Fatal Pulmonary Hemorrhagic Infarction Caused by Pulmonary Vein Thrombotic Occlusion During Venoarterial Extracorporeal Membrane Oxygenation

Kohei Masaki,1 MD, Toru Hashimoto,1,2 MD, Masato Katsuki,1 MD, Kisho Ohtani,1 MD, Taiki Higo,1 MD, Tomoki Ushijima,1 MD, Yoshihisa Tanoue,2,3 MD, Akira Shiose,3 MD and Hiroyuki Tsutsui,1 MD

Summary
A 20-year-old man with arrhythmogenic right ventricular cardiomyopathy (ARVC) was resuscitated from ventricular fibrillation. He was transferred to our hospital because of progressive multiorgan dysfunction despite mechanical circulatory support with peripheral venoarterial extracorporeal membrane oxygenation (VA-ECMO) and intra-aortic balloon pump (IABP). At admission to our hospital, chest X-ray showed bilateral complete lung opacification, and echocardiography revealed a massive thrombus occupying the left atrium (LA) and left ventricle (LV). Conversion to central ECMO with transapical LV venting and thrombectomy were performed. The huge LA thrombus occluded all pulmonary veins (PVs). Despite the surgery and intensive care, complete lung opacity remained, and he died of multiorgan failure associated with sepsis. Autopsy demonstrated bilateral pulmonary multiple red infarctions, and histopathology showed alveolar wall necrosis with extensive hemorrhage, confirming a diagnosis of pulmonary hemorrhagic infarction. Extensive pulmonary infarction was attributable to PV occlusion due to massive LA thrombus. PV thrombosis should be considered when refractory lung opacities are encountered during VA-ECMO and necessitates early intervention.

Key words: Pulmonary vein thrombosis, Intracardiac thrombosis, Left ventricular venting, Arrhythmogenic right ventricular cardiomyopathy

Extracorporeal membrane oxygenation (ECMO) supports heart and lung function in refractory cardiopulmonary failure. Among the most frequent complications is ECMO-associated coagulopathy, which has high morbidity and mortality. Although intracardiac and intra-aortic thrombosis during ECMO support is not very frequent, it is critical because thromboembolic events may result in devastating outcome. Intracardiac thrombosis during ECMO support typically occurs in the left ventricle (LV) or aortic root, while thromboses in the left atrium (LA) and pulmonary vein (PV) have been rarely reported. The outcome of PV thrombosis during ECMO support has not been well recognized either. Here, we present a case of PV thrombosis associated with massive left atrial thrombus during venoarterial ECMO (VA-ECMO), which resulted in extensive pulmonary hemorrhagic infarction and fatal outcome.

