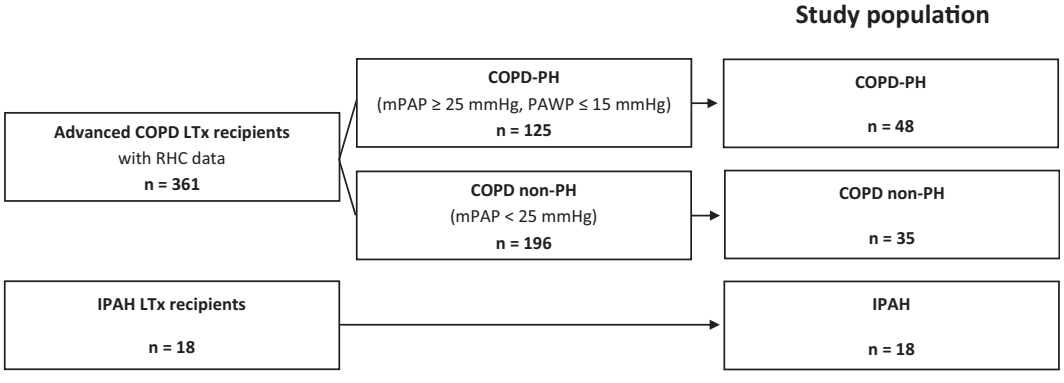

Figure 1. Study population. A total of 101 explanted lungs from transplant recipients with RHC data from pre-transplant hemodynamic evaluation. A random selection of 35/196 COPD non-PH patients were included in the analysis. Forty-eight patients with pre-capillary COPD were included, comprising a random selection of 35/110 patients with mild–moderate pre-capillary PH (mPAP 25–34 mmHg) and 13/15 with severe pre-capillary COPD-PH (unavailable histological material in two patients). Explanted lungs from 18 patients with IPAH were used as reference.

Table 1. Semi-quantitative grading scheme describing pulmonary venous hypertensive (VH) lesions of increasing complexity.

0	No discernible pulmonary venous remodeling
	- Thin-walled vessel
	- Narrow fibrous intima and discrete muscle layer
	- Single elastic lamina
1	Arterialization *or* intimal fibrosis
	- Intimal fibroelastic thickening and increased cellularity (myofibroblastic)
	- Mild elastic lamina duplication/splitting tendency
	- Mild combinations of arterialization (smooth muscle cell hypertrophy) and intimal fibrosis can occur
2	Arterialization *and* intimal fibrosis
	- Intimal fibrotic thickening and increased cellularity due to myofibroblast proliferation and deposition of collagen and elastin
	- Severe elastic lamina duplication/splitting and multi layering (often fully concentric)
	- Generally more severe arterialization and intimal fibrosis

arterialization; VH grade 2 = substantial intimal fibrosis and arterialization in conjunction. Pulmonary vascular venous changes were assessed overall and the most severe and widespread vascular lesion determined the overall degree of venous remodeling as reflected by the VH grade.

Statistical analysis

Continuous data are expressed as median (interquartile range [IQR]). Explorative correlation analysis between ordinal variables and continuous variables was investigated using Spearman's rank-order correlation test. Two-tailed asymptotic significance levels are displayed. Correlation between ordinal variables with expected monotonous relationship was analyzed using Goodman and Kruskal's Gamma (IBM SPSS/PAWP Statistics 22, Armonk, NY, USA). A significance level of $\alpha = 0.05$ was applied.

Results

Venous remodeling was explored in COPD non-PH (n = 35), pre-capillary COPD-PH (n = 48), and IPAH (n = 18) patients. Consequently, explanted lungs from 101 transplant recipients with increasing hemodynamic severity were analyzed (Fig. 1). Baseline characteristics are summarized in Table 2. The median time from evaluation to transplantation was 372 (IQR = 194–777) days.

Pathological alterations of veins were present in all groups, with the following incidences of VH grade 0/1/2: 34/66/0% in COPD non-PH; 19/71/10% in COPD-PH; and 11/61/28% in IPAH (Fig. 2). Fig. 3 illustrates the spectrum of pulmonary venous remodeling according to the introduced grading scheme, with elastin stains particularly related to remodeled veins.

