

# Surgical Treatment of Adult Williams-Beuren Syndrome with Pulmonary Arteriovenous Fistula

Xiaojie Zhang, Shiqiang Wang, Gangping Huang

Department of Cardiac Surgery, Zhejiang University Sir Run Run Shaw Hospital, Zhejiang, China

## ABSTRACT

Williams-Beuren syndrome (WBS) is a genetic disease involving the gene deletion of a chromosome. It is sporadically caused by the disruption of the elastin gene at the locus 7q11.23, and it occurs in as many as 1:7,500 individuals [Zucker 2018].

WBS includes cardiac lesions and a wide spectrum of congenital malformations with cardiovascular disorders, representing the most worrisome ones. The most typically frequent cardiovascular anomalies primarily comprise supra-valvular aortic stenosis, peripheral pulmonary stenosis, mitral regurgitation, and aortic coarctation [Matisoff 2015].

Other main features include central nervous system and connective tissue involvement, mainly with a characteristic elfin face, mental and growth retardation, and hypercalcemia. We report a rare case of WBS with right pulmonary arteriovenous fistula (PAVF), associated with supra-valvular aortic membrane stenosis, mitral regurgitation, and aortic coarctation. The patient underwent two-stage surgical treatment with satisfactory results at 5 years of follow-up.

This case study was approved by the local research ethics board. Written informed consent was obtained from this patient.

## CASE REPORT

A 28-year-old male with a characteristic elfin facial appearance was admitted to our hospital because of heart failure and dyspnea. He complained of cough and sputum after cold for half a month, which did not improve after treatment, and gradually appeared cyanosis after exercise one week prior with dyspnea. He was unable to lie flat at night. The patient's medical history was remarkable for decreased physical growth and motor developmental disorders and mental retardation. Owing to his peculiar face and mental retardation, fluorescence in situ hybridization analysis performed when he was a child revealed the hybridization signal on only one

chromosome 7. In this patient, he underwent bilateral inguinal hernia repair. Physical examination revealed a 3/6 harsh systolic murmur, decreased palpable bilateral femoral pulses, and an elevated pressure gradient of 40 mmHg between his upper and lower limb (130/40 mmHg, 90/35 mmHg, respectively). Emergent Troponin T was normal, and D-dimer was negative. NT pro-BNP was increased (4265pg/ml). The serum calcium level (2.16 mmol/L) was low. Arterial blood gas showed low carbon dioxide (32mmHg) and oxygen partial pressure (65mmHg) when inhaling 41% oxygen. Emergent chest computed tomography scan angiography showed pulmonary edema, massive pleural effusion, and enlarged heart shadow. ECG monitoring suggested atrial fibrillation rhythm, with an average ventricular rate of 114 beats/min (Figure 1A). (Figure 1) Ultrasound examination of both lower limbs showed no thrombus. Transthoracic echocardiography indicated moderate-to-severe mitral valve regurgitation and a supra-valvular aortic membrane stenosis without coronary stenosis. The preoperative peak systolic pressure gradient of stenosis was 85mmHg. Simultaneously, echocardiography also demonstrated severe local ascending aortic coarctation with a 6.2mm diameter 2cm above the aortic valve annular. The pulmonary valve and pulmonary stenosis were not seen. With diuretic treatment and amiodarone to control the heart rate, the symptoms of heart failure were satisfactorily relieved. Arterial blood gas still showed low carbon dioxide (32mmHg) and oxygen partial pressure (71mmHg) on inhaling 33% oxygen. Computer tomography angiography of the aorta showed pulmonary arteriovenous fistula in the anterior basal segment of the right lower lobe in addition to ascending aortic coarctation and abdominal aortic coarctation which was a long segment (with 0.8cm diameter). (Figure 2) Chest computed tomography scan angiography showed that pulmonary edema and massive pleural effusion disappeared (Figure 3A).

