Cardiology in the Young

cambridge.org/cty

Recurrent coarctation in Williams syndrome: novel approach of drug-eluting stent implantation

Aphrodite Tzifa[1], Konstantinos S. Mylonas[1] and Antonios Halapas[2]

[1]Department of Congenital Heart Disease, Mitera Hospital, Hygeia Group, Athens, Greece and [2]Department of Transcatheter Heart Valves, Hygeia Hospital, Athens, Greece

Brief Report

Cite this article: Tzifa A, Mylonas KS, and Halapas A (2020) Recurrent coarctation in Williams syndrome: novel approach of drug-eluting stent implantation. *Cardiology in the Young* **30**: 294–297. doi: 10.1017/S1047951119003202

Received: 4 October 2019
Revised: 11 December 2019
Accepted: 12 December 2019
First published online: 16 January 2020

Keywords:
Williams syndrome; aortic coarctation; drug-eluting stent; Zotarolimus; CHD

Author for correspondence:
Dr A. Tzifa, MD(Res), FRCPCH, Consultant Paediatric Cardiologist, Department of Congenital Heart Disease, Mitera Hospital, Hygeia Group, ErythrouStavrou 6, 15123 Marousi, Athens, Greece. Tel: +306908999961; E-mail: atzifa@mitera.gr

Abstract

Patients with Williams syndrome often present with abnormalities of the vascular wall of the aorta and/or the pulmonary artery. Surgery may result in restenosis of the affected vessel. Herein, we report a case of an infant with multiple recurrences of aortic coarctation successfully treated with Zotarolimus drug-eluting stent.

Case presentation

A 5-day-old term, 3 kg female was born at our institution. Heart murmur was detected and aortic coarctation was diagnosed. Through lateral thoracotomy, an end-to-end anastomosis was performed. The aortic wall was unusually hard and fluorescence in situ hybridization examination confirmed the diagnosis of Williams syndrome. The infant returned at the age of 2 months with severe recoarctation, peak echocardiographic gradient 130 mmHg (mean = 79 mmHg), with diastolic tail. On MRI and cardiac catheterisation, long-segment stenosis was appreciated (Fig 1a to c). Maximum diameter at the restenosis site measured 1.7 mm. Gadolinium contrast dropout was noted on three-dimensional MRI angiography due to extreme stenosis. Surgical consultation was against reoperation at this vessel diameter, hence angioplasty was suggested. The lesion was successfully ballooned with a Traveler 3.5 × 20 mm balloon (Abbott), upgraded to a non-compliant NC Euphora RX 5 × 15 mm (Medtronic) and finally a 6-mm Tyshak balloon (NuMED) (Fig 1d). Post-angioplasty, right axillary artery pressure dropped from 194/77 to 97/62 mmHg. Haemodynamic gradient dropped from 100 mmHg (ascending aortic pressure –AoA 194/77 mmHg, descending aorta –AoD 94/62 mmHg) to 39 mmHg (AoA 86/30/54 mmHg, AoD 47/30 mmHg). Peak echocardiographic gradient fell from 130 to 70 mmHg max (mean = 35 mmHg).

The lesion gradually restenosed within the next 3 months. On catheterisation, long-segment restenosis was noted more distally to the original lesion. Peak echocardiographic gradient measured 120 mmHg (mean = 75 mmHg), with prominent diastolic tail. The stenosis was re-ballooned with a non-compliant NC Euphora RX, 5 × 15 mm balloon (Medtronic), followed by a 6-mm Tyshak balloon. Haemodynamic gradient dropped from 99 mmHg (AoA 170/78 mmHg, AoD 71/45 mmHg) to 28 mmHg (AoA 110/40 mmHg to AoD 82/42 mmHg). Peak echocardiographic gradient fell from 120 to 46–50 mmHg (mean = 25 mmHg).

The patient remained clinically well for 1 year. However, subsequent monthly reviews revealed gradual long-segment restenosis. Double antihypertensive therapy was required. Peak echocardiographic gradient measured 105 mmHg (mean = 52 mmHg), with diastolic tail. Catheterisation was performed again at the age of 18 month. Both femoral arteries were found completely occluded with collateral network, hence access was obtained via a 4-Fr sheath placed in the right axillary artery. Repeat angioplasty was deemed unsuitable. Therefore, a 5 × 15 mm Resolute Onyx™ drug-eluting stent was implanted (Medtronic). The affected lesion was completely covered (Fig 2a and b). Baseline gradient of 80 mmHg (AoA 150/75 mmHg, AoD 70/48 mmHg) fell to 15 mmHg (AoA 92/52 mmHg to AoD 77/50 mmHg). Peak echocardiographic gradient fell from 105 to 45 mmHg (mean = 22 mmHg). Following this intervention, the patient was started on aspirin and clopidogrel which she has continued to this date (aka 19 months since the procedure and 18 months after the CT angiography). Aspirin will be continued indefinitely. Clopidogrel was adjusted for weight according to somatic growth up to 1- year post-stent implantation and has been left at the same dose since. It will empirically be discontinued at 2 years post-catheterisation. The patient has remained clinically well and free from further interventions. Echocardiographic max Doppler gradient has remained stable at 50 mmHg (mean = 20–25 mmHg) (Supplementary material Fig S1). CT angiography 18 months post-implantation showed good stent apposition without evidence of intimal