Accordingly, the highest incidence of severe venous remodeling, corresponding to VH grade 2, was observed in IPAH, with a lower incidence in the COPD-PH group, but was not detected in COPD non-PH. Similarly, the lowest proportion of non-remodeled veins (VH grade 0) was observed in IPAH, while most frequently observed in COPD non-PH. Intimal fibrosis, usually without elaborate arterialization (VH grade 1), was quite evenly distributed among the groups.

Venous remodeling in COPD

Analysis of COPD patients showed that the extent of venous remodeling, assessed by VH grade scores, was statistically significantly higher in COPD-PH than in COPD non-PH (median rank 45.92 versus 36.63, Mann–Whitney *U*-test $P = 0.033$).

Explorative correlation analyses were conducted to assess the relationship between venous remodeling and hemodynamic indices in advanced COPD. We observed a modest positive correlation between the degree of venous remodeling, assessed by VH grade scores, and the systolic PAP ($r_s = 0.239$, $P = 0.032$) as well as the mPAP ($r_s = 0.235$, $P = 0.032$), whereas remaining hemodynamic indices did not correlate to the degree of venous remodeling (Table 3, Fig. 4).

Diffusion capacity for carbon monoxide (DL_{CO}) correlated modestly and inversely to the degree of venous remodeling ($r_s = -0.285$, $P = 0.027$; DL_{CO} % of predicted $r_s = -0.246$, $P = 0.056$), while no other pulmonary function variable correlated significantly (Table 3). Moreover, the analysis did not demonstrate a correlation between the extent of venous remodeling and PaO_2 ($r_s = -0.018$, $P = 0.883$) or $PaCO_2$ ($r_s = 0.202$, $P = 0.086$) (Table 3, Fig. 4).

Arterio-venous remodeling relationship in COPD

Progressive arterial lesions previously described in explanted lungs of advanced COPD patients, assessed by a modified Heath–Edwards (HE) six-grade classification scheme,[5,7] were included in a correlation analysis. Of 84 COPD patients included in this study, six (7%) showed no structural alterations, 24 (29%) presented with medial thickening of muscular arteries, 25 (30%) displayed further cellular intimal proliferation, and 26 (31%) had additional concentric intimal fibrosis, corresponding modified HE grades 0–3.

Table 2. Clinical baseline characteristics.

	COPD Non-PH (n = 35)	COPD-PH (n = 48)	IPAH (n = 18)
Age (years)	52.9 (48.7–58.8)	54.8 (50.6–58.4)	31.3 (20.6–47.8)
BMI (kg/m^2)	20.1 (18.5–24.6)	21.8 (18.8–24.1)	23.2 (20.5–25.7)
Gender (No. female [%])	23 (66)	21 (44)	12 (67)
Arterial blood gas values (mmHg)			
PaO_2	66.3 (60.7–72.3)	63.4 (55.7–71.7)	68.2 (56.6–74.8)
$PaCO_2$	42.0 (38.3–47.3)	46.2 (42.7–57.4)	29.6 (26.4–33.0)
Pulmonary function tests			
FEV_1 (L)	0.7 (0.6–0.8)	0.6 (0.5–0.7)	2.4 (1.7–3.4)
FEV_1 (% predicted)	23.6 (20.8–30.4)	18.6 (15.0–22.7)	84.7 (71.5–87.0)
FVC (L/s)	1.9 (1.5–2.2)	1.7 (1.3–2.1)	3.1 (2.6–4.3)
FVC (% predicted)	57.5 (48.3–66.1)	42.0 (33.3–57.0)	88.0 (81.3–95.5)
FEV_1/FVC (s^{-1})	0.4 (0.3–0.4)	0.4 (0.3–0.4)	0.8 (0.7–0.8)
TLC (L)	7.6 (6.2–8.6)	8.1 (6.8–9.3)	4.8 (4.4–6.3)
TLC (% predicted)	128 (113–146)	129 (117–143)	98 (91–103)
RV (L)	5.2 (3.9–5.9)	6.2 (4.7–7.1)	1.7 (1.4–2.4)
RV (% predicted)	259 (226–304)	295 (242–330)	116 (93–126)
DL_{CO} (mmol/min/kPa)	2.4 (1.8–3.7)	1.9 (1.4–2.6)	5.4 (4.5–5.6)
DL_{CO} (% predicted)	30.4 (20.5–41.1)	22.5 (15.2–25.7)	56.0 (45.5–72.2)
K_{CO} (mmol/min/kPa/L)	0.6 (0.4–0.8)	0.5 (0.4–0.7)	1.2 (1.0–1.4)
K_{CO} (% predicted)	41.0 (26.3–51.0)	32.2 (23.0–43.1)	61.2 (31.6–68.7)
Hemodynamics			
PAP (mmHg)			
Systolic	28 (25–31)	43 (37–48)	83 (74–103)
Diastolic	14 (8–17)	22 (19–26)	39 (30–45)
Mean	18 (14–22)	30 (27–36)	53 (48–70)
mRAP (mmHg)	5 (4–6)	9 (7–10)	8 (6–16)
PAWP (mmHg)	9 (8–11)	12 (10–14)	16 (10–21)
CO (L/min)	5.0 (4.2–5.8)	5.5 (4.6–6.8)	3.5 (3.0–4.4)
CI (L/min/m^2)	2.9 (2.6–3.4)	3.0 (2.7–3.6)	2.0 (1.6–2.6)
PVR (WU)	1.8 (1.0–2.6)	3.5 (2.7–4.3)	11.7 (8.4–17.6)