The patient underwent a two-step surgery for repairing most of the hemodynamically significant thoracic malformations. First, percutaneous surgical intervention was performed. Selective angiography of the right pulmonary artery confirmed the diagnosis of a solitary PAVF in the right lower lobe with feeding arteries, with a diameter of 3 mm in the narrowest segment of the feeding arteries. Percutaneous transcatheter embolization of the PAVF was then performed. A 6 Fr, 100 cm guiding catheter was placed over a stiff exchange wire. A passage between the artery and vein was achieved using a 5 Fr, 125 cm coaxial catheter in order to set the tip of the guiding catheter into the proximal portion of the feeding artery. Three intravascular coils were selected to occlude the feeding artery

Received February 11, 2022; accepted March 30, 2022.

Correspondence: Xiaojie Zhang, Zhejiang University Sir Run Run Shaw Hospital, Zhejiang, China (e-mail: [drzhangxiaojie@zju.edu.cn](mailto:drzhangxiaojie@zju.edu.cn)).

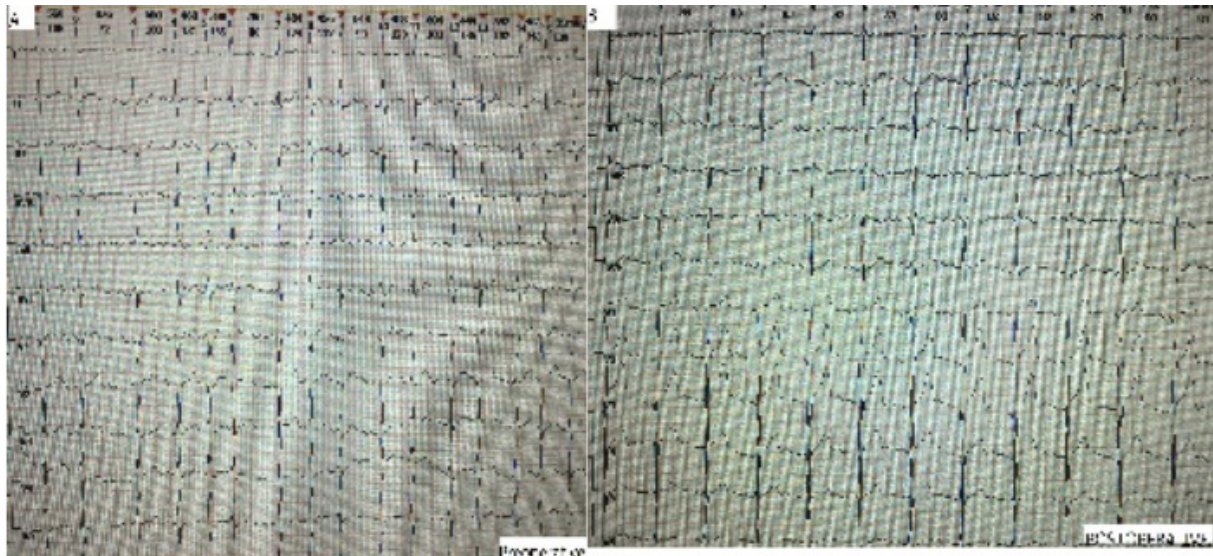


Figure 1. Preoperative and postoperative electrogram

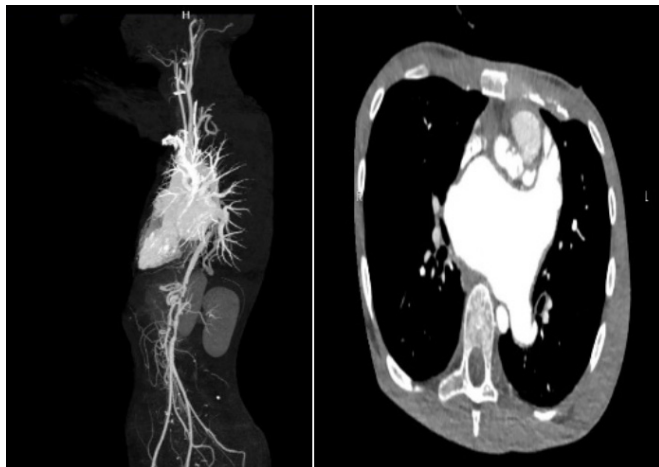


Figure 2. Preoperative computer tomography angiography of aorta

(respectively 4mm\*15cm, 4mm\*8cm, 3mm\*14cm). Repeat angiography confirmed complete occlusion of the vessel within 5 min. A week later, he underwent a next-step surgery for repairing the significant malformations through a median sternotomy. First, Cox IV radiofrequency ablation for atrial fibrillation was performed. Second, when the enlarged left atrium and left ventricle were found to be the cause of the mitral regurgitation, reduction annuloplasty of the mitral valve was used. At last, an inverted Y-shaped incision was made to longitudinally cut the local coarctation of the ascending aorta until it reached the membranous stenosis ring and was horizontally enlarged to expose and cut out the membranous stenosis ring and showed the coronary ostia were normal. The inverted Y-shaped aorta incision was transverse sutured. The cross-clamp time was 146 minutes, and the total bypass time was 178 minutes. Atrial fibrillation rhythm became sinus rhythm immediately after surgery. Mitral regurgitation

