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ADVANCED IN AORTIC ROOT SURGERY

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Abstract

The aortic root is often affected by aneurysmal degeneration of the ascending aorta or dissection. It is important for the clinician to be familiar with current guidelines and recommendations for detection, monitoring, and intervention of the aneurysmal aortic root. Timely surgical referral to an experienced aortic center allows for close monitoring and possible intervention that may preserve the aortic valve in appropriate cases and avoid disastrous complications such as aortic dissection, rupture, or death. Patients with bicuspid aortic valve syndrome or connective tissue disorders (e.g., Marfan syndrome) are particularly at risk and should be followed aggressively. Whenever possible, attempts should be made to preserve or repair the aortic valve using valve-sparing aortic root replacement techniques. This article provides an overview of recent advances in management of the aortic root, including guidelines for surgical intervention, technical procedures, and outcomes.

Introduction and Anatomy

The anatomic space between the aorta and the left ventricle is called the aortic root and includes, from top to bottom, the sinotubular junction (which separates the aortic root from the ascending aorta), aortic sinuses, aortic cusps, and aortic annulus (aorto-ventricular junction).[1] The three aortic cusps have a crescent shape and often are of different sizes, but the length of the base of a cusp is consistently 1.5 times longer than the length of its free margin. Therefore, a large cusp will have a proportionally longer annulus, free margin, intercommissural distance, and a larger sinus of Valsalva. The non-coronary and right cusps and sinuses of Valsalva are usually larger than the left cusp and sinus. The aortic annulus is a tridimensional structure that, for practical purposes, is measured as the maximal distance along a single horizontal plane at the level of its nadir. In childhood, the diameter of the aortic annulus is approximately 20% larger than the sinotubular junction (STJ). As the elastic fibers of the arterial wall change with increasing age, the STJ dilates and becomes equal in diameter to the aortic annulus and in later life, especially in cases of aortic stenosis, is usually 10% larger than the annulus.

Aortic Root Pathology and Surgical Indications

Ascending aortic aneurysms often cause dilatation of the STJ with consequent aortic insufficiency due to lack of coaptation of the cusps (Figure 1). One or more aortic sinuses may also become dilated in patients with ascending aortic aneurysm, but the aortic annulus often remains unchanged. Patients with ascending aortic aneurysms and aortic insufficiency are usually in their sixth or seventh decade of life. If the aortic cusps are normal or minimally elongated along their free margins, it is possible to reconstruct the aortic root, repair the cusps if necessary, and re-establish aortic valve competence.

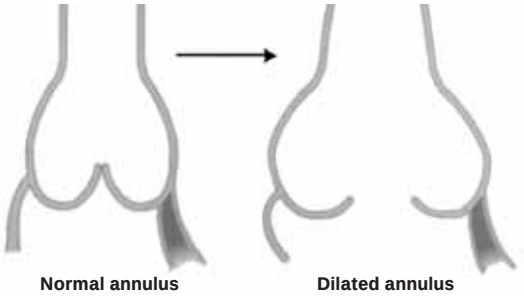

Figure 1. Aortic root dilatation as cause of aortic insufficiency.[29]
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The mechanism of aortic insufficiency in patients with aortic root aneurysm is more complicated. Dilatation of the aortic root often starts at the level of the sinuses of Valsalva (Figure 1). As wall tension increases, the STJ begins to dilate. The aortic annulus may also dilate in these patients, further complicating the mechanism of aortic insufficiency by widening the fibrous subcommissural triangles of the non-coronary aortic cusp. Depending on the rate of expansion of the aneurysm, the cusps may or may not become elongated and overstretched and develop stress fenestrations along the commissural areas, rendering them unsuitable for aortic valve repair.

Figure 2. Annuloaortic ectasia as commonly encountered in Marfan syndrome.