BMI, body mass index; CI, cardiac index; CO, cardiac output; COPD, chronic obstructive pulmonary disease; DL_{CO}, diffusion capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IPAH, idiopathic pulmonary arterial hypertension; K_{CO}; carbon monoxide transfer coefficient; mRAP, mean right atrial pressure; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RV, residual volume; TLC, total lung capacity.

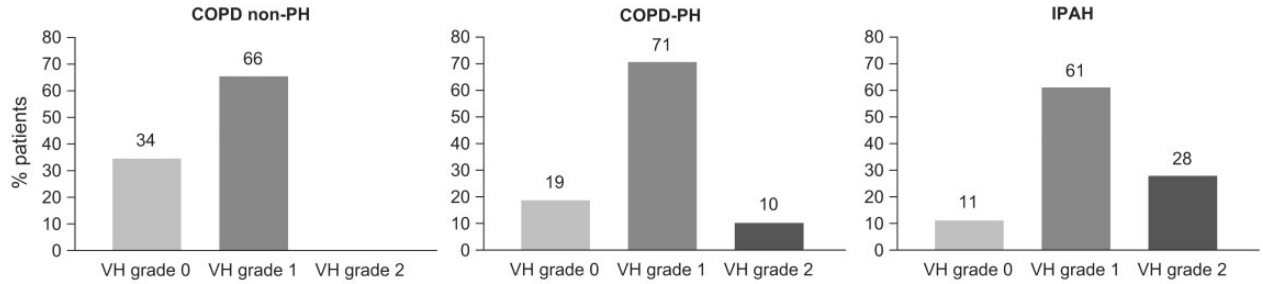

Figure 2. Incidences of venous remodeling in pre-specified groups according to the severity of venous remodeling assessed by VH-classification.

