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CASE REPORT OPEN ACCESS

Recurrence of Pulmonary Hypertension After Unilateral Lung Transplantation: Histological Evidence of Vasoconstrictive Mechanism

Satoshi Akagi[1] | Megumi Kondo[1] | Koichi Ichimura[2] | Takehiro Tanaka[3] | Seiichiro Sugimoto[4] | Kentaro Ejiri[1] | Kazufumi Nakamura[5] | Shinsuke Yuasa[1]

[1]Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan | [2]Department of Pathology, Hiroshima City Hiroshima Citizens Hospital, Hiroshima, Japan | [3]Department of Pathology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan | [4]Department of General Thoracic Surgery and Organ Transplant Center, Okayama University Hospital, Okayama, Japan | [5]Center for Advanced Heart Failure, Okayama University Hospital, Okayama, Japan

Correspondence: Satoshi Akagi (akagi-s@cc.okayama-u.ac.jp)

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ABSTRACT

Pulmonary hypertension (PH) is widely recognized as a disease driven by both vasoconstriction and vascular remodeling. Vasoconstriction is thought to play a predominant role in the early stages of PH, whereas the contribution of vascular remodeling increases as the disease progresses. However, clinical or histological evidence of this pathological progression has not been reported. We describe a case of recurrent PH after unilateral right lung transplantation, ultimately requiring bilateral transplantation 9 years later, and discuss the pathogenesis of PH based on histological findings in the transplanted normal lungs and changes in pulmonary blood flow observed by lung perfusion scintigraphy. Serial lung perfusion scintigraphy revealed a dynamic shift in pulmonary blood flow, initially favoring the transplanted lung, followed by a gradual decline. Histological examination demonstrated that the right lung of the second transplantation showed minimal vascular remodeling. These findings provide compelling evidence that vasoconstriction was the predominant contributor to PH after the first transplantation, offering unique insight into early PH pathobiology.

1 | Introduction

Pulmonary hypertension (PH) is a life-threatening disease with elevated pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR). The pathological features of PH include pulmonary vasoconstriction and vascular remodeling, resulting in luminal narrowing of small pulmonary arteries. Vasoconstriction is caused by an imbalance between vasoconstrictors and vasodilators, particularly excessive endothelin signaling and reduced nitric oxide and prostacyclin activity. Vascular remodeling involves proliferation of pulmonary artery endothelial and smooth muscle cells, medial hypertrophy, and intimal thickening [1]. It has been proposed that vasoconstriction precedes vascular remodeling during the development of PH [2]; however, this sequence has not been clearly demonstrated in clinical settings. Lung transplantation provides a unique opportunity to study pulmonary vascular pathophysiology in humans. In particular, unilateral lung transplantation creates a condition in which a previously normal lung is suddenly exposed to marked changes in pulmonary blood flow and shear stress. Here, we report a case of recurrent PH after unilateral lung transplantation that ultimately required bilateral lung transplantation. By integrating serial hemodynamic measurements, lung perfusion scintigraphy, and histological evaluation of explanted lungs, we provide insights into the relative roles of vasoconstriction and vascular remodeling in PH progression.

2 | Case Presentation

An 18-year-old man was diagnosed at 7 years of age with PH associated with pulmonary artery hypoplasia. Right heart catheterization revealed a mean PAP (mPAP) of 51 mmHg, a pulmonary artery wedge pressure (PAWP) of 5 mmHg, cardiac output (CO) of 2.5 L/min, and a PVR of 18.6 Wood units. Lung perfusion scintigraphy showed pulmonary blood flow distribution of 55% to the right lung and 45% to the left lung (Figure 1A). A unilateral living-donor lung transplantation of the right lung was performed. One year after transplantation, hemodynamics improved, with an mPAP of 30 mmHg, PAWP of 12 mmHg, CO of 3.2 L/min, and PVR of 5.6 Wood units. Lung perfusion scintigraphy demonstrated marked redistribution of blood flow, with 84% to the transplanted right lung and 16% to the native left lung (Figure 1A). Five years after transplantation, pulmonary hemodynamics worsened, with an mPAP of 41 mmHg, PAWP of 13 mmHg, CO of 3.6 L/min, and PVR of 7.7 Wood units, accompanied by redistribution of pulmonary blood flow (70% right, 30% left) (Figure 1A). Eight years after transplantation, pulmonary hemodynamics had deteriorated further, with an mPAP of 73 mmHg, PAWP of 13 mmHg, CO of 3.9 L/min, and PVR of 15.4 Wood units, and pulmonary blood flow was 64% to the right lung and 36% to the left lung (Figure 1A). Despite the initiation of PH-targeted therapies, PH progressed, and the patient was re-listed for lung transplantation. One year later, bilateral cadaveric lung transplantation was performed.

