REVIEW

Cardiovascular disease in Williams syndrome

R. Thomas Collins II[a,b]

Purpose of review
Williams syndrome is a multisystem disorder seen with some regularity at most pediatric centers and usually fairly often at larger centers. Cardiovascular abnormalities, because of elastin deficiency, are the leading cause of morbidity and mortality in patients with Williams syndrome. The present article presents a review of the most recent developments regarding the cardiovascular issues in Williams syndrome.

Recent findings
Cardiovascular abnormalities occur in 80% of patients with Williams syndrome, the majority of which are arterial stenoses. The stenoses seen in Williams syndrome now appear to arise from deficient circumferential arterial growth. Pharmacological therapies aimed at improving the vascular stenoses have shown some promise in animal models. Surgical outcomes for supravalvar aortic stenosis are good at most centers. Transcatheter interventions are largely ineffective in Williams syndrome. Multilevel surgical pulmonary artery reconstruction has excellent results for peripheral pulmonary artery stenosis. Periprocedural risk stratification and management algorithms may decrease the risk of cardiovascular complications.

Summary
Cardiovascular abnormalities are a major determining factor in the clinical picture and trajectory of patients with Williams syndrome. Advances in surgical techniques, medical therapeutic options, and periprocedural management hold promise for significant improvements in the cardiovascular outcomes of these patients.

Keywords
anesthesia, cardiovascular, medical, surgery, Williams syndrome

INTRODUCTION

Williams syndrome (Online Mendelian Inheritance in Man #194050), or Williams–Beuren syndrome, is a multisystem, congenital disorder affecting approximately one in 10 000 live births [1]. Williams syndrome occurs as the result of a deletion of approximately 1.5–1.8 Mb on chromosome 7q11.23 [2]. The deletion includes 26–28 genes and is almost always *de novo*; however, familial cases have been reported [3]. The *ELN* gene, which encodes the protein elastin, is located near the middle of the commonly deleted region [4]. Deletion of one of the *ELN* alleles, resulting in hemizygosity of *ELN*, is responsible for the vascular abnormalities seen in Williams syndrome [5].

THE ROLE OF ELASTIN IN CARDIOVASCULAR ABNORMALITIES

Elastin comprises approximately 50% of the dry weight of the aorta, and is found throughout the arterial tree [6]. Elastin provides distensibility and recoil, allowing for the storage of energy in the arterial wall during systolic distension and the release of the stored energy during diastolic recoil. This feature of elastin improves the efficiency of the cardiovascular system via the Windkessel effect, a physical phenomenon by which noncontinuous, pulsatile energy can be stored and subsequently released as a continuous stream. In the aorta, the pulsatile flow from the heart is stored in the distended wall during systole. Subsequently, as the aortic wall recoils during diastole, it continues to push the blood further into the distal arterial tree. Thus, via the Windkessel effect, the pulsatile flow from the heart is transformed to continuous flow at the distal arterial bed and capillary level [7]. In

[a]The Department of Pediatrics, Division of Cardiology, Stanford University School of Medicine and [b]The Department of Pediatrics, Division of Cardiology, Lucile Packard Children's Hospital Stanford, Palo Alto, California, USA

Correspondence to R. Thomas Collins II, MD, Stanford University School of Medicine, 750 Welch Road, Suite 321, Palo Alto, CA 94304, USA. Tel: +1 650 736 7419; e-mail: tomcollins@stanford.edu

Curr Opin Pediatr 2018, 30:000–000

DOI:10.1097/MOP.0000000000000664

KEY POINTS

- Cardiovascular abnormalities, which occur in the large majority of patients with Williams syndrome, are the leading cause of morbidity and mortality.
- Transcatheter interventions for arterial stenoses in Williams syndrome are rarely of any benefit and may be detrimental.
- In the right hands, multilevel, surgical pulmonary artery reconstruction can have exceptional results in patients with Williams syndrome.
- The risk of cardiovascular events in the periprocedural period can likely be mitigated against in patients with Williams syndrome using a risk stratification plan and periprocedural management algorithm.

addition, the Windkessel effect decreases the afterload on the heart and is vital for coronary artery perfusion during diastole, thereby impairing ventricular function [8].

Prior studies have reported that elastin haploinsufficiency results in subendothelial migration and vascular smooth muscle cell hyperplasia causing encroachment on the vascular lumen and arterial stenoses [9,10]. However, recent work by Jiao *et al.* [11▪] has shown that deficient circumferential growth, and not vascular smooth muscle cell proliferation, is the primary determinant of aortic luminal narrowing in the setting of elastin haploinsufficiency and moderate vascular disease. This represents a significant shift in the understanding of the pathophysiology of arterial stenoses in Williams syndrome, one that could shift the approach to future medical therapies [12].

