Successful Recanalization of Thrombotic Occlusion in Pulmonary Artery Stent Using Sonothrombolysis

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INTRODUCTION

Recently, it has been shown that intermittent high–mechanical index impulses from a diagnostic transthoracic ultrasound system can recanalize acutely thrombosed vessels in animal models of arteriovenous graft thrombosis[1] and acute myocardial infarction during an intravenous infusion of ultrasound contrast agent.[2,3] The safety and success of this technique in large animal models have led to the first clinical investigation of this technique in acute ST-segment elevation myocardial infarction,[4] which is ongoing at our institution. This has demonstrated that diagnostic high–mechanical index impulses applied transthoracically before invasive angiography increased the early recanalization rate of the culprit coronary artery to nearly 60% before percutaneous intervention.[4] Although intravascular ultrasound catheters have been used for pulmonary artery thrombi,[5] there is no published report regarding the use of intravenous microbubbles and transthoracic ultrasound for the treatment of pulmonary embolism.

CASE DESCRIPTION

We report a case of postoperative heart surgery for hypoplastic left heart syndrome and current diagnosis of left pulmonary artery stent thrombosis followed by embolism.

A 13-month-old girl was born at 40 weeks' gestational age with a prenatal diagnosis of hypoplastic left heart syndrome. At birth, her weight was 3.0 kg, length was 48 cm, and Apgar scores were 8/9/9. She also had a small atrial septal defect and a patent ductus arteriosus. On day 3, she underwent hybrid open heart surgery including pulmonary artery banding and stent implantation in the ductus arteriosus (Express 7 × 19 mm; Boston Scientific, Fremont, CA). On day 7 a balloon atrial septostomy was performed to increase atrial septal defect size. Echocardiography at this time demonstrated a non-restrictive atrial septal defect, a peak instantaneous gradient of about 100 mm Hg through the pulmonary bandings, and a patent ductus arteriosus, with preferential flow direction from the aorta to the pulmonary artery (peak gradient 31 mm Hg).

The infant was eventually discharged on day 38 and at 1 year underwent a Norwood-Glenn procedure, which consisted of an atrial septectomy, a lateral-terminal aortopulmonary anastomosis creating a new exclusive outlet path for the systemic flow, debanding of both branch pulmonary arteries, and an anastomosis between the superior vena cava and right pulmonary artery. The ductus arteriosus with the stent was resected. A new 5-mm stent was placed in the left pulmonary artery (Express 7 × 19 mm), which had some grade of stenosis. On the first postoperative day, she developed hypotension and bradycardia. Urgent echocardiography demonstrated absence of flow in the left pulmonary artery at the exact stent location.

Treatment with intravenous heparin was started immediately. Because of persistent respiratory distress, cyanosis, and hypotension, the infant underwent diagnostic pulmonary angiography, which confirmed left pulmonary artery embolism. The vessel had a second stenting, which resulted in improved oxygenation and hemodynamic recovery. Unfortunately, on the 23rd postoperative day the patient once again developed severe hypotension and hypoxemia, with a decrease in oxygen saturation to 61%. Repeat catheterization detected recurrent pulmonary artery stent thrombosis and multiple thromboemboli to all left pulmonary branches (Figure 1A, Video 1). A left pulmonary artery catheter was placed, and after a bolus of 0.05 mg/kg of alteplase, a 24-hour complementary infusion at 5 mg/kg/h was initiated. On the following day, before any additional procedure was performed, transthoracic echocardiography demonstrated unsuccessful recanalization of left main pulmonary artery (Figure 2A). At the same time, selective left pulmonary artery angiography demonstrated persistence of occlusion of all lobe branches and extensive thrombi involving the main left pulmonary artery (Figure 1B, Video 2).

