Aortic Root Replacement for Children With Loeys-Dietz Syndrome

Nishant D. Patel, MD, Diane Alejo, BA, Todd Crawford, MD, Narutoshi Hibino, MD, Harry C. Dietz, MD, Duke E. Cameron, MD, and Luca A. Vricella, MD

Division of Cardiac Surgery, Department of Surgery, and The McKusick-Nathans Institute of Genetic Medicine, The Johns Hopkins Medical Institutions, Baltimore, Maryland

Background. **Loeys-Dietz syndrome (LDS) is an aggressive aortopathy with a proclivity for aortic aneurysm rupture and dissection at smaller diameters than other connective tissue disorders. We reviewed our surgical experience of children with LDS to validate our guidelines for prophylactic aortic root replacement (ARR).**

Methods. **We reviewed all children (younger than 18 years) with a diagnosis of LDS who underwent ARR at our institution. The primary endpoint was mortality, and secondary endpoints included complications and the need for further interventions.**

Results. **Thirty-four children with LDS underwent ARR. Mean age at operation was 10 years, and 15 (44%) were female. Mean preoperative root diameter was 4 cm. Three children (9%) had composite ARR with a mechanical prosthesis, and 31 (91%) underwent valve-sparing ARR. Concomitant procedures included arch replacement in 2 (6%), aortic valve repair in 1 (3%), and patent foramen ovale closure in 16 (47%). There was no operative mortality. Two children (6%) required late replacement of the ascending aorta, 5 (15%) required arch replacement, 1 (3%) required mitral valve replacement, and 2 (6%) had coronary button aneurysms/pseudoaneurysms requiring repair. Three children required redo valve-sparing ARR after a Florida sleeve procedure, and 2 had progressive aortic insufficiency requiring aortic valve replacement after a valve-sparing procedure. There were 2 late deaths (6%).**

Conclusions. **These data confirm the aggressive aortopathy of LDS. Valve-sparing ARR should be performed when feasible to avoid the risks of prostheses. Serial imaging of the arterial tree is critical, given the rate of subsequent intervention.**

(Ann Thorac Surg 2017;103:1513–8)

Loeys-Dietz syndrome (LDS) is an autosomal dominant connective tissue disorder characterized by generalized arterial tortuosity, hypertelorism, and a broad/bifid uvula or cleft palate [1] resulting from mutations in the transforming growth factor beta receptor (TGFBR) 1 and 2, Mothers against decapentaplegic homolog 3 (SMAD3), and transforming growth factor beta ligand (TGFB) genes. The life-threatening feature of LDS is the widespread arterial involvement, tortuosity, and risk of dissection and rupture, which occurs at younger ages and at smaller aortic diameters than other connective tissue disorders. In this report, we share our intermediate experience of aortic root replacement (ARR) in children with LDS.

Patients and Methods

After obtaining Institutional Review Board approval, we retrospectively reviewed the medical records of all children less than 18 years of age who had ARR with the diagnosis of LDS. A waiver for individual consent was granted by our Institutional Review Board. The diagnosis of LDS was confirmed with genetic analysis and clinical phenotype in collaboration with colleagues from the McKusick Department of Medical Genetics and the Connective Tissue Disorders Clinic at the Johns Hopkins Hospital.

Data were collected from hospital records and outpatient follow-up records. Variables collected included demographics, medical and surgical history, operative data, preoperative and postoperative cardiovascular imaging, postoperative complications, and further interventions on the arterial tree. Mortality data were obtained from autopsy records (when available), death certificates, and outpatient reports. Statistical analyses were performed using STATA 9.0 (StataCorp, College Station, TX) software. Continuous variables are reported as mean ± SD,

Accepted for publication Jan 9, 2017.

Presented at the Sixty-third Annual Meeting of the Southern Thoracic Surgical Association, Naples, FL, Nov 9–12, 2016.

Address correspondence to Dr Vricella, 1800 Orleans St, Zayed 7107, Baltimore, MD 21287; email: lvricella@jhmi.edu.

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2017.01.053

unless otherwise noted. Follow-up was 100% complete, and mean follow-up was 5.4 years.

Results

Preoperative Clinical Characteristics

Between July 1992 and July 2015, 34 children with a confirmed diagnosis of LDS underwent ARR. Fifteen (44.1%) were female. Mean age at operation was 10.2 ± 5.1 years. Two (5.9%) had a prior sternotomy. One patient (2.9%) presented with a type A aortic dissection, and 3 (8.8%) had a bicuspid aortic valve. Mean preoperative aortic root diameter was 4.0 ± 0.9 cm, with a mean Z score of 7.8 ± 3.0.

