Cardiology in the Young (2017), **27**, 1959–1965
doi:10.1017/S1047951117002116

Original Article

Landmark lecture: Perloff lecture: Tribute to Professor Joseph Kayle Perloff and lessons learned from him: aortopathy in adults with CHD*

Koichiro Niwa†

Department of Cardiology, Cardiovascular Center, St Luke's International Hospital, Tokyo, Japan

Abstract Marfan syndrome, bicuspid aortic valve, and/or coarctation of the aorta are associated with medial abnormalities of the ascending aortic or para-coarctation aorta. Medial abnormalities in the ascending aorta are prevalent in other type of patients with a variety of CHDs such as single ventricle, persistent truncus arteriosus, transposition of the great arteries, hypoplastic left heart syndrome, and tetralogy of Fallot, encompassing a wide age range and may predispose to dilatation, aneurysm, and rapture necessitating aortic valve and root surgery. These CHDs exhibit ongoing dilatation of the aortic root and reduced aortic elasticity and increased aortic stiffness that may relate to intrinsic properties of the aortic root. These aortic dilatation and increased stiffness can induce aortic aneurysm, rapture of the aorta, and aortic regurgitation, but also provoke left ventricular hypertrophy, reduced coronary artery flow, and left ventricular failure. Therefore, a new clinical entity can be used to call this association of aortic pathophysiological abnormality, aortic dilation, and aorto-left ventricular interaction – "aortopathy".

Keywords: Aortic dilatation; aortopathy; Joseph Perloff; cystic medial necrosis; aortic elasticity

Received: 21 August 2017; Accepted: 5 December 2017

A Tribute to Professor Joseph Kayle Perloff

Born in New Orleans, Dr Perloff enrolled in Tulane University and graduated with a Bachelor of Arts in English literature. He served in the United State Navy in the Pacific.

After World War II, Dr Perloff decided to go to medical school and obtained premedical credentials at the University of Chicago. He entered Louisiana State University School of Medicine and graduated in 1951. Following graduation, he spent 3 years at the Mount Sinai Hospital in New York as an intern and resident in Pathology and Medicine, where he met her wife Margie. He was awarded a Fulbright Fellowship to the Institute of Cardiology, National Heart Hospital, London, where he worked with Dr Paul Hamilton Wood, and learned the skill of physical examination of the heart and circulation. Now he is widely known as the father of physical examination. Dr Paul Wood is famous as nominator of the Eisenmenger syndrome and Wood unit for pulmonary vascular resistance.

After returning from England, Dr Perloff completed a medical residency at Georgetown University Medical Center in Washington, DC, followed by a National Institute of Health-sponsored fellowship in Cardiology. After rising to full professor in 1970, he accepted the position as the Chief of the Cardiovascular medicine at the University of Pennsylvania School of Medicine in Philadelphia. In 1977, he relocated to the University of California, Los Angeles, and later in 1983, he was named to the newly endorsed Streisand/American Heart Association Chair as Professor of Medicine and Pediatrics.

*Presented at the 2017 Seventh World Congress of Pediatric Cardiology & Cardiac Surgery (WCPCCS 2017), Barcelona, Spain, 16–21 July, 2017. Presented Friday, 21 July, 2017.

†Presidents of the Japanese Society for Adult Congenital Heart Disease and Asia Pacific Society for Adult Congenital Heart Disease.

Correspondence to: K. Niwa, MD, PhD, FAHA, FACC, FJCC, Department of Cardiology, Cardiovascular Center, St luke's International Hospital, Tokyo 1048560, Japan. Tel: 81335415151; Fax: 81355507194; E-mail: kniwa@aol.com

Dr Perloff gave an American Heart Association lecture in 1972 entitled "The Pediatric Congenital Cardiac Becomes a Post-Operative Adult: The Changing Population of Congenital Heart Disease". The lecture appeared in *Circulation* as the first publication on what was destined to become a new cardiovascular subspecialty – CHD in adults. Few cardiologists could deal with this evolving field. Therefore, Dr Perloff was soon joined by Dr John Child and Dr David Skorton, who together established the UCLA Adult Congenital Heart Disease Center in 1978.