Histological evaluation using Elastica van Gieson staining was conducted on the explanted right lung from the first transplantation and on both lungs from the second transplantation (Figure 1B). The right lung from the first transplantation showed intimal and medial thickening of peripheral pulmonary arteries without plexiform lesions or capillary proliferation. At the second transplantation, the left lung exhibited similar arterial remodeling, whereas the right lung showed only minimal arterial thickening. Peripheral pulmonary arteries were categorized as fully muscularized, partially muscularized, or non-muscularized. Fully muscularized arteries predominated in the right lung from the first transplantation and in the left lung from the second transplantation, whereas non-muscularized arteries were most frequent in the right lung from the second transplantation (Figure 1C).

3 | Discussion

This case offers a unique human model to explore the relative contributions of vasoconstriction and vascular remodeling in the progression of PH. Two major paradigms have been proposed to explain PH pathobiology: one emphasizing sustained vasoconstriction and hemodynamic stress, and the other focusing on irreversible vascular remodeling, often referred to as the cancer paradigm [3, 4]. While both mechanisms undoubtedly contribute to disease progression, their relative dominance at different disease stages remains uncertain.

Following unilateral lung transplantation, pulmonary blood flow was abruptly redirected toward the transplanted lung, resulting in a marked increase in shear stress. Despite this hemodynamic burden, histological analysis of the transplanted lung obtained at the second transplantation demonstrated only minimal intimal and medial thickening, with preservation of

