

Cardiovascular Disease in Williams Syndrome

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Williams syndrome (WS), also referred to as Williams-Beuren syndrome (Online Mendelian Inheritance in Man 194050), is a congenital, multisystem disorder involving the cardiovascular, connective tissue, and central nervous systems.¹ WS occurs in ≈ 1 in 10000 live births² as a result of the de novo deletion of ≈ 1.55 to 1.83 Mb on chromosome 7q11.23.³ Familial cases can occur but are far less common than de novo cases.⁴ The deletion involves 26 to 28 genes, including the *ELN* gene, which codes for the protein elastin.⁵ Hemizygoty of the *ELN* gene coding for elastin has been demonstrated to be responsible for the vascular pathology in WS.⁶ The remaining 25 to 27 deleted genes contribute to the phenotypic findings in patients with WS and have recently been reviewed in detail elsewhere.⁵

In 1961, Williams et al⁷ reported their experience with 4 patients with supravalvular aortic stenosis (SVAS), mental retardation, and abnormal facial features. The following year, Beuren and colleagues⁸ reported similar findings in 5 patients, and they subsequently reported detailed cardiac and angiographic data from 10 such patients.⁹ Their findings, combined with other characteristic features, led both groups to theorize that a previously unrecognized syndrome was the likely origin, a theory that led to the eponym Williams-Beuren syndrome.

Diagnosis

After the reports of Williams et al⁷ and Beuren et al⁸ were published, the basis for the diagnosis of WS was the presence of a constellation of distinctive phenotypic characteristics. Genetic analysis at that time was limited essentially to karyotyping and microscopic inspection of individual chromosomes, which Beuren et al⁹ reported in 3 of their patients. With improved molecular genetics diagnostic techniques, Ewart et al¹⁰ used fluorescent in situ hybridization to demonstrate hemizygoty of the *ELN* locus in patients with WS. This method is now the standard for establishing the diagnosis of WS (Figure 1).

Clinical Manifestations

As a result of the size of the deletion in WS, the phenotypic features seen commonly are numerous, and a complete discussion of them is beyond the scope of this article. However, several classic features are worthwhile noting.

Before the reports of Williams et al⁷ and Beuren et al⁸ several authors had reported on hypercalcemia, mental retardation, and failure to thrive in small groups of patients with elf-like facial features.¹¹ This gave rise to the moniker “elfin facies

syndrome”, by which WS was referred. Careful examination of the facial features of 2 patients reported by Bongiovanni et al¹² is consistent with the diagnosis of WS. The constellation of facial features often seen in WS includes a broad forehead; periorbital fullness; a stellate pattern of the irises; a flattened nasal bridge with an upturned nose; a long philtrum with a wide mouth and full lips; high, rounded cheeks; and a pointed chin (Figure 2).

In addition to typical facial features, patients with WS have a characteristic ebullient personality profile that is classically referred to as the cocktail personality. Patients with WS are hypersocial and garrulous and have a relative verbal strength that belies a mean IQ of 50 to 60.¹³ Although their verbal communication skills are relatively strong, 50% to 90% of patients meet diagnostic criteria for anxiety disorder, attention deficit-hyperactivity disorder, or phobic disorder.⁵

Hypercalcemia, which was a prominent feature in the report of Bongiovanni et al,¹¹ has been reported to occur in up to 50% of patients with WS.¹⁴ This finding is most commonly seen in infancy and typically resolves during childhood.¹²

Cardiovascular Features of Williams Syndrome

Cardiovascular defects are the most common cause of death in patients with WS.⁵ Structural cardiovascular abnormalities occur in $\approx 80\%$ of all WS patients¹⁵ and are present in up to 93% of WS patients presenting in the first year of life.¹⁶ Although a number of cardiovascular abnormalities are common to WS, the majority consist of some form of arterial stenosis.¹⁵

Pathophysiology of Arterial Stenoses

Elastin constitutes $\approx 50\%$ of the dry weight of the normal aorta¹⁷ and is the product of extensively cross-linked tropo-elastin monomers. Elastin is characterized by a high degree of reversible distensibility, including the ability to deform significantly with small forces.¹⁸ In the arterial system, this characteristic allows the storage of energy in the form of arterial distension during systole and the subsequent release of the stored energy via vascular recoil during diastole, a principle known as the Windkessel effect, which greatly improves the efficiency of the cardiovascular system.¹⁹

In the arterial tree, smooth muscle cells produce the large majority of elastin, with some also being produced by endothelial cells and adventitial fibroblasts.¹⁸ Elastin polymers form elastic fibers that are arranged into concentric rings of elastic lamellae around the arterial lumen. Each elastic lamella