After obtaining family consent for compassionate use, a decision was made to perform two-dimensional image-guided transthoracic sonothrombolysis, which has been used at our hospital to emergently recanalize coronary arteries and the microcirculation in acute myocardial infarction.[1] This was performed using transthoracic high–mechanical index impulses from a diagnostic transducer associated with the use of commercially available microbubble (SonoVue; Bracco, Milan, Italy) for therapy, for a period of 50 min. This specific use of SonoVue microbubbles is off-label. Ultrasound with high–mechanical index impulses (1.7 MHz, mechanical index 1.3) and 20-μsec pulse duration was applied in the second left intercostal space, with the beam directed to the pulmonary artery, sweeping the ultrasound beam to insonify the upper left pulmonary lobe and the superior part of the inferior left pulmonary lobe, during intravenous bolus injection of microbubbles (0.1 mL each injection) followed by saline injection (Figure 3). The total dose of microbubbles used was 6 mL.

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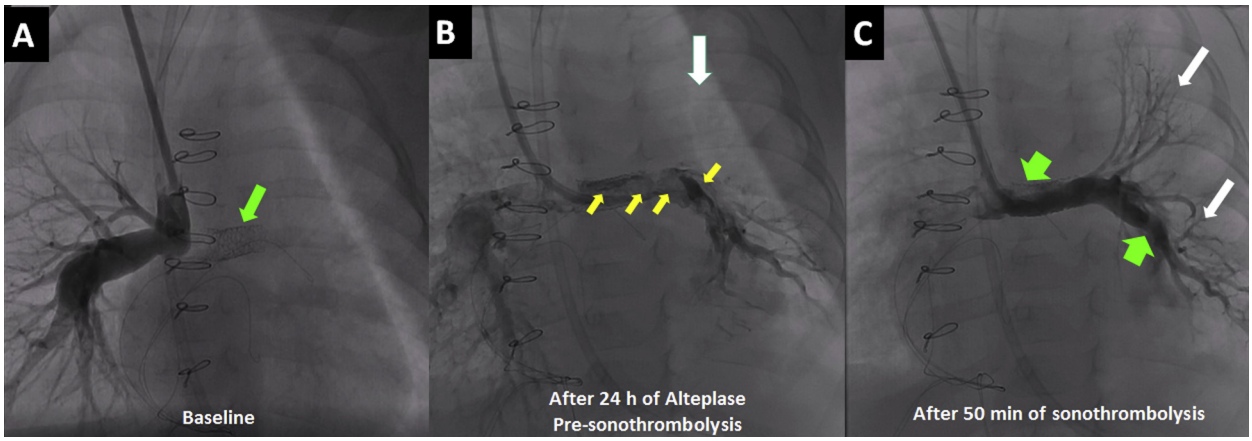

Figure 1 **(A)** Twenty-four hours before sonothrombolysis and immediately before the infusion of alteplase, a contrast injection in the main pulmonary artery demonstrated complete occlusion of the left pulmonary artery branch (*green arrow*). **(B)** Angiography with contrast injection in the left pulmonary artery demonstrating thrombotic occlusion of all lobe branches and multiple thrombi (negative images indicated by *yellow arrows*) and the absence of flow in the upper left pulmonary lobe (*white arrow*). **(C)** At 50 min of sonothrombolysis, observe the recanalization of flow to the main pulmonary artery branch with presence of residual thrombi (*green arrows*) but with flow to the lung periphery (*white arrows*).