Dr Perloff has enjoyed worldwide acclaim as a visiting professor and lecturer. He received numerous national and international awards: an Honorary degree on occasion of the 650th anniversary of the founding of Charles University in Prague; International Symposium on Adult Congenital Heart Disease, Santorini, Greece, was held in honour of Dr Perloff; the Laennec Society Commemorative lecture, Hakone, Japan; named lecture at the Japanese Society for ACHD Tokyo; Carl J Wiggers Memorial lecture of the American Heart Association; The UCLA School of Medicine's highest academic honour – The awards of extraordinary Merit; and Lifetime Achievement Award American College of Cardiology.

Dr Perloff is the author of 13 editions of three books, 250 journal articles, and over 90 chapters. The books include the Clinical Recognition of Congenital Heart Disease, 6th edition; Congenital Heart Disease in Adults, 3rd edition; Physical Examination of the Heart and Circulation, 4th edition.

He made a great contribution not only at the national and international Congress but also at the meeting of Japanese Cardiac Society, visiting Japan six times, including twice to The Congress of Japanese Society for Adult Congenital Heart Disease.

Finally, we extended our sincere appreciation to Professor Joseph K. Perloff for his enormous contribution to our Society. His legacy is not only that of a master of children, teacher, and researcher, but he is quite literally credited with fathering an entire field of medicine, that of adult CHD. His contributions to cardiology are incredible; they will keep guiding and leading us forever, giving us an everlasting pioneering spirit.

Dr Perloff will continue to show us a way to the future, and we will always share his dream.

We extend our sincere appreciation to Professor Joseph K. Perloff for his enormous contribution to Cardiology especially ACHD field (Fig 1).

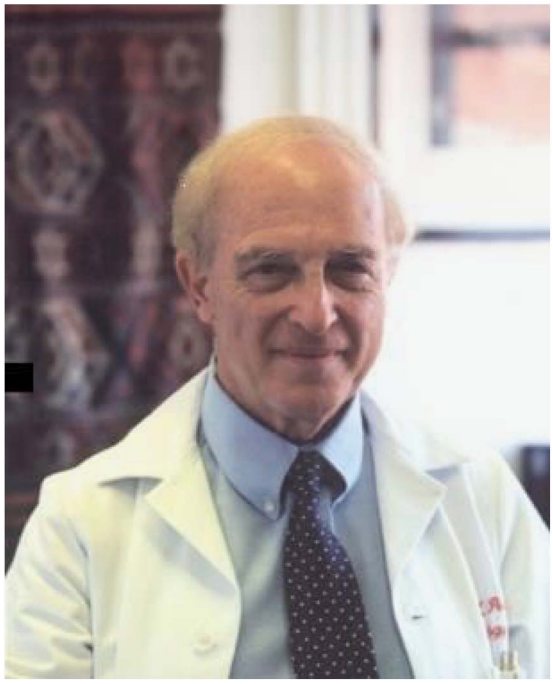

Figure 1.
Joseph K. Perloff, MD (December, 1924 to 8 August, 2014).

Aortic dilation in Marfan syndrome, Turner syndrome, bicuspid aortic valve, and coarctation of the aorta is well recognised, and these disorders are consistently associated with the ascending aortic and/or para-coarctation medial abnormalities.[1–3] CHD such as single ventricle, persistent truncus arteriosus, transposition of the great arteries, hypoplastic left heart syndrome, and tetralogy of Fallot are also associated with aortic medial abnormalities, aortic dilatation, and aortic regurgitation.[1] Aortic medial abnormalities – the so-called cystic medial necrosis – reach their severest form in Marfan syndrome and annuloaortic ectasia, and are prevalent and qualitatively similar but seldom quantitatively as marked in a wide variety of CHDs with a wide age range.[1] This aortic medial abnormality possibly reflects a common developmental fault that weakens and attenuates the aortic wall. These CHDs with aortic dilatation are often associated with decreased elasticity and increased stiffness of the aorta.[4–6] These aortic pathophysiological changes are negatively influencing on the systemic ventricular function because of the increased afterload and ventricular hypertrophy.[5]

