Original paper

Pulmonary vascular alterations in explanted lung after transplantation

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Widespread pulmonary destruction and fibrosis can be seen in end-stage pulmonary diseases. This situation causes vascular remodeling of the pulmonary circulation and pulmonary hypertension. Lung transplantation is an alternative treatment for end-stage pulmonary diseases. The purpose of this study is to research pathological vascular alterations retrospectively in explanted lungs with or without pulmonary hypertension.

57 explanted lungs were evaluated for occlusive intimal fibroelastosis, smooth muscle proliferation, medial hypertrophy, intimal cellular or fibrous thickening, hemosiderosis, plexiform lesion, angiomatoid lesion, arteriosclerosis, venopathy, capillary duplication and arteriovenous malformation. Both systolic and mean pulmonary artery pressures were defined. The relationship between vascular patterns and pulmonary hypertension was investigated.

Pathological vascular alterations in explanted lungs with or without pulmonary hypertension included medial hypertrophy (80.71%), intimal cellular or fibrous thickening (80.7%), arteriosclerosis (77.19%), smooth muscle proliferation (55.3%) and arteriovenous malformation (50.3%). Hemosiderosis (12.5%), plexiform lesion (14%) and venopathy (21%) were less frequent pathological vascular alterations. Capillary duplication was common in secondary pulmonary hypertension and was statistically meaningful.

Although medial hypertrophy and intimal thickness were seen in pulmonary hypertension, they can also be observed in end-stage pulmonary diseases without pulmonary hypertension. Interstitial capillary duplication was an important histopathological finding in end-stage lung diseases with pulmonary arterial hypertension.

Key words: pulmonary hypertension, pulmonary remodeling, lung transplantation, vasculopathy, arteriovenous malformations.

Introduction

Interstitial lung diseases, chronic obstructive lung disease (COPD), bronchiectasia, Kartegener syndrome, and α-1 thyripsin deficiency are chronic progressive diseases, which bring about worsening of the respiratory condition leading to death. These diseases are resulting end-stage pulmonary diseases. Patients with end-stage pulmonary diseases are prone to developing pulmonary hypertension [1].

The extension of fibrosis and reduction of alveoli are leading causes of vascular changes and pulmonary hypertension. Pulmonary vascular lesions in end-stage idiopathic pulmonary fibrosis, Langerhans cell histiocytosis and obliterative bronchiolitis were investigated previously [2, 3, 4]. However, the correlation between histopathologic pulmonary vascular features and pulmonary hypertension in end-stage pulmonary diseases is not available. Lung transplantation is an acceptable treatment for end-stage pulmonary diseases, which provides longer survival time and life quality. The explanted lung is the most important source for histopathological investigation of end-stage pulmonary diseases. Therefore we designed a retrospective study on explanted specimens. The objectives of the study were as follows: (1) to evaluate pulmonary vascular changes underlying vascular remodeling in end-stage pulmonary diseases (2) to correlate pulmonary hypertension with vascular changes.

Materials and methods

Patients

The Medical Expertise Training Committee has reviewed and approved this study, and all the patients signed an informed consent form. This was a retrospective study of 57 patients who underwent single and double lung transplantation in our center from December 2013 to January 2019. Age, gender, transplantation indication and type of transplantation were retrieved. The transplantation indication of our cases was divided into three groups as emphysematous, fibrotic and suppurative.

Pathological examination of explanted lungs

All explanted lungs were fixed with 10% buffered formalin. For each specimen, at least ten blocks of lung tissue taken macroscopically had abnormal appearing lungs, of which the upper (four blocks), middle (two blocks) and lower lobes (four blocks) were available. Vascular resection margin and bronchial resection margin were sampled. The pathological specimens were sectioned and stained with hematoxylin and eosin (HE), elastic Verhoeff Van Gieson stain for vessel identification, an masson trichrom for fibrosis, Prussian blue for hemosiderosis .

Pulmonary vessels were analyzed in all sections. The following modifications were investigated: occlusive intimal fibroelastosis, smooth muscle proliferation, medial hypertrophy, intimal cellular or fibrous thickening, hemosiderosis, plexiform lesion, angiomatoid lesion, atherosclerosis, venopathy, capillary duplication and arteriovenous malformation. Vascular abnormalities were reported as present or absent.

Atherosclerotic lesions were evaluated in the vascular resection margin. When calcification was observed with atheromatous plaque consisting of foamed macrophage and connective tissue at the vascular surgery border, it was evaluated as an atherosclerotic lesion [5]. Areas consisting of dilated vessels with different diameters and wall thickness were recorded as arterio-venous malformations (6). Diffuse intimal fibrosis or chronic perivenous inflammation and occlusion findings in the veins were evaluated as venopathy. Verhoeffs elastic stain was used to separate the veins from the arteries [4]. Increased number of congested alveolar capillaries in interstitium in the areas where the lung preserves its structure was evaluated as capillary duplication [2]

Occlusive intimal fibroelastosis, smooth muscle proliferation, medial hypertrophy, intimal cellular or fibrous thickening, hemosiderosis, plexiform lesion and angiomatoid lesion investigated in the parenchyma were the patterns used for the histological grading of hypertensive pulmonary arterial hypertension [7, 8, 9].