CAMBRIDGE UNIVERSITY PRESS

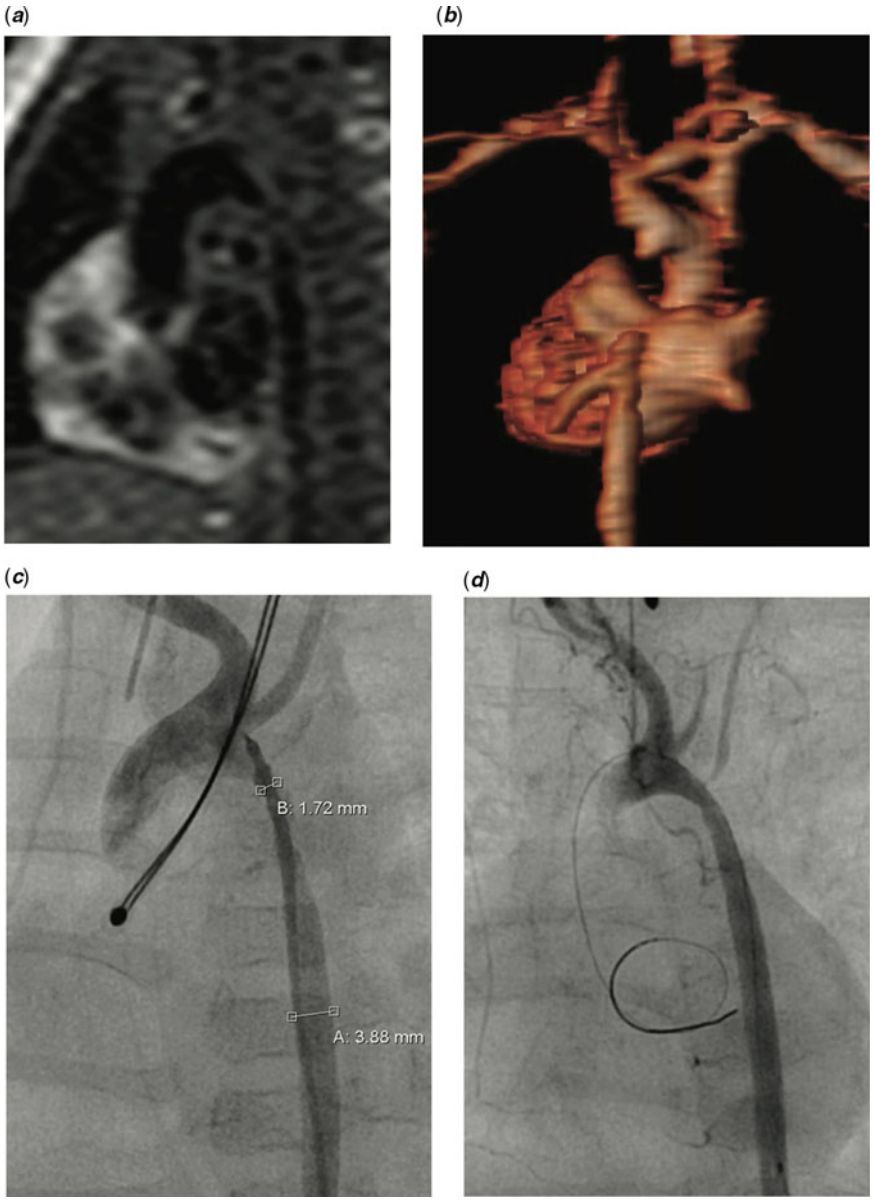

Figure 1. (***a***) Black blood sagittal MRI section, showing severe recoarctation, (***b***) three-dimensional reconstruction with gadolinium dropout at the site of the coarctation due to the severity of the stenosis, (***c***) angiographic view of the coarctation showing the narrowest point estimated at 1.7 mm, (***d***) initial balloon angioplasty – final result.

proliferation (Fig 2c and d). The patient's femoral pulses are well palpable and four-limb blood pressures measure an upper–lower peak gradient of 20 mmHg.