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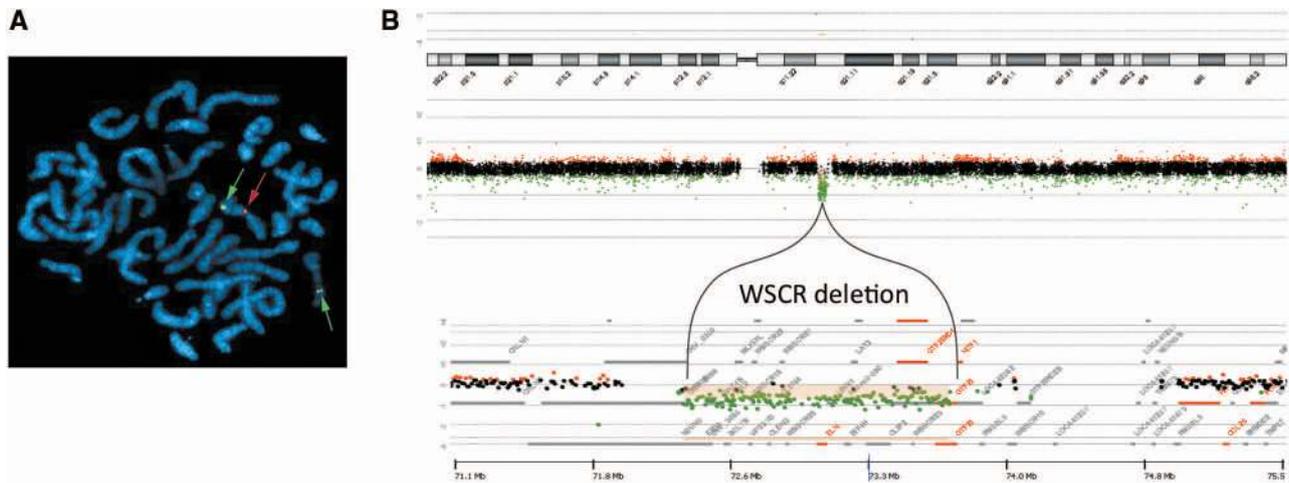


Figure 1. Laboratory diagnosis of Williams syndrome. Fluorescence in situ hybridization (A) demonstrates 1 normal chromosome 7 with 2 hybridization signals. The presence of the elastin gene (*ELN*) is marked by a red fluorescence signal (red arrow). The second chromosome 7 shows no evidence of *ELN*. The green fluorescing signals on each chromosome 7 are control genes (green arrows). A schematic of chromosome 7 (B) from an Agilent 244K microarray demonstrates a cluster of green hybridization signals consistent with a loss of ≈ 1.5 Mb from the Williams syndrome critical region (WSCR). Reprinted from Pober⁵ with permission from the publisher. Copyright © 2010, Massachusetts Medical Society.

alternates with a ring of smooth muscle, forming a lamellar unit.²⁰ The elastic lamellae allow an artery to respond to the increased hemodynamic stress of cardiac systole and to maintain sufficient blood pressure during diastole.²¹ Patients with WS and with hemizygosity of *ELN* lack the elasticity of the arterial tree provided by normal elastin and thereby have increased arterial stiffness.²²

Elastin also serves to regulate phenotypic modulation, proliferation, and migration of vascular smooth muscle cells. In the absence of elastin, pervasive subendothelial migration and proliferation of vascular smooth muscle cells occur, resulting in occlusion of the vascular lumen.²³ Murine models of *ELN* haploinsufficiency display marked arterial medial hypertrophy

and subsequent arteriopathy,²⁴ findings that are strikingly similar to those found in patients with WS²⁵ (Figure 3).

Supravalvar Aortic Stenosis

SVAS was the cardiovascular lesion first reported by Williams et al⁷ and has been found to be the most common cardiovascular abnormality.¹⁵ The incidence of SVAS has been reported to be 45% to 75% in patients with WS.^{12,15,29,30} Two types of SVAS are typically seen in patients with WS: a discrete, hourglass narrowing at the sinotubular junction or a diffuse, long-segment stenosis of the ascending aorta³¹ (Figure 4). The hourglass type of SVAS is the more common of the two,^{33,34} occurring in $\approx 75\%$ of children.³⁵ The diffuse type of SVAS often is associated with stenoses of the brachiocephalic vessels.^{35,36}

The natural history of SVAS in WS depends on the severity of the lesion at presentation or follow-up.¹⁵ Historically, SVAS in patients with WS has been thought to tend to progress, but this expected observation, as demonstrated in Table 1, is not in keeping with the majority of publications. Review of the reports that led to the expectation of progression of SVAS casts doubt on the accuracy of the conclusion. Giddins and colleagues³⁷ first reported that SVAS might be progressive in a cohort of 10 patients with WS in 1989. Significant sampling bias was introduced in that only those patients with SVAS of a severity to warrant at least 2 cardiac catheterizations were included. In a cohort of 32 patients with SVAS, Eronen and colleagues³⁰ reported that SVAS tended to progress, a conclusion based on the observation that 3 patients <1 year of age underwent SVAS intervention compared with 7 patients 1 to 15 years of age who underwent SVAS intervention. In an incomplete follow-up sample, Kececioglu et al³¹ reported progression of SVAS severity in 11 of 21 patients. Kim and colleagues⁴¹ also reported progression of SVAS severity; however, the study was cross-sectional, not longitudinal, and the conclusion was based on the finding that the severity of



Figure 2. Facial characteristics of Williams syndrome. This photograph of a boy with Williams syndrome demonstrates a number of the typical facial features, including a broad forehead, mild periorbital fullness, stellate irises, an upturned nose, a long philtrum, full lips, a small chin, and prominent cheeks. (Informed consent has been obtained from the patient's legally authorized representative to publish identifying details.)