Pulmonary hemodynamic assessment

Pulmonary artery pressure is normally lower than systemic blood pressure. Normal mean pulmonary artery pressure is 10-15 mmHg, and systolic pulmonary artery pressure is 18-25 mmHg, at rest. However, systolic pulmonary artery pressure that is higher than 40 mmHg is referred to as pulmonary hypertension. Pulmonary hypertension is used to describe an increase in pulmonary artery pressure. Both systolic and mean pulmonary artery pressures were defined by either echocardiography (ECHO) or pulmonary catheterization [10].

Statistical analysis

The pathological data were expressed using statistical analyses, which were conducted using the SPSS statistical software package (version 17.0, SPSS, Chicago, Illinois, United States). The t-test and one-way ANOVA test (Scheffe test and Tamhane test) were used to analyze the potential differences between study groups. In cases where a difference was detected between the groups, the Levene test was used to check the differences between the variances and to identify which group was the source of the difference. The variances were not equal when p values were < 0.05 based on the Levene test; variances were considered equal when p values were > 0.05 based on the Levene test. Based on t-tests and one-way ANOVA test (Scheffe test and Tamhane test), p values of < 0.05 were considered statistically significant [11].

Table I. The demographical properties of lung transplant recipients

Parameters/Patient characteristics	Emphysematous (range/n; %)	Fibrotic (range/n; %)	Suppurative (range/n; %)	General average/ Total (range/n; %)
Age at transplant	54.2 year (28-65)	44.4 year (25-61)	37.7 year (19-59)	46.9 year (19-65)
Sex				
Male	19 (33.3%)	24 (42.1%)	5 (8.8%)	48 (84.2%)
Female	1 (1.8%)	5 (8.8%)	3 (5.2%)	9 (15.8%)
Transplant Indication				
COPD-emphysema	19 (33.3%)	NA	NA	19 (33.3%)
A-1 antitrypsin deficiency	1 (1.8%)	NA	NA	1 (1.8%)
Idiopathic pulmonary fibrosis	NA	14 (24.6%)	NA	14 (24.4%)
Silicosis	NA	5 (8.8%)	NA	5 (8.8%)
Langerhans' cell histiocytosis	NA	3 (5.2%)	NA	3 (5.2%)
Non-specific interstitial pneumonia	NA	2 (3.5%)	NA	2 (3.5%)
Alveolar lipoproteinosis	NA	1 (1.8%)	NA	1 (1.8%)
Bronchiolitis obliterans	NA	1 (1.8%)	NA	1 (1.8%)
Adult respiratory distress syndrome	NA	1 (1.8%)	NA	1 (1.8%)
Graft versus host disease	NA	1 (1.8%)	NA	1 (1.8%)
Lymphanjioleiomyomatosis	NA	1 (1.8%)	NA	1 (1.8%)
Bronchiectasis	NA	NA	7* (12.3%)	7 (12.2%)
Cystic fibrosis	NA	NA	1 (1.8%)	1 (1.8%)
Type of transplant				
Bilateral sequential lung transplantation	19 (33.3%)	25 (43.9%)	7 (12.3%)	51 (89.5%)
Single lung transplantation	1 (1.8%)	4 (7.0%)	1 (1.8%)	6 (10.5%)

NA – not applicable; COPD – chronic obstructive pulmonary disease

** – Two patients in this category was bronchiectasis secondary to Kartagener's Syndrome*

Results

Characteristics of the patients

A total of 57 cases were included in the study between 2013 and 2019. Bilateral sequential lung transplantation was performed in 51 (89.5%) cases and single lung transplantation was performed in six (10.5%) cases. The youngest of 48 male and nine female patients was 19 years old and the oldest was 65 years old. The cases (n = 57) were divided into three groups as emphysematous (n = 20), fibrotic (n = 29) and suppurative (n = 8; Table I).

The fibrotic group consisted of idiopathic pulmonary fibrosis (IPF), Non-specific interstitial pneumonia (NSIP), silicosis, Langerhans' cell histiocytosis, alveolar lipoproteinosis, bronchiolitis obliterans (BO), adult respiratory distress syndrome, graft versus host disease and lymphanjioleiomyomatosis. The youngest patient in the fibrotic group was 25 and the oldest was 61 years old. Twenty-four were men and five were women. The most frequently observed patients in the fibrotic group were those diagnosed with IPF (n = 14).

The emphysematous group consisted of COPD (n = 19) and α 1-antitrypsin deficiency (n = 1). The age range of patients ranged from 28 to 65, with 19 male patients and one female patient.