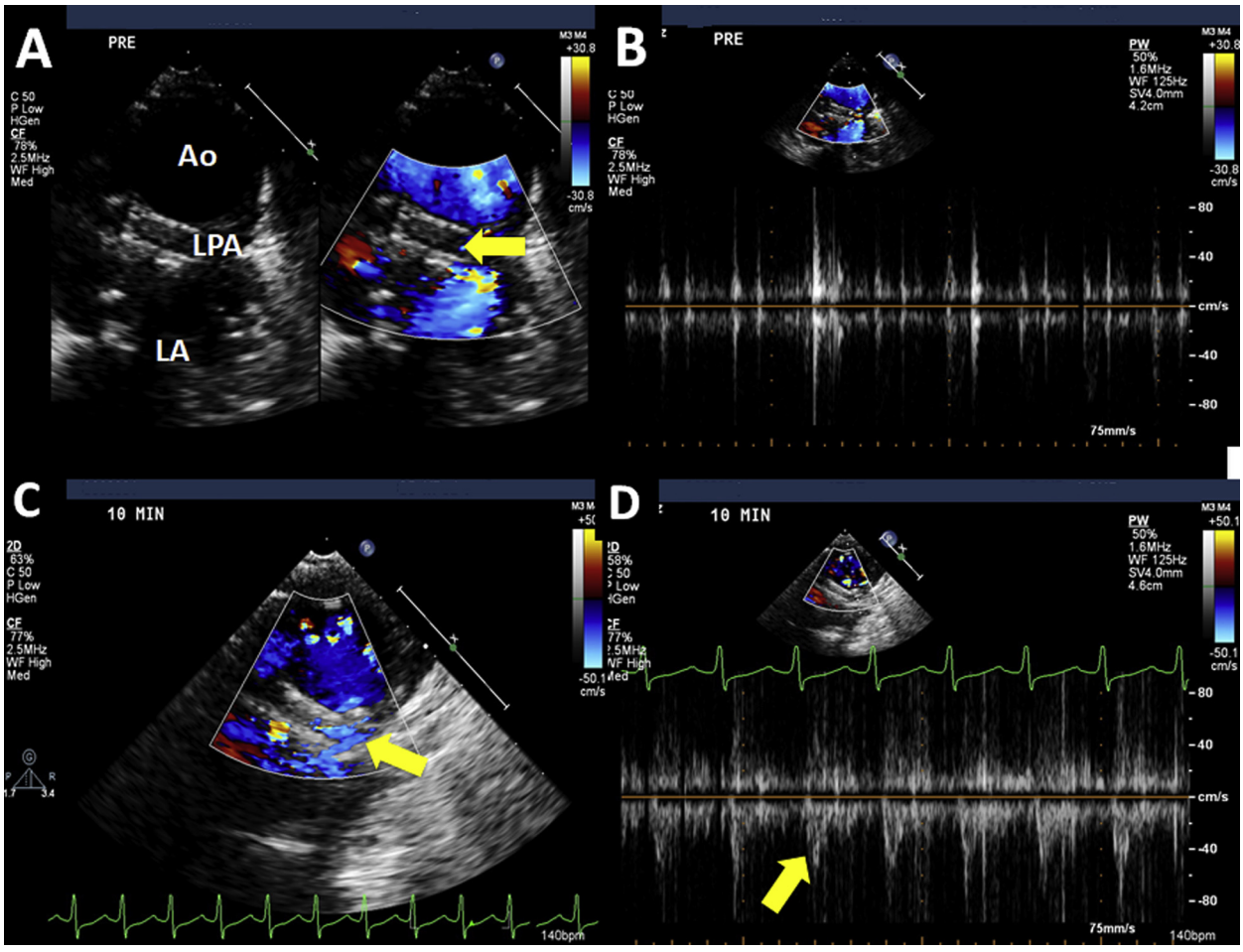

Figure 2 Two-dimensional and color Doppler images demonstrating absence of flow in the left pulmonary artery, where the stent was placed **(A)**. Pulsed-wave Doppler confirming absence of signal with the sample volume placed in the left main pulmonary artery **(B)**. At 50 min of sonothrombolysis, two-dimensional color flow **(C)** and Doppler **(D)** signs of left pulmonary artery recanalization are observed (*yellow arrows*). *Ao*, Aortic arch; *LA*, left atrium; *LAP*, left pulmonary artery branch.