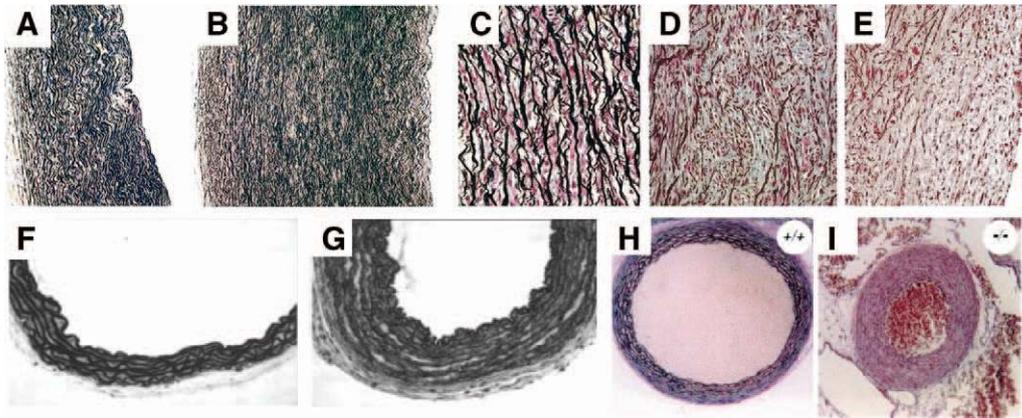


Figure 3. Arterial abnormalities in elastin deficiency. Photomicrographs of transverse sections of the ascending aorta stained with Movat pentachrome from a healthy 2-year-old child (A) and a 2-year-old child with Williams syndrome (B) demonstrate an increased arterial wall diameter resulting from medial hypertrophy. Increased magnification of the tunica media of the aorta reveals parallel elastic lamellae separated by single layers of smooth muscle cells in a healthy 2-year-old child (C). Similarly, increased magnification of the medial (D) and neointimal (E) layers of a stenotic region of the aorta in a 2-year-old patient with Williams syndrome reveals disorganization of the tunica media with multiple clusters of smooth muscle cells separated by thin, fragmented elastic fibers (D) and intimal thickening of the aorta composed by numerous smooth muscle cells surrounded by elastin-poor extracellular matrix (E). Reprinted from Urbán et al²⁶ with permission from the publisher. Copyright © 2002, Elsevier. Knockout mouse models of *ELN* deficiency demonstrate significant aortic medial hypertrophy (G) compared with controls (F). From Hirano E, Knutsen RH, Sugitani H, Ciliberto CH, Mecham RP. Functional rescue of elastin insufficiency in mice by the human elastin gene. *Circ Res*. 2007;101:523-531.²⁷ A homozygous knockout mouse model for *ELN* deletion reveals neonatal obstructive disease in the aorta (I) compared with a control (H). Reprinted from Li et al²⁸ with permission from the publisher. Copyright © 1998, Macmillan Publishers Ltd.

SVAS was greater in the older patients than in the younger patients ($R=0.32$). Thus, these studies include significant methodological issues that limit their scientific validity, and they are not in keeping with the majority of studies. Therefore, although SVAS severity can progress, especially in patients with a moderate or severe degrees of stenosis, it remains stable in the majority of patients.

Findings Associated With SVAS

Although SVAS can occur in isolation, it is frequently associated with other cardiovascular lesions. Brown and colleagues⁴² reported ≥ 1 associated congenital cardiac abnormalities in 75% of patients with SVAS. In their report of 242 patients with WS who had undergone cardiac catheterization or surgery, Pham et al⁴³ reported that SVAS was associated with

pulmonary artery stenoses or aortic arch abnormalities in 58% of children. Coronary artery abnormalities, whether ostial stenosis or arterial dilation, are seen in up to 45% of patients with SVAS^{15,34,41} and likely contribute to sudden death in patients with WS.⁴⁴ Aortic valve abnormalities are also seen regularly in the setting of SVAS. These lesions are addressed separately.

Pulmonary Arterial Stenosis

Pulmonary artery stenosis (PAS) is the second most common cardiovascular abnormality in WS.¹⁵ The incidence of PAS in WS depends on the age at the time of presentation; PAS is more common in patients in the first year of life than at older ages.¹⁶ The reported range of incidence of PAS in WS is 37% to 75%, with the majority of studies reporting an incidence of $\approx 40\%$.^{15,30,33,45}

The stenoses seen in the pulmonary arterial bed most commonly occur in the branch and peripheral pulmonary arteries. Although discrete stenosis can be seen, diffuse stenoses involving large segments of the pulmonary arterial tree are frequently encountered⁴⁶ (Figure 5). Supravalvar pulmonary stenosis is also seen but is less common, occurring in $\approx 12\%$ of all patients with WS¹⁵ and 20% of those presenting in the first year of life.¹⁶

The natural history of PAS in WS is one of improvement, which has been described in multiple studies.^{16,37,38} This natural history is likely related to the change in arterial medial tension that occurs in the postnatal period. Pulmonary arterial concentrations of elastin normally decrease in the first few months of life, at a time when pulmonary vascular resistance is normalizing.¹⁷ Theoretically, the decrease in pulmonary arterial pressure lessens the arterial medial tension in the pulmonary arteries, decreasing the role of elastin. As a result, there is improvement in the arterial stenoses as the patient grows.