obviously was improved. The pressure gradient between the upper and lower extremities did not change after surgery, and the cardiac echocardiography at discharge indicated that the peak blood flow in the ascending aorta still was high (4.2m/s), with an average pressure gradient of 72mmHg. Pathological findings showed that the septal fibrous tissue was accompanied by local myxoid degeneration. The patient was discharged 15 days after surgery. (Figures 3B and 3C).

During follow-up, sinus rhythm was maintained (Figure 1B). The above cardiac indexes improved year after year. After 5 years, the peak blood flow in the ascending aorta decreased to 2.4m/s, and the average pressure gradient was 10mmHg. (Figure 4) The inner diameter of the vessel at the stenosis also dilated from 6mm to 14mm while sinus rhythm was kept, and the mitral valve was normal.

## DISCUSSION

WBS is a multiple system disorder because of elastin deficiency. Literature showed that approximately 80% of patients with WBS have cardiovascular malformations, of which the most common cardiovascular malformation is arterial stenosis, in addition to ventricular septal defect, atrial septal defect, mitral valve insufficiency, aortic valve insufficiency and other rare intracardiac malformations [Zucker 2018]. Supervalvular aortic stenosis (SVAS) is the most prevalent the arterial stenosis occurring in approximately 45-75% of patients with WBS, of which the spectrum ranges from discrete circumferential thickening of the aorta at the sinotubular junction to diffuse involvement of the ascending, transverse, and descending aorta with varying degrees of hypoplasia and narrowing; SVAS may worsen with time [Matisoff 2015; Panfilov 2020]. Hills et al. showed the cardiovascular-associated mortality risk and risk of sudden death in the WBS was 25–100 times higher than that of the general population and cardiovascular disease was the

