



HAL
open science

Klippel-Trenaunay syndrome as a rare cause of chronic thromboembolic pulmonary hypertension

A. Seferian, X. Jaïs, L. Savale, M. Jevnikar, M.-R. Ghigna, J. Weatherald, S. Assoun, E. Fadel, G. Simonneau, O. Sitbon, et al.

► **To cite this version:**

A. Seferian, X. Jaïs, L. Savale, M. Jevnikar, M.-R. Ghigna, et al.. Klippel-Trenaunay syndrome as a rare cause of chronic thromboembolic pulmonary hypertension. *Respiratory Medicine and Research*, 2019, 76, pp.48 - 53. 10.1016/j.resmer.2019.06.002 . hal-03487523

HAL Id: hal-03487523

<https://hal.science/hal-03487523>

Submitted on 20 Jul 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Klippel-Trenaunay syndrome as a rare cause of chronic thromboembolic pulmonary hypertension

Andrei Seferian, MD^{1,2,3}, Xavier Jaïs, MD^{1,2,3}, Laurent Savale, MD, PhD^{1,2,3}, Mitja Jevnikar, MD^{1,2,3}, Maria-Rosa Ghigna, MD⁴, Jason Weatherald, MD⁵, Sandra Assoun, MD^{1,2,3}, Elie Fadel, MD, PhD⁶, Gérald Simonneau, MD^{1,2,3}, Olivier Sitbon, MD, PhD^{1,2,3}, Marc Humbert, MD, PhD^{1,2,3}, David Montani, MD, PhD^{1,2,3}

1- Univ. Paris-Sud, Faculté de Médecine, Université Paris-Saclay, Le Kremlin-Bicêtre, France

2- INSERM UMR_S 999, Hôpital Marie Lannelongue, Le Plessis-Robinson, France

3- Assistance Publique - Hôpitaux de Paris (AP-HP), Service de Pneumologie, Centre de Référence de l'Hypertension Pulmonaire, Hôpital Bicêtre, Le Kremlin-Bicêtre, France.

4. Service d'anatomopathologie, Hôpital Marie Lannelongue, Le Plessis-Robinson, France

5. University of Calgary, Department of Medicine & Libin Cardiovascular Institute of Alberta

6. Service de Chirurgie Thoracique, Hôpital Marie Lannelongue, Le Plessis-Robinson, France

Running head: CTEPH associated with Klippel-Trenaunay syndrome

Corresponding author:

Montani David, MD, PhD

Centre de Référence de l'Hypertension Pulmonaire, Service de Pneumologie, Hôpital Bicêtre, Assistance Publique, Hôpitaux de Paris

78 rue du Général Leclerc, 94270 Le Kremlin-Bicêtre, France.

Tel: (33) 1 45 21 79 72; Fax: (33) 1 45 21 79 71;

e-mail: david.montani@aphp.fr

ABSTRACT

Klippel-Trenaunay syndrome (KTS) is a congenital disorder characterized by cutaneous capillary malformations, soft-tissue and bone hypertrophy, and multiple capillary, venous or lymphatic malformations. KTS is associated with recurrent thromboembolic events.

We reported herein five cases of chronic thromboembolic pulmonary hypertension (CTEPH) associated with KTS (age min-max 26-50 years old, 3 male/ 2 female). Hemodynamics showed severe pulmonary hypertension (PH) with pulmonary vascular resistance ranging from 5.6 to 18.3 Wood units (WU), associated with marked clinical impairment (NYHA functional class III or IV in 4 patients). Computed tomography (CT) of the chest and pulmonary angiography confirmed proximal CTEPH accessible to surgical intervention in one patient and distal forms of CTEPH in 4 patients. Evolution after pulmonary endarterectomy showed hemodynamic normalization, while the patients with distal CTEPH had severe outcomes with 2 early deaths after PH diagnosis (44 and 35 months respectively). One patient with distal CTEPH was still alive 16 years after diagnosis on specific PH therapy and one was transplanted after 15 years because of right heart failure (death after 12 months). Histological analysis of the lung explants showed typical chronic thromboembolic material specific for CTEPH. In conclusion, KTS may be complicated by severe CTEPH requiring careful anticoagulation and multidisciplinary follow-up in expert centers to screen for disease potentially accessible to endarterectomy. In the modern management era of CTEPH, balloon pulmonary angioplasty will certainly be an interesting option in patients with inoperable disease.