Historical perspective

In 1928, Maude Abbott[7] mentioned in her textbook of CHD that "the presence of a bicuspid aortic valve appears to indicate, at least in a portion of the cases in which it occurs, a tendency for spontaneous rapture". In 1972, McKusick[3] reported that the association of bicuspid aortic valve and cystic medial necrosis is more than coincidence, and cystic medial necrosis was defined as follows:[8] non-inflammatory smooth muscle cell loss; fragmentation of elastic fibres;

https://doi.org/10.1017/S1047951117002116 Published online by Cambridge University Press

and accumulation of basophilic ground substance within cell-depleted areas of the medial layer of the vessel wall. Edwards et al[9] reported that among 119 necropsy specimens with aortic dissection, 11 were from bicuspid aortic valve (9%). Roberts et al[2] also reported that among 186 necropsy specimens with aortic dissection, 14 were from bicuspid aortic valve (7.5%) with a mean age of 52; they also found severe degeneration of the elastic fibre in the aortic wall in 90% of them. High incidence of bicuspid aortic valve among patients with aortic dissection suggests a causative relationship between bicuspid aortic valve and aortic dissecting aneurysm. Hahn et al[10] and Nistri et al[11] reported that there is a high prevalence of aortic root enlargement in bicuspid aortic valve, which occurs irrespective of altered haemodynamics, suggesting that both bicuspid aortic valve and aortic root dilatation may reflect a common developmental defect. It has been recognised that patients with aortic valve disease have a tendency to dilate aortic root followed by dissection, and those harbour cystic medial necrosis in the aortic media. Bicuspid aortic valve was the first non-syndromic CHD in which aortic dissection and dilation were reported.[12] In 2001, Niwa et al[1] reported that aortic medial abnormalities – the so-called cystic medial necrosis – are prevalent in a wide variety of CHDs with dilated aortic root. After that, progressive aortic dilatation and regurgitation in various types of CHD regardless of intracardiac repair have been continuously reported.[13–30]

CHDs associated with aortic dilatation (Table 2)

Bicuspid aortic valve and the Ross procedure

Aortic dissection is found to be nine times more prevalent in bicuspid aortic valve patients than in those with tricuspid valve.[13] Aortic dilation begins during childhood in bicuspid aortic valve patients, regardless of the presence of aortic stenosis.[14] Histologic abnormalities in the ascending aorta in bicuspid aortic valve patients are similar to those found in Marfan syndrome patients.[1]

From recent report on the Ross procedure,[15] in 118 patients with the Ross procedure with a mean age of 34 years and a follow-up of 44 months (bicuspid aortic valve in 81%), diameter of the sinuses of valsalva increased from 31 ± 0.4 to 33 ± 0.5 mm. In 13/118 (11%), the diameter ranged from 40 to 51 mm, and 7/118 (6%) developed moderate aortic regurgitation, and three (3%) required aortic valve replacement. The predicted probability of no or trivial aortic regurgitation decreased from 63% in the early postoperative period to 24% after 16 years.[16] The most common cause for the failure of the Ross procedure has been reported to be pulmonary autograft dilation.[17] Dilation of the pulmonary autograft after the Ross procedure occurs because of an intrinsic abnormality of the pulmonary root in patients with congenital aortic valve disease.

Coarctation of the aorta

Isner et al[18] examined by light microscopic features of coarctation segment in 33 patients, with ages ranging from 1 day to 15 years, and found cystic medial necrosis, deletion, and disarray of elastic tissue in all 33 specimens. Remarkable finding observed is this pathological abnormality is found as early as in a neonate, and it suggests cystic medial necrosis in the aortic wall in coarctation of the aorta is possibly intrinsic.

Tetralogy of Fallot

Among the cyanotic CHD, tetralogy of Fallot was the first in which aortic dilation was recognised.[19,20] Aortic dilatation is a well-known feature of unrepaired tetralogy of Fallot and correlates well with severity of right ventricular outflow tract stenosis, and is greatest in tetralogy of Fallot and pulmonary atresia. Aortic regurgitation in unrepaired tetralogy of Fallot imposes volume overload on both ventricles.[21] A significant subset of adults late after repair of tetralogy of Fallot exhibits progressive aortic root dilatation that may lead to aortic regurgitation and predispose to dissection and rapture. The aortic dilatation relates medial abnormalities coupled with previous long-standing volume overload of the ascending aorta (right to left shunting through malalignment type ventricular septal defect). This dilatation and histological abnormalities have been found from as early as infants.[22] Overall, 15% of repaired tetralogy of Fallot in adults have been reported to have a dilated aortic root.[23] Different from the Marfan syndrome, aortic aneurysm and dissection/rapture were, rarely as low as five cases, reported in tetralogy of Fallot (Fig 2). This is possibly because histological abnormality in the aorta in tetralogy of Fallot is less severe than those of Marfan syndrome.[1]