Discussion

Williams syndrome results from a microdeletion in chromosome 7 (q11.23 region). This deletion involves several genes, including the ELN elastin-encoding gene. Structural cardiac and vascular disease occurs in about 80% of patients, most commonly supravalvar aortic stenosis and branch pulmonary artery stenosis.[1] Due to the elastin deficiency, coarctation of the aorta, mid-aortic syndrome, as well as coronary, renal and mesenteric artery stenosis have also been described.[1] Coarctation in these patients may manifest as discrete stenosis or a long-segment narrowing.[2] Patch implantation is successful in most cases of Williams infants with long-segment coarctation.[3] In our patient, vessel diameter was only 1.7 mm, which was considered to be too narrow for effective patch enlargement. Long-segment stenosis, rapid recoarctation following balloon angioplasty, as well as the fact that balloon angioplasty may trigger intimal proliferation further, prompted us to stent the lesion. Cohen et al recently reported successful use of drug-eluting balloons in a Williams patient with branch pulmonary artery in-stent stenosis.[4] Angioplasty with a drug-eluting balloon was performed for in-stent restenosis and to remodel the distal pulmonary vessels bilaterally. This resulted in immediate improvement of the in-stent restenosis and resultant decrease in the right ventricular pressure. The antiproliferative effects of drug-eluting balloons may be of benefit in Williams arteriopathy. We chose a drug-eluting stent, based on the same hypothesis that the drug might minimise the risk of in-stent restenosis.

Drug-eluting balloons and drug-eluting stents have been tried in adults for both coronary lesions and peripheral femoropopliteal artery stenosis.[5,6] In recent years, their use in paediatric cardiac interventions has anecdotally increased. Lee et al recently reported on nine newborns who underwent stent implantation in the arterial duct with a sirolimus-eluting single stents.[7] The Zotarolimus Resolute Onyx™ stent is a new generation drug-eluting

https://doi.org/10.1017/S1047951119003202 Published online by Cambridge University Press

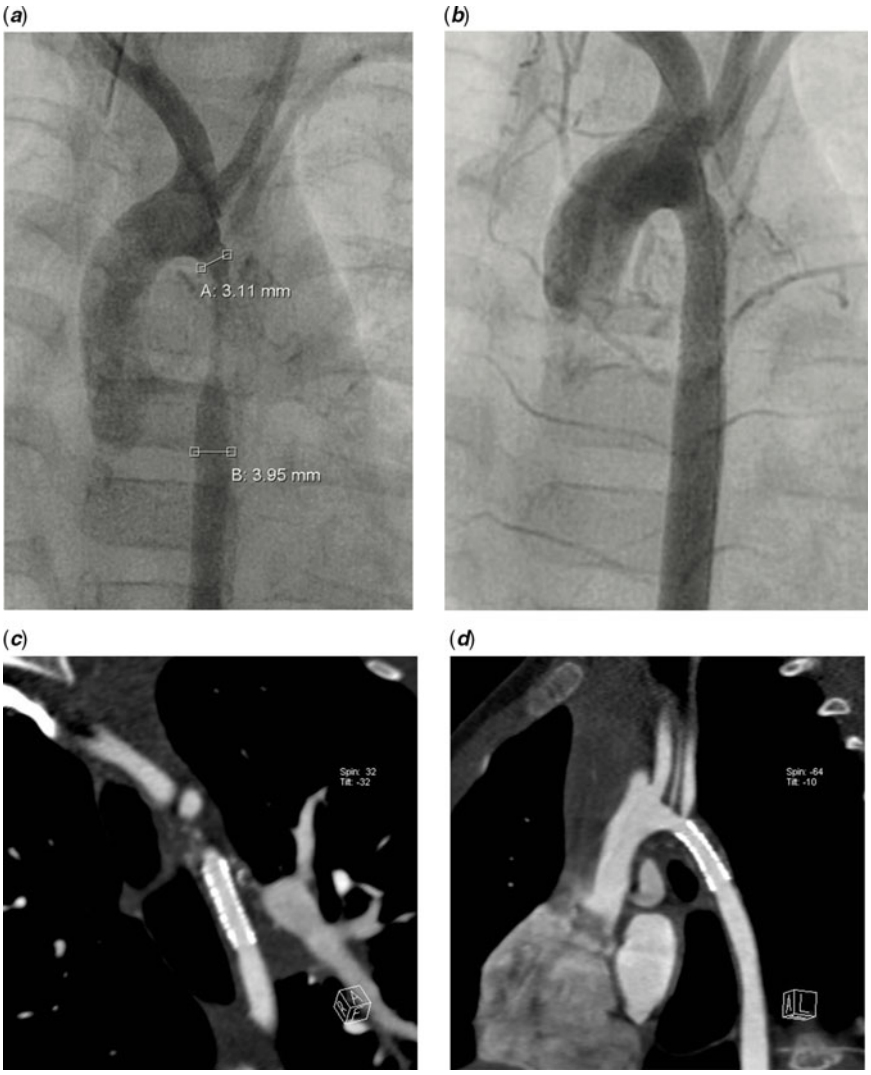

Figure 2. Implantation of a 5 × 15 mm Resolute Onyx™ drug-eluting sten (Medtronic) with an excellent angiographic result: (***a***) pre-stenting and (***b***) post-stenting, (***c***–***d***) CT angiography at 18 months post-implantation revealed no intimal in-stent growth.