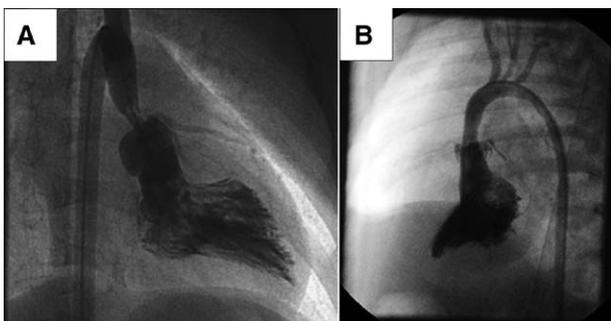


Figure 4. Supravalvar aortic stenosis. A, An anterior–posterior projection angiogram demonstrates a severe, discrete stenosis of the aorta at the level of the sinotubular junction. The ascending aorta above the sinotubular junction is normal in caliber, consistent with the classic hourglass form of supravalvar aortic stenosis. Reprinted from Stone et al³² with permission from the publisher. Copyright © 2012, Elsevier B, A lateral projection angiogram demonstrates moderate supravalvar aortic stenosis with diffuse, long-segment involvement of the entire thoracic aorta. Stenosis of the aortic arch vessels is present.

Table 1. Long-Term Outcome of SVAS in Williams Syndrome

Author (Year)	Patients With SVAS, n	Follow-Up, y	SVAS Worsened, n (%)	SVAS Stable, n (%)	SVAS Improved, n (%)
Giddins et al ³⁷ (1989)	7	6.7	6 (86)	1 (14)	...
Wren et al ³⁸ (1990)	9	...	7 (78)	2 (22)	...
Zalzstein et al ³³ (1991)	35	7.1	13 (37)	22 (63)	...
Kececioglu et al ³¹ (1993)	21	11	11 (52)	9 (43)	1 (5)
Wessel et al ³⁹ (1994)	45	12.9	13 (29)	32 (71)	...
Wang et al ^{39a} (1999)	15	6	2 (13)	10 (67)	3 (20)
Collins et al ⁴⁰ (2010)	121	8.9	12 (10)	93 (77)	16 (13)
Total	253	...	64 (25)	169 (67)	20 (8)

SVAS indicates supralvalvar aortic stenosis.

Coronary Artery Abnormalities in SVAS

Coronary artery abnormalities are often associated with congenital SVAS.⁴⁷ Some investigators have recommended that every patient with SVAS should be considered at risk for myocardial ischemia.⁴⁸ Coronary artery involvement in patients with WS may manifest as coronary ostial stenosis, diffuse coronary artery stenosis, coronary artery dilation, or obstruction to coronary artery inflow by the aortic valve, the sinotubular ridge, or a combination of both (Figure 6).

In recent medical literature, coronary ostial stenosis is the most commonly reported coronary abnormality, occurring in $\approx 5\%$ of all patients with WS¹⁵ and 9% of those presenting in the first year of life.¹⁶ However, these estimates are likely to be below the true prevalence because the majority of patients in those studies did not have evaluations of the coronary arteries, by either imaging or inspection at surgery. Stamm et al³⁴ reported a prevalence of coronary ostial stenosis of 45% in their surgical series of patients with SVAS. Ostial stenosis is more frequent in patients with WS and severe vascular disease⁴¹; in those patients with stenosis of the thoracic aorta (STA), coronary ostial stenosis had a prevalence of $\approx 19\%$.⁴⁰ The diagnosis of coronary ostial stenosis is difficult to make and is usually made only at the time of cardiac catheterization or surgery when a coronary probe cannot be passed easily into the coronary artery. The increasing use of cardiac magnetic resonance imaging and cardiac computed tomography will likely increase the likelihood of the diagnosis of coronary ostial stenosis, leading to a higher true prevalence than previously reported.

The pathophysiology of coronary ostial stenosis can be complex. Inflow to the coronary arteries can be restricted by

adhesion of the aortic leaflet edge to the narrowed sinotubular junction.⁴⁸ The coronary ostia may also become narrowed by the overhanging, stenosing SVAS ring,⁵⁰ resulting in reduced diastolic coronary arterial flow.⁴⁵ Alternatively, high pressure proximal to the SVAS is transmitted to the coronary arteries and may result in severe dysplasia and narrowing of these arteries.⁵¹

Dilated and tortuous coronary arteries are seen commonly in patients with SVAS.^{52–54} Numerous investigators have reported that dilation of the coronary arteries is seen more frequently than stenosis.^{41,55–57} van Son and colleagues⁵⁰ reported that coronary ostial stenosis was more common than dilation in the left coronary artery, whereas dilation was more common than stenosis in the right coronary artery. Furthermore, Kim et al⁴¹ reported that in those patients with the hourglass type of SVAS, 80% had coronary arterial dilation, whereas those with long-segment stenosis demonstrated coronary ostial stenosis. Marked dilation and aneurysm of the coronary arteries can be seen,⁵⁸ with the lumen of the proximal coronary artery being as large as the aorta itself.⁵⁹

The pathophysiology of coronary arterial dilation has been suggested to be the result of the increased pressure and turbulence to which the coronary arteries are subjected by left ventricular ejection into a small, noncompliant chamber⁵⁷ (Figure 6B).