The most frequent indications for aortic root replacement are primarily aortic root aneurysm, aortic dissection, or endocarditis involving the root.[2] Annuloaortic ectasia is a form of aneurysmal dilatation of the proximal ascending aorta and aortic annulus that is often associated with Marfan syndrome (Figure 2). It can also be a complication due to tertiary syphilis. Aortic root aneurysm and aortic dissections, if not treated, can lead to significant morbidity and mortality. Timely surgical

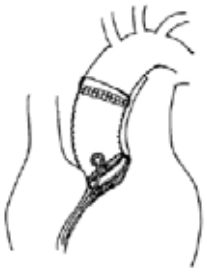

Figure 3. Modified Bentall procedure for aortic root replacement.[30]
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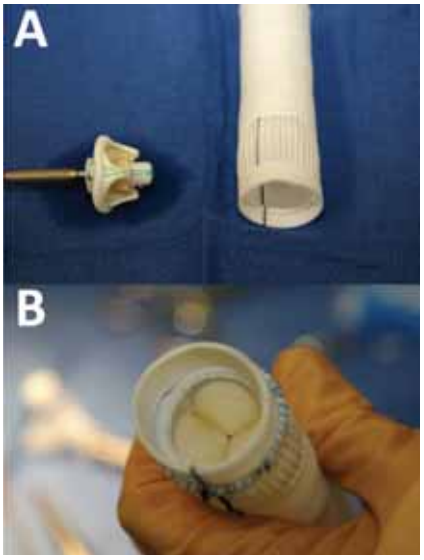

Figure 4. Construction of biologic valve conduit using Gelweave Valsalva™ graft.

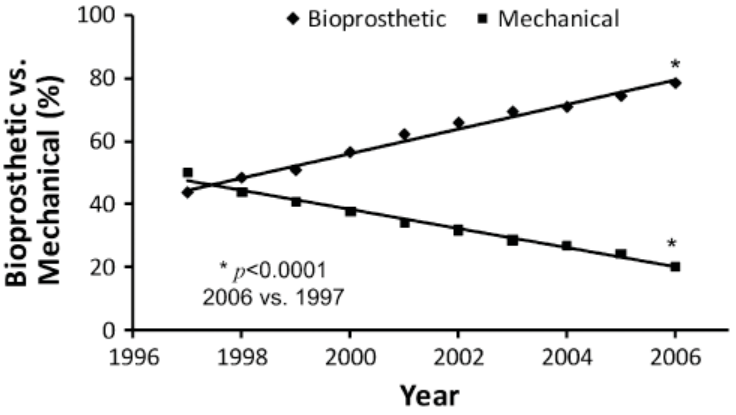

Figure 5. Society of Thoracic Surgeons trend for bioprosthetic vs. mechanical valve implantation.[31] Reprinted with permission from Elsevier/The American Association for Thoracic Surgery.

repair of the diseased root usually takes the form of aortic root replacement with or without a valve-sparing approach. This could be achieved as a composite prosthesis or as separate elements. An ascending aortic aneurysm can be simply fixed by a tube graft replacement of the ascending aorta with satisfactory results.[3] Modified Bentall procedures eliminate the entire aortic root tissue and, with this, the risk of future annular dilatation and associated aortic insufficiency or recurrent aneurysm (Figure 3).[3]

Acute aortic dissection involving the ascending aorta requires emergent surgery. The minimum operation required is to replace the ascending aorta to prevent extension of the tear into the root, which could cause aortic or coronary insufficiency; to prevent rupture of the ascending aorta; and to minimize the likelihood of extension of the tear into the head vessels, causing cerebral ischemia. While replacing the ascending aorta achieves the above goals, this operation may not stabilize the aortic root. In cases where the root is dilated or involved in the dissection, replacement of the aortic sinuses is indicated.

Most patients with aortic root aneurysms are asymptomatic and have no physical signs if they have no aortic insufficiency. Some patients may complain of vague chest pain. Severe chest pain is suggestive of rapid expansion or intimal tear with dissection. Echocardiography establishes the diagnosis and provides information regarding the aortic cusps. Computed tomography scan and magnetic resonance imaging of the chest are also diagnostic and useful in providing information regarding the entire thoracic aorta. Surgery is recommended when the transverse diameter of the aortic root exceeds 55 mm.[4-6] If the aortic valve can be preserved, surgery should be considered when the transverse diameter of the aortic root reaches 45–50 mm, if there is aortic size growth >5 mm per year, or if the patient is symptomatic.[7-8] This size criterion is also used for patients with genetic abnormalities, those with a family history of acute aortic dissection, and in patients with a bicuspid aortic valve.[9]