Table 1. Structural cardiovascular abnormalities in patients with Williams syndrome

Structural abnormality	Frequency
Supravalvar aortic stenosis	35–65% [13,16,17]
Peripheral pulmonary artery stenosis	37–61% [13,17,18]
Long-segment stenosis of the thoracic aorta[a]	6–14% [17,19]
Ventricular septal defect	8–21% [13,17]
Supravalvar pulmonary stenosis	12% [12]
Abnormal mitral valve	20% [13]
Mitral valve prolapse	15% [20,21]
Mitral valve regurgitation	14% [21]
Abnormal aortic valve	18% [13]
Aortic insufficiency	10% [13]
Abnormal aortic valve cusps	7% [13]
Bicuspid aortic valve	5–12% [13,20]
Valvar aortic stenosis	4% [13]
Coronary artery anomalies	11–27% [13,22]
Ostial stenosis	5–9% [12,13]
Dilated coronary arteries[b]	19–23% [22,23]
ALCAPA	Rare [12]
Atrial septal defect	3–6% [13,17]
Ebstein anomaly	Rare [24–26]
Tetralogy of Fallot	Rare [17,27,28]
Total anomalous pulmonary venous return	Rare [29–31]
Complete atrioventricular canal defect	Rare [32]
Double-chambered right ventricle	Rare [33]
Aortopulmonary window	Rare [15]
Interrupted aortic arch	Rare [34]
Pulmonary artery sling	Rare [35]

[a]Long-segment stenosis of the thoracic aorta is often incorrectly referred to as coarctation of the aorta.
[b]In cases of severe supravalvar aortic stenosis; ALCAPA, anomalous left coronary artery arising from the pulmonary artery.

CARDIOVASCULAR ABNORMALITIES IN WILLIAMS SYNDROME

Structural cardiovascular abnormalities, the majority of which are stenotic lesions, are the leading cause of morbidity and mortality in patients with Williams syndrome [3]. Cardiovascular defects occur in approximately 80% of patients with Williams syndrome [13], a number that increases to 93% in those who present in the 1st year of life [14]. Supravalvar aortic stenosis (SVAS) occurs in approximately 55% of patients with Williams syndrome who present in the 1st year of life [14] and 45% of those who present thereafter [13]. The natural history of SVAS lesion severity is mostly one of stability [15]. Branch or peripheral pulmonary artery stenosis (PAS) occurs in approximately 60% of patients presenting in the 1st year of life [14] and ≈40% of those who present thereafter [15]. The natural history of PAS is one of progressive improvement. A number of other structural cardiac abnormalities are common in Williams syndrome, with rarer lesions like Ebstein anomaly of the tricuspid valve also having been reported (Table 1).

Other nonstructural cardiovascular issues are common in patients with Williams syndrome. Of those, hypertension is the most common, occurring in 40–50% [36]. Renal artery stenosis, which can be a significant contributor to hypertension, has been reported to occur in 7–58% of patients with Williams syndrome [13,37–39,40▪▪]. However, a significant number of patients do not have an identifiable cause for hypertension [41]. Notably, the risk of hypertension is decreased in patients whose deletion includes *NCF1* [42]. Another less common, but highly concerning, issue for patients with Williams syndrome is a significantly increased risk of sudden

death. Sudden death is 25–100 times more common in patients with Williams syndrome than the general population [43,44], with the cause being incompletely understood. The majority of events have been in the periprocedural setting [45▪], and are often associated with the concomitant presence of bilateral outflow tract obstruction and coronary artery stenosis [43], though this is not always the case [43,46]. Prolongation of the corrected QT (QTc) interval on ECG is present in 13% of patients with Williams syndrome [46], which may be a contributing factor in the increased risk of sudden death [47]. Notably, an increased risk of sudden death has not been reported in nonsyndromic elastin arteriopathy, a condition caused by mutations in *ELN* and characterized by a cardiovascular phenotype nearly identical to Williams syndrome. QTc prolongation is not associated with nonsydromic elastin arteriopathy [48], suggesting that the QTc prolongation in Williams syndrome could play a role in the increased risk of sudden death.

MANAGEMENT OF CARDIOVASCULAR ISSUES IN PATIENTS WITH WILLIAMS SYNDROME

Medical management

Medical therapies to address cardiovascular issues in Williams syndrome are largely directed toward the treatment of hypertension. When considering hypertension and subsequent management thereof, it is imperative to determine if renal artery stenosis is present. Angiotensin converting enzyme inhibitors (ACEI), which are often first-line therapy for hypertension in the general population, are generally, relatively contraindicated in the setting of renal artery stenosis, as they pose a risk of renal dysfunction [49]. Conversely, calcium channel blockers of the dihydropiridine class are often the first line of therapy for hypertension in Williams syndrome, as they are effective and do not carry a risk in the setting of renal artery stenosis [15]. β-blockers are another option for hypertension management, and they may have additional benefits regarding potential arrhythmia risk and sudden death [15].