Other Systemic Arterial Stenoses

It has become increasingly clear that the elastin haploinsufficiency in WS results in a systemic arteriopathy.⁴⁸ This systemic arteriopathy manifests at sites other than the supra-valvar aortic region and the pulmonary vascular bed in $\approx 20\%$

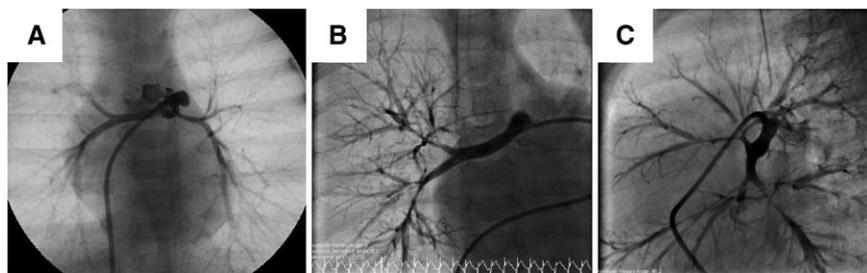


Figure 5. Peripheral pulmonary arterial stenosis. **A**, An anterior-posterior projection angiogram demonstrates severe stenosis of the right and left pulmonary arteries, with the left being more stenotic than the right. The distal pulmonary vascular bed also reveals severe, diffuse stenoses. **B**, Anterior-posterior and lateral (**C**) projection angiograms of a catheter in the right pulmonary artery demonstrate severe stenoses of the distal branch pulmonary arteries with a characteristic snowflake appearance of the pulmonary vascular bed.

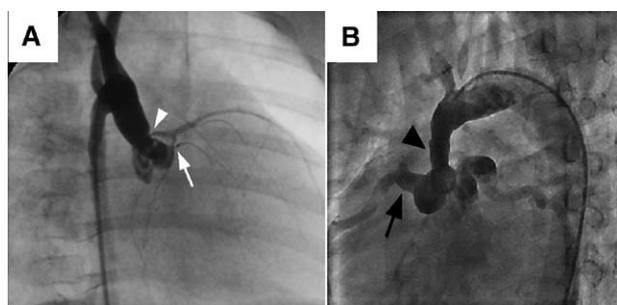


Figure 6. Coronary artery abnormalities. **A**, An anterior-posterior angiogram demonstrates severe stenosis of the origin of the left main coronary artery (white arrowhead), diffusely narrowed coronary arteries, and severe stenosis of a branch of the left circumflex coronary artery (white arrow). **B**, A lateral projection angiogram demonstrates severe, long-segment supravalvar aortic stenosis (black arrowhead) and marked dilation of the coronary arteries (black arrow). Reproduced from Salahuddin et al⁴⁹ with permission from the publisher. Copyright © 2010, BMJ Publishing Group Ltd.

of patients.¹² The most common site for these stenoses is the thoracic aorta.¹⁵

STA, sometimes referred to as middle aortic syndrome,³⁹ may include discrete coarctation at the aortic isthmus but also includes long-segment narrowing that may involve the aorta from the supravalvar region to the diaphragm and beyond, a finding first reported by Beuren et al⁹ (Figure 7). The frequency of STA is uncertain because the range of incidence from multiple studies is 2% to 70%.^{15,33,43,39,60,61} About half of the patients with STA will have mild disease, whereas one quarter have moderate stenosis and the remaining one quarter have severe stenosis. The incidence of other systemic arterial stenoses is increased in patients with STA,^{15,40} indicating that STA is a marker for worsened generalized arteriopathy. Progression of STA can be seen in moderate and severe stenoses, with some patients demonstrating rapid progression over short periods of time. These patients usually manifest progression within the first year of life.^{62,63}

Renal artery stenosis (RAS) has been reported in 7% to 58% of patients with WS.^{12,15,61,64} RAS is usually found at the origin of the renal arteries. Rose et al⁶¹ demonstrated that isolated RAS is rare and is usually seen in combination with STA. In the presence of STA, RAS occurs in 16% of patients.⁴⁰ Rose and colleagues¹² demonstrated that ~40% of patients with WS with systemic hypertension have RAS. Systemic hypertension is present in ~50% of adult patients with WS.

Systemic arterial stenoses can be seen at other sites throughout the arterial tree. The remaining most common sites are the neck and limbs, abdominal aorta, mesenteric arteries, and intracranial vessels.¹⁵

Other Structural Cardiac Abnormalities

Although arterial stenoses represent the large majority of cardiovascular abnormalities in patients with WS, a number of other structural cardiac abnormalities are seen with regularity. Ventricular septal defects are present in 4% to 9% of all patients with WS^{15,45} and up to 21% of those presenting in the first year of life.¹⁶ The defects are

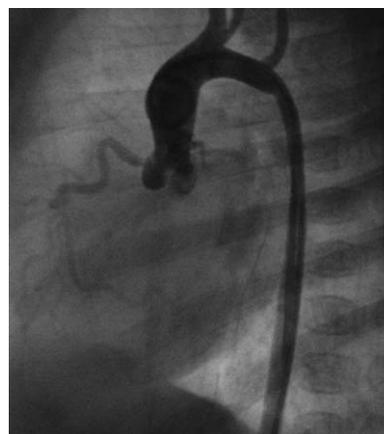


Figure 7. Stenosis of the thoracic aorta. A lateral projection angiogram demonstrates a normal ascending and transverse aorta with a long-segment stenosis of the thoracic aorta from the proximal descending aorta to the level of the diaphragm.

muscular ventricular septal defects in 75% of children, with the remainder often being conoventricular (perimembranous).^{15,65} Ventricular septal defects in the setting of a complete atrioventricular canal defect⁶⁶ and tetralogy of Fallot^{30,67,68} have been reported.