Operative Data

Three children (8.8%) had composite ARR with a mechanical prosthesis, and 31 (91.2%) had a valve-sparing ARR. Of the children who underwent valve-sparing ARR, 1 had root remodeling, 2 had reimplantation with a straight tube graft, 3 had a Florida Sleeve operation, and 25 had reimplantation with a Valsalva graft. Concomitant procedures included arch replacement in 2 patients (5.9%), patent ductus arteriosus closure in 3 (8.8%), aortic valve repair in 1 (2.9%), atrial septal defect closure in 7 (20.6%), and patent foramen ovale closure in 16 (47.1%). Mean cardiopulmonary bypass time was 143.3 ± 22.0 minutes, and mean aortic cross-clamp time was 101.6 ± 17.7 minutes. The most common graft size chosen among all children was a 24-mm graft.

Survival and In-Hospital Complications

There was no operative mortality. Late death occurred in 2 children (5.9%); the causes of their death are unknown, but likely involved some form of vascular catastrophe. Kaplan-Meier survival was 95% at 10 years (Fig 1).

In-hospital complications included pneumonia in 3 children. There were no episodes of thromboembolism or endocarditis. Two children (5.9%) required late replacement of the ascending aorta, 5 (14.7%) required arch replacement, 1 (2.9%) required mitral valve replacement, and 2 (5.9%) had coronary button aneurysms/pseudoaneurysms requiring repair. Two children (5.9%) had progressive aortic insufficiency after a Florida sleeve procedure and required redo valve-sparing ARR. A third child who had a Florida sleeve procedure had dilation of the coronary keyholes required redo valve-sparing root replacement. Two children (5.9%) in this study had progressive aortic insufficiency requiring aortic valve replacement after a valve-sparing procedure. Freedom from intervention on the aortic root, aortic valve or residual aorta was 54% at 10 years (Fig 2).

Comment

Loeys-Dietz syndrome is categorized into four subtypes [2]. The presence of an aneurysm or dissection along with a mutation in TGFBR1 (LDS 1), TGFBR2 (LDS 2), SMAD3 (LDS 3), or TGFB2 (LDS 4) is sufficient for the diagnosis of LDS (Table 1). The medical and surgical management are similar across the four subtypes despite some variability in expression.

The life-threatening feature of LDS is its progressive aortic aneurysmal disease. In particular, patients with LDS 1 and 2 are at higher risk for aortic catastrophe. These patients were found to rupture at early ages and at smaller aortic diameters than other connective tissue/aneurysmal syndromes [1, 3, 4], with reports of

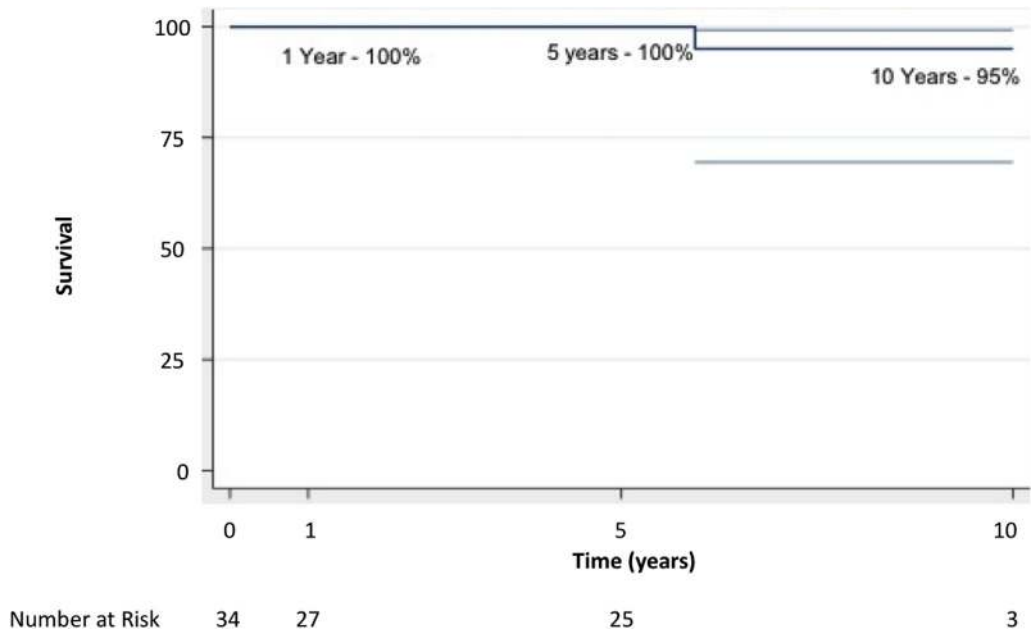

Fig 1. Kaplan-Meier survival curves. (The pale lines represent 95% confidence intervals.)

