

Enhanced EP4 Expression in a Pulmonary Artery Aneurysm With Dissection in a Patient With Pulmonary Arterial Hypertension

Satoshi Akagi, MD, PhD; Kazufumi Nakamura, MD, PhD;
Utako Yokoyama, MD, PhD; Shingo Kasahara, MD, PhD; Toshihiro Sarashina, MD;
Kentarō Ejiri, MD; Hiroshi Ito, MD, PhD

Pulmonary artery (PA) aneurysm is sometimes found in patients with pulmonary arterial hypertension (PAH), and PA dissection is a rare but life-threatening complication. The pathological background of PA aneurysms and dissection remains poorly understood.

A 29-year-old man was diagnosed with PAH associated with patent ductus arteriosus (PDA; Movie I in the [Data Supplement](#)) and was in World Health Organization functional class II. Chest radiography showed an enlargement of the PA (Figure 1A). Contrast-enhanced computed tomography demonstrated large PA aneurysm with a diameter of 72 mm (Figure 1B). His PA pressure was 58/33 (44) mmHg, and PA wedge pressure was 6 mmHg. We closed the PDA with a coil. Seven years after the diagnosis, he was transported to our hospital with sudden chest pain and deteriorating consciousness. Systemic blood pressure was 92/63 mmHg, heart rate was 83/min, and oxygen saturation was 98% with 3 L/min of oxygen administered. A chest radiography showed marked enlargement of the PA (Figure 1C). Contrast-enhanced computed tomography demonstrated the expansion of a PA aneurysm with a diameter of 105 mm and a dissection in the main PA (Figure 1D). The patient underwent emergency surgery for reconstruction of the right ventricular outflow tract and to perform bilateral PA plication (Figure 1E and 1F). Because PH remained after surgery, we administered tadalafil and ambrisentan. His PA pressure was 41/16 (24) mmHg at 8 months after surgery.

We investigated elastic fiber formation and prostaglandin E receptor type 4 (EP4) expression in the resected PA. In histological analysis, moderate-to-severe elastic fiber degradation was observed in the area of the PA aneurysm and dissection (Figure 2A and 2B). The elastic fibers were hypoplastic in PDA (Figure 2C). The right PA was formed by normal elastic fibers (Figure 2D). Immunohistochemistry demonstrated that EP4 expression was enhanced in the area of the PA aneurysm,

dissection (Figure 2E and 2F), and PDA (Figure 2G). EP4 was not expressed in the right PA (Figure 2H).

PA aneurysm is a rare disease with an estimated prevalence of 8 in 109 571 consecutive postmortem examination.¹ It is seen in patients with PAH, congenital heart diseases with left-to-right shunting, connective tissue diseases, systematic vasculitis, infections, chronic pulmonary embolism, and trauma. Although the mechanism of PA aneurysm remains poorly understood, elevation of PA pressure caused by PAH or high flow because of left-to-right shunting, resultant mucoid degeneration of the media, and fragmentation of elastic fibers are probably causes of a PA aneurysm. Particularly, congenital heart disease with left-to-right shunting has been recognized as the major reason for PA aneurysm. High flow because of left-to-right shunting increases shear stress of the PA and promotes aneurysm formation. However, high PA pressure or high flow do not always lead to a PA aneurysm. Other unknown factors are, therefore, involved in the mechanism of the PA aneurysm formation.

Our immunohistochemistry analysis gave a hint regarding the mechanism of a PA aneurysm formation. Histological analysis of this case showed degradation of elastic fibers and enhanced EP4 expression in the area of the PA aneurysm and dissection. A previous study showed that EP4 expression was increased in a human abdominal aortic aneurysm.² Stimulation of EP4 enhances matrix metalloproteinases-2 activation and interleukin-6 production, and regional inflammation weakens the arterial wall to promote the formation of an abdominal aortic aneurysm. Interestingly, EP4 expression was also enhanced in PDA in this case. A previous study showed that EP4 expression was increased in a human PDA.³ Furthermore, PDA is known to be the most frequent congenital heart defects associated with a PA aneurysm.¹ EP4 overexpression in PA and PDA might contribute to the formation of a PA aneurysm and dissection in patients with PAH.