The suppurative group consisted of patients with bronchiectasis (n = 7) and cystic fibrosis (n = 1). Two patients in the bronchiectasis group were followed by Kartagener's Syndrome. Five were male and three were female. The youngest was 19 and the oldest was 59 years old.

The relationship between pulmonary hypertension and pathological vascular changes

Pathological vascular alterations in explanted lung with or without pulmonary hypertension were medial hypertrophy (80.71%), intimal cellular or fibrous thickening (80.7%), arteriosclerosis (77.19%), smooth muscle proliferation (54.3%) and arteriovenous malformation (50.3%) (Fig. 1). Hemosiderosis (12.5%), plexiform lesion (14%) and venopathy

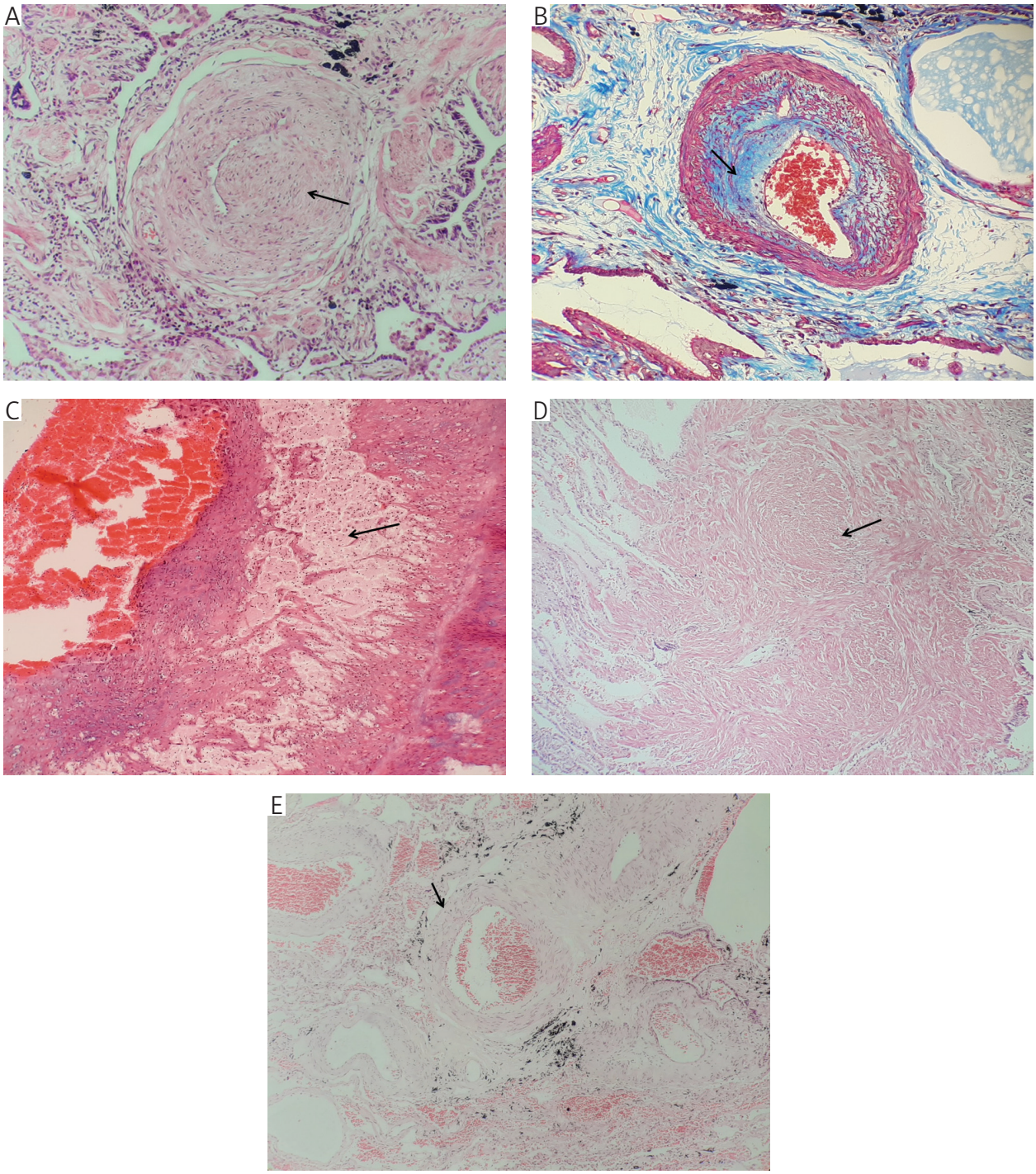

Fig. 1. A) Example of a pulmonary artery demonstrating medial muscle hypertrophy. Arrow shows thickened media (HE, magnification 100×). B) Arrow shows intimal fibrous thickening due to collagen deposition (Masson's trichrome, magnification 100×). C) Arrow shows atheromatous plaque consisting of foamed macrophage and connective tissue in the vascular resection margin (HE, magnification 100×). D) Arrow shows smooth muscle proliferation in the interstitium (HE, magnification 40×). E) Arteriovenous malformation consisting of dilated vessels. Arrow shows dilated vessels (HE, magnification 40×)

(21%) were less frequent pathological vascular alterations (Fig. 2).