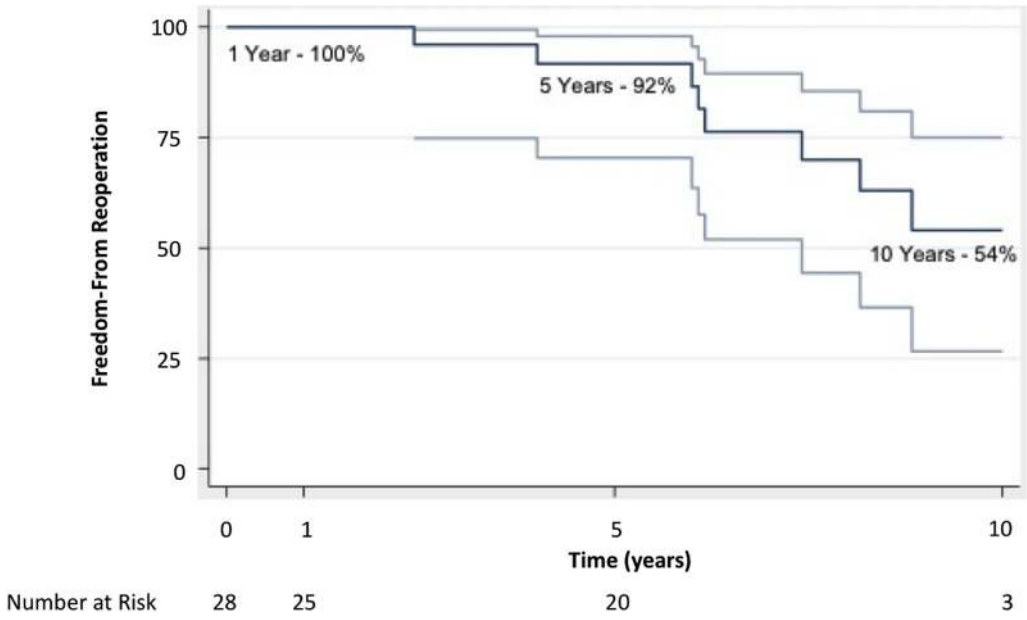

Fig 2. Freedom from intervention on the aortic root, aortic valve, or residual aorta. (The pale lines represent 95% confidence intervals.)

aortic dissection in children as young as 3 months [4, 5]. Early diagnosis and frequent surveillance with the goal of elective surgical treatment are critical to improving life expectancy. Our current guidelines for the cardiovascular care of patients with LDS are detailed in Table 2.

Certain congenital heart defects are more common among LDS children compared with the normal population, and should be managed according to standard surgical guidelines regardless of the aortic root disease. In this study, concomitant congenital repairs included patent ductus arteriosus closure in 3 children (8.8%), atrial septal defect closure in 7 (20.6%), and patent foramen ovale closure in 16 (47.1%).

Unlike patients with infantile Marfan syndrome, children with LDS rarely manifest significant mitral or tricuspid pathology in early childhood. None of the LDS children in this study had mitral or tricuspid repair at the time of aortic root replacement. Among adult patients with LDS, mitral valve pathology results from severe bileaflet prolapse and annular dilation. We have addressed mitral valve regurgitation in adults with LDS with a combination of a ring annuloplasty and the creation of a double-orifice mitral valve by placing an Alfieri edge-to-edge suture.

Our current guidelines for aortic root replacement in LDS are given in Table 3. For LDS type 1 and type 2, we recommend aortic root replacement at a threshold of 4 cm because these are the more aggressive subtypes. However, among children with LDS 1 and 2, there are certain genotypes that are known to be even more aggressive for which we proceed with surgical intervention when the aortic annulus is large enough (greater than 2 cm) to accommodate an adult-size composite mechanical prosthesis. Children with LDS type 3, which is caused by mutations in SMAD3, have more moderately aggressive disease. Therefore, for children with LDS type 3, we will proceed with ARR at 4.0 cm to 4.5 cm. Children with LDS type 4 due to mutations in TGFB2 have a milder phenotype and so our threshold for intervention is slightly higher, at 4.5 cm. However, even among these children, those with a concerning family history of aortic catastrophe may warrant earlier intervention.