From the Department of Cardiovascular Medicine (S.A., K.N., T.S., K.E., H.I.) and Department of Cardiovascular Surgery (S.K.), Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan; and Department of Cardiovascular Research Institute, Yokohama City University Graduate School of Medicine, Japan (U.Y.).

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Correspondence to Satoshi Akagi, MD, PhD, Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan. E-mail akagi-s@cc.okayama-u.ac.jp

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Disclosures

None.

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KEY WORDS: aneurysm ■ computed tomography ■ dissection ■ patent ductus arteriosus ■ prostaglandins ■ pulmonary artery ■ pulmonary hypertension

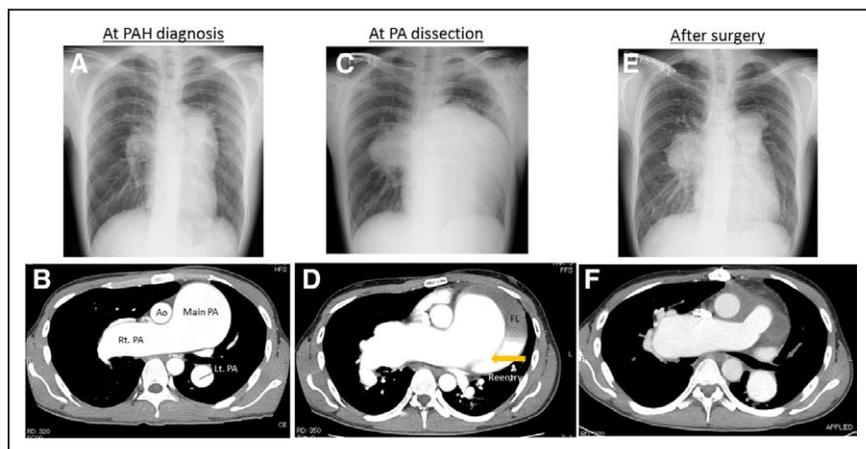


Figure 1. Chest radiography and contrast-enhanced computed tomography. **A** and **B**, At pulmonary arterial hypertension (PAH) diagnosis. **C** and **D**, At PA dissection. Arrow indicates the reentry in the distal main PA. **E** and **F**, After surgery. Ao indicates aorta; FL, false lumen; Lt, left; PA, pulmonary artery; and Rt, right.

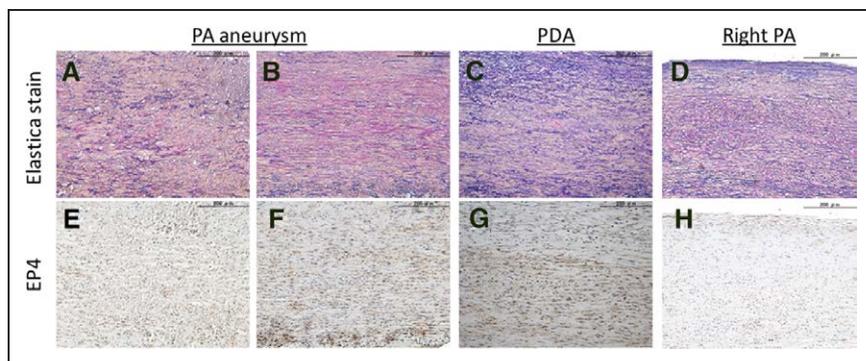


Figure 2. Elastica staining and immunohistochemistry for prostaglandin E receptor type 4 (EP4) in the pulmonary artery (PA) and patent ductus arteriosus (PDA). **A–D**, Elastica staining. **E–H**, Immunohistochemistry for EP4. Mild-to-severe elastic fiber degradation was observed in the area of the PA aneurysm (**A** and **B**). Elastic fibers were hypoplastic in PDA (**C**) and normal in right PA (**D**). EP4 expression was enhanced in the area of the PA aneurysm and dissection (**E** and **F**) and PDA (**G**). EP4 was not expressed in the right PA (**H**). Scale bars = 200 μ m.

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Video legend

Movie I. 3D volume rendered PA image of contrast-enhanced computed tomography.

Patent ductus arteriosus was observed.