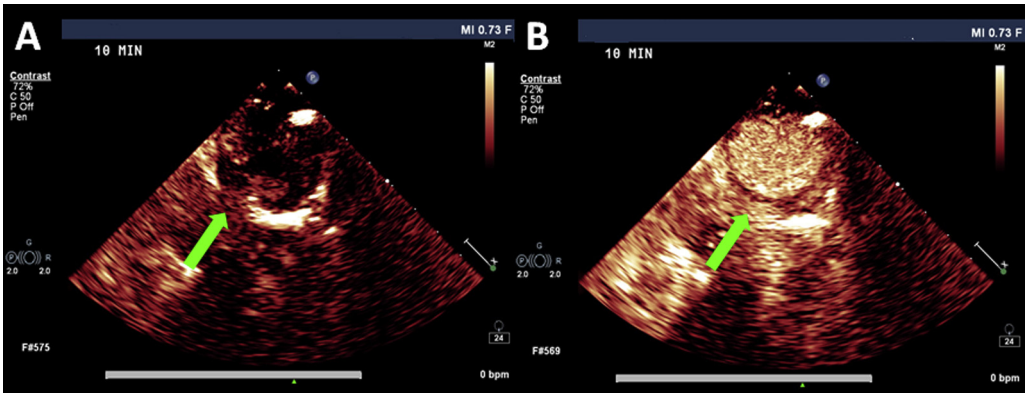

Figure 3 Low–mechanical index two-dimensional echocardiography of the left main pulmonary artery demonstrating microbubbles passing through the thrombotic occlusion. Images are acquired immediately after **(A)** and 2 sec after microbubble destruction by high–mechanical index impulses **(B)**, where the presence of microbubbles can be detected (*arrows*).

After 50 min of this application, two-dimensional, Doppler, and diagnostic ultrasound contrast (Video 3), as well as pulmonary angiography, confirmed recanalization (Figure 2B). Angiography also demonstrated flow to the main pulmonary artery branch and to the periphery of the lung, although residual thrombi were evident in the distal vasculature (Figure 1C, Video 4). This was associated with an improvement in systemic oxygenation (from 64% baseline to 78% after sonothrombolysis). Angiographic patency in the left pulmonary artery and branches was evident after sonothrombolysis. After sonothrombolysis, the child became hemodynamically stable, with improvement of saturation. However, on the 25th day after sonothrombolysis, she was diagnosed with *Pseudomonas aeruginosa* systemic infection, leading to a septic state that was difficult to manage. The child presented an irresponsive cardiac arrest by pulseless electric activity and died.

DISCUSSION

In this case we demonstrated, for the first time, that transthoracic ultrasound–induced microbubble cavitation can be used in patients with pulmonary artery thromboembolism. The mechanism for thrombus dissolution appears to be the mechanical effects of cavitation, which dissolve the thrombus either in the presence or absence of a low-dose fibrinolytic agent.[6] The application of this approach in patients with acute pulmonary embolism is unprecedented in the literature. The application seems particularly advantageous in younger patients because of the proximity of vascular structures to allow improved penetration of transcutaneously applied ultrasound impulses. The role of sonothrombolytic therapy with concurrent pharmacologic thrombolysis needs to be explored in the setting of pulmonary embolism. The longer pulse duration of the high–mechanical index impulse (which was increased to 20 μsec for this case study) may increase the effectiveness of the technique for larger intravascular chronic venous thrombi or catheter-related thrombi.[7] The residual thrombi in the pulmonary vasculature after treatment was not associated with obvious clinical consequence in this patient, but we do recognize that the effects of distal embolization after ultrasound and microbubble treatment need to be systematically examined.

Using microbubbles as a cardiac ultrasound contrast agent in children is still not approved by the US Food and Drug Administration, and it is currently contraindicated in the presence of right-to-left cardiac shunts and hypoxia, both conditions present in this case. Some publications, however, have reported that ultrasound contrast is safe in these patients.[8-10]

CONCLUSION

Intravenous microbubbles associated with transthoracic application of ultrasound were able to recanalize pulmonary artery obstruction in a child with congenital heart disease. The application of the new therapeutic approach of sonothrombolysis may be potentially useful for patients with pulmonary embolism.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.case.2018.11.006.

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