Although the modified Bentall operation is viewed by many as the gold standard, valve-sparing root replacement has become a safe and reliable alternative for appropriately selected younger patients with LDS, with low risk of mortality, aortic valve failure, and need for reintervention on the aortic root [6]. Five patients who had valve-sparing root replacement required reoperation

Table 1. Loeys-Dietz Syndrome Classification

LDS Subtype	Gene	Other Disorders Reported
1	*TGFBR1*	TAAD (previously, LDS 1a, 1b, 2a, 2b)
2	*TGFBR2*	TAAD, MFS2 (previously, LDS 1a, 1b, 2a, 2b)
3	*SMAD3*	Aneurysms-osteoarthritis syndrome
4	*TGFB2*	Aortic and cerebral aneurysm, arterial tortuosity, and skeletal manifestations

LDS = Loeys-Dietz syndrome; MFS2 = Marfan syndrome type 2; SMAD3 = Mothers against decapentaplegic homolog 3; TAAD = thoracic aortic aneurysm and dissection; TGFB = transforming growth factor-beta; TGFBR = transforming growth factor-beta receptor.

Table 2. Guidelines for Cardiovascular Care

Routine Cardiovascular Care
Yearly echocardiogram; shorter interval depending on extent of aortic disease
Angiotensin-receptor blockade, beta-blocker, or angiotensin-converting enzyme inhibitor for strict control of hypertension
Avoidance of contact/competitive sports, isometric exercises, strenuous exercise, blows to head/chest
Avoidance of stimulants and vasoconstrictors
Subacute bacterial endocarditis prophylaxis for patients with artificial valves
Atrial fibrillation and arrhythmia management per normal protocol
Cardiac surgery consultation when approaching surgical thresholds for intervention

on the aortic valve or root. Three of these 5 patients had undergone a Florida sleeve procedure [7]: one of them had dilated coronary keyholes requiring redo valve-sparing root replacement; in another, the sleeve migrated distally and required conversion to a reimplantation procedure; and a third had annular dilation requiring redo valve-sparing root replacement and aortic valve repair. Based on these initial outcomes with the Florida sleeve at our institution, we have abandoned this procedure in favor of conventional valve-sparing root replacement (reimplantation).

The other two late failures in this series had conventional valve-sparing operations. One 9-month-old child who had valve-sparing root replacement with a straight tube graft had a dilated annulus, progressive aortic insufficiency, and a dilated arch and ascending aneurysm that required redo sternotomy, composite root replacement, and arch and ascending aneurysm repair 98 months after his initial operation. A second child required composite root replacement 74 months after valve-sparing root replacement after severe aortic insufficiency developed secondary to the annulus prolapsing below the graft due to a torn subannular suture below the right coronary leaflet.

We have previously reported our experience with valve-sparing root replacement [6]. Our operative technique for the majority of patients who had valve-sparing root replacement was a modified David V procedure in which the native aortic valve was resuspended within a Dacron graft with prefashioned pseudosinuses (Gelweave Valsalva graft; Vaskutek, Renfrewshire, Scotland, UK). Although we initially adopted the Yacoub remodeling procedure, our reintervention rate in the connective tissue patient population was high due to annular dilation and progressive aortic insufficiency. Subsequently, we switched to the reimplantation procedure when the Valsalva graft became available.

Our contraindications to valve-sparing root replacement are the presence of severe leaflet fenestrations and leaflet asymmetry, acute dissection in the unstable patient, and bicuspid aortic valves with extensive calcification. For these children, composite root replacement with a mechanical prosthesis remains a safe and reproducible option. Our technical approach to valve-sparing root replacement in children with LDS is similar to that for patients with other aortopathies. Notably, in a small number of children with LDS 1 and 2, we placed additional subannular sutures in the area of the aortomitral curtain to improve stabilization. The remainder of our operative approach is the same, including selection of graft size, which is based on the optimal sinotubular junction diameter. We then select a graft that is 2 mm to 3 mm larger than the optimal sinotubular junction diameter as the graft will be seated around the aortic root complex.