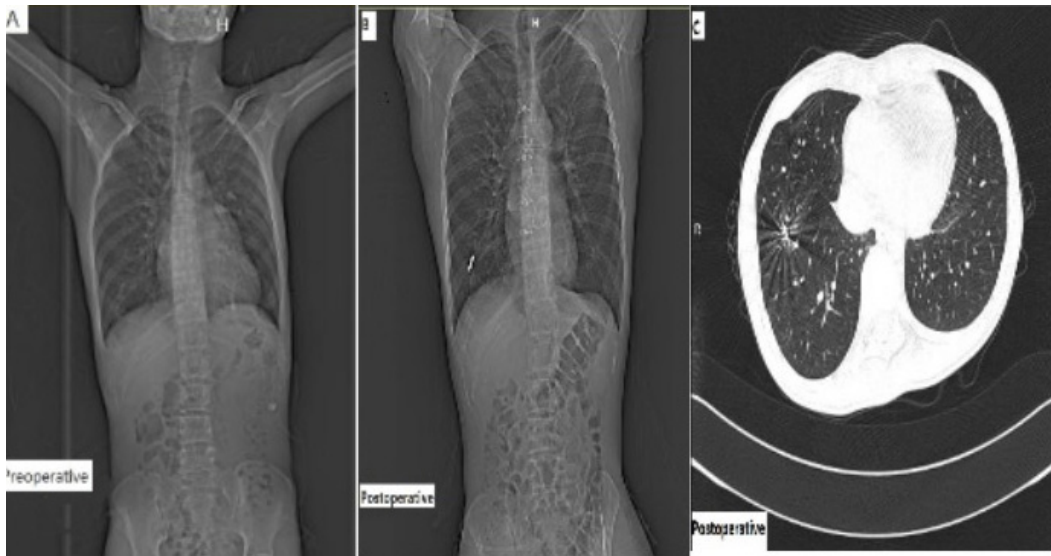


Figure 3. Preoperative and postoperative chest computer tomography

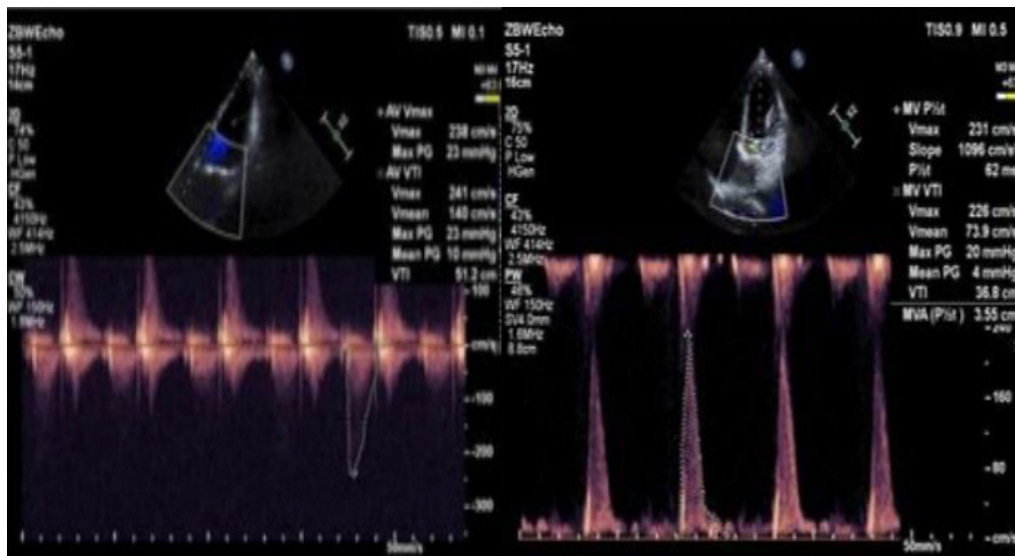


Figure 4. Postoperative echocardiogram

main cause of morbidity and mortality in WBS [Hills 2017]. So, the cardiovascular malformations of Williams syndrome are a significant therapeutic target. Depending on the type, location, severity of those cardiovascular malformations, and time of onset, about one in three of the patients with WBS may require transcatheter intervention or surgery [Collins 2013]. In our case, the WBS patient was an adult with SVAS that included the membranous stenosis above the sinotubular junction, local ascending aorta coarctation, and long-segment abdominal aorta coarctation, with the whole segment of dysplastic aorta whose lumen was mild narrow. It caused severe supravalvular aortic stenosis and needed surgical treatment. Patch repair, ascending aorta replacement, and catheter intervention have shown good results for SVAS; the inverted Y-shaped incision was performed

and transversely sutured so as to not only relieve SVAS but also widen the anastomosis to avoid postoperative restenosis [Pober 2010; Kaushal 2010]. Enlargement of mitral annulation was the cause of mitral regurgitation in this patient. At present, there is no consensus on whether mitral valve replacement or mitral valve formation is the treatment for mitral regurgitation in patients with WBS. Abdominal aortic coarctation was not treated.