The fibrotic, emphysematous and suppurative groups were compared in terms of the frequency of the histopathological parameters investigated (Table II). Occlusive intimal fibroelastosis and smooth muscle proliferation were more common in the fibrotic group than in the emphysematous group ($p < 0.05$, $p = 0.013$, $p = 0.012$). Intimal cellular or fibrous thickening was more common in the

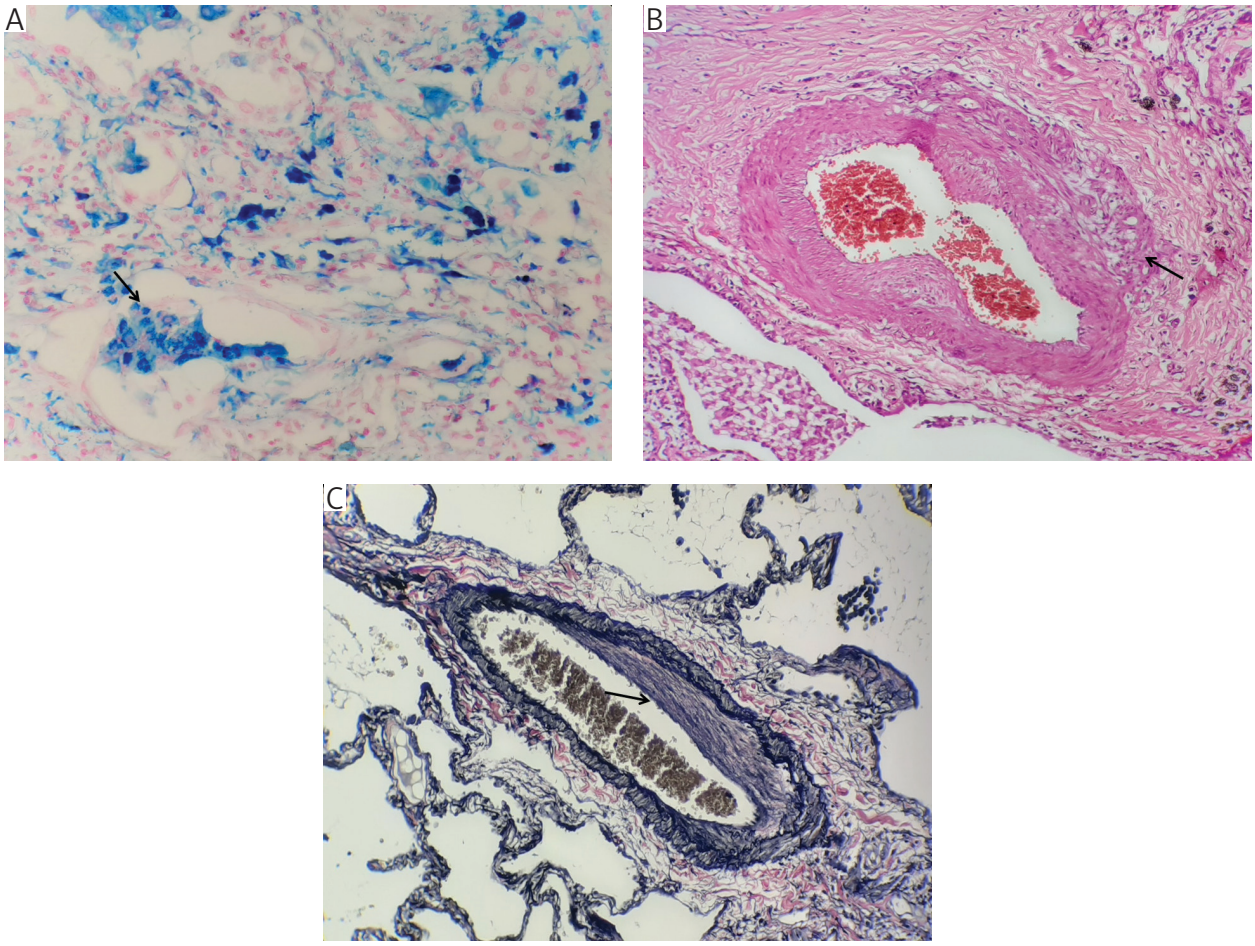

Fig. 2. A) Iron deposition is found in alveolar macrophages. Arrow shows iron deposition in macrophages and interstitium (Prussian blue, magnification 400×). B) Arrow shows an artery and an adjacent plexiform proliferation of primitive endothelial tubules and capillaries (HE, magnification 100×). C) Venopathy characterized by intimal thickening with fibrous tissue. Arrow shows fibrous tissue in the intima (elastic Verhoeff Van Gieson, magnification 100×)

emphysematous group than in the suppurative group ($p < 0.05$, $p = 0.014$). Plexiform lesions were more common in the fibrotic group than in the emphysematous group ($p < 0.05$, $p = 0.034$). Arteriovenous malformations were more common in the emphysematous and suppurative groups than in the fibrotic group ($p < 0.05$, $p = 0.01$, $p = 0.01$). There was no difference between the groups in terms of the frequency of other histopathological parameters.