Key words: Klippel-Trenaunay syndrome, Pulmonary hypertension, Chronic thromboembolic pulmonary hypertension, endarterectomy

INTRODUCTION

The Klippel-Trenaunay syndrome (KTS) is a rare congenital disorder characterized by the clinical triad of: 1) capillary malformations (port-wine stain); 2) soft tissue and bone hypertrophy or, occasionally hypotrophy; and 3) atypical, mostly lateral varicosity, without significant arteriovenous shunting. KTS is, in most of the cases, a sporadic event with an incompletely elucidated etiology, but most likely due to a mesodermal abnormality that occurs during early fetal development¹. It is associated with a higher risk for thromboembolic events of up to 22%^{2,3}. Incomplete resolution of the vascular obstruction after a pulmonary embolism may lead to chronic thromboembolic pulmonary hypertension (CTEPH). The most effective therapy for CTEPH is pulmonary thromboendarterectomy, which is reserved for the proximal forms of the disease⁴. Recently, for technically inoperable cases balloon pulmonary angioplasty (BPA) and pulmonary hypertension (PH) - targeted medical therapy became available as part of a multimodal, individualized patient approach in specialized PH centers⁵⁻⁷.

We present a series of 5 cases of patients with KTS and CTEPH referred to the French Referral Centre for Pulmonary Hypertension. Clinical, functional and hemodynamic parameters, management and survival of these patients are presented in **Table 1**.

Case 1

A 50-year-old male with KTS diagnosed in childhood was directly admitted to intensive care unit with acute pulmonary embolism. He had a previous history of pulmonary embolism seven years prior and, at that time, life-long oral anticoagulation therapy (OAT) therapy had been initiated. Elevated pulmonary arterial pressures on echocardiography suggested a severe pulmonary hypertension (PH), confirmed on right heart catheterization (RHC): mean pulmonary arterial pressure (mPAP) of 61 mmHg, cardiac index (CI) of 1.46l/min/m² and pulmonary vascular resistance (PVR) of 18.3 Woods unit (WU). Ventilation perfusion lung scan, angiography and chest computer tomography were more in keeping with CTEPH with proximal lesions (**Figure 1 A-D**). Thus, pulmonary thromboendarterectomy was performed after a 3-month period of bridge-therapy by oral phosphodiesterase type 5 inhibitors (PDE5-i). Surgery resulted in good reperfusion of the pulmonary arteries (**Figure 1E**). Typical intimal fibrosis, associated with chronic and more recent thromboembolic material were found on histological analysis. Six months later, the patient was in NYHA FC I and had a normal CI that allowed the discontinuation of PDE5-i. The patient was lost on follow-up 48 months after diagnosis of CTEPH.

Case 2

A 42-year-old female with KTS diagnosed at birth was admitted for acute sub-segmental pulmonary embolism, with normal right ventricular function on echocardiography. In the context of KTS, she had a history of splenectomy for a giant splenic angioma and multiple amputations of her right lower limb due to frequently infected superficial low-flow arteriovenous malformations extending into the pelvis (**Figure 2A**). The patient was treated with low molecular weight heparin (LMWH) and placement of an inferior vena cava filter was not feasible. Two months later, despite well-conducted anticoagulation therapy the patient had a second episode of pulmonary embolism, complicated by a stroke secondary due to systemic embolization through a patent *foramen ovale*. After two months, the patient had a complete neurological recovery and was in NYHA FC III. RHC showed moderate PH with

mPAP of 46mmHg, CI of 3.1 l/min/m² and PVR 7.41 WU. Radiological features confirmed an absence of surgically accessible thromboembolic material (**Figure 2B-D**), and an oral dual endothelin receptor antagonist was added with significant improvement (mPAP= 33 mmHg, CI= 4.2 l/min/m², PVR= 3.6 WU). The patient died from pelvic hemorrhagic complications 44 months after diagnosis of CTEPH.