Complete transposition of the great artery with arterial switch operation

Aortic dilation and aortic regurgitation are well-known complications after arterial switch operation in complete transposition of the great artery.[24,25] Freedom from aortic regurgitation and aortic valve replacement was 69 and 97% at 15 years, respectively.[24] Neo-aortic valve regurgitation was severe in 3.7% and trivial to mild in 81% at mid-term

https://doi.org/10.1017/S1047951117002116 Published online by Cambridge University Press

Case reports
Ascending Aortic Dissection(10), Large Aneurysm(1)

	Sex Age (y)	Diagnosis	AoSize (mm)	AR	Aorta	Journal
Kim WH	M, 23	TOF	70	severe	Dissection	IJC 2005
Wijesekera VA	M, 60	TOF	55	severe	Dissection	IJC 2014
Rathi VK	M, 36	TOF	93x83	ND	Dissection	IJC 2005
Konstantinov IE	M, 18	TOF chr 22q11 del	60X70	mild	Dissection	JTCS 2010
Dearani JA	M, 26	VSD PA	ND	ND	Dissection	SEM TCSPCSA
Egan M	M, 26	HLHS Fontan	78	Severe	Dissection	Ped Card 2009
Stolla M	M, 15	HLHS TCPC	70	ND	Dissection	JTCS2014
Cleuziou J	M, 27	DORV-VSD-PS	85	mod	Large Aneurysm	Ann Th S 2006
Nowitz A	F, 41	dTGA Mustard	70	severe	Dissection	JCardiovasc Anesth2013
Sharma R	F, 42	dTGA Mustard	70	severe	Dissection	AsiaCardvasc ann2013
Personal commun	M, 28	TA Fontan	56	ND	Dissection	Not reported

Figure 2.
Case reports. Ascending Aortic Dissection (n = 10), Large Aneurysm (n = 1).

follow-up.[25] Cystic medial necrosis is observed in both neo-aorta and pulmonary artery in neonate; therefore, histological aortic abnormality in transposition of the great arteries is one of the causes of this aortic dilatation.[26] Progressive dilation of the neo-aortic root becomes out of proportion to somatic growth, and the incidence of aortic regurgitation increases with age. Previous pulmonary artery banding, older age at repair, and presence of ventricular septal defect are the risk factors for aortic regurgitation.[27]

Hypoplastic left heart syndrome

Neo-aortic root dilation and aortic regurgitation after staged reconstruction for hypoplastic left heart syndrome are known complications, and these progress over time. Cohen[28] followed 53 patients with hypoplastic left heart syndrome after Fontan procedure for 9 years and found neo-aortic root progressively dilated out of proportion to the body size, with 98% having a z-score >2 at most recent follow-up. Neo-aortic regurgitation was present in 61%. Therefore, difference of arterial histology may be one of the causes of this regurgitation.

Other CHDs

Dilated aortic root is found in the majority of operated truncus arteriosus patients; however, none has dissection or rapture.[29] In this disorder, anatomical truncal valve abnormality and regurgitation is common, and therefore, the role of dilatation of the aorta on truncal valve regurgitation is unclear. Aortic dissection after CHD is found in patients with Fontan,[30] but the incidence of aortic dissection in CHD other than bicuspid aortic valve and coarctation of the aorta is extremely rare, which are different from Marfan and related genetic disorders.

Pathophysiology and cause of aortic dilatation

Histopathological abnormalities in various CHDs

In a study by Niwa et al[1], in 88 (10 different diagnoses) CHD patients with dilated aorta with age of 3 weeks to 81 years (32 ± 6 years) (48 male and 40 female patients), surgical biopsy aortic specimens were obtained, and cystic medial necrosis in the aortic media was observed in all of these patients (Table 1).

Cause of aortic dilatation in CHD (Table 1) and histology of the aortic media

Independent variables that alter the structure of ascending aortic media include Marfan syndrome, annuloaortic ectasia or Turner syndrome, and systemic hypertension,[31] ageing,[32] and pregnancy,[33] and others (Table 2). Marfan syndrome is characterised by a defect in the chromosome 15 gene that codes for fibrillin-1,[34] in the absence of which elastin is more readily degraded by metalloproteinase.[35] Deletion of TGF-β receptor has a relation to aortic dilatation.[36] The genetic fault in Marfan syndrome apparently impairs aortic medial elastic fibres more extensively than impairment in CHD, and the

https://doi.org/10.1017/S1047951117002116 Published online by Cambridge University Press

Table 1. CHDs associated with aortic dilatation in adults.