Before transplantation, systolic and mean pulmonary artery pressures were detected by ECHO or pulmonary artery catheterization. Pulmonary hypertension was defined as a mean pulmonary artery pressure > 25 mmHg or systolic pulmonary artery pressure > 40 mmHg. It was observed that there was no statistically significant difference between patients with normal pulmonary artery pressure and those with pulmonary hypertension in terms of histopathological parameters other than capillary duplication (Fig. 3). Capillary duplication is more common and statistically significant in patients with pulmonary hypertension than in those without pulmonary hypertension (13 [22.81%] vs. 4 [7.02%], $p < 0.05$, $p = 0.038$; Table III).

Discussion

The main function of the lung is to change carbon dioxide in the blood to oxygen. The pulmonary vascular system is specialized to perform this function. The pulmonary vascular structure receives the entire cardiac output. Pulmonary circulation is low-pressure to distribute cardiac output to all parts of the lung and is 10 mmHg at rest. Structural changes in explant lungs in patients undergoing lung transplantation disrupt carbon dioxide and oxygen exchange. Pulmonary parenchymal loss leads to vascular remodeling [12]. Not only primary disease but also vascular changes are observed in explant materials. The morphological features of this remodeling determines the clinical situation. The most important finding of vascular changes is pulmonary hypertension. Parenchymal diseases of the lung are one of the most important causes of pulmonary hypertension. However,

Table II. Statistical analyses of pathological parameters between emphysematous, fibrotic, and suppurative groups, neglecting pulmonary pressure

Parameter (Total %)	Lung Pathology Group	Positive (n/%)	Negative (n/%)	Statistics (One-way ANOVA) (A vs. B [Test method; p value])
Occlusive intimal fibroelastozis (29.83%)	Emphysematous	2 (3.51%)	18 (31.58%)	Emphysematous vs. fibrotic (Tamhane; $p < 0.05$, $p = 0.013$)
	Fibrotic	13 (22.81%)	16 (28.07%)	
	Suppurative	2 (3.51%)	6 (10.52%)	
Smooth muscle proliferation (54.38%)	Emphysematous	6 (10.52%)	14 (24.56%)	Emphysematous vs. fibrotic (Scheffe; $p < 0.05$, $p = 0.012$)
	Fibrotic	21 (36.84%)	8 (14.04%)	
	Suppurative	4 (7.02%)	4 (7.02%)	
Medial hypertrophy (80.71%)	Emphysematous	14 (24.56%)	6 (10.52%)	No statistically significance was calculated between groups
	Fibrotic	25 (43.86%)	4 (7.02%)	
	Suppurative	7 (12.29%)	1 (1.75%)	
Intimal cellular or fibrous thickening (80.7%)	Emphysematous	13 (22.81%)	7 (12.28%)	Emphysematous vs. suppurative (Tamhane; $p < 0.05$, $p = 0.014$)
	Fibrotic	25 (43.85%)	4 (7.02%)	
	Suppurative	8 (14.04%)	0 (0.0%)	
Hemosiderosis (10.53%)	Emphysematous	1 (1.75%)	19 (33.33%)	No statistically significance was calculated between groups
	Fibrotic	4 (7.03%)	25 (43.86%)	
	Suppurative	1 (1.75%)	7 (12.28%)	
Plexiform lesion (14.03%)	Emphysematous	0 (0.0%)	20 (35.08%)	Emphysematous vs. fibrotic (Tamhane; $p < 0.05$, $p = 0.034$)
	Fibrotic	6 (10.52%)	23 (40.35%)	
	Suppurative	2 (3.51%)	6 (10.52%)	
Angiomatoid lesion (45.62%)	Emphysematous	10 (17.54%)	10 (17.55%)	No statistically significance was calculated between groups
	Fibrotic	14 (24.57%)	15 (26.32%)	
	Suppurative	2 (3.51%)	6 (10.52%)	
Arteriosclerosis (77.19%)	Emphysematous	15 (26.32%)	5 (8.77%)	No statistically significance was calculated between groups
	Fibrotic	25 (43.85%)	4 (7.02%)	
	Suppurative	4 (7.02%)	4 (7.02%)	
Venopathy (21.06%)	Emphysematous	8 (14.04%)	12 (21.05%)	No statistically significance was calculated between groups. However, the relationship between emphysematous and fibrotic groups was near significance border (Tamhane; $p = 0.076$)
	Fibrotic	3 (5.27%)	26 (45.61%)	
	Suppurative	1 (1.75%)	7 (12.28%)	
Capillary duplication (29.83%)	Emphysematous	4 (7.02%)	16 (28.07%)	No statistically significance was calculated between groups
	Fibrotic	10 (17.54%)	19 (33.33%)	
	Suppurative	3 (5.27%)	5 (8.77%)	
Arteriovenous malformation (50.88%)	Emphysematous	16 (28.08%)	4 (7.02%)	Emphysematous vs. Fibrotic (Scheffe; $p < 0.05$, $p = 0.01$) Fibrotic vs. suppurative (Scheffe; $p < 0.05$, $p = 0.01$)
	Fibrotic	6 (10.52%)	23 (40.35%)	
	Suppurative	7 (12.28%)	1 (1.75%)	