Case 3

A 42-year-old male with KTS known since adolescence was referred for evaluation of progressive exertional dyspnea, which had progressed over the last 6 months. He was previously treated with oral anticoagulants for one year after an episode of deep vein thrombosis with concurrent asymptomatic sub-segmental pulmonary embolism. The patient was in NYHA FC III and RHC demonstrated severe PH (mPAP= 54 mmHg, CI of 2.54 l/min/m², PVR= 11 WU). No proximal thromboembolic material was found on radiological examinations and inhaled prostacyclin was initiated but later switched to an oral dual endothelin receptor antagonist after 1 year because of prostacyclin-related side-effects. After 6 years, a decrease in the CI prompted the addition of a PDE5-i with satisfactory response. The patient is still alive 16 years after initial diagnosis on dual oral therapy.

Case 4

A 26-year-old female, with a history of typical KTS diagnosed when she was 2-years-old and splenectomy for splenic angioma was referred to our department three months after an episode of left femoral deep vein thrombosis complicated by an acute pulmonary embolism. She was in NYHA FC III with a 6-minute walking distance of 383 m. RHC showed severe pre-capillary PH (mPAP of 70 mmHg, CI of 2.68 l/min/m², PVR= 11.9 WU). The ventilation perfusion lung scan showed sub-segmental non-matched perfusion defects confirmed by angiography and chest computer tomography. Oral dual endothelin receptor antagonist was initiated and an inferior vena cava filter was inserted. The patient deteriorated after 13 months requiring addition of a PDE5-i and continuous intravenous prostacyclin. No

improvement was observed, and the patient was listed for lung transplantation, but died due to irreversible end-stage right heart failure 11 months later.

Case 5

A 46-year-old male with KTS since birth was referred for evaluation of progressive exertional dyspnea, which progressed over the last 12 months. At 18 years of age, varicose veins and a deep vein thrombosis of the left lower limb required thrombolysis and placement of an IVCF that was still patent. The patient was in NYHA FC II and RHC showed a mPAP of 51 mmHg, a CI of 3.9 l/min/m² and PVR of 5.6 WU. Radiological features suggested a distal form of CTEPH. At the time of diagnosis, epoprostenol was the only available specific PAH therapy and this option was refused by the patient. Six years later, inhaled prostacyclin was initiated in the context of increasing dyspnea (NYHA FC III) and hemodynamic deterioration. Side-effects associated with inhaled iloprost and further clinical and hemodynamical deterioration prompted a switch to *i.v.* epoprostenol after 4 years. Because of clinical worsening, an oral dual endothelin receptor antagonist was added but right heart failure prompted for urgent lung transplantation 15 years after diagnosis of CTEPH. Histological analysis of the explanted lungs showed typical chronic thromboembolic material with recent thrombosis (**Figure 3**). The patient died of post-transplant lymphoproliferative disorder 12 months after transplantation.

DISCUSSION

KTS is a rare complex vascular malformation that generally involves capillaries, veins and lymphatics. Recently, genetic studies in patients with vascular malformations showed that mutations in PI3K-AKT pathway are found in patients with KTS^{8,9} opening the door for clinical studies for the use of targeted molecules like rapamycin an inhibitor of mTOR1 that interacts with the altered pathway¹⁰. A multidisciplinary approach is needed from the early stages of the disease usually during childhood with the aim of preventing the most severe complications: hemorrhage, recurrent infections and thromboembolic events^{1,2,11}. The risk for thromboembolic events is up to 22% in patients with KTS^{1,2,12} and is probably due to a hypercoagulability mechanism at sites of vascular malformations, with blood stagnation and activation of coagulation. This phenomenon suggested by high levels of specific coagulation markers like fibrinogen, prothrombin, D-dimer or von Willebrand factor, occurs within the distorted, enlarged veins and is the trigger of thrombotic events^{2,13,14}.

Like previously reported KTS-associated CTEPH patients, deep vein thrombosis has been objectively described in 3 of our patients. In addition, four patients had a history of acute symptomatic pulmonary embolism. Anticoagulation therapy with vitamin K antagonists was preferred for 4 patients and an inferior vena cava filter was placed in 2 patients. Pulmonary embolism recurrence was recorded in one patient. Despite previous reports that suggested that LMWH are more effective for patients with extensive vascular malformations and thromboembolic events¹³, the patient treated with LMWH experienced also recurrence of pulmonary embolism. Magnetic resonance venography by showing extensive pelvis and abdominal malformations ruled out placement of IVCF for the rest of the patients. There is sometimes a difficult balance between the risk for bleeding associated with the malformations and the need for a anticoagulant therapy. Our data suggest that efficacy of the anticoagulant therapy depends on the extension of vascular malformations and that perhaps local surgery could play a more important role. None of our patients received direct oral anticoagulants, mainly as we present a historic cohort as there are some drug interactions between direct oral anticoagulants and PAH targeted therapies¹⁵. As part of their follow-up

for KTS, all our patients were also periodically evaluated by phlebologists, hematologists and plastic surgeons.