Operative Strategies

Where the aortic root is extensively destroyed by dissection or endocarditis, or if there is aneurysmal enlargement of the root, then aortic root repair is warranted for improved short- and long-term outcomes.[10] The most common form of aortic root repair is the modified Bentall operation involving replacement of the aortic valve, sinuses of Valsalva, and the ascending aorta with reimplantation of the coronary ostia into the new Dacron aortic graft. This can be performed by using a number of options, such as composite valve-graft conduits (mechanical or biologic), aortic root allografts or xenografts, and valve-sparing root replacements. Axillary artery cannulation, through an 8 mm end-to-side graft, has proven to be an excellent tool for any aortic procedure by allowing the surgeon to maintain all options for repair of the root, ascending, and arch. It is currently our preferred approach.

Modified Bentall Procedures: Composite Valve-Graft Conduit (Mechanical and Tissue)

The most popular prosthesis for aortic root replacement is a pre-manufactured composite mechanical valve and Dacron tube graft conduit. Alternatively, a composite biologic valve-conduit can be constructed at the time of operation (Figure 4). This can be easily performed on the back table by selecting a graft 5 mm larger than the stented valve (e.g., a #23 stented porcine/pericardial valve sutured into a #28 mm Dacron tube graft). These biologic valve conduits are often used in older patients or others who would like to avoid the need for anticoagulation. As demonstrated by Society of Thoracic Surgeons data (Figure 5), there has been a significant decline in the number of mechanical valves used as biologic valve durability has improved over the past 10–15 years. Many active patients in their 40s and 50s or younger are requesting biologic valves to avoid the potential hazards of anticoagulation and the associated lifestyle modification that would be required with mechanical valves.[11]

Some of the more recent advances involving aortic root replacement using composite biologic valve conduits include forward planning for subsequent operations or interventions, particularly on patients presenting to surgery at a young age. In particular, as the use of these composite biologic valve conduits become more popular in younger patients, minor technical adjustments at the time of initial aortic root repair may lead to a significantly simpler subsequent operation. One of these modifications is use of the De Paulis Gelweave Valsalva™ graft conduit (Terumo Cardiovascular Systems Corporation, Ann Arbor, MI) that allows for a more geometric reconstruction of the root that

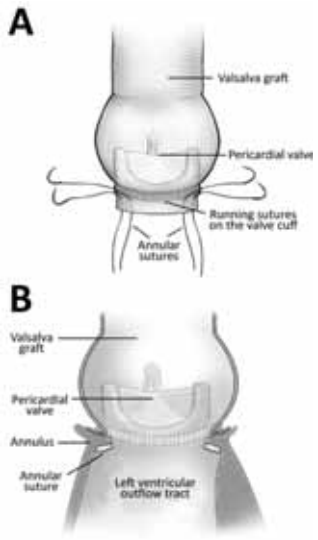

Figure 6. (A) Supra-annular composite biologic valve conduit using the Valsalva graft. (B) Composite graft seated above the annulus using proximal skirt of the graft below valve attachment.[13]

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Figure 7. (A) Mechanical valve conduit (On-X Ascending Aortic Prosthesis). (B) Freestyle® xenograft aortic root.

(A) Image courtesy of On-X Life Technologies, Incorporated™. Used with permission. (B) Copyright Medtronic, Inc. Used with permission

mimics the billowing of sinuses of Valsalva. This conduit has several potential short- and long-term advantages, including decreasing the need for significant coronary ostia mobilization when reimplanting the coronary buttons into the graft — thus rendering this portion of the procedure easier, especially during a redo operation, endocarditis or aortic dissection where adhesions are problematic. This graft may also confer a long-term benefit as it allows for a more physiologic closure of aortic valve cusps and coronary perfusion, which may improve long-term durability of the biologic valve. This also has the potential added benefit of displacing the coronaries away from the aortic annulus, rendering future transcatheter aortic valve interventions (TAVI) less prone to coronary obstruction.