pulmonary hypertension does not develop clinically in every patient, even in the end-stage. In our study, we observed medial hypertrophy in the artery walls with intimal cellular or fibrous thickening, which is a symptom of pulmonary arterial hypertension, even in patients with normal pulmonary blood pressure. These two vascular changes are the two most common findings in patients with PAH in many studies [2, 3]. Although the pathogenesis of PAH is not fully understood, it suggests that intimal cellular or fibrous thickening and medial hypertrophy in the artery walls do not constitute PAH alone. This may be

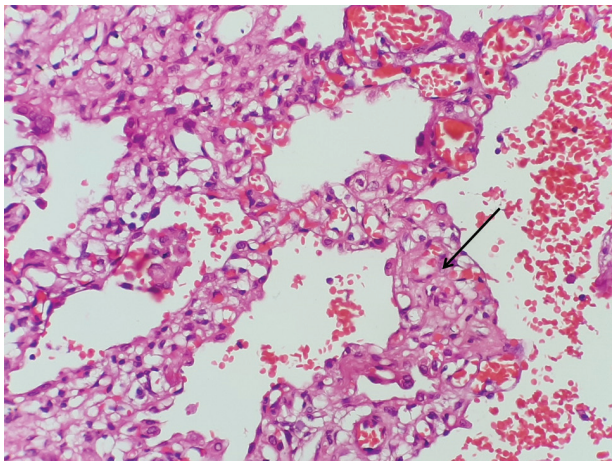

Fig. 3. There are many capillaries within an alveolar septum . Arrow shows capillary duplication in the interstitium. (HE, magnification 400×)

a common sign of vascular remodeling or loss of alveolar function independent of etiology.

The most important difference between primary PAH and secondary PAH is that plexiform and angiomatoid lesions are less frequent in secondary PAH [13]. In our cases, plexiform lesions were observed at a rate of 14.03%. In our study, we more frequently observed plexiform lesions in the fibrotic group than in the emphysematous group. This may be due to the fact that vascular remodeling induced by fibrosis in patients forming the fibrotic group uses mechanisms similar to those of primary PAH.

Colombat *et al*. detected different types of vascular changes in areas where patients with IPF retain their normal structure. Occlusion of pulmonary venules, alveolar capillary multiplication and muscular hyperplasia in the arteries are the most common vascular

Table III. Statistical analyses of pathological parameters between secondary pulmonary hypertension cases with normal pulmonary pressure cases after lung transplantation

Parameter	Positive or Negative	Pulmonary Hypertension Group (mean PAB ≥ 25 mmHg) (n/%) Group-A	Normal Pulmonary Pressure Group (mean PAB < 25 mmHg) (n/%) Group-B	Statistics (t-test) (A vs. B [Test method; p value])
Occlusive Intimal Fibroelastozis	Positive	13 (22.82%)	5 (8.77%)	No statistically significance was calculated between Group A and B (p = 0.092)
	Negative	19 (33.33%)	20 (35.08%)	
Smooth Muscle Proliferation	Positive	17 (29.82%)	14 (24.57%)	No statistically significance was calculated between Group A and B (p = 0.832)
	Negative	15 (26.32%)	11 (19.29%)	
Medial Hypertrophy	Positive	28 (49.12%)	18 (31.58%)	No statistically significance was calculated between Group A and B (p = 0.163)
	Negative	4 (7.02%)	7 (12.28%)	
Intimal Cellular or Fibrous Thickening	Positive	27 (47.38%)	19 (33.33%)	No statistically significance was calculated between Group A and B (p = 0.436)
	Negative	5 (8.77%)	6 (10.52%)	
Hemosiderosis	Positive	5 (8.77%)	2 (3.51%)	No statistically significance was calculated between Group A and B (p = 0.393)
	Negative	27 (47.37%)	23 (40.35%)	
Plexiform Lesion	Positive	6 (10.52%)	2 (3.51%)	No statistically significance was calculated between Group A and B (p = 0.234)
	Negative	26 (45.62%)	23 (40.35%)	
Angiomatoid Lesion	Positive	16 (28.07%)	10 (17.54%)	No statistically significance was calculated between Group A and B (p = 0.461)
	Negative	16 (28.07%)	15 (26.32%)	
Arteriosclerosis	Positive	24 (42.11%)	20 (35.08%)	No statistically significance was calculated between Group A and B (p = 0.662)
	Negative	8 (14.04%)	5 (8.77%)	
Venopathy	Positive	5 (8.77%)	7 (12.28%)	No statistically significance was calculated between Group A and B (p = 0.277)
	Negative	27 (47.37%)	18 (31.58%)	
Capillary Duplication	Positive	13 (22.81%)	4 (7.02%)	Group A vs. Group B (p < 0.05, p = 0.038)
	Negative	19 (33.33%)	21 (36.84%)	
Arteriovenous Malformation	Positive	15 (26.32%)	14 (24.57%)	No statistically significance was calculated between Group A and B (p = 0.503)
	Negative	17 (29.82%)	11 (19.29%)	