Recently, Owens *et al.* [50▪▪] have reported important findings from their study of renal hemodynamics and blood pressure (BP) in an elastin heterozygous ($ELN^{+/-}$) murine model. Although BP in the $ELN^{+/-}$ mice was similar to wild-type controls, renal vascular resistance was increased and renal blood flow was lower. Further, there was damage to the glomerular filtration barrier at the level of the podocyte foot processes, a finding independent of BP, indicating elastin deficiency produces structural defects in the kidney. Further, the renal interlobar artery basal tone and myogenic response were noted to be elevated in $ELN^{+/-}$, a finding that was normalized by the administration of candesartan, an AT1 blocker (ARB). These findings suggest that ARBs could be an attractive antihypertensive therapy for patients with Williams syndrome, though cautious use would be required in the setting of renal artery stenosis, as ARBs can have similar effects to ACEI.

Pharmacological therapies to treat arterial stenosis

Effective medical therapies aimed at improving the vascular abnormalities in patients with Williams syndrome have so far been elusive. However, multiple recent studies in murine models of elastin haploinsufficiency have shown promising results that may 1 day translate into effective therapies for patients.

Minoxidil, a K_{ATP} channel opener and vasodilator used for hypertension therapy, has been known for 20 years to increase arterial elastin content [51]. Slove *et al.* [52] subsequently reported similar findings of increased aortic elastin concentration in elastin deficient rats treated with minoxidil; however, they reported better results from diazoxide, a different K_{ATP} channel opener. In 2017, Coquand-Gandit *et al.* [53▪] reported minoxidil increases tropoelastin and induced elastin expression in aged, adult mice. More recently, Knutsen *et al.* [54▪▪] reported their results of minoxidil administration in the $ELN^{-/-}$ murine model. They found that minoxidil decreased arterial stiffness, improved arterial diameter, and restored blood flow to the carotid and cerebral arteries. The findings persisted for weeks following discontinuation of the medication. Although these results suggest that oral therapy with minoxidil has the potential to improve the arterial abnormalities in Williams syndrome, they must be considered with caution. The measures used by Knutsen *et al.* to assess arterial stiffness are BP-dependent. Since the BPs were lower in treated $ELN^{-/-}$ mice, decreased arterial stiffness would be expected to also be found, as was the case. It is unclear from the described methodology if the authors controlled for BP in their analysis. Another factor to consider in this study is the arterial wall thickness was actually increased in the treated mice. Because the stain used in the presented histological slides specifically stains for elastin, other components of the arterial wall that contribute to wall thickness cannot be delineated. In addition, promising results in animal models do not always translate into highly successful therapies in humans [55,56]. Further investigation of the arterial effects of minoxidil in patients with Williams syndrome will need to be conducted. Nevertheless, the results of these

studies are highly encouraging with regard to future potential use in patients with Williams syndrome. Further, given its proven benefit in the treatment of hypertension in the general population, the incorporation of minoxidil into the antihypertensive armamentarium for patients with Williams syndrome seems reasonable in appropriate clinical contexts.

Rapamycin, which blocks cellular proliferation via inhibition of the mammalian target of rapamycin complex, has also shown promising results in laboratory and mouse models. Kinnear *et al.* [57] first reported the use of rapamycin in smooth muscle cell cultures derived from induced pluripotent stem cells from patients with Williams syndrome. In that study, rapamycin decreased the pathologic smooth muscle cell proliferation rate. In 2013, Li *et al.* [58] reported that rapamycin reduced smooth muscle cell proliferation and aortic obstruction in $ELN^{-/-}$ mouse pups and prevented medial hyperlamellation in heterozygotes. Notably, the improvement in the vascular findings did not result in increased lifespan of the mice. This finding has not, thus far, been reproduced in humans. More recently, Jiao *et al.* [59▪] have shown that rapamycin and its analogs prevent aortic fibrosis and stiffening. Although these studies using rapamycin in cell cultures and mice are encouraging, no studies with rapamycin have been done in patients with Williams syndrome. Further, rapamycin therapy comes with significant side effects that will need to be considered.

Laboratory testing for other potential therapies has shown some promise, but the data are limited. The inhibition of microRNA-29 in cell cultures has been shown to increase elastin in the extracellular matrix [60]. Similarly, the inhibition of extracellular signal-regulated kinases 1/2 phosphorylation increases elastin synthesis [61]. Misra *et al.* [62] have recently reported that celengitide, an integrin β3 and β5 inhibitor, decreases arterial muscularization, and stenosis.

Taken together, there are multiple pharmacological therapies that show promise in laboratory models of elastin haploinsufficiency. Although data from studies of these therapies in patients with Williams syndrome are currently unavailable, the results from the laboratory studies hold significant hope that beneficial pharmacological therapies will be elucidated that will improve the vascular phenotype in patients with Williams syndrome, hopefully to such a degree as to avoid the need for surgical intervention.

Surgical management

Interventions for the various cardiovascular abnormalities seen in Williams syndrome, whether catheter-based or surgical, are performed in one-third of patients, with 75% of those undergoing their first intervention by 5 years of age [13]. The risk for major adverse cardiovascular events (in-hospital death, cardiac arrest, or postoperative mechanical circulatory support) in patients with Williams syndrome who undergo heart surgery is significantly increased in those who undergo surgery for bilateral outflow tract obstruction; complex left ventricular (LV) outflow tract obstruction; and procedures involving coronary artery repair [63].