Supra-annular placement of the biologic valve within the conduit can have significant potential benefits. This can be performed by implanting the biologic valve 2–3 mm into the Valsalva graft (using a running 4-0 polypropylene suture) and allowing a 2- to 3-ring skirt at the proximal end of the graft. Non-everting pledgeted 2-0 polyester sutures are placed on the aortic annulus. Those sutures are subsequently passed through the Valsalva graft collar below the sewing cuff of the prosthetic valve (Figure 6). Theoretically, the Valsalva conduit reduces the tension of coronary buttons compared with the conventional tube graft. It also creates more space between the biologic valve struts and coronary buttons and may decrease the risk of coronary button complications.

Passing the annular sutures through the graft collar is the major advantage of this technique. Because the valve is seated above the aortic annulus, this technique allows the surgeon to place a larger-sized valve than the annulus, which is especially helpful for patients with a small aortic annulus. The effective orifice area becomes the left ventricular outflow tract, not the internal diameter of the prosthetic valve. The valve position is slightly higher compared with a technique passing the annular sutures through the valve cuff; however, the coronary buttons do not need to be placed higher because the Valsalva graft creates space between the valve and the graft wall. These techniques may allow the surgeon to reoperate on the valve only, without compromising the root structure if the prosthetic valve has become degenerated.[12] The use of the Valsalva graft allows for a larger space in the root to facilitate both resection of the old valve and replacement of a new prosthesis. Another potential advantage is possible future deployment of percutaneous aortic valve prostheses inside such a biologic valve conduit. Having a larger valve orifice allows a larger-sized percutaneous valve to be deployed, while displacing the coronary buttons away from the biologic valve may decrease the risk of coronary occlusion complications. Mortality rates in the literature for such operations have been reported as 2–7%.[13, 14] Recently, the Columbia group described a technique for aortic root replacement using the 3F stentless equine biologic aortic valve (ATS Medical, Inc., Minneapolis, MN) within the Gelweave Valsalva graft with excellent short-term results and very low mean transvalvular gradients (4.0 ± 1.7 mmHg).

Modified Bentall Procedures: Allografts and Xenografts

Alternatives to biologic or mechanical valve conduits include xenograft (porcine) aortic root replacements (e.g., Medtronic Freestyle®) and cadaveric aortic root allografts (e.g., Cryolife CryoValve® Aortic Valve Allograft) (Figure 7). The stentless design of both these grafts offers a potential for improved hemodynamics over stented tissue valves. Both of these options are used in patients who want to avoid lifelong anticoagulation and have low rates of infection. Allografts are offered as a complete aortic graft from the aortic valve to the arch and often include the anterior leaflet of the mitral valve. This provides the surgeon with flexibility to replace the ascending aorta and use of the anterior leaflet for reconstruction of any defects within the root, as can be seen in endocarditis. However, allografts are occasionally limited in availability, tend to be more difficult to implant, and have suboptimal durability secondary to accelerated calcification. Aortic allograft implantation is currently performed less frequently and is often reserved for patients with aortic root abscess. Porcine aortic roots are treated with glutaraldehyde fixation at low pressures and anti-calcification treatment to maintain structure and potentially improve durability. A recent study by Yacoub and colleagues compared the Freestyle xenograft to allograft root replacement in a randomized fashion. Late survival was similar after homograft versus Freestyle root replacement. However, Freestyle aortic root replacement was associated with significantly less progressive aortic valve dysfunction and a lower need for reoperations.[15]

Aortic Valve-Sparing Root Procedures

Aortic valve-sparing procedures involve replacement of the aortic root and proximal ascending aorta while leaving the native aortic valve in situ. Candidates for this operation are patients who develop aortic root pathology, with or without aortic insufficiency, but with normal aortic valve cusps. Patients with ascending aortic aneurysm and aortic insufficiency often have a dilated STJ but normal or minimally dilated aortic sinuses and normal cusps, and all that is needed to restore aortic valve competence is to reduce the diameter of the STJ at the time the ascending aorta is replaced.[16, 17]