The incidence of CTEPH after symptomatic pulmonary embolism ranges from 0.4% to 6.2%, giving a pooled incidence of 3.4%¹⁶⁻¹⁸. In the literature, there are previously reported cases of CTEPH complicating KTS¹⁹⁻²¹ or other extensive vascular malformations but to our knowledge the present study represents the most extensive series of CTEPH cases complicating KTS. In addition to the vascular malformations, splenectomy, a known risk factor for CTEPH²² was noted in 2 patients. Clinical, functional and hemodynamic data at time of diagnosis showed severe disease for all 5 patients, in accordance with previous reports^{2,21,23}. The outcome was favorable in the patient with proximal disease that returned to normal hemodynamics after pulmonary thromboendarterectomy. The others had distal forms and specific PAH therapies available at time of diagnosis (prostacyclin agonists, endothelin-receptor antagonists, phosphodiesterase type-5 inhibitors) were initiated with variable responses. One patient is still in follow-up in our clinic 16 years later with the same evolution pattern as commonly observed in CTEPH.

Besides lifelong anticoagulation, surgical endarterectomy is the treatment of choice in patients with proximal CTEPH affecting large pulmonary arteries. However, around half of CTEPH patients are not operated, mainly because of distal lesions inaccessible to surgery. For technically inoperable cases, PH medical therapy is recommended with or without balloon pulmonary angioplasty performed in experienced centers²⁴.

For severe PH patients refractory to treatment, lung transplantation is the last therapeutic option²⁰. In recent years, careful timing of the decision helped improve overall survival that however remains rather low at about 50% at 5 years²⁵. KTS was not considered a contraindication for transplantation. Two patients were listed for lung transplantation, but unfortunately both died: one before the procedure due to irreversible, end-stage heart failure, while the other was transplanted and died of post-transplant lymphoproliferative disorder. From the histological analysis of the explanted lungs we can assume that there is no specific

pattern in CTEPH associated with KTS compared to CTEPH patients both exhibiting chronic and more recent thromboembolic material.

In conclusion, KTS requires specific multidisciplinary follow-up and prompt evaluation of unexplained dyspnea. CTEPH is a rare but severe complication of pulmonary embolism occurring in the context of KTS. Distal forms of CTEPH were associated with a poor prognosis. No standard therapy could be determined and therefore each case must be examined individually. In the modern management era of CTEPH, balloon pulmonary angioplasty will certainly be an interesting option in patients with inoperable disease. Proximal CTEPH associated with KTS had a good prognosis in one patient and therefore high-resolution computer tomography of the chest and pulmonary angiography are needed to discriminate these patients.