PAVF is a congenital pulmonary vascular malformation that previously has not been reported in patients with William's syndrome. It can result in hypoxemia, even cyanosis, and heart failure in severe cases because of the left-to-right shunt at the pulmonary level. Although the relevance of this association is not clear to date, PAVF can exacerbate pathophysiologically the hypoxemia of WBS. In this WBS patient, severe hypoxemia

still occurred after heart failure improved. Transcatheter intervention currently is considered to be the most minimally invasive surgical method with the best effect.

Literature verified that patients with Williams syndrome are at high risk with anesthesia, especially when undergoing cardiac procedures. These risks can be mitigated with an appropriate plan and adherence to the hemodynamic goals for non-cardiac procedures. It is necessary for WBS patients with cardiovascular complications to adequately prepare for operation when considering the higher risk for anesthesia-related adverse events and major adverse cardiac events following surgery [Brown 2018]. In the present case, a two-step surgical treatment strategy was adopted, in which pulmonary arteriovenous fistula embolization being a non-cardiac surgery was taken first under local anesthesia to improve hypoxemia and tolerance for secondary cardiovascular surgery and reduce the incidence of anesthesia-related adverse events and major adverse cardiac events following surgery.

Almost all patients with WBS require multiple encounters with the healthcare system for the management of medical or surgical problems because they still have elastin deficiency-related vasculopathy, hypertension, intellectual disability, and social problems after surgery. So, it is necessary to have a long-term follow-up for WBS after treatment. In the present case, since abdominal aortic coarctation was not managed, there was no immediate significant decrease in pressure gradient or flow rate of supervalvular aortic stenosis after surgery. Follow-up observation was maintained after the operation. It was not until 5 years later that these indicators returned to normal, while mitral valve repair and Cox IV radiofrequency ablation for atrial fibrillation still is satisfactory. Follow-up will continue to observe the patient's abdominal aortic coarctation and other issues.

## ACKNOWLEDGMENT

This article was supported by grants from the Natural Science Foundation of Zhejiang Province (LY19H020010).

## CONCLUSION

The management of WBS patients requires a multidisciplinary group, including cardiovascular physicians, cardiovascular surgery, mental health, and endocrinology. In addition to long-term follow-up after surgery to observe cardiovascular complications, attention should be paid to hypertension, diabetes, and mental health and social problems.

## REFERENCES

- Brown ML, Nasr VG, Toohey R, et al. 2018. Williams Syndrome and Anesthesia for Non-cardiac Surgery: High Risk Can Be Mitigated with Appropriate Planning. *Pediatric cardiology*. 39(6): p. 1123-1128.
- Collins RT, 2nd. 2013. Cardiovascular disease in Williams syndrome. *Circulation*. 127(21): p. 2125-34.
- Hills JA, Zarate YA, Danylchuk NR, et al. 2017. Advanced cardiovascular imaging in Williams syndrome: Abnormalities, usefulness, and strategy for use. *Am J Med Genet A*. 173(5): p. 1194-1199.
- Kaushal S, Backer CL, Patel S, et al. 2010. Midterm outcomes in supra-valvular aortic stenosis demonstrate the superiority of multisinus aortoplasty. *Ann Thorac Surg*. 89(5): p. 1371-7.
- Matisoff AJ, Olivieri L, Schwartz JM, et al. 2015. Risk assessment and anesthetic management of patients with Williams syndrome: a comprehensive review. *Paediatr Anaesth*. 25(12): p. 1207-15.
- Panfilov DS, Saushkin VV, Kozlov BN. 2020. Cardiovascular abnormalities in patient with Williams-Beuren syndrome. *Eur J Cardiothorac Surg*. 58(1): p. 196-198.
- Pober BR. 2010. Williams-Beuren syndrome. *N Engl J Med*. 362(3): p. 239-52.
- Zucker EJ. 2018. Syndromes with aortic involvement: pictorial review. *Cardiovasc Diagn Ther*. 8(Suppl 1): p. S71-S81.