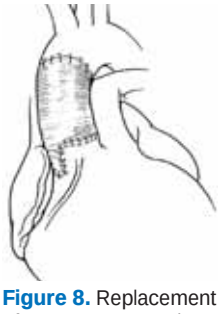

Figure 8. Replacement of one or more aortic sinuses is feasible when necessary.[32]

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In an important paper by Lawrie and DeBakey, a durable repair was presented for a large number of patients with preserved valve function and dissecting aneurysm by placing a tube replacement and conserving the aortic root, excluding patients with Marfan syndrome.[3] Durability of this repair would be increased by performing AV resuspension at the commissural level. Occasionally in patients with severe aortic

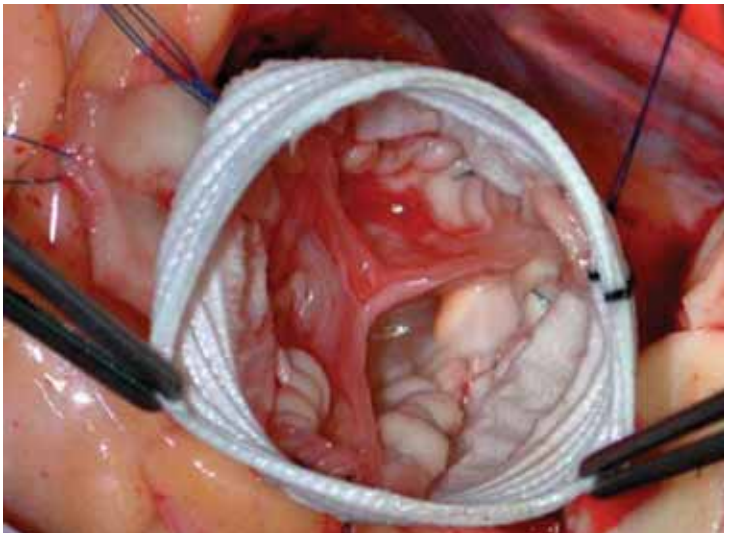

Figure 9. Valve-sparing root replacement using the reimplantation technique.

insufficiency, one or more cusps remain nearly normal because of the asymmetric nature of aortic root dilatation. If the non-coronary aortic sinus is dilated or altered by aortic dissection, a neosinus can be created by tailoring the graft with a tongue of tissue that is sutured directly to the aortic annulus (Figure 8).

There are two types of aortic valve-sparing operations for patients with aortic root aneurysm: remodeling of the aortic root (described by Yacoub[18]) and reimplantation of the aortic valve (described by David[4]) (Figure 9). In the remodeling procedure, the three aortic sinuses are excised, and a properly tailored tubular Dacron graft of diameter equal to the estimated diameter of the STJ is sutured to the aortic annulus. The coronary arteries are then reimplanted into their respective sinuses. Remodeling of the aortic root replaces all three aortic sinuses but does not stabilize the aortic valve annulus and therefore leads to delayed dilatation of the aortic annulus.

Remodeling of the aortic root may be inappropriate for patients with Marfan syndrome or annuloaortic ectasia because the annulus may continue to dilate and cause late aortic insufficiency[7, 19-22] The aortic valve reimplantation technique avoids this potential late complication by excising the aortic sinuses and reimplanting the aortic valve into a Dacron graft, thus stabilizing the annulus. It has been suggested that the presence of the aortic sinuses is important for normal cusp motion and, potentially, cusp durability.[23-25] Several modifications to the reimplantation procedure were introduced to create neoaortic sinuses, including use of the Gelweave Valsalva graft mentioned above.[26, 27] Short- and long-term outcomes for these procedures have been encouraging. David et al. reported that freedom from moderate aortic insufficiency at 10 years was 80 ± 7%, and freedom from severe aortic insufficiency was 98 ± 1%. Preserving the normal anatomic structure of the aortic cusps is the key element in the success of the procedures and serves to highlight the importance of the patient selection process.

Aortic valve-sparing root procedures have acceptable results, with long-term stable outcomes of the aortic valves even in patients with aortic insufficiency, bicuspid valve, and connective tissue disorders such as Marfan syndrome and Loeys-Dietz syndrome.[28] Many of these long-term results require validation as they are mostly reported by the originator of the operative approach.