REFERENCES

- 1 Gloviczki P, Driscoll DJ. Klippel-Trenaunay syndrome: current management. *Phlebology* 2007; 22:291-298
- 2 Gianlupi A, Harper RW, Dwyre DM, et al. Recurrent pulmonary embolism associated with Klippel-Trenaunay-Weber syndrome. *Chest* 1999; 115:1199-1201
- 3 Baskerville PA. [Thromboembolic disease and congenital venous abnormalities]. *Phlebologie* 1987; 40:531-536
- 4 Dartevielle P, Fadel E, Mussot S, et al. Chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2004; 23:637-648
- 5 Bouvaist H, Thony F, Jondot M, et al. Balloon pulmonary angioplasty in a patient with chronic thromboembolic pulmonary hypertension. *Eur Respir Rev* 2014; 23:393-395
- 6 Ogawa A, Matsubara H. Balloon Pulmonary Angioplasty: A Treatment Option for Inoperable Patients with Chronic Thromboembolic Pulmonary Hypertension. *Front Cardiovasc Med* 2015; 2:4
- 7 Simonneau G, D'Armini AM, Ghofrani HA, et al. Predictors of long-term outcomes in patients treated with riociguat for chronic thromboembolic pulmonary hypertension: data from the CHEST-2 open-label, randomised, long-term extension trial. *Lancet Respir Med* 2016; 4:372-380
- 8 Kurek KC, Luks VL, Ayturk UM, et al. Somatic mosaic activating mutations in PIK3CA cause CLOVES syndrome. *Am J Hum Genet* 2012; 90:1108-1115
- 9 Luks VL, Kamitaki N, Vivero MP, et al. Lymphatic and other vascular malformative/overgrowth disorders are caused by somatic mutations in PIK3CA. *J Pediatr* 2015; 166:1048-1054 e1041-1045
- 10 Youssefian L, Vahidnezhad H, Baghdadi T, et al. Fibroadipose hyperplasia versus Proteus syndrome: segmental overgrowth with a mosaic mutation in the PIK3CA gene. *J Invest Dermatol* 2015; 135:1450-1453
- 11 Muluk SC, Ginns LC, Semigran MJ, et al. Klippel-Trenaunay syndrome with multiple pulmonary emboli--an unusual cause of progressive pulmonary dysfunction. *J Vasc Surg* 1995; 21:686-690
- 12 Baskerville PA, Ackroyd JS, Lea Thomas M, et al. The Klippel-Trenaunay syndrome: clinical, radiological and haemodynamic features and management. *Br J Surg* 1985; 72:232-236
- 13 Mazoyer E, Enjolras O, Laurian C, et al. Coagulation abnormalities associated with extensive venous malformations of the limbs: differentiation from Kasabach-Merritt syndrome. *Clin Lab Haematol* 2002; 24:243-251
- 14 Huiras EE, Barnes CJ, Eichenfield LF, et al. Pulmonary thromboembolism associated with Klippel-Trenaunay syndrome. *Pediatrics* 2005; 116:e596-600
- 15 Margelidon-Cozzolino V, Delavenne X, Catella-Chatron J, et al. Indications and potential pitfalls of anticoagulants in pulmonary hypertension: Would DOACs become a better option than VKAs? *Blood Rev* 2019
- 16 Simonneau G, Torbicki A, Dorfmuller P, et al. The pathophysiology of chronic thromboembolic pulmonary hypertension. *Eur Respir Rev* 2017; 26
- 17 Pengo V, Lensing AW, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med* 2004; 350:2257-2264
- 18 Becattini C, Agnelli G, Pesavento R, et al. Incidence of chronic thromboembolic pulmonary hypertension after a first episode of pulmonary embolism. *Chest* 2006; 130:172-175
- 19 Johnson JN, Driscoll DJ, McGregor CG. Pulmonary thromboendarterectomy in Klippel-Trenaunay syndrome. *J Thorac Cardiovasc Surg* 2010; 140:e41-43
- 20 Walder B, Kapelanski DP, Auger WR, et al. Successful pulmonary thromboendarterectomy in a patient with Klippel-Trenaunay syndrome. *Chest* 2000; 117:1520-1522

- 21 Oduber CE, Gerdes VE, van der Horst CM, et al. Vascular malformations as underlying cause of chronic thromboembolism and pulmonary hypertension. *J Plast Reconstr Aesthet Surg* 2009; 62:684-689; discussion 689
- 22 Jais X, loos V, Jardim C, et al. Splenectomy and chronic thromboembolic pulmonary hypertension. *Thorax* 2005; 60:1031-1034
- 23 Bonderman D, Nowotny R, Skoro-Sajer N, et al. Bosentan therapy for inoperable chronic thromboembolic pulmonary hypertension. *Chest* 2005; 128:2599-2603
- 24 Kim NH, Delcroix M, Jais X, et al. Chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2019; 53
- 25 Fadel E, Mercier O, Mussot S, et al. Long-term outcome of double-lung and heart-lung transplantation for pulmonary hypertension: a comparative retrospective study of 219 patients. *Eur J Cardiothorac Surg* 2010; 38:277-284