The decision to perform aortic arch replacement at the time of aortic root replacement remains challenging, especially in the pediatric population, in which most of the LDS children present with dilated roots but normal arch dimensions. Our experience has demonstrated that in the absence of aortic dissection, LDS patients are more likely to require arch intervention after elective root replacement than children with Marfan syndrome. Conversely, with aortic dissection, the rate of arch interventions is similar between LDS and Marfan patients. Our current practice is not to proceed with routine total arch replacement in LDS children in an effort to avoid circulatory arrest and minimize aortic cross-clamp time, as well as to avoid additional suture lines that may increase the risk of bleeding or late pseudoaneurysm formation. Currently, we take an individualized approach to concomitant aortic arch repair based on dimensions (more than 4 cm), rate of growth (more than 0.5 cm per year), severity of craniofacial features, genotype, and family history.

Postoperative surveillance of LDS children is critical given the high incidence of reoperation on either the root or residual aorta (Fig 2). Surveillance includes echocardiography every 3 to 6 months for the first year after surgery. After 1 year, serial echocardiography is performed every 6 months to 1 year. We obtain full cardiovascular imaging from head to toes with either magnetic resonance angiography or computed tomography

Table 3. Surgical Thresholds for Aortic Root Replacement in Children With Loeys-Dietz Syndrome 1, 2, and 3

System	Threshold
Aortic root, children	Delay surgery until annulus >2.0 cm to accommodate adult size graft Aortic root diameter of 4 cm Rapidly expanding aorta[a], severe craniofacial features; strong family history of early aortic catastrophe may warrant earlier surgical intervention

[a] More than 0.5 cm per year.

angiography with three-dimensional reconstruction preoperatively. Imaging is repeated after 1 year, and subsequent full-body imaging is determined based on findings, but should occur at least every 2 years.

Optimal medical management in LDS children includes routine beta-blockade [8] to reduce hemodynamic stress on the vasculature. Whereas others promote the use of angiotensin-converting enzyme inhibitors [9, 10], we prescribe angiotensin-receptor blockers owing to the specific mechanism of action on the TGFB signaling cascade [11].

Our experience with aortic root replacement for children with LDS confirms the need for an aggressive approach. We attempt to utilize a valve-preserving strategy whenever possible and prefer the reimplantation technique over remodeling or the Florida sleeve owing to improved hemostasis and stabilization of the aortic annulus, which is of particular importance in the LDS population. The high incidence of subsequent reintervention among children with LDS confirms the need for meticulous and frequent cardiovascular imaging of the entire arterial tree.

References

1. Loeys BL, Chen J, Neptune ER, et al. A syndrome of altered cardiovascular, craniofacial, neurocognitive, and skeletal development caused by mutations in TGFBR1 or TGFBR2. Nat Genet 2005;37:275–81.
2. MacCarrick G, Black JH, Bowdin S, et al. Loeys-Dietz syndrome: a primer for diagnosis and management. Genet Med 2014;16:576–87.
3. Williams JL, Loeys BL, Nwakanma LU, et al. Early surgical experience with Loeys-Dietz: a new syndrome of aggressive thoracic aortic aneurysm disease. Ann Thorac Surg 2007;83(Suppl):785–90.
4. Loeys BL, Schwarze U, Holm T, et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. N Engl J Med 2006;355:788–98.
5. Malhotra A, Westesson PL. Loeys-Dietz syndrome. Pediatr Radiol 2009;39:1015.
6. Patel ND, Arnaoutakis GJ, George TJ, et al. Valve-sparing aortic root replacement in Loeys-Dietz syndrome. Ann Thorac Surg 2011;92:556–60.
7. Hess PJ, Harman K, Klodell CT, et al. Early outcomes using the Florida sleeve repair for correction of aortic insufficiency due to root aneurysms. Ann Thorac Surg 2009;87:1161–9.
8. Shores J, Berger KR, Murphy EA, Pyeritz RE. Progression of aortic dilation and the benefit of long-term beta-adrenergic blockade in Marfan's syndrome. N Engl J Med 1994;330:1335–41.
9. Yetman AT, Beroukhim RS, Ivy DD, Manchester D. Importance of the clinical recognition of Loeys-Dietz syndrome in the neonatal period. Pediatrics 2007;119:e1199–202.
10. Everitt MD, Pinto N, Hawkins JA, Mitchell MB, Kouretas PC, Yetman AT. Cardiovascular surgery in children with Marfan syndrome or Loeys-Dietz syndrome. J Thorac Cardiovasc Surg 2009;137:1327–32.
11. Matt P, Habashi J, Carrel T, Cmaeron DE, van Eyk JE, Dietz HC. Recent advances in understanding Marfan syndrome: should we now treat surgical patients with losartan? J Thorac Cardiovasc Surg 2008;135:389–94.