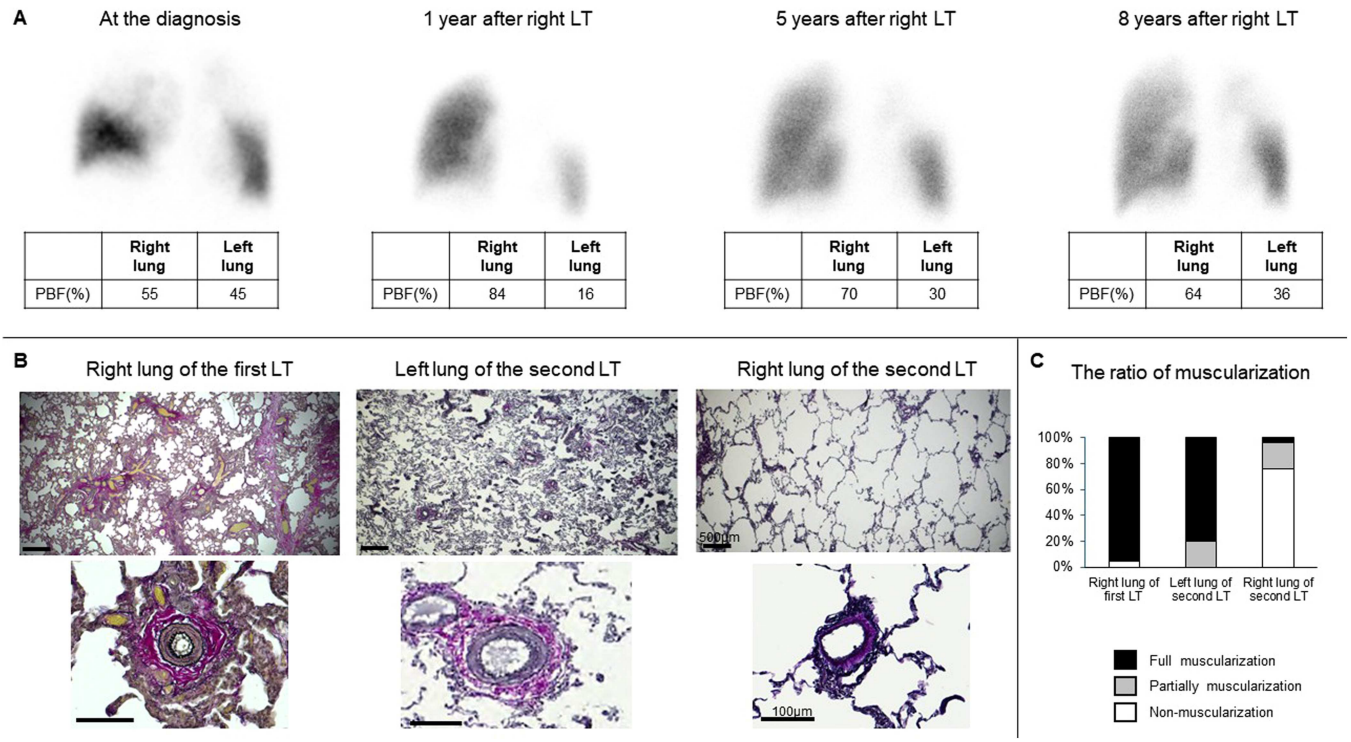

FIGURE 1 | (A) Lung perfusion scintigraphy before and after unilateral lung transplantation. PBF: a ratio of pulmonary blood flow. (B) Historical findings of peripheral pulmonary arteries in the right lung of the first lung transplantation, and the right and left lungs of the second lung transplantation. Bar of upper figures = 500 μm. Bar of lower figures = 100 μm. (C) The ratio of muscularization. Black is full muscularization. Gray is partially muscularization. White is non-muscularization.

non-muscularized peripheral pulmonary arteries. This dissociation between hemodynamics and structural remodeling strongly suggests that vasoconstriction, rather than fixed anatomical obstruction, was the primary driver of PH recurrence.

Our findings have important clinical implications. First, they provide rare histological support for the concept that early PH may be predominantly functional rather than structural. Second, they suggest that therapeutic strategies targeting vasoconstriction may remain effective even in advanced clinical scenarios, provided that irreversible remodeling has not occurred. Finally, this case highlights the potential value of integrating functional imaging and histology to refine PH phenotyping in the era of precision medicine.

There are several limitations in interpreting the findings of this case. First, the possibility of sampling error cannot be completely ruled out, as the histological analysis was performed using limited tissue samples, which may not fully represent the overall pathological features of the lung. Second, subtle or early vascular remodeling may not have been detectable using routine histological staining. Finally, because this report describes a single case, the generalizability of these findings remains limited.

In conclusion, this case suggests that PH recurrence after unilateral lung transplantation may occur even in the absence of marked vascular remodeling, raising the possibility that vasoconstriction may play an important role in early-stage PH. These findings may provide insights into PH pathobiology and could have implications for future therapeutic strategies.

Author Contributions

Satoshi Akagi was the lead author and was responsible for collecting the data, drafting, and editing the manuscript. Megumi Kondo and Seiichiro Sugimoto collected the data. Koichi Ichimura and Takahiro Tanaka validated the histological findings. Kentaro Eijiri, Kazufumi Nakamura, and Shinsuke Yuasa supervised and critically revised the manuscript. Shinsuke Yuasa is the guarantor of this article and takes full responsibility for the integrity of the data and accuracy of the analysis.

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Ethics Statement

Institutional review board approval was not required for this single-patient case report.

Consent

Written consent was obtained from the patient for publication of this report.

Conflicts of Interest

The authors declare no conflicts of interest.

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