Conclusions

Aortic root repair is the treatment of choice for patients with aortic root pathology. Improvements in surgical technique, including cardiopulmonary bypass, myocardial protection, cerebral protection, and anesthetic management, have resulted in improved perioperative and long-term outcomes following aortic root repair. With improvements in bioprosthetic valve durability and fewer problems associated with anticoagulation, patients and surgeons are increasingly choosing composite biologic valve grafts with excellent short- and long-term outcomes — typically less than 5% mortality for elective procedures. Advances in technology and techniques include using the Valsalva graft, which re-establishes the anatomic and physiologic function of the root in the form of pseudosinuses. Also, supra-annular implantation of the valve conduit has allowed for improvements in hemodynamic parameters (reduced gradients) and potentially improved valve durability while allowing for easier possible reintervention surgically or via percutaneous valve implantation. In the future, as endovascular technology develops ways to navigate the coronary ostia, branched and fenestrated grafts may play a role in aortic root repair.

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References

1. Fazel SS, David TE. Aortic valve-sparing operations for aortic root and ascending aortic aneurysms. Curr Opin Cardiol. 2007 Nov;22(6):497-503.
2. Olson LJ, Subramanian R, Edwards WD. Surgical pathology of pure aortic insufficiency: a study of 225 cases. Mayo Clin Proc. 1984 Dec;59(12):835-41.
3. Lawrie GM, Earle N, DeBakey ME. Long-term fate of the aortic root and aortic valve after ascending aneurysm surgery. Ann Surg. 1993 Jun;217(6):711-20.
4. David TE, Feindel CM. An aortic valve-sparing operation for patients with aortic incompetence and aneurysm of the ascending aorta. J Thorac Cardiovasc Surg. 1992 Apr;103(4):617-21.
5. Gott VL, Greene PS, Alejo DE, Cameron DE, Naftel DC, Miller DC, et al. Replacement of the aortic root in patients with Marfan's syndrome. N Engl J Med. 1999 Apr 29;340(17):1307-13.
6. Aicher D, Langer F, Lausberg H, Bierbach B, Schafers HJ. Aortic root remodeling: ten-year experience with 274 patients. J Thorac Cardiovasc Surg. 2007 Oct;134(4):909-15.
7. Athanasiou T, Jones C, Jin R, Grunkemeier GL, Ross DN. Homograft implantation techniques in the aortic position: to preserve or replace the aortic root? Ann Thorac Surg. 2006 May;81(5):1578-85.
8. Elefteriades JA. Natural history of thoracic aortic aneurysms: indications for surgery, and surgical versus nonsurgical risks. Ann Thorac Surg. 2002 Nov;74(5):S1877-80.
9. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE Jr., et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the diagnosis and management of patients with thoracic aortic disease. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons,and Society for Vascular Medicine. J Am Coll Cardiol. 2010 Apr 6;55(14):e27-e129.