Surgery is most often performed for SVAS, and in the large majority of cases, surgery for SVAS is undertaken by 15 years of age [13,17,64]. In a large, single-center cohort of all patients with SVAS (41% with Williams syndrome), survival for SVAS surgery was $90 \pm 7\%$ at 5 years and $82 \pm 10\%$ at 20 years [65]. In that cohort, need for subsequent SVAS surgery was low. Recently, Roemers *et al.* [66] reported a single-center experience of 49 patients (24/49, 49% with diagnosed Williams syndrome) who underwent SVAS repair and had follow-up of up to 52 years. Those authors found no difference in outcomes for symmetrical (Brom's three-patch technique or slide aortoplasty) versus asymmetrical (single patch or inverted Y-shaped patch) techniques. Need for reoperation for SVAS was reported in 16% of cases, the majority of which (6/8, 75%) had a prior history of discrete SVAS. In the setting of the diffuse-type of SVAS, wherein the whole aorta is stenotic, some authors have reported that as many as 35% will require reintervention [67].

Interventions for PAS have largely been transcatheter in nature [13]. This approach in a cohort of patients with Williams syndrome was first reported by Geggel *et al.* [68]. On the contrary, the literature reporting transcatheter dilation of the pulmonary arteries is not particularly convincing of its benefit in Williams syndrome. In Geggel's original report, the mean right ventricular (RV) pressure did not change as a result of the balloon dilation. Further, the difference between the RV and systemic BPs, referred to as the RV-to-aorta ratio (RV : Ao), only decreased greater than 20% in four of the 39 procedures. Subsequently, Cunningham reported on transcatheter outcomes in 69 patients (23 with Williams syndrome) who underwent transcatheter dilation for PAS [69]. In the patients with Williams syndrome, the RV : Ao did not change. Further, the need for reintervention was very high; 75% at 5 years for transcatheter and 23% at 5 years for surgical. In addition, transcatheter stent implantation in patients with Williams syndrome can often induce a marked neointimal hyperplasia response resulting in worse arterial stenosis [70,71]. As such, stent implantation in patients with Williams syndrome should largely be avoided.

Although outcomes for surgical intervention of PAS in patients with Williams syndrome have been suboptimal at most institutions, multilevel surgical pulmonary artery reconstruction, as reported by Mainwaring *et al.* [72], has been shown to carry a high degree of success. Mid-term results of patients who have undergone this surgical approach (including 19 patients with Williams syndrome) indicate a decrease of RV : Ao from 0.88 ± 0.07 preoperatively to 0.40 ± 0.04 postoperatively, with a maintenance of the outcome over 4 ± 3 years of follow-up [73▪▪]. When contrasted against the results of transcatheter interventions, multilevel surgical pulmonary artery reconstruction should be the first-line management strategy in patients with Williams syndrome.

Orthotopic heart transplantation is an option for many children and young adults with congenital heart disease. Only recently have González-López *et al.* [74▪] reported the first case of heart transplant in a patient with Williams syndrome. Because of a range of considerations regarding the success of heart transplantation, such as likely marked afterload on both the RV (due to PAS) and the LV (due to diffuse aortic stenosis), most patients with Williams syndrome would not be viable candidates.

Periprocedural and anesthesia management

As previously noted, sudden death is markedly increased in patients with Williams syndrome, most often in the periprocedural period. Olsen *et al.* [75] published their experience of 108 anesthestic events in 29 patients over a 35-year period. Twelve anesthetic administrations (11%) were associated with a cardiac complication, two of which included cardiac arrest (1.9%), including one patient who died (0.9% mortality). In 2016, Latham *et al.* [76] reported their experience of 141 anesthestic events in 48 patients (42 with Williams syndrome) over a 23-year period. In that study, 16 anesthetic administrations (11%) were associated with intraprocedural complications, seven of which were cardiac arrests (5% of anesthetics). In total, 25% of patients experienced intraprocedural complications. Bilateral outflow tract obstruction was common in those who had complications.

The risk of complications reported by both Olsen *et al.* and Latham *et al.* far exceed that seen by this author in hundreds of patients with Williams syndrome at three different institutions. The reasons for these differences may include a number of things such as era of the studies; change in management over time; lack of a Williams syndrome-specific approach to periprocedural management at the study institutions; differences in experience level with Williams syndrome; and recall bias. Nevertheless, because of the increased risk, whatever the level, increasing attention and periprocedural planning are being given to patients with Williams syndrome. As a result, two recent articles have been published

Table 2. Risk stratification and prehydration plan prior to anesthetic administration in patients with Williams syndrome