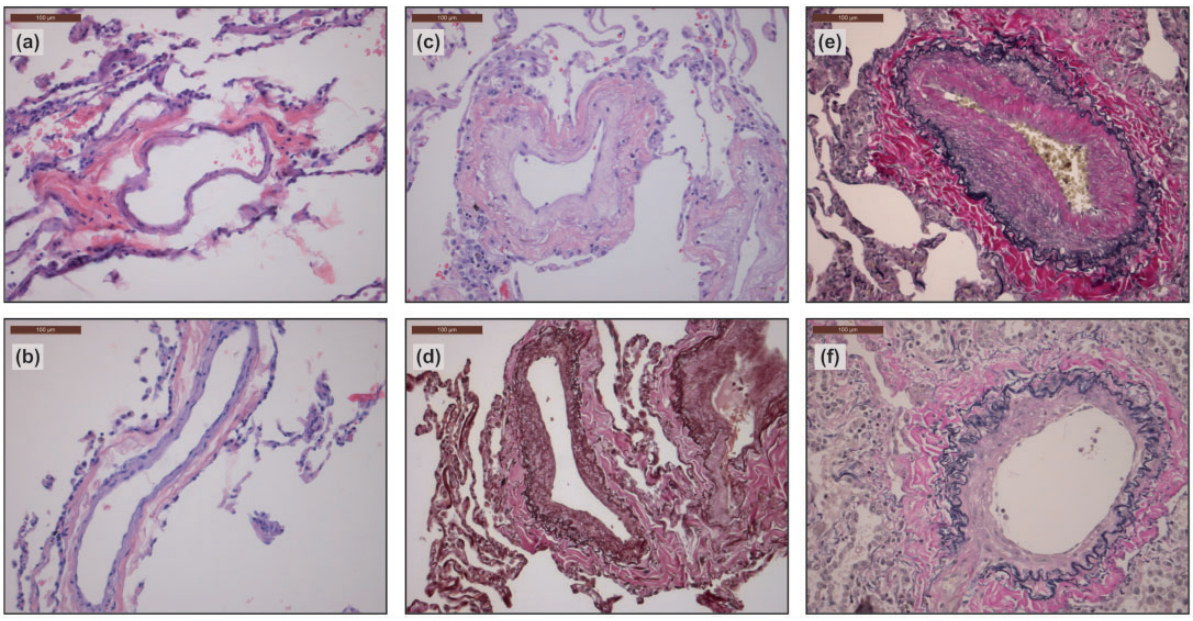

Figure 3. Histological examples of venous vascular remodeling. (a, b) VH grade 0 = vein without remodeling. Thin-walled vessel with discrete intima, delicate single-layered elastic lamina and discernable smooth muscle cells (H&E staining). (c, d) VH grade I = veins with increased vessel wall thickness, mainly due to fibroelastic deposition in the intima and a slight degree of myofibroblast proliferation. Prominent splitting/duplication of the elastic lamina. ((c) H&E staining; (d) Alcian/van Gieson/elastin staining). (e, f) VH grade 2 = increased vessel wall thickness, with more pronounced collagen and elastin deposition including myofibroblast proliferation in the intima and media. Multilayering of a split/duplicated elastic lamina in a concentric pattern combined with smooth muscle cell hypertrophy. ((e) Alcian/van Gieson/elastin staining; (f) Verhoeff staining).

Two (2%) had additional complex structural lesions comprising plexiform lesions with or without angiomatoid lesions, corresponding to modified HE grades 4–5, while no COPD patient presented with necrotizing arteritis (modified HE grade 6). The degree of venous remodeling in COPD, as denoted by VH classification, correlated positively and moderately to the severity of arterial remodeling ($G = 0.408$, $P = 0.014$).

Discussion

This study describes the frequency and severity of venous structural lesions in IPAH as well as advanced COPD with and without accompanying PH. While arterial remodeling is well-documented, venous remodeling is increasingly attracting attention in different forms of PH. However, pulmonary veins remain difficult to study. Lung venous endothelium and smooth muscle cells lack unique molecular markers to aid identification and distinction from pre-capillary vessels in humans.[8] In this study, the anatomical localization was used to isolate veins, which provides a histological distinguishing feature of the present.

Severe venous remodeling, a composite of substantial arterialization and intimal fibrosis (VH grade 2), was exclusively observed in patients with PH, and most frequently in IPAH. Moreover, the majority of IPAH patients predominantly displayed intimal fibrosis with subtle features of arterialization in veins (VH grade 1). Thus, structural alterations of the venous vasculature seem apparent in IPAH, suggesting that the disease is not exclusively restricted to the arterial vasculature, thereby challenging the traditional dogma. This finding is in agreement with observed increases in intimal and adventitial thickness of pulmonary venous walls in primary PH[9] and recently described pronounced muscular remodeling of septal veins in PAH lungs carrying *BMPR2* mutation.[10] It is noteworthy that the observed intensity of venous intimal fibrosis, irrespective of assigned grade, was not as severe as is typically characteristic for the extensive and diffuse fibrous occlusion of veins in PVOD[11,12] (Fig. 5). Furthermore, plexiform lesions (focal obliterative lesions of endothelial cell channels lined by smooth muscle cells, myofibroblasts and connective tissue matrix, typically considered a hallmark of PAH[13]) were present in 17 of 18 IPAH patients, which are not routinely observed in PVOD.[14]

The pathogenic pathways and possible genetic mediators accountable for pulmonary venous remodeling remain unknown, although mutations in *EIF2AK4* have been linked PVOD.[15] Nonetheless, venous remodeling may be more common in different clinical forms of PH than anticipated. Venous fibrotic lesions have been identified in chronic thromboembolic PH[16] while both arterialization as well as increased media, intima, and adventitial thickness of pulmonary veins in PH secondary to left heart disease have been described.[17–19] Here, we extensively describe venous remodeling in COPD. Histological analysis showed that intimal fibrosis with subtle arterialization (VH grade 1) was frequent in COPD-PH. It was also apparent in the

Table 3. Correlation between venous remodeling and clinical variables in COPD.