Case Report
A 20-year-old man suffered ventricular fibrillation after exercise and was resuscitated with peripheral VA-ECMO and intra-aortic balloon pump (IABP) at a tertiary hospital. Coronary angiography demonstrated no stenocclusive lesion. He had been referred to a clinic because of electrocardiographic abnormality at medical checkup when he was admitted to a college the previous year; his electrocardiogram showed inverted T waves in V1-3 leads without right bundle branch block. Although echocardiography demonstrated dilatation of the right ventricle (RV) and right atrium (RA) without left ventricular dysfunction (Supplemental Figure 1), he did not have further investigation because he was asymptomatic. Thereafter, he once experienced syncope with seizure during exercise but was diagnosed as heat stroke at that time. Arrhythmogenic right ventricular cardiomyopathy (ARVC) was suspected based on these past medical histories and findings. The echocardiography after VA-ECMO implementation at the first hospital revealed no apparent intracardiac thrombi (Supplemental Figure 2). He was transferred to our hospital on day 5 after resuscitation owing to the deterioration of multiorgan dysfunction and lower limb malperfusion.
His cardiac contractility had not recovered at all, and the aortic valve opening was absent. On admission to our hospital, chest X-ray showed bilateral complete lung opacification (Figure 1A). Electrocardiogram showed poor R wave progression in all leads (Supplemental Figure 3). Echocardiography demonstrated akinesis of both ventricles and revealed a massive thrombus occupying the LA and extending into the LV despite anticoagulation therapy with unfractionated heparin (Figure 1B). No apparent thrombus formation was observed in the RA and RV by echocardiography and contrast-enhanced computed tomography scan (Supplemental Figure 4). Plasma D-dimer level was elevated at 14.3 μg/mL. Laboratory investigation did not reveal any prothrombotic disorders, including protein C or S deficiency, antithrombin III deficiency, antiphospholipid antibody syndrome, and heparin-induced thrombocytopenia. Conversion to central VA-ECMO and thrombectomy were urgently performed to improve systemic perfusion with adequate LV decompression and prevent thromboembolic insults. During the surgery, intracardiac exploration revealed a huge LA thrombus occluding all of the PVs and attaching to the mitral complex in the LV (Figure 2A and B). Despite the successful surgery and postoperative intensive care under central ECMO, complete lung opacity improved only partially (Figure 3), and cardiac contractility was not restored. Although listing for heart-lung transplantation was considered, he died of multiorgan failure associated with sepsis 2 weeks after central ECMO surgery. Macroscopic observation at autopsy demonstrated multiple red infarction in both lungs (Figure 4A), and histopathology of the lungs showed alveolar wall necrosis with extensive hemorrhage (Figure 4B), confirming a diagnosis of pulmonary hemorrhagic infarction. Extensive pulmonary infarction was attributable to PV occlusion due to massive LA...
thrombus in the present case. The histological finding of the right ventricular myocardium showed degenerated and diminished cardiomyocytes with extended fibrofatty tissue replacement, compatible with ARVC (Figure 5). In contrast, the histopathology of the LV tissue demonstrated coagulative necrosis associated with inflammatory cell infiltration, fibrinous deposits, and microthrombi, suggesting ischemic changes caused by tissue malperfusion (Supplemental Figure 5).

Discussion

Hemorrhagic and coagulation complications are the most frequent adverse events during VA-ECMO support. Clot formation within the ECMO circuit or oxygenator is not rare, and thromboembolic complication during VA-ECMO support has high mortality and morbidity. Intracardiac and intra-aortic thrombosis is relatively less but is the worst situation that would lead to life-threatening consequences, including acute neurogenic events, acute limb ischemia, and multiorgan infarctions. Intracardiac thrombosis mostly occurs in the LV or aortic root and less frequently in the RV and LA.

Pulmonary infarction typically occurs in patients with pulmonary embolism associated with pulmonary venous hypertension secondary to long-standing left heart failure, and obesity and cigarette smoking also raise a risk of developing pulmonary infarction following pulmonary embolism. PV occlusion also causes pulmonary infarction. It has been reported that PV stenosis or occlusion following catheter ablation of the PVs for atrial fibrillation causes pulmonary infarction. It has also been demonstrated that a huge left atrial myxoma occluded PVs, leading to pulmonary infarction necessitating pneumectomy. PV thrombosis after lung transplant causes pulmonary infarction and graft dysfunction. PV thrombotic occlusion associated with massive LA thrombus during VA-ECMO is a rare and potentially lethal manifestation. In the present case, the patient developed massive LA thrombus during ECMO support despite anticoagulation therapy with unfractionated heparin under no prothrombotic background. Intracardiac thrombosis was likely attributable to failure of LV decompression by initial support with VA-ECMO and IABP before transfer. Early LV decompression...
sition by percutaneous ventricular assist device (Impella), percutaneous transseptal LA venting, or percutaneous transpulmonary venting might have prevented thrombus formation.\textsuperscript{4,11} Surgical LV venting is also among alternatives if available. Although no consensus guideline recommending when to perform LV venting exists, it should be placed when persistent aortic valve closure, severe aortic regurgitation, refractory pulmonary edema due to LV overload, and pulmonary hemorrhage are observed.\textsuperscript{11} Prophylactic LV venting should be considered if LV dysfunction is severe and expected to be persistent. Anticoagulation therapy should at least be intensified when LV venting procedure is not shortly available.