Marfan syndrome
Turner syndrome
Bicuspid aortic valve
Coarctation of the aorta
Tetralogy of Fallot
Single ventricle with pulmonary atresia or stenosis
Persistent truncus arteriosus
Transposition of the great arteries
Hypoplastic left heart syndrome
Fontan procedure

Table 2. Variables alter structure of ascending aortic media.

1. Systemic hypertension
2. Aeging
3. Pregnancy
4. Chromosome abnormality: Marfan syndrome, Turner syndrome, Noonan syndrome
5. Gene abnormality: fibrillin-1 defect (15q21.1)
6. Deletion of TGF-β receptor, ALK5 signalling in neural crest cell
7. Metalloproteinase and elastin
8. Haemodynamic abnormality (increased aortic flow)
9. Intrinsic abnormality of the aortic wall in CHDs

incidence of ascending aortic dilatation, dissection or rapture is higher and the degree of aortic root medial lesions is greater in the former than in the latter.

Genetics in aortic dilatation in CHD

On comparing patients with A-P phenotype (R-L cusp fusion) bicuspid aortic valve with R-L phenotype (R-N cusp fusion), the former is more common in men and has a larger stiffer at the sinus of Valsalva and smaller at the ascending aorta and aortic arch than the latter.[37] This aortic shape difference is possibly due to inborn error of the aortic wall than due to haemodynamic effect.[38] Therefore, bicuspid aortic valve phenotype can predict elastic properties of the ascending aorta and has potential impact on clinical outcomes.

Overall, 50.9% prevalence of fibrillin-1 gene polymorphisms or mutations is found in tetralogy of Fallot patients with dilated aorta and there is more than eight times risk for aortic dilation in patients with these variants.[39] In 10/93 (10.8%) patients with chromosome 22q11.2 partial deletion without conotruncal abnormality, aortic dilation is found,[40] and chromosome 22q11.2 partial deletion may be one of the risk factors of aortic dilatation.[23]

Aortic root dilation and aortic elastic properties

Chong[6], in a study conducted on 67 children with 8.3 years after tetralogy of Fallot repair, observed aortic dilation (z-score >2) in 61–88% of them; moreover, significantly increased stiffness, reduced strain, and distensibility of the aorta were observed in aortic dilators. Senzaki et al[5], in a study comparing 38 repaired tetralogy of Fallot patients with 55 controls, reported that the former had higher characteristic of impedance and pulse wave velocity, lower total peripheral arterial compliance, higher arterial wave reflection, and also observed that the increase in aortic wall stiffness was closely associated with the increase in the aortic root diameter. Therefore, central and peripheral arterial wall stiffness is characteristically increased after tetralogy of Fallot repair. Abnormal arterial elastic properties have negative impact on left ventricle and provoke aortic dilatation, and it may induce left ventricular hypertrophy, systolic, and diastolic dysfunction of the left ventricle. Furthermore, in repaired tetralogy of Fallot patients, increased augmentation indices have been reported.[41]

In patients after arterial switch operation, decreased aortic elasticity and distensibility are confirmed by increased pulse wave velocity[42] and increased stiffness index.[43]

These aortic pathophysiological abnormalities are observed in the other types of CHD with aortic dilatation. These characteristics induce aortic dilation and aortic regurgitation,[4,5] and increased pulsatile load on left ventricle followed by decreased cardiac output, and also provoke decreased coronary blood flow that may negatively influence on the left ventricular function.[44] Aortic regurgitation may also develop and progress due to stiffness of aortic root.

We can recognise this pathophysiological abnormality of the aorta and abnormal aortoventricular interaction as a clinical entity "Aortopathy".

Conclusions

A subset of adult patients with CHD exhibits ongoing dilatation of the aortic root and reduced aortic elasticity, which may relate to intrinsic properties of the aortic root. This new concept of aortic dilatation is shifting a paradigm of aortic dilatation from so called post-stenotic dilatation to primary intrinsic aortopathy. These aortic dilatation and increased stiffness can induce aortic aneurysm, rapture, and aortic regurgitation, but also provoke left ventricular hypertrophy, reduced coronary artery flow, and left ventricular failure. We can recognise this association of aortic pathophysiological abnormality, aortic dilation, and aortic–ventricular interaction as a new clinical entity – "Aortopathy".

Acknowledgement

The author thanks Marjolie Perloff MA, PhD and Jamil Aboulhosn MD, PhD, for providing photos and data on him, Joseph Perloff MD.

Financial Support

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

Conflicts of Interest

None.