	Venous remodeling	
	Correlation coefficient	*P* value
Age (years)	0.162	0.148
BMI (kg/m^2)	0.060	0.597
Arterial blood gas values		
PaO_2 (mmHg)	−0.018	0.883
$PaCO_2$ (mmHg)	0.202	0.086
Pulmonary function tests		
FEV_1 (L)	−0.153	0.173
FEV_1 (% predicted)	−0.148	0.191
FVC (L/s)	−0.151	0.178
FVC (% predicted)	−0.173	0.128
FEV_1/FVC (s^{-1})	−0.005	0.961
TLC (L)	−0.017	0.633
TLC (% predicted)	−0.056	0.633
RV (L)	0.039	0.749
RV (% predicted)	0.034	0.778
DL_{CO} (mmol/min/kPa)	−0.285	0.027
DL_{CO} (% predicted)	−0.246	0.056
K_{CO} (mmol/min/kPa/L)	−0.185	0.149
K_{CO} (% predicted)	−0.193	0.136
Hemodynamics		
PAP (mmHg)		
Systolic	0.239	0.032
Diastolic	0.185	0.151
Mean	0.235	0.032
mRAP (mmHg)	0.023	0.869
PAWP (mmHg)	0.198	0.080
CO (L/min)	−0.014	0.910
CI (L/min/m^2)	−0.128	0.331
PVR (WU)	0.133	0.261

BMI, body mass index; CI, cardiac index; CO, cardiac output; COPD, chronic obstructive pulmonary disease; DL_{CO}, diffusion capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; K_{CO}; carbon monoxide transfer coefficient; mRAP, mean right atrial pressure; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RV, residual volume; TLC, total lung capacity.

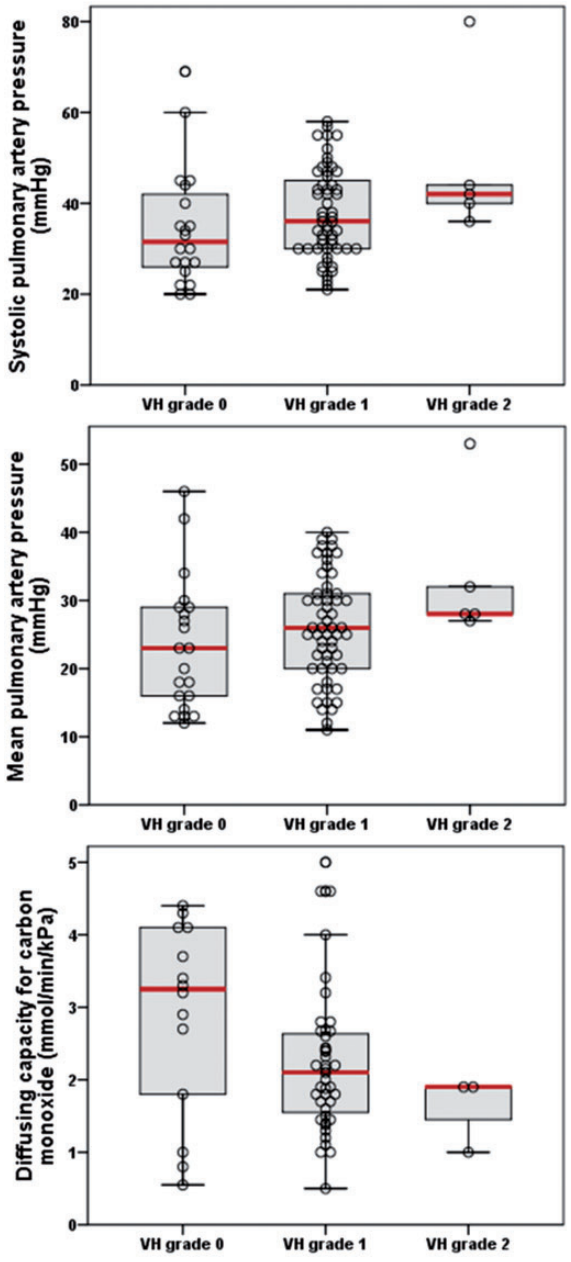

Figure 4. Plots of selected correlations according to VH-grade allocation.