In the present case, the patient experienced severe pulmonary hemorrhagic infarction as a consequence of pulmonary venous hypertension due to thrombotic occlusion of all the PVs. PV thrombosis was considered to be primarily associated with LA and LV thrombi caused by inadequate LV venting, while coagulopathy due to ECMO and inflammatory response to extracorporeal circulation might also have contributed to the intrapulmonary coagulopathic state.\textsuperscript{1,2,12} Severe RV systolic dysfunction and subsequent pulmonary artery flow reduction might also have contributed to thrombus formation in the PVs. Extensive pulmonary hemorrhagic infarction was suggested by complete lung opacities in chest X-ray images, which was refractory despite aggressive diuresis and ultrafiltration. The diagnosis of pulmonary hemorrhagic infarction was pathologically proven as shown in Figure 3.

**Conclusion**

PV thrombosis is an uncommon complication; however, it should be considered as a differential diagnosis when refractory lung opacities are encountered during VA-ECMO support. PV thrombosis would necessitate intensification of anticoagulation therapy, thrombolysis, or even surgery, such as lung lobectomy and pneumonectomy, to rescue patients. Delayed intervention might result in lethal outcome in severe acute PV thrombosis.

**Disclosure**

Conflicts of interest: None declared.

**References**

1. Eckman PM, Katz JN, El Banayosy A, Bohula EA, Sun B, van Diepen S. Veno-arterial extracorporeal membrane oxygenation for cardiogenic shock: an introduction for the busy clinician. Circulation 2019; 140: 2019-37.
2. Williams B, Bernstein W. Review of venoarterial extracorporeal membrane oxygenation and development of intracardiac thrombosis in adult cardiothoracic patients. J Extra Corpor Technol 2016; 48: 162-7.
3. Miniati M, Bottai M, Ciccotosto C, Roberto L, Monti S. Predictors of pulmonary infarction. Medicine 2015; 94: e1488.
4. Alfuadhi KM, Hassan HH, Abdullah H, Sherbini M. Pulmonary vein occlusion and lung infarction complicating non-treated moderate single pulmonary vein stenosis after radiofrequency ablation of atrial fibrillation. BJ R Case Rep 2017; 3: 20160091.
5. Stevens LH, Hornuth DA, Schmidt PE, Atkins S, Fehrenbacher JW. Left atrial myxoma: pulmonary infarction caused by pulmonary venous occlusion. Ann Thorac Surg 1987; 43: 215-7.
6. Sertic F, Crespo MM, Milas B, Bermudez C. Early diagnosis and management of pulmonary vein thrombosis following lung transplant. J Thorac Cardiovasc Surg 2019; 157: e419-21.
7. Denton EJ, Rischin A, McGiffin D, et al. Refractory pulmonary edema caused by late pulmonary vein thrombosis after lung transplantation: a rare adverse event. Ann Thorac Surg 2016; 102: e197-9.
8. Leibowitz DW, Smith CR, Michler RE, et al. Incidence of pulmonary vein complications after lung transplantation: a prospective transesophageal echocardiographic study. J Am Coll Cardiol 1994; 24: 671-5.
9. Weis F, Beiras-Fernandez A, Bruegger D, et al. Huge intracardiac thrombosis in a patient on veno-arterial extracorporeal membrane oxygenation support. Interact Cardiovasc Thorac Surg 2009; 8: 247-9.
10. Bottio T, Angelini A, Testolin L, Bonato R, Thiene G, Gerosa G. How an undiscovered extensive peripheral pulmonary venous thrombosis destroyed a heart transplant: a case report. Transplant Proc 2004; 36: 1551-3.
11. Xie A, Forrest P, Loforte A. Left ventricular decompression in veno-arterial extracorporeal membrane oxygenation. Ann Cardiothorac Surg 2019; 8: 9-18.
12. Millar JE, Fanning JP, McDonald CI, McAuley DF, Fraser JF. The inflammatory response to extracorporeal membrane oxygenation (ECMO): a review of the pathophysiology. Crit Care 2016; 20: 387.