Aortic valve abnormalities have been described in surgical reports in up to 50% of cases of SVAS.⁴⁸ Adhesion of the leaflets of the aortic valve to the sinotubular junction, which may result in myocardial ischemia as a result of the obstruction of coronary blood flow, is the most common aortic valve abnormality in patients with SVAS,⁶⁹ occurring in as many as half of patients.³⁴ This fusion, or tethering, of the aortic valve to the sinotubular junction has been reported in association with sudden cardiac death in patients with WS who had SVAS.⁷⁰ The aortic valve may be thickened in up to 30% of patients with SVAS.⁵⁹ Bicuspid aortic valve has been reported in 25% to 39% of patients with SVAS^{71,72} and in 5% to 12% of patients with WS.^{16,65}

Mitral valve abnormalities are also common in patients with WS. Mitral valve prolapse is seen in 9% to 27% of patients^{45,65,67,73} and is mild in 85% of them. Mitral regurgitation also occurs in ~15% of patients and is mild in 80% of them.⁷³

In contrast to mitral valve involvement, the tricuspid valve is seldom reported to be involved in patients with WS.⁷⁴ Ebstein anomaly of the tricuspid valve has been reported rarely.⁷⁵⁻⁷⁷

Sudden Cardiac Death

Sudden cardiac death in a patient with WS was first reported by Rashkind et al.⁷⁸ The risk of sudden cardiac death is 25 to 100 times greater than that in the general population.^{44,79} The reason of this increased risk of sudden death is not completely understood. A large number of cardiovascular collapses and deaths in patients with WS have been in the perioperative and perianesthetic setting.⁸⁰ The risk of sudden cardiovascular collapse appears to be greater in the presence of bilateral outflow tract obstruction,⁴³ especially with coronary arterial stenosis.⁴⁴ However, sudden death has been reported in the absence of autopsy evidence of outflow tract or coronary obstruction.^{43,81} More recently, prolongation of

the corrected QT interval (QTc) on ECG has been shown to be present in 13% of patients with WS and may contribute to the increased risk of sudden death.⁸² In addition, ventricular ectopic complexes and arrhythmias have been correlated with the presence of QTc prolongation in patients with WS, which may indicate a role for microvascular ischemia in the QTc prolongation.⁸³

ECG Abnormalities

Patients with WS often undergo ECGs, but data on the findings of ECGs in these patients are limited. In addition to the abnormalities of cardiac repolarization previously mentioned, ventricular hypertrophy is frequently seen. Right ventricular hypertrophy on ECG will be found in ≈60% of patients, whereas left ventricular hypertrophy on ECG is demonstrated in 40% of patients.⁸⁴

Screening for Cardiovascular Abnormalities

Because cardiovascular abnormalities occur in 80% of patients with WS, detailed cardiovascular screening is imperative.¹⁵ Once the diagnosis of WS is made, all patients should undergo an evaluation by a pediatric cardiologist.¹² In addition to a thorough history and physical examination, the initial cardiologic evaluation should include an ECG and complete echocardiogram. If cardiovascular abnormalities are found, individualized follow-up should be dictated by the patient's age and lesion severity. Because of the increased risk of ventricular ectopic complexes and arrhythmias, arrhythmia screening with 24-hour ambulatory ECG monitoring should be considered.⁸³

Four-extremity blood pressure measurements should be obtained on every patient if possible.⁴⁰ However, physiological caveats must be considered in this special population. In those patients with SVAS, the Coanda effect, the tendency of a moving fluid to attach itself to a surface and move along it, often produces discrepant blood pressure measurements that may mimic STA or coarctation.⁸⁵ Diffuse STA occurs in ≈15% of patients with WS.⁴⁰ Echocardiography may not demonstrate the stenosis, but the physical examination typically reveals diminished pulses and blood pressures in the lower extremities.⁴⁰ The aortic arterial branches, whether subclavian, carotid, or femoral arteries, may have stenoses, which can result in abnormal findings on blood pressure measurements. If the possibility of significant STA cannot be ruled out, imaging with cardiac computed tomography, magnetic resonance angiography, or cardiac catheterization should be considered.⁴⁰ The use of cardiac catheterization for advanced imaging has been advocated because it allows emergent use of extracorporeal membrane oxygenation should the patient have acute cardiovascular decompensation.⁸⁶

Close attention should be paid to bruits on physical examination. Abdominal bruits are not uncommon in patients with WS and may herald the presence of RAS.^{12,64} If an abdominal bruit is discovered, renal ultrasonography with Doppler interrogation should be undertaken. Otherwise, renal ultrasonography is recommended at puberty and every 5 years thereafter.¹² Bruits in the neck may indicate the presence of stenoses of the brachiocephalic vessels.

Any patient with WS and neurological findings, including headaches, should undergo an evaluation for intracranial stenoses.⁸⁷ In a large cohort of patients, the majority of whom did not have cranial imaging, intracranial stenoses were reported to occur in 1% of patients,¹⁵ but the true incidence of intracranial stenoses is unknown.⁸⁸

Management of Structural Cardiovascular Abnormalities

Medical Management

Depending on the severity of the lesions, a large number of patients can be followed up clinically without immediate intervention. Table 2 outlines the author's recommended cardiovascular evaluation and follow-up strategy. Those patients who present in the first year of life are at an increased risk of progression of arterial stenoses compared with those who present later.¹⁶ For this reason, follow-up visits every 3 months during the first year of life are suggested, which is more frequent than the 2001 recommendations of the American Academy of Pediatrics.¹² Patients with moderate to severe degrees of stenoses should be re-evaluated on a more frequent basis because progression can occur rapidly. During follow-up visits, the decision for echocardiographic re-evaluation can be determined on the basis of physical examination findings.