COPD non-PH group, which may be expected given the fact that even arterial remodeling is evident in smokers and in COPD without PH.[5,20] Furthermore, the COPD non-PH group surely included patients with "borderline-PH" hemodynamic characteristics, in whom a vascular component and future manifest PH is likely as a consequence of hemodynamic progression.[21,22] However, the composite of marked arterialization and intimal fibrosis (VH grade 2) was only identified in COPD, when PH was present. Accordingly, advanced venous lesions similar to those observed in IPAH can be observed in COPD when PH is present. Interestingly, explorative correlation analysis suggested a positive relationship between the degree of venous remodeling and hemodynamic severity in COPD. More specifically, correlation to systolic and mPAP was observed. The relationship was modest and should be interpreted with respect to the variability and study design. Nevertheless, the association seems physiologically congruent and in accordance with the previously described (stronger) association between arterial structural lesions and hemodynamic severity in advanced COPD.[5] Whether venous remodeling, in this context, represents a cause or

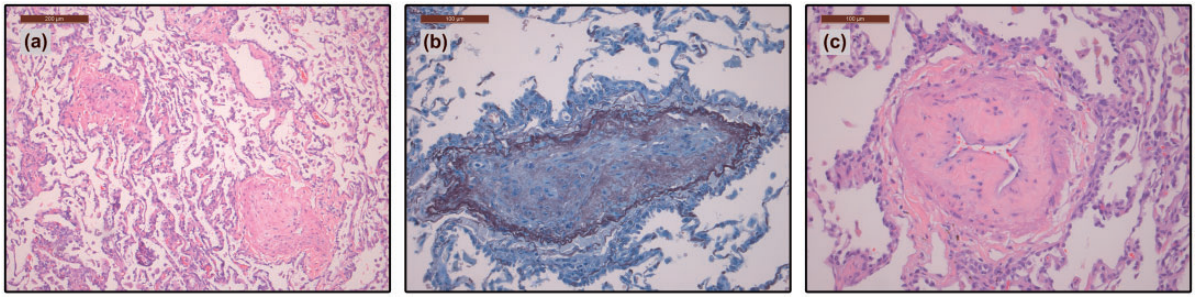

Figure 5. Venous vascular remodeling in a patient who underwent lung transplantation due to pulmonary veno-occlusive disease at our institution. (a) Partial and total occlusion of pre-septal veins with loose, cushion-like intimal fibrosis in addition to a slight capillary hemangiomatosis and numerous siderophages in the alveolar lumina. (H&E staining). (b) Totally obstructed pre-septal vein with occlusive fibroelastosis and duplication of external elastic lamina (Orcein staining). (c) Sub-totally and severely occluded pre-septal vein with cushion-like loose collagenous intimal fibrosis (H&E staining).

consequence of hemodynamic worsening remains to be clarified. Notably, the degree of arterial and venous remodeling in COPD correlated positively suggesting that both pre-capillary and post-capillary vessels in COPD react to stimuli which promote vascular remodeling. Chronic exposure to hypoxia plays a pivotal role in the development of arterial remodeling.[23] Pulmonary veins, similar to pulmonary arteries, exhibit high sensitivity to hypoxia[24] and chronic exposure can perpetuate venous arterialization,[25] which is in keeping with the overall observations of venous remodeling in advanced COPD. It should be mentioned that simultaneous presence of both noteworthy arterial and venous lesions not necessarily implied severe COPD-PH. This could suggest that "vascular phenotypes" in COPD-PH may also be evident in the mild–moderate COPD-PH spectrum. Interestingly, venous remodeling correlated negatively to DL_{CO} in the explorative correlation analysis. Consequently, DL_{CO} may potentially aid identification of COPD patients with noteworthy venous remodeling alike its supportive role in detection of PVOD in presumed PAH.[26] In this context, it is noteworthy that DL_{CO} has been identified as an independent predictor of mortality in COPD-PH.[27]

Various PH phenotypes, including COPD-PH and IPAH as shown, seem to include structural alterations of veins,[16–19] whereas PVOD ultimately represents a rare manifestation of PH with excessive venous structural changes.[28] The consequences of venous remodeling in non-PVOD PH are unknown. In particular, the specific influence of venous remodeling on the efficacy of pharmacological PAH treatment requires clarification. At present, it is challenging to relate vascular remodeling to responsiveness of pharmacological therapies or outcome, since sequential routine or even experimental biopsies are avoided due to the risk of severe complications in PH. Nonetheless, elaborate remodeling of post-capillary vessels in PH may aggravate the clinical course and alter the response to specific PAH therapy, similar to its role in PVOD.[12] Surely, the identification of pathogenic pathways, genetic mediators, and novel methods to identify patient phenotypes with venous remodeling is necessary to allow for a better understanding of the clinical implications of venous involvement in PH and may provide a basis for treatment differentiation.