10. Musci M, Weng Y, Hubler M, Amiri A, Pasic M, Kosky S, et al. Homograft aortic root replacement in native or prosthetic active infective endocarditis: twenty-year single-center experience. J Thorac Cardiovasc Surg. 2010 Mar;139(3):665-73.
11. Zehr KJ, Orszulak TA, Mullany CJ, Matloobi A, Daly RC, Dearani JA, et al. Surgery for aneurysms of the aortic root: a 30-year experience. Circulation. 2004 Sep 14;110(11):1364-71.
12. Albertini A, Dell'Amore A, Zussa C, Lamarra M. Modified Bentall operation: the double sewing ring technique. Eur J Cardiothorac Surg. 2007 Nov;32(5):804-6.
13. Tabata M, Takayama H, Bowdish ME, Smith CR, Stewart AS. Modified Bentall operation with bioprosthetic valved conduit: Columbia University experience. Ann Thorac Surg. 2009 Jun;87(6):1969-70.
14. Tang GH, Borger MA. Aortic root replacement surgery: indications, techniques and outcomes. Expert Rev Cardiovasc Ther. 2005 Sep;3(5):845-56.
15. El-Hamamsy I, Clark L, Stevens LM, Sarang Z, Melina G, Takkenberg JJ, et al. Late outcomes following freestyle versus homograft aortic root replacement: results from a prospective randomized trial. J Am Coll Cardiol. 2010 Jan 26;55(4):368-76.
16. Dapunt OE, Galla JD, Sadeghi AM, Lansman SL, Mezrow CK, de Asla RA, et al. The natural history of thoracic aortic aneurysms. J Thorac Cardiovasc Surg. 1994 May;107(5): 1323-32.
17. Coady MA, Rizzo JA, Goldstein LJ, Elefteriades JA. Natural history, pathogenesis, and etiology of thoracic aortic aneurysms and dissections. Cardiol Clin. 1999 Nov;17(4):615-35; vii.
18. Sarsam MA, Yacoub M. Remodeling of the aortic valve anulus. J Thorac Cardiovasc Surg. 1993 Mar;105(3):435-8.
19. Hagan PG, Nienaber CA, Isselbacher EM, Bruckman D, Karavite DJ, Russman PL, et al. The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. JAMA. 2000 Feb 16;283(7):897-903.
20. Neri E, Toscano T, Papalia U, Frati G, Massetti M, Capannini G, et al. Proximal aortic dissection with coronary malperfusion: presentation, management, and outcome. J Thorac Cardiovasc Surg. 2001 Mar;121(3):552-60.
21. Tsai TT, Bossone E, Isselbacher EM, Nienaber CA, Evangelista A, Fang J, et al. Clinical characteristics of hypotension in patients with acute aortic dissection. Am J Cardiol. 2005 Jan 1;95(1): 48-52.
22. de Paulis R, Tomai F, Bertoldo F, Ghini AS, Scaffa R, Nardi P, et al. Coronary flow characteristics after a Bentall procedure with or without sinuses of Valsalva. Eur J Cardiothorac Surg. 2004 Jul;26(1):66-72.
23. Erbel R, Alfonso F, Boileau C, Dirsch O, Eber B, Haverich A, et al. Diagnosis and management of aortic dissection. Eur Heart J. 2001 Sep;22(18):1642-81.
24. Moore AG, Eagle KA, Bruckman D, Moon BS, Malouf JF, Fattori R, et al. Choice of computed tomography, transesophageal echocardiography, magnetic resonance imaging, and aortography in acute aortic dissection: International Registry of Acute Aortic Dissection (IRAD). Am J Cardiol. 2002 May 15;89(10):1235-8.
25. Nienaber CA, von Kodolitsch Y, Nicolas V, Siglow V, Piepho A, Brockhoff C, et al. The diagnosis of thoracic aortic dissection by noninvasive imaging procedures. N Engl J Med. 1993 Jan 7;328(1):1-9.
26. Boyer JK, Gutierrez F, Braverman AC. Approach to the dilated aortic root. Curr Opin Cardiol. 2004 Nov;19(6):563-9.
27. Elefteriades JA. Indications for aortic replacement. J Thorac Cardiovasc Surg. 2010 Dec;140(6 Suppl):S5-9; discussion S45-51.
28. Williams JA, Loeys BL, Nwakanma LU, Dietz HC, Spevak PJ, Patel ND, et al. Early surgical experience with Loeys-Dietz: a new syndrome of aggressive thoracic aortic aneurysm disease. Ann Thorac Surg. 2007 Feb;83(2):S757-63; discussion S85-90.
29. Feindel CM, David TE. Aortic valve sparing operations: basic concepts. Int J Cardiol. 2004 Dec;97 Suppl 1:61-6.
30. Zhang C, Ni Y, Shi L, Jin T. The treatment of recurrent aortic prosthetic detachment with modified Bentall procedure: results of two cases. J Thorac Cardiovasc Surg. 2009 Sep;138(3): 770-1.
31. Brown JM, O'Brien SM, Wu C, Sikora JA, Griffith BP, Gammie JS. Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database. J Thorac Cardiovasc Surg. 2009 Jan;137(1):82-90.
32. David TE. Surgical treatment of ascending aorta and aortic root aneurysms. Prog Cardiovasc Dis. 2010 Mar-Apr;52(5):438-44.