Low risk (standard anesthetic care)	Moderate risk (morning IV placement and hydration ≥2 h prior to anesthetic)	High risk[a] (admit preceding evening with IV fluid administration overnight[b])
Age >20 years	Hypertension	Age <3 years
No cardiac involvement greater than mild supravalvar or branch PAS	Moderate supravalvar or branch PAS	History of adverse cardiovascular event
Normal ECG	Mild bilateral outflow tract obstruction	Preprocedural arrhythmia
No renal artery involvement	Renal artery stenosis	Bilateral outflow tract obstruction of ≥moderate severity
	Renal dysfunction	SVAS gradient of ≥40 mmHg *and* the presence of left ventricular hypertrophy
	QTc on ECG >450 ms, but <500 ms	Coronary artery involvement
	Airway abnormalities, lung disease, or severe gastroesophageal reflux	Diffuse stenosis of the thoracic aorta
		Right ventricular pressure ≥75% systemic
		≥Moderate left or right ventricular hypertrophy
		Symptoms or ECG signs of ischemia
		QTc on ECG ≥ 500 ms

IV, intravenous catheter; ms, milliseconds; PAS, pulmonary artery stenosis; PICC, peripherally inserted central venous catheter; QTc, corrected QT interval on ECG; SVAS, supravalvar aortic stenosis. Adapted with permission [45▪].

[a]If patient has prior history of obstructive lesions that have been surgically repaired, then he/she should NOT be considered to be high risk. Rather, determination of risk should be based on current anatomic issues.

[b]Reliable IV placement is imperative. Strong consideration should be given to having placement performed by the vascular access team. In addition, for certain patients with particularly high-risk lesions (significant coronary arterial stenosis and outflow tract obstruction), placement of a PICC line should be considered, especially if the patient is to go on to have a surgical procedure.

outlining periprocedural risk stratification and management plans aimed at mitigating the risk of cardiovascular complications [45▪,77]. Table 2 outlines the risk stratification system and preprocedural hydration plan used by this author.

CONCLUSION

Cardiovascular abnormalities are present in the large majority of patients with Williams syndrome, and the need for interventions is common. Advancements in surgical techniques provide options for significant improvements in the cardiovascular disease burden for these patients. Recent cell culture and animal model work suggest that successful pharmacological therapies aimed at ameliorating the vascular abnormalities in Williams syndrome will soon be realized, thus decreasing the need for surgery. Periprocedural cardiovascular complications are much more common in patients with Williams syndrome than the general populations. If used appropriately, recently published periprocedural risk stratification and management guidelines may decrease periprocedural complications significantly.

Acknowledgements

None.

Financial support and sponsorship

The current work was supported, indirectly, by the Division of Cardiology, Department of Pediatrics, Stanford University School of Medicine, Palo Alto, California, USA.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Strømme P, Bjørnstad PG, Ramstad K. Prevalence estimation of Williams syndrome. J Child Neurol 2002; 17:269–271.
2. Adams GN, Schmaier AH. The Williams–Beuren syndrome – a window into genetic variants leading to the development of cardiovascular disease. PLoS Genet 2012; 8:e1002479.
3. Pober BR. Williams–Beuren syndrome. N Engl J Med 2010; 362:239–252.
4. Lowery MC, Morris CA, Ewart A, *et al.* Strong correlation of elastin deletions, detected by FISH, with Williams syndrome: evaluation of 235 patients. Am J Hum Genet 1995; 57:49–53.
5. Keating MT. Genetic approaches to cardiovascular disease: supravalvular aortic stenosis, Williams syndrome, and long-QT syndrome. Circulation 1995; 92:142–147.
6. Leung DY, Glagov S, Mathews MB. Elastin and collagen accumulation in rabbit ascending aorta and pulmonary trunk during postnatal growth. Correlation of cellular synthetic response with medial tension. Circ Res 1977; 41:316–323.
7. Metafratzi ZM, Efremidis SC, Skopelitou AS, de Roos A. The clinical significance of aortic compliance and its assessment with magnetic resonance imaging. J Cardiovasc Magn Reson 2002; 4:481–491.
8. Ohtsuka S, Kakihana M, Watanabe H, Sugishita Y. Chronically decreased aortic distensibility causes deterioration of coronary perfusion during increased left ventricular contraction. J Am Coll Cardiol 1994; 24:1406–1414.
9. Karnik SK. A critical role for elastin signaling in vascular morphogenesis and disease. Development 2003; 130:411–423.
10. Urban Z, Riazi S, Seidl TL, *et al.* Connection between elastin haploinsufficiency and increased cell proliferation in patients with supravalvular aortic stenosis and Williams–Beuren syndrome. Am J Hum Genet 2002; 71:30–44.
11. ▪ Jiao Y, Li G, Korneva A, *et al.* Deficient circumferential growth is the primary determinant of aortic obstruction attributable to partial elastin deficiency. Arterioscler Thromb Vasc Biol 2017; 37:930–941.

These authors report that arterial stenosis in elastin deficient mice is the result of deficient circumferential growth, as opposed to smooth muscle cell proliferation, which has been the widely held explanation for the pathology. This finding has the potential to redirect therapeutic approaches to patients with Williams syndrome.