Certain limitations of the study should be borne in mind. First, pulmonary veins are histologically difficult to distinguish from arteries. Given the current lack of unique pulmonary venous molecular markers, the anatomical localization is a reasonable distinctive feature although aberrations may occur in disease states. The analysis concerned a unified assessment of both inter- and intralobular veins (i.e. septal and non-septal veins) without uniform random sampling. Accordingly, the study does not allow for definite conclusion regarding the hetero- or homogeneity of remodeling in septal versus non-septal veins or the dissemination of venous remodeling related to particular lung segments. Subjectively, both septal and non-septal veins in a particular specimen presented with similar degrees of remodeling, which furthermore seemed to be equally distributed throughout the respective lung segments. Second, semi-quantitative analysis relies on subtle differences and could be subject to interpretation bias despite our efforts to avoid bias by blinding the observer to clinical and hemodynamic characteristics. Accordingly, the study design and methodology should be considered in the interpretation of the results. Nonetheless, a planimetric description is a relevant and a natural first step before more extensive and rigorous analysis with prospective computerized morphometric analysis of perfusion-fixated and dye-injected venous vessels, which can provide additional detailed insights of the venous structure, despite inherent difficulties of vessel calibration due to post-mortem vessel contraction.[29] Third, histological samples from explanted lungs may not be representative of the pathoanatomy during evaluation for transplantation. As the evolution of the vascular remodeling component over time is incompletely understood, pulmonary vascular alterations may have occurred after index RHC.

In conclusion, venous remodeling comprising intimal fibrosis and features of arterialization to a variable extent, is frequently encountered in advanced COPD and IPAH. Occasionally, venous remodeling in COPD reaches the

same advanced degree as in IPAH, when PH is present. In exploratory correlation analysis, venous remodeling in COPD correlated with the hemodynamic severity, diffusion capacity for monoxide, and the extent of arterial remodeling. This finding needs further clarification by use of state-of-the-art morphometric analysis suitable for PH. The clinical importance of venous remodeling in PH and the implications for PAH specific treatment require further investigation.

Conflict of interest

The author(s) declare that there is no conflict of interest.

Funding

This study was supported by The Heart-Center Research Foundation, Copenhagen University Hospital, Rigshospitalet, Denmark.