FIGURE LEGENDS

Figure 1 Review of a patient with KTS/CTEPH and proximal perfusion defects

A. Contrast-enhanced high-resolution computed tomography of the chest - pulmonary arteries reformatted by using maximal intensity projection (MIP) showing bilateral proximal thromboembolic material; **B.** V/Q lung scan with multiple non-matched perfusion defects: right basal pyramid, right superior lobe, left inferior lobe; **C.** Angiography (right anterior view) showing proximal thromboembolic lesions; **D.** Fully dissected thromboembolic material extracted after thromboendarterectomy

Figure 2 Review of a patient with KTS/CTEPH and distal perfusion defects

A. Magnetic resonance imaging (T1) showing multiple vascular malformations of the pelvis and of the lower limb; **B.** V/Q lung scan with multiple sub-segmental non-matched perfusion defects; **C., D.** Angiography (left profile and right profile views respectively) showing narrowed pulmonary arteries with distal thromboembolic material.

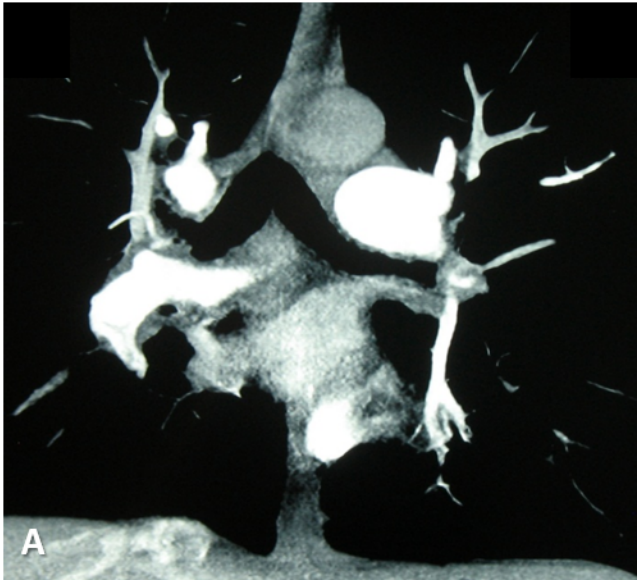
Figure 3 Histological analysis from explanted lungs of a KTS/CTEPH patient (Haematoxylin & Eosin Stain)

A. Recent thromboembolic lesion; **B.** Organized thrombus in an elastic pulmonary artery; **C., D.** Organized thrombi within pre-acinar pulmonary arteries, forming “colander-like” lesions

Table 1. Clinical, functional and hemodynamic parameters and outcomes of CTEPH associated with KTS patients

	Age at PH diagnosis	Gender	Thromboembolic history	NYHA FC	6MWD m	mPAP mmHg	CI l/min/m ²	PVR Wood units	Form of CTEPH	Pulmonary thromboendarterectomy	Specific PH therapy	Evolution
1	50	M	PE 7 years prior to diagnosis 2 nd PE at time of diagnosis	IV	n/a	61	1.46	18.3	Proximal	Yes	PDE5-i	Hemodynamic normalization 48 months after diagnosis
2	42	F	PE 3 months before diagnosis	III	n/a	46	3.11	7.4	Distal	No	ERA	Death 44 months after diagnosis due to hemorrhagic complications
3	42	M	DVT at asymptomatic PE 6 months prior to diagnosis	III	415	54	2.54	11	Distal	No	ERA PDE5-i	Alive 16 years after diagnosis
4	26	F	DVT and PE 3 months prior to diagnosis	III	383	70	2.68	11.9	Distal	No	ERA PDE5-i IV Prostacyclin	Death 35 months after diagnosis on transplantation list
5	46	M	DVT at young age	II	n/a	51	3.91	5.6	Distal	No	ERA Inhaled Prostacyclin	Death 12 months after lung transplantation / 15 years after diagnosis

6MWD: 6-minute walk distance; CI: cardiac index; DVT: deep vein thrombosis; IVC: inferior vena cava filter; LMWH: low-molecular weight heparin; NYHA FC: New York Heart Association functional class; mPAP: mean pulmonary artery pressure, N/A: not available; NYHA: New York Heart Association; PE: pulmonary embolism; TPR: total pulmonary resistance; ERA: endothelin receptor antagonist; PDE5-i: phosphodiesterase type 5 inhibitor; PVR: pulmonary vascular resistance



VENTILATION

PERFUSION