lesions [2]. In our study, although there was no difference between the groups, medial hypertrophy was common in the fibrotic group.

Fartoukh and colleagues have observed intimal fibrosis and medial hypertrophy in the arteries in patients with Langerhans cell histiocytosis. Venular obliteration, hemosiderosis and capillary dilation were observed in one-third of the cases. Similar changes were also observed in the unaffected areas of the parenchyma in half of the cases. In the same study, intimal fibrosis and medial hypertrophy in the arteries were observed in patients with pulmonary hypertension, COPD and IPF. They detected veno-occulusive-like disease characterized by venular obliteration, hemosiderosis and capillary dilation only in patients with Langerhans cell histiocytosis [3]. We detected only 10.53% of our hemosiderosis cases. Although it was observed most frequently in the fibrotic group, we did not see a statistically significant difference between the groups.

Smooth muscle hyperplasia in the parenchyma is observed in patients with severe pulmonary hypertension [14, 15]. However, although none of our cases had severe PAH, we detected smooth muscle hyperplasia in 54.38% of the cases. We think that in patients with secondary PAH, parenchymal smooth muscle hyperplasia is not directly proportional to the severity of blood pressure and is due to parenchymal changes caused by primary disease.

Arteriosclerosis is the focal thickening of the intima that causes serious diseases such as heart attack and cerebrovascular diseases. Studies have shown that the thickness of the internal elastic laminate of the arteries affects arterial involvement. The internal elastic lamina of the peripheral arteries is thinner and not dense. Therefore it is more involved than the cerebral arteries [16]. In our study, we observed arteriosclerosis findings characterized by atheroma plaques and calcification at the vascular surgical margin in 77.19% of the explant lungs. Studies have shown that coronary artery disease is higher in transplant candidates with fibrotic lung disease than in patients with emphysema. Therefore the inflammatory process in end-stage lung diseases is not only limited to the lungs but is a systemic process [17, 18]. This situation explains the frequency of histopathological findings of arteriosclerosis in our cases.

It is the third group of PAH that is secondary to lung diseases and hypoxia, according to the Evian classification. Hypoxia is the primary cause. Small pulmonary artery vasoconstriction underlies the pathogenesis. The prognosis depends on the severity of the pulmonary disease rather than the hemodynamic disorder. Histopathologically, medial hypertrophy and smooth muscle proliferation spread to the periphery in small arteries. Pulmonary capillary hemangiomatosis, on the other hand, is a proliferation of capillaries in the interstitium that causes pulmonary hypertension [19]. Studies have shown that interstitial capillary proliferation develops in the lungs of patients who develop PAH on the fibrotic ground associated with systemic sclerosis [20]. In our study, a statistically significant difference was observed between patients with normal pulmonary artery pressure and those with PAH in terms of interstitial capillary duplication. Interstitial capillary duplication is histologically similar to capillary hemangiomatosis. In our study, we found that secondary hypertension is an important histopathological finding in end-stage lung diseases.

Although pulmonary hypertension is a disease of the arteries, venous diseases are also an important entity in this group. Both arterial and venous remodeling are observed in all forms of pulmonary hypertension, including interstitial lung diseases. Saggar *et al.* detected venopathy consisting of obliteration, perivenous mononuclear cell infiltration and secondary capillary congestion in pulmonary veins in bronchiolitis obliterans patients with pulmonary hypertension [4]. Normal pulmonary veins do not have a double elastic layer and contain a thin muscular layer. When remodeling, they cannot be distinguished from the artery as "arterialized". Therefore it is difficult to examine venous remodeling without certain molecular markers [21]. In our study, we examined the interlobular septa and the subpleural areas by applying verhoff elestica paint, in which the veins can be observed more easily in terms of venopathy. We detected venopathy most frequently in the emphysematous group. However, we could not detect its relationship with pulmonary hypertension. Stacher *et al*. did not find a relationship between venous remodeling and arterial media and intima thickness in patients with pulmonary arterial hypertension and scleroderma [22]. The remodeling of pulmonary veins and venules is at the forefront, especially in patients with PAH due to connective tissue diseases. These patients are therefore resistant to PAH treatment [23]. Genetic studies on mRNA and protein levels in lung explants have shown that pulmonary venous occlusive disease shares more features with IPF than PAH [24].