stent that delivers a synthetic analogue of Sirolimus, which inhibits the m-TOR activity leading to inhibition of cell cycle progression from the G_1 to the S phase, thus minimising neointimal hyperplasia and the risk of in-stent restenosis.[8,9] We chose a Zotarolimus drug-eluting stent based on its known safety profile. Indeed, based on available Zotarolimus pharmacokinetic data, systemic safety margins of ≥78-fold have been established for the Resolute Onyx™ stent at 380 μg due to the extended elution of Zotarolimus from the BioLinx® polymer, meaning that we delivered 78 × less drug than what it would be considered unsafe.[9]

At 18-month follow-up our patient has not developed recoarctation, arterial hypertension, or other significant adverse effects. Most recent echocardiography and CT angiography revealed that the stent is of good diameter with no collapse and laminar pulsatile forward flow. Further surgery will most likely be required when the patient is of a suitable age and weight to undergo a more definitive surgical procedure, although even this may be avoided, if further dilation and potentially cautious intentional stent fracture manages to deal with growth-related restenosis.[10]

Conclusion

Drug-eluting stents may be used in recoarctation patients with abnormal vascular wall to decrease neointimal proliferation and prevent rapid restenosis. Due to the small available diameters of such stents of up to 5 mm, it is anticipated that re-interventions for stent dilation and/or stent fracture or a reoperation may be required in the future. Therefore, such procedures may not be definitive but offer palliation in patients when imminent surgery carries a high risk with low success rate.

Supplementary Material. To view supplementary material for this article, please visit https://doi.org/10.1017/S1047951119003202

Financial Support. This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflicts of Interest. None.

References

1. Mannarino S, Collins RT 2nd. Cardiovascular disease in Williams syndrome. Circulation 2013; 127: 2125–2134.
2. Collins RT 2nd, Kaplan P, Rome JJ. Stenosis of the thoracic aorta in Williams syndrome. Pediatr Cardiol 2010; 31: 829–833.
3. Mannarino S, Keizman E, Pasotti M, Codazzi AC, De Sando E, Giamberti A. A rare case of discrete aortic coarctation in Williams-Beuren syndrome. Diagnostic and therapeutic considerations. Pediatr Med Chir 2015; 37: pmc.2015.120.

4. Cohen JL, Glickstein JS, Crystal MA. Drug-coated balloon angioplasty: a novel treatment for pulmonary artery in-stent stenosis in a patient with Williams Syndrome. Pediatr Cardiol 2017; 38: 1716–1721.
5. Scheinert D, Duda S, Zeller T, et al. The LEVANT I (Lutonix paclitaxel-coated balloon for the prevention of femoropopliteal restenosis) trial for femoropopliteal revascularization: first-in-human randomized trial of low-dose drug-coated balloon versus uncoated balloon angioplasty. J Am Coll Cardiol Cardiovasc Interv 2014; 7: 10–19.
6. Palmerini T, Benedetto U, Biondi-Zoccai G, et al. Long-term safety of drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. J Am Coll Cardiol 2015; 65: 2496–2507.
7. Lee KJ, Seto W, Benson L, Chaturvedi RR. Pharmacokinetics of sirolimus-eluting stents implanted in the neonatal arterial duct. Circ Cardiovasc Interv 2015; 8: e002233.doi: 10.1161/CIRCINTERVENTIONS.114.002233
8. Wessely R, Schomig A, Kastrati A. Sirolimus and Paclitaxel on polymer-based drug-eluting stents: similar but different. J Am Coll Cardiol 2006; 47: 708–714.
9. Burke SE, Kuntz RE, Schwartz LB. Zotarolimus (ABT-578) eluting stents. Adv Drug Deliv Rev 2006; 58: 437–446.
10. Khan A, Qureshi A, Justino H. Comparison of drug eluting versus bare metal stents for pulmonary vein stenosis in childhood. Catheter Cardiovasc Interv 2019; 94: 233–242.

https://doi.org/10.1017/S1047951119003202 Published online by Cambridge University Press