Patients presenting after the first year of life have a decreased, although not absent, likelihood of arterial stenosis progression. Those with severe stenoses are nearly certainly likely to require intervention, whereas those with moderate stenoses are most likely to remain stable.¹⁵ Patients with mild degrees of arterial stenoses are highly unlikely to have progression of arterial stenoses to a degree that would necessitate intervention,¹⁵ and less aggressive cardiovascular follow-up can be undertaken.

Therapeutic options for systemic hypertension in patients with WS must take into consideration the potential presence of RAS. Thus, the use of angiotensin-converting enzyme inhibitors is contraindicated unless RAS has been definitively ruled out. Data-based recommendations for antihypertensive therapies cannot be made.⁸⁸ However, calcium channel blockers of the dihydropyridine type are effective medications for the treatment of hypertension in patients with WS. The use of β -blocker therapy for hypertension has the attractive additional benefit of potentially decreasing the risk of ventricular arrhythmia or an increased adrenergic response, as well as sudden death, in patients with prolongation of the QTc.

Surgical Management

Approximately 20% of patients with WS will require surgical or transcatheter interventions for cardiovascular abnormalities, the large majority of which will be needed by 15 years of age.^{15,67} The need for intervention is increased to ≈30% in those who present during the first year of life.¹⁶

Surgical intervention is most commonly undertaken for SVAS^{15,45} because transcatheter balloon angioplasty has been found to be ineffective.⁶⁷ Surgical approaches to SVAS have evolved over time, with the current most common technique being the use of an inverted Y-shaped patch,³⁵ especially

Table 2. Cardiovascular Evaluation and Follow-Up of Patients With Williams Syndrome*

Examination every 3 mo during the first year of life, then annually until 5 y of age, and biennially or triennially thereafter

4-Extremity blood pressures at each visit until adolescence

ECG at each visit to assess QTc

24-h Ambulatory ECG at 1 y of age, annually until 5 y of age, and then biennially

Echocardiography at presentation, at least annually until 5 y of age, and then as needed if heart disease is present

CT or MRI of the aorta if severe SVAS is present; imaging of head and neck vessels should also be considered

Renal ultrasound if hypertensive or if abdominal bruits are auscultated

Ultrasound of carotids if carotid bruits are present

CT indicates computed tomography; MRI, magnetic resonance imaging; and SVAS, supravalvar aortic stenosis.

*Cardiovascular management should be performed by a pediatric cardiologist well versed in the care of patients with Williams syndrome.

when augmentation of the ascending aorta is necessary.⁴² The modified Brom (3-sinus) technique has been shown to have excellent midterm outcomes without the need for reintervention⁸⁹ and is increasingly being used. Other techniques such as the apicoaortic conduit⁹⁰ are used less commonly. In a study cohort with 41% WS patients, the overall survival of patients with SVAS was estimated at $90\pm 7\%$, $84\pm 9\%$, and $82\pm 10\%$ at 5, 10, and 20 years, respectively.⁹¹ Freedom from late reoperation in the same cohort was estimated at $97\pm 4\%$, $93\pm 7\%$, and $86\pm 10\%$ at 5, 10, and 20 years, respectively. However, in those patients with the diffuse type of SVAS, as many as 35% will require reintervention.⁴²

Transcatheter intervention is most commonly used for peripheral PAS.¹⁵ Geggel et al⁴⁶ have reported that central pulmonary arteries do not respond well to balloon angioplasty. However, the intrapulmonary segments of the pulmonary arteries respond better to balloon dilation, especially when undertaken in a serial manner. A significant issue reported by Geggel and colleagues is pulmonary arterial aneurysm formation after balloon angioplasty. Wessel et al³⁹ previously reported that high degrees of PAS are tolerated well without intervention, which, when combined with the high frequency of complications from transcatheter interventions, led Geggel et al⁴⁶ to recommend frequent noninvasive observation in the asymptomatic patient with subsystemic right ventricular pressures. Transcatheter vascular stenting has been used infrequently in patients with WS.^{15,43,46} Rapid failure of arterial stenting in patients with WS has been reported, and the resected arterial wall demonstrates extensive fibrosis and intimal and smooth muscle cell proliferation.^{92,93} In-stent stenosis in patients with WS is likely related to an abnormal arterial response to injury caused by stent implantation in the setting of decreased arterial elastin.²³

STA does not require surgical or transcatheter intervention in $\approx 70\%$ of patients with WS. Those patients with STA requiring intervention are highly likely to need intervention before 5 years of age, and the risk of reintervention is $>50\%$.⁴⁰ Furthermore, those who undergo reintervention have an 80% likelihood of undergoing another subsequent reintervention.

Because of the decreased likelihood of successful intervention and the attendant risks of the procedures, conservative, noninterventional management of patients with STA should be considered.

Periprocedural Management

As noted previously, sudden cardiovascular collapse during the periprocedural period has been reported multiple times in patients with WS. To date, no studies have evaluated anesthetic regimens in patients with WS, and no data-driven recommendations are available. Medley et al⁹⁴ have recommended preoperative thyroid screening. Those authors also recommended against the use of succinylcholine because of a theoretical risk of a hyperkalemic response and recommended titrating neuromuscular blockade with intraoperative monitoring of train of four. Burch and colleagues⁸⁰ have published anesthetic goals in patients with congenital SVAS, including patients with WS, that can be summarized as follows: maintain sinus rhythm at an age-appropriate heart rate, ensure an adequate preload while avoiding rapid shifts in intravascular volume, avoid anesthetic strategies associated with negative inotropic effects and decreased systemic vascular resistance (ie, propofol, Sodium Pentothal, sevoflurane, isoflurane, and desflurane), and treat hypotension aggressively (phenylephrine, ephedrine, or low-dose epinephrine may be appropriate, depending on the status of the patient).