DISCUSSION

DR JORGE D. SALAZAR (Boston, MA): My congratulations to Dr Patel and colleagues from the Johns Hopkins Hospital for an excellent paper and presentation, in particular, the admirable surgical outcomes. I do thank you for providing me a copy of the manuscript well in advance. It is much appreciated.

You report a valve-sparing approach in 91% of patients with no early deaths but only 54% freedom from valve reintervention at 10 years. My first question, does this change your philosophy regarding valve preservation or sparing, or can you share your technical modifications that have been developed to achieve better valve preservation?

DR PATEL: The reintervention rate included patients that had either reintervention on the aortic root, the valve or the residual aorta. In this series, only 5 of the 31 valve-sparing patients required a reoperation for failure of the valve-sparing procedure. Our technical modifications with this particular patient population have been minimal. In certain children, especially those with particularly aggressive mutations, we have added additional subannular sutures in the region of the aortomitral curtain. Otherwise, our hemostatic suture line, our distal suture line, and the management of our coronary buttons have remained the same.

DR SALAZAR: As I am sure you will agree, it seems like the primary issue is really fixing the annulus below it with a graft, and some of us have taken, with high-risk patients like this, to actually using pledgeted sutures there instead of the way Duke taught me, without pledgets. Is that something that you have developed or do you think there actually may be some use for in this high-risk population?

DR PATEL: Dr Cameron's current technique utilizes three pledgeted subannular sutures.

DR SALAZAR: A second question. Given the demonstrated high risks for aortic catastrophe in this population and the excellent surgical results, is there an advantage to waiting until 4 cm, especially if valve preservation strategies improve?

DR PATEL: That is a very difficult question and I do not think we have the actual data to suggest that proceeding at a smaller aortic diameter would be beneficial. What we do know is that over the last two years, 4 cm in most patients seems to be right, but we do know that even among patients who have Loeys-Dietz syndrome type 1 and 2 with a very aggressive phenotype and very particularly bad acting mutations, it is beneficial to proceed with a root replacement at diameters around 2 cm. So, there are certain patients who do benefit from earlier intervention.

This is where having a collaboration with a genetic institute like we have with Dr Dietz is particularly beneficial, because he follows these patients and their families regularly and can identify those patients with more aggressive mutations who should get intervention earlier.

DR SALAZAR: I think that is an excellent answer. It seems that most of these patients end up having problems, and given the excellent surgical results as you have demonstrated, earlier intervention may be warranted.

A third question and my last question. Given your experience with the postoperative natural history of Loeys-Dietz patients,

can a similar argument be made for more aggressive empiric interventions on the aortic arch and ascending aorta? In other words, is there really an advantage to waiting?

DR PATEL: So, once again, a difficult question and I do not think we have all the right data. In adults, we know that for patients who have aortic dissection, the rate of arch intervention between Marfan patients and Loeys-Dietz syndrome patients is the same. In the absence of dissection, children with Loeys-Dietz syndrome have a significantly higher rate of arch intervention in the future. So, I think there is a role for concomitant arch repair at the time of a root replacement. In children specifically, we are not aggressive with replacing the arch, because these children are coming in for elective root replacement with normal arch dimensions.

But once again, I think this is where the genetics and the phenotype really play an important role, because if we can identify those patients who are at high risk of aortic catastrophe, particularly in the arch, we could potentially intervene at a smaller diameter and younger ages.

DR SALAZAR: Well, I suspect, and I assume that your data would bear this out, that it is somewhat unpredictable and that genetics may guide us but not ultimately determine which patients will come back, and therefore it may be worthwhile considering a more aggressive strategy with such excellent results. Congratulations.

DR PATEL: I also have to tell you, I have to thank you, because when I was a college student, Dr Baumgartner set up this intersession program where we shadowed cardiac surgeons. The very first operation I saw was a root replacement that you did with Dr Cameron, and I got hooked. My wife also blames you for that. (Laughter)

DR SALAZAR: Well, I am honored to be at blame. Thank you.