12. Angelov SN, Zhu J, Hu JH, Dichek DA. What's the skinny on elastin deficiency and supravalvular aortic stenosis? Arterioscler Thromb Vasc Biol 2017; 37:740–742.
13. Collins RT, Kaplan P, Somes GW, Rome JJ. Long-term outcomes of patients with cardiovascular abnormalities and Williams syndrome. Am J Cardiol 2010; 105:874–878.
14. Collins RT, Kaplan P, Somes GW, Rome JJ. Cardiovascular abnormalities, interventions, and long-term outcomes in infantile Williams syndrome. J Pediatr 2010; 156:253–258.e1.
15. Collins RT. Cardiovascular disease in Williams syndrome. Circulation 2013; 127:2125–2134.
16. Sadler LS, Pober BR, Grandinetti A, *et al.* Differences by sex in cardiovascular disease in Williams syndrome. J Pediatr 2001; 139:849–853.
17. Del Pasqua A, Rinelli G, Toscano A, *et al.* New findings concerning cardiovascular Manifestations emerging from long-term follow-up of 150 patients with the Williams–Beuren syndrome. Cardiol Young 2009; 19:563–565.
18. Yau EKC, Lo IFM, Lam STS. Williams–Beuren syndrome in the Hong Kong Chinese population: retrospective study. Hong Kong Med J 2004; 10:22–27.
19. Collins RT, Kaplan P, Rome JJ. Stenosis of the thoracic aorta in Williams syndrome. Pediatr Cardiol 2010; 31:829–833.
20. Hallidie-Smith KA, Karas S. Cardiac anomalies in Williams–Beuren syndrome. Arch Dis Child 1988; 63:809–813.
21. Collins RT. Mitral valve diseases in Williams syndrome – case report and review of the literature. Echocardiography 2012; 29:373–374.
22. Kim YM, Yoo SJ, Choi JY, *et al.* Natural course of supravalvar aortic stenosis and peripheral pulmonary arterial stenosis in Williams' syndrome. Cardiol Young 1999; 9:37–41.
23. Stamm C, Li J, Ho SY, *et al.* The aortic root in supravalvular aortic stenosis: the potential surgical relevance of morphologic findings. J Thorac Cardiovasc Surg 1997; 114:16–24.
24. Changela V, Maheshwari S, Bhat M. Williams syndrome and Ebstein's anomaly: a rare association. Ann Pediatr Cardiol 2009; 2:165–166.
25. Williams DA, Cook AL. An infant with Williams–Beuren syndrome and Ebstein anomaly. Cardiol Young 2010; 20:445–447.
26. Patil SJ, Madhusudhan BG, Shah S, Suresh PV. Facial phenotype at different ages and cardiovascular malformations in children with Williams–Beuren syndrome: a study from India. Am J Med Genet 2012; 158A:1729–1734.
27. Eronen M, Peippo M, Hiippala A, *et al.* Cardiovascular manifestations in 75 patients with Williams syndrome. J Med Genet 2002; 39:554–558.
28. Pernot C, Worms AM, Marcon F, Admant P. Williams–Beuren facies with mental retardation and tetralogy of Fallot. Pediatrie 1984; 39:53–58.
29. Park HK, Heinle JS, Morales DLS. Williams syndrome and obstructed total anomalous pulmonary venous return: a previously unreported association. Ann Thorac Surg 2012; 94:289–291.
30. Ferrero GB, Biamino E, Sorasio L, *et al.* Presenting phenotype and clinical evaluation in a cohort of 22 Williams–Beuren syndrome patients. Eur J Med Genet 2007; 50:327–337.
31. Shimamoto T, Ikeda T, Koshiji T, *et al.* A successful surgical repair of total anomalous pulmonary venous connection associated with Williams syndrome. Kyobu Geka 1997; 50:405–408.
32. Nakamoto S. Williams syndrome associated with complete atrioventricular septal defect. Heart 2003; 89:e15.
33. Mazumdar J, Sarkar R, Badveli A, Majumder B. Double chamber right ventricle in Williams syndrome: a rare cardiac anomaly reported. Springerplus 2016; 5:275.
34. Harris LC, Nghiem QX. Idiopathic hypercalcemia of infancy with interruption of the aortic arch. J Pediatr 1968; 73:84–88.
35. Okagawa H, Kimura K, Okuno M, *et al.* Case of Williams elfin facies syndrome with pulmonary artery sling. Int J Cardiol 1993; 42:295–297.
36. Broder K, Reinhardt E, Ahern J, *et al.* Elevated ambulatory blood pressure in 20 subjects with Williams syndrome. Am J Med Genet 1999; 83:356–360.
37. Committee on Genetics. American Academy of Pediatrics: healthcare supervision for children with Williams syndrome. Pediatrics 2001; 107: 1192–1204.
38. Rose C, Wessel A, Pankau R, *et al.* Anomalies of the abdominal aorta in Williams–Beuren syndrome – another cause of arterial hypertension. Eur J Pediatr 2001; 160:655–658.