Medical Management of QTc Prolongation

Because prolongation of the QTc may occur with or without concomitant structural cardiovascular abnormalities, ongoing ECG screening should be considered in all patients with WS on at least a biennial basis. Those whose QTc interval suggests prolongation (≥ 440 milliseconds) should be referred to a pediatric cardiologist well versed in the care of patients with WS, and consultation with an electrophysiologist is recommended. Assessment should include elucidation of other risk factors for sudden death, review of medications that may contribute to QTc prolongation, and an enhanced adrenergic state. Strong consideration should be given to treatment with β -blocker therapy for those with QTc prolongation, especially before the initiation of attention deficit–hyperactivity disorder medications.⁸² Furthermore, all patients with WS who are maintained on attention deficit–hyperactivity disorder medications should undergo repeat ECG at appropriate intervals, with or without β -blocker therapy.⁸² In patients with long-QT syndrome, a QTc ≥ 500 milliseconds is a high-risk indicator for sudden death.⁹⁵ Genetic testing has been recommended for any asymptomatic patient with QT prolongation in the absence of other clinical conditions that might prolong the QT interval, as defined by a QTc >480 milliseconds (prepuberty) or >500 milliseconds (adults).⁹⁶ Because patients with WS have other clinical conditions that might prolong the QT interval, it is the author's practice to undertake genetic testing for WS patients with a QTc ≥ 500 milliseconds.

Developing Therapies

Currently, medical therapeutic options for cardiovascular issues in patients with WS are limited primarily to the

treatment of hypertension or dysrhythmias. However, a number of potentially beneficial therapies have been reported in animal studies.

The use of minoxidil has been shown to increase elastin content significantly in the abdominal aorta, superior mesenteric, and renal arteries.⁹⁷ The presumed mechanism of action is via decreased tissue elastase activity. Minoxidil was initially developed as an antihypertensive and could be an attractive therapeutic option for the treatment of hypertension in patients with WS with the possible added effect of increasing arterial elastin content.

Multiple agents affect elastin synthesis regulation and could potentially serve as therapeutic options in patients with WS. Transforming growth factor- β increases the expression of multiple extracellular matrix genes, including elastin, through increases in transcription or stabilization.⁹⁸ Aldosterone increases elastin mRNA levels, tropoelastin synthesis, and elastic fiber deposition in a dose-dependent manner.⁹⁹ The elastogenic effect of aldosterone is mediated via a mineralocorticoid receptor-independent mechanism involving insulin-like growth factor-1 receptor signaling.¹⁰⁰ Glucocorticoids upregulate tropoelastin expression in the fetal lung,¹⁰¹ possibly via a similar corticosteroid pathway. Interestingly, the aldosterone receptor antagonist eplerenone has been shown to increase arterial collagen content in patients with hypertension.¹⁰² Similarly, eplerenone and spironolactone have been reported to increase elastic fiber formation in dermal layers.¹⁰³ These results suggest a possible role for aldosterone antagonists in the treatment of the arterial stenoses most commonly present in patients with WS.

Matrix metalloproteinases cause the breakdown of extracellular matrix proteins such as collagen and elastin.¹⁰⁴ Petrincic et al¹⁰⁵ have shown in rat models that doxycycline, a matrix metalloproteinase inhibitor, prevents the fragmentation and destruction of elastin. Other investigators have shown in porcine models that the use of matrix metalloproteinase inhibitors results in higher elastin density with less intimal hyperplasia in the vessel wall of treated animals.¹⁰⁴ In that study, neointimal hyperplasia was significantly reduced in Gore-Tex grafts in animals treated with matrix metalloproteinase inhibitors, a finding that may be translatable to transcatheter stent implantations.

Tissue-engineered blood vessels are being developed and hold promise for surgical treatment options for significant arterial stenoses.¹⁰⁶ Elastin-mimetic polypeptides can be fabricated into nonwoven fabrics of fiber networks that mimic native elastin scaffolds. Tubular constructs that could be used as an arterial substitute have been produced by fiber deposition.¹⁰⁷

Summary

WS is a complex, multisystem disorder with significant cardiovascular manifestations. Arterial stenoses make up the large majority of cardiovascular issues in patients with WS. Although all patients with WS need early and ongoing cardiovascular evaluation and follow-up, most patients will not require cardiovascular interventions. In those patients who do undergo surgical and catheter-based interventions, the results are favorable, although long-segment STA remains

very difficult to treat. Sudden death in patients with WS is significantly greater than in the general population, and expert periprocedural care of these patients is paramount. Prolongation of the QTc is common in patients with WS, and conservative management with medications should be considered. The potential for groundbreaking advancements in medical therapies is present in already available pharmaceutical agents; these potential therapies need to be investigated in meaningful ways.

Disclosures

None.

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KEY WORDS: aortic stenosis, supravalvular ■ cardiovascular diseases ■ genetics ■ heart diseases ■ humans ■ pulmonary artery ■ Williams syndrome