In our study, we detected arteriovenous malformation in 50.8% of all cases in all three groups, mostly in the emphysematous group. The most common cause of pulmonary arteriovenous malformations is hereditary hemorrhagic telangiectasia [25]. Acquired arteriovenous malformation; infections such as hepatic cirrhosis, mitral stenosis, actinomycosis, cystosomiasis, tuberculosis, hydatid cyst develop as a result of metastatic carcinoma or trauma. Neovascularization in the area of inflammation is the main mechanism for the development of arteriovenous malformation [26]. Prolonged inflammation is also

included in the etiology of PAH. Especially perivascular lymphoid infiltrations consisting of lymphocytes have been shown to correlate with pulmonary vascular remodeling parameters and hemodynamic parameters in PAH. The interaction between specialized cells and soluble factors creates an inflammatory response to infection, trauma and autoimmunity [22, 27, 28]. Our study is the first study to emphasize that arteriovenous malformation in end-stage lung diseases is a sign of vascular remodeling.

Vascular remodeling is a complex process playing a role in cellular adaptation mechanisms and numerous molecules in end-stage lung diseases. Changes in the TGFß signal pathway, especially mutations in the TGF-β receptor superfamily, are the underlying cause of PAH [29]. Growth factors are potent mitogens and chemoattractants for vascular cells such as smooth muscle cells, fibroblasts and endothelial cells. The binding of growth factors to tyrosine kinase receptors initiates major signaling pathways, causing cell proliferation, migration and apoptosis resistance [30]. Genetic factors create PAH through exaggerated cellular response, chronic inflammatory stimuli, exacerbation of metabolic changes, and accumulation of DNA damage. The metabolic flexibility and changes in cell activities play an important role in the pathogenesis of PAH [21]. Myofibroblasts can occur with epithelial mesenchymal passage from epithelial cells. At the same time, TGF-β stimulation activates fibroblasts, causing myofibroblast formation. Studies have shown that TGF-β also plays an important role in idiopathic pulmonary fibrosis [31]. TGF-β leads to fibrosis with tenascin-C secretion and promotes repair. However, both processes are disrupted by oxidative damage [32]. Similar to the role of TGF-β in pulmonary fibrosis, TGF-ß provides airway remodeling in patients with COPD [33]. All these studies reveal that the processes that cause disruptions in the normal lung structure also cause vascular remodeling. However, this does not fully explain the differences in vascular patterns.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the resulting disease (COVID-19) has caused a worldwide pandemic that causes mortality and morbidity. Most COVID-19 patients have mild symptoms or asymptomatic. However, acute respiratory distress syndrome (ARDS) develops in 10% of the cases. Mortality is 60% in this group. Lungs being the main target organ in COVID-19, metabolic and hematological changes are the most important causes of mortality. Pathological changes are caused by an excessive response of immune cells such as macrophages and mast cells. Mast cells are producers of histamine. They increase the production of IL-1. IL-1 is a pleiotropic cytokine that is active in inflammation and immunity [34]. IL-1 causes hypotension. It does this by causing a decrease in systemic blood pressure, a decrease in vascular resistance, an increase in heart rate, and leukocyte aggregation. IL-1 induces thromboxane B2 (TxB2) releases in activated neutrophils and macrophages. An increase in thromboxane can induce leukocyte aggregation and systemic inflammation, which would account for bronchopneumonia, microtrombi, ischemic lesions, pulmonary emboli, or pulmonary infarct. Therefore, drugs that reduce IL-1 are recommended in the treatment of COVID-19 [35, 36]. Immunological mechanisms that play a role in pulmonary remodeling in the COVID-19 will also be guiding in terms of the mechanisms and treatment principles of vascular changes in end-stage lung diseases.

Vascular remodeling patterns are important findings that affect the clinical situation, treatment and prognosis in end-stage lung diseases. Although medial hypertrophy and intimal thickness were seen in pulmonary hypertension, they can be observed in end-stage pulmonary diseases without pulmonary hypertension. Interstitial capillary duplication is histologically similar to capillary hemangiomatosis. In our study, we found that capillary duplication is common histopathological finding in explanted lung with secondary pulmonary hypertension. Also, arteriosclerosis and arteriovenous malformation were other pulmonary vascular alterations that were detected in end-stage pulmonary diseases.

The authors declare no conflict of interest.

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