References

1. Humbert M, Morrell NW, Archer SL, et al. Cellular and molecular pathobiology of pulmonary arterial hypertension. *J Am Coll Cardiol* 2004; 43(12 Suppl S): 13S–24S.
2. Jeffery TK and Morrell NW. Molecular and cellular basis of pulmonary vascular remodeling in pulmonary hypertension. *Prog Cardiovasc Dis* 2002; 45(3): 173–202.
3. Tuder RM, Marecki JC, Richter A, et al. Pathology of pulmonary hypertension. *Clin Chest Med* 2007; 28(1): 23–42, vii.
4. Andersen KH, Iversen M, Kjaergaard J, et al. Prevalence, predictors, and survival in pulmonary hypertension related to end-stage chronic obstructive pulmonary disease. *J Heart Lung Transplant* 2012; 31(4): 373–380.
5. Carlsen J, Hasseriis AK, Boesgaard S, et al. Pulmonary arterial lesions in explanted lungs after transplantation correlate with severity of pulmonary hypertension in chronic obstructive pulmonary disease. *J Heart Lung Transplant* 2013; 32(3): 347–354.
6. Orens JB, Estenne M, Arcasoy S, et al. International guidelines for the selection of lung transplant candidates: 2006 update–a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2006; 25(7): 745–755.
7. Heath D and Edwards JE. The pathology of hypertensive pulmonary vascular disease; a description of six grades of structural changes in the pulmonary arteries with special reference to congenital cardiac septal defects. *Circulation* 1958; 18(4 Part 1): 533–547.
8. Tuder RM, Archer SL, Dorfmüller P, et al. Relevant issues in the pathology and pathobiology of pulmonary hypertension. *J Am Coll Cardiol* 2013; 62(25 Suppl): D4–12.
9. Chazova I, Loyd JE, Zhdanov VS, et al. Pulmonary artery adventitial changes and venous involvement in primary pulmonary hypertension. *Am J Pathol* 1995; 146(2): 389–397.
10. Ghigna M-R, Guignabert C, Montani D, et al. BMPR2 mutation status influences bronchial vascular changes in pulmonary arterial hypertension. *Eur Respir J* 2016; 48(6): 1668–1681.
11. Mandel J, Mark EJ and Hales CA. Pulmonary veno-occlusive disease. *Am J Respir Crit Care Med* 2000; 162(5): 1964–1973.
12. Montani D, Price LC, Dorfmuller P, et al. Pulmonary veno-occlusive disease. *Eur Respir J* 2009; 33(1): 189–200.
13. Pietra GG, Capron F, Stewart S, et al. Pathologic assessment of vasculopathies in pulmonary hypertension. *J Am Coll Cardiol* 2004; 43(12 Suppl S): 25S–32S.
14. Montani D, O'Callaghan DS, Savale L, et al. Pulmonary veno-occlusive disease: recent progress and current challenges. *Respir Med* 2010; 104 Suppl: S23–32.
15. Eyries M, Montani D, Girerd B, et al. EIF2AK4 mutations cause pulmonary veno-occlusive disease, a recessive form of pulmonary hypertension. *Nat Genet* 2014; 46(1): 65–69.
16. Dorfmüller P, Günther S, Ghigna M-R, et al. Microvascular disease in chronic thromboembolic pulmonary hypertension: a role for pulmonary veins and systemic vasculature. *Eur Respir J* 2014; 44(5): 1275–1288.
17. Heath D and Edwards JE. Histological changes in the lung in diseases associated with pulmonary venous hypertension. *Br J Dis Chest* 1959; 53(1): 8–18.
18. Wagenvoort CA. Morphologic changes in intrapulmonary veins. *Hum Pathol* 1970; 1(2): 205–213.
19. Hunt JM, Bethea B, Liu X, et al. Pulmonary veins in the normal lung and pulmonary hypertension due to left heart disease. *Am J Physiol Lung Cell Mol Physiol* 2013; 305(10): L725–736.
20. Santos S, Peinado VI, Ramírez J, et al. Characterization of pulmonary vascular remodelling in smokers and patients with mild COPD. *Eur Respir J* 2002; 19(4): 632–638.
21. Weitzenblum E, Sautegeau A, Ehrhart M, et al. Long-term course of pulmonary arterial pressure in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1984; 130(6): 993–998.
22. Kessler R, Faller M, Weitzenblum E, et al. 'Natural history' of pulmonary hypertension in a series of 131 patients with chronic obstructive lung disease. *Am J Respir Crit Care Med* 2001; 164(2): 219–224.
23. Wrobel JP, Thompson BR and Williams TJ. Mechanisms of pulmonary hypertension in chronic obstructive pulmonary disease: a pathophysiologic review. *J Heart Lung Transplant* 2012; 31(6): 557–564.
24. Gao Y and Raj JU. Role of veins in regulation of pulmonary circulation. *Am J Physiol Lung Cell Mol Physiol* 2005; 288(2): L213–226.
25. Wagenvoort CA and Wagenvoort N. Pulmonary veins in high-altitude residents: a morphometric study. *Thorax* 1982; 37(12): 931–935.
26. Montani D, Achouh L, Dorfmüller P, et al. Pulmonary veno-occlusive disease: clinical, functional, radiologic, and hemodynamic characteristics and outcome of 24 cases confirmed by histology. *Medicine (Baltimore)* 2008; 87(4): 220–233.
27. Hurdman J, Condliffe R, Elliot CA, et al. Pulmonary hypertension in COPD: results from the ASPIRE registry. *Eur Respir J* 2013; 41(6): 1292–1301.
28. Brewer DB and Humphreys DR. Primary pulmonary hypertension with obstructive venous lesions. *Br Heart J* 1960; 22: 445–448.
29. Wright JL, Petty T and Thurlbeck WM. Analysis of the structure of the muscular pulmonary arteries in patients with pulmonary hypertension and COPD: National Institutes of Health nocturnal oxygen therapy trial. *Lung* 1992; 170(2): 109–124.