39. Bouchireb K, Boyer O, Bonnet D, *et al.* Clinical features and management of arterial hypertension in children with Williams–Beuren syndrome. Nephrol Dial Transplant 2010; 25:434–438.

40. ■■ Hills JA, Zarate YA, Danylchuk NR, *et al.* Advanced cardiovascular imaging in Williams syndrome: abnormalities, usefulness, and strategy for use. Am J Med Genet 2017; 173:1194–1199.

The article profiles the utility of advanced cardiovascular imaging in patients with Williams syndrome, demonstrating that tomographic imaging (computed tomography or MRI) should be performed to assess the renal arteries if strong clinical indicators are present, as Doppler ultrasound provides suboptimal assessment.

41. Cherniske EM, Carpenter TO, Klaiman C, *et al.* Multisystem study of 20 older adults with Williams syndrome. Am J Med Genet 2004; 131A:255–264.

42. Del Campo M, Antonell A, Magano LF, *et al.* Hemizygosity at the *NCF1* gene in patients with Williams–Beuren syndrome decreases their risk of hypertension. Am J Hum Genet 2006; 78:533–542.

43. Bird LM, Billman GF, Lacro RV, *et al.* Sudden death in Williams syndrome: report of ten cases. J Pediatr 1996; 129:926–931.

44. Wessel A, Gravenhorst V, Buchhorn R, *et al.* Risk of sudden death in the Williams–Beuren syndrome. Am J Med Genet 2004; 127A:234–237.

45. ■ Collins RT, Collins MG, Schmitz ML, Hamrick JT. Peri-procedural risk stratification and management of patients with Williams syndrome. Congenit Heart Dis 2017; 12:133–142.

The work provides a comprehensive synthesis of periprocedural management of patients with Williams syndrome, including a risk stratification schema aimed at decreasing the risk of anesthetic-related events.

46. Collins RT, Aziz PF, Gleason MM, *et al.* Abnormalities of cardiac repolarization in Williams syndrome. Am J Cardiol 2010; 106:1029–1033.

47. Collins RT. Clinical significance of prolonged QTc interval in Williams syndrome. Am J Cardiol 2011; 108:471–473.

48. McCarty HM, Tang X, Swearingen CJ, Collins RT. Comparison of electrocardiographic QTc duration in patients with supravalvar aortic stenosis with versus without Williams syndrome. Am J Cardiol 2013; 111:1501–1504.

49. Hricik DE, Dunn MJ. Angiotensin-converting enzyme inhibitor-induced renal failure: causes, consequences, and diagnostic uses. J Am Soc Nephrol 1990; 1:845–858.

50. ■■ Owens EA, Jie L, Reyes BAS, *et al.* Elastin insufficiency causes hypertension, structural defects and abnormal remodelling of renal vascular signaling. Kidney Int 2017; 92:1100–1118.

The article presents important data on renal vascular resistance, blood flow, and structural changes in elastin insufficiency, apart from hypertension. The use of angiotensin receptor blockade reversed the findings, which suggests that the use of that class of medication could be beneficial for patients with Williams syndrome.

51. Tsoporis J, Keeley FW, Lee RM, Leenen FH. Arterial vasodilation and vascular connective tissue changes in spontaneously hypertensive rats. J Cardiovasc Pharmacol 1998; 31:960–962.

52. Slove S, Lannoy M, Behmoaras J, Pezet M. Potassium channel openers increase aortic elastic fiber formation and reverse the genetically determined elastin deficit in the BN rat. Hypertension 2013; 62:794–801.

53. ■ Coquand-Gandit M, Jacob MP, Fhayli W, *et al.* Chronic treatment with minoxidil induces elastic fiber neosynthesis and functional improvement in the aorta of aged mice. Rejuven Res 2017; 20:218–230.

The work demonstrates that elastin synthesis can be reinitiated in senescent mice and, as a result, aortic mechanics can be improved. These findings may be translatable to patients with Williams syndrome with resultant increased elastin production and improvement of the vascular pathology.

54. ■■ Knutsen R, Beeman SC, Broekelmann TJ, *et al.* Minoxidil improves vascular compliance, restores cerebral blood flow and alters extracellular matrix gene expression in a model of chronic vascular stiffness. Am J Physiol Heart Circ Physiol 2018; 20:218.

The article reports significant improvements in arterial mechanics and function in an elastin-deficient mouse model treated with oral minoxidil. These results strongly suggest oral minoxidil could be used to improve the vascular pathology in patients with Williams syndrome.

55. Habashi JP, Judge DP, Holm TM, *et al.* Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. Science 2006; 312:117–121.

56. Lacro RV, Dietz HC, Sleeper LA, *et al.* Atenolol versus losartan in children and young adults with Marfan's syndrome. N Engl J Med 2014; 371:2061–2071.

57. Kinnear C, Chang WY, Khattak S, *et al.* Modeling and rescue of the vascular phenotype of Williams–Beuren syndrome in patient induced pluripotent stem cells. Stem Cells Transl Med 2012; 2:2–15.

58. Li W, Li Q, Qin L, *et al.* Rapamycin inhibits smooth muscle cell proliferation and obstructive arteriopathy attributable to elastin deficiency. Arterioscler Thromb Vasc Biol 2013; 33:1028–1035.

59. ■ Jiao Y, Li G, Li Q, *et al.* mTOR (mechanistic target of rapamycin) inhibition decreases mechanosignaling, collagen accumulation, and stiffening of the thoracic aorta in elastin-deficient mice. Arterioscler Thromb Vasc Biol 2017; 37:1657–1666.

The article reports the effectiveness of rapamycin on decreasing aortic stiffness in elastin-deficient mice, a therapeutic benefit that could have significant clinical impact on patients with Williams syndrome.

60. Zhang P, Huang A, Ferruzzi J, Mecham RP. Inhibition of microRNA-29 enhances elastin levels in cells haploinsufficient for elastin and in bioengineered vessels – brief report. Arterioscler Thromb Vasc Biol 2012; 32:756–759.

61. Lannoy M, Slove S, Louedec L, *et al.* Inhibition of ERK1/2 phosphorylation: a new strategy to stimulate elastogenesis in the aorta. Hypertension 2014; 64:423–430.

62. Misra A, Sheikh AQ, Kumar A, *et al.* Integrin β3 inhibition is a therapeutic strategy for supravalvular aortic stenosis. J Exp Med 2016; 213:451–463.

63. Hornik CP, Collins RT, Jaquiss RD, *et al.* Adverse cardiac events in children with Williams syndrome undergoing cardiovascular surgery: an analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database. J Thorac Cardiovasc Surg 2015; 149:1516–1522.e1.

64. Bruno E, Rossi N, Thüer O, *et al.* Cardiovascular findings, and clinical course, in patients with Williams syndrome. Cardiol Young 2003; 13:532–536.

65. Deo SV, Burkhart HM, Schaff HV, *et al.* Late outcomes for surgical repair of supravalvar aortic stenosis. Ann Thorac Surg 2012; 94:854–859.

66. Roemers R, Kluin J, de Heer F, *et al.* Surgical correction of supravalvar aortic stenosis: 52 years' experience. World J Pediatr Congenit Heart Surg 2018; 9:131–138.

67. Brown JW, Ruzmetov M, Vijay P, Turrentine MW. Surgical repair of congenital supravalvular aortic stenosis in children. Eur J Cardiothorac Surg 2002; 21:50–56.

68. Geggel RL, Gauvreau K, Lock JE. Balloon dilation angioplasty of peripheral pulmonary stenosis associated with Williams syndrome. Circulation 2001; 103:2165–2170.

69. Cunningham JW, McElhinney DB, Gauvreau K, *et al.* Outcomes after primary transcatheter therapy in infants and young children with severe bilateral peripheral pulmonary artery stenosis. Circ Cardiovasc Interv 2013; 6:460–467.

70. Apostolopoulou SC, Kelekis NL, Laskari C, *et al.* Restenosis and pseudoaneurysm formation after stent placement for aortic coarctation in Williams syndrome. J Vasc Interv Radiol 2002; 13:547–548.

71. Mookerjee J, Roebuck D, Derrick G. Restenosis after aortic stenting. Cardiol Young 2004; 14:210–211.

72. Mainwaring RD, Sheikh AY, Punn R, *et al.* Surgical outcomes for patients with pulmonary atresia/major aortopulmonary collaterals and Alagille syndrome. Eur J Cardiothorac Surg 2012; 42:235–240.

73. ■■ Mainwaring RD, Hanley FL. Surgical techniques for repair of peripheral pulmonary artery stenosis. Semin Thorac Cardiovasc Surg 2017; 29:198–205.

In this work, the surgical technique for multilevel pulmonary artery reconstruction is detailed and outstanding mid-term outcomes are reported in 37 cases, 19 of which had Williams syndrome. This surgical approach represents a paradigm shift in the management of the severe peripheral pulmonary stenosis that can be seen in Williams syndrome.

74. ■ González-López M-T, Pérez-Caballero-Martínez R, Granados-Ruiz M-Á, *et al.* End-stage ischemic heart failure and Williams–Beuren syndrome: a unique scenario for pediatric heart transplantation. Pediatr Transplant 2016; 20:472–476.

This is the first report of orthotopic heart transplantation in a patient with Williams syndrome.

75. Olsen M, Fahy CJ, Costi DA, *et al.* Anaesthesia-related haemodynamic complications in Williams syndrome patients: a review of one institution's experience. Anaesth Intensive Care 2014; 42:619–624.

76. Latham GJ, Ross FJ, Eisses MJ, *et al.* Perioperative morbidity in children with elastin arteriopathy. Paediatr Anaesth 2016; 26:926–935.

77. Matisoff AJ, Olivieri L, Schwartz JM, Deutsch N. Risk assessment and anesthetic management of patients with Williams syndrome: a comprehensive review. Pediatr Anesth 2015; 25:1207–1215.