References

1. Niwa K, Perloff JK, Bhuta SM, et al. Structural abnormalities of great arterial walls in congenital heart disease. Light and electron microscopic analyses. Circulation 2001; 103: 393–400.
2. Roberts CS, Roberts WC. Dissection of the aorta associated with congenital malformation of the aortic valve. J Am Coll Cardiol 1991; 17: 712–716.
3. Mckusick VA. Association of congenital bicuspid aortic valve and Erdheim's cystic medial necrosis. Lancet 1972; I: 1026–1027.
4. Seki M, Kurishima C, Kawasaki H, et al. Aortic stiffness and aortic dilation in infants and children with tetralogy of Fallot before corrective surgery: evidence for intrinsically abnormal aortic mechanical property. Eur J Cardiothorac Surg 2012; 41: 277–282.
5. Senzaki H, Iwamoto Y, Ishido H, et al. Arterial haemodynamics in patients after repair of tetralogy of Fallot: influence on left ventricular after load and aortic dilatation. Heart 2008; 94: 70–74.
6. Chong WY, Wong WH, Chiu CS, et al. Aortic root dilation and aortic elastic properties in children after repair of tetralogy of Fallot. Am J Cardiol 2006; 97: 905–909.
7. Perloff JK. Congenital aortic stenosis. Congenital aortic regurgitation. In: Perloff JK, Marelli AJ, (eds). Clinical Recognition of Congenital Heart Disease, 6th edn. Elsevier Saunders Company, Philadelphia, PA, 2012. P74–75.
8. Erdheim J. Medionecrosis aortae idiopathica-cystica. Virchows Arch Pathol Anat 1930; 276: 186.
9. Edwards WD, Leaf DS, Edwards JE. Dissecting aortic aneurysm associated with congenital bicuspid aortic valve. Circulation 1978; 57: 1022–1025.
10. Hahn RT, Roman MJ, Mogtader AH, et al. Association of aortic dilation with regurgitant, stenotic and functionally normal bicuspid aortic valves. J Am Coll Cardiol 1992; 19: 283–288.
11. Nistri S, Sorbo MD, Marin M, et al. Aortic root dilatation in young men with normally functioning bicuspid aortic valves. Heart 1999; 82: 19–22.
12. Reid RT. Bicuspid aortic valve associated with aneurysmal dilatation of the ascending aorta. Med J Aust 1952; 2: 628–629.
13. Larson EW, Edwards WD. Risk factors for aortic dissection: a necropsy study of 161 cases. Am J Cardiol 1984; 53: 849–855.
14. Gurvitz M, Chang RK, Drant S, et al. Frequency of aortic root dilation in children with a bicuspid aortic valve. Am J Cardiol 2004; 94: 1337–1340.
15. de Sa M, Moshkovitz Y, Butany J, David TE. Histologic abnormalities of the ascending aorta and pulmonary trunk in patients with bicuspid aortic valve disease: clinical relevance to the Ross procedure. J Thorac Cardiovasc Surg 1999; 118: 588–594.
16. Elkins RC, Thompson DM, Lane MM, et al. Ross operation: 16-year experience. J Thorac Cardiovasc Surg 2008; 136: 623–630.
17. David TE, Omran A, Ivanov J, et al. Dilation of the pulmonary autograft after the Ross procedure. J Thorac Cardiovasc Surg 2000; 119: 210–220.
18. Isner JM, Donaldson RF, Fulton D, et al. Cystic medial necrosis in coarctation of the aorta: a potential factor contributing to adverse consequences observed after percutaneous balloon angioplasty of coarctation sites. Circulation 1987; 75: 689–695.
19. Niwa K. Aortic root dilatation in tetralogy of Fallot long-term after repair-histology of the aorta in tetralogy of Fallot: evidence of intrinsic aortopathy. Int J Cardiol 2005; 103: 117–119.
20. Rieker RP, Berman MA, Stansel Jr HC. Postoperative studies in patients with tetralogy of Fallot. Ann Thorac Surg 1975; 19: 17–26.
21. Capelli H, Ross D, Somerville J. Aortic regurgitation in tetrad of Fallot and pulmonary atresia. Am J Cardiol 1982; 49: 1979–1983.
22. Tan JL, Davlouros PA, McCarthy KP, et al. Intrinsic histological abnormalities of aortic root and ascending aorta in tetralogy of Fallot: evidence of causative mechanism for aortic dilatation and aortopathy. Circulation 2005; 112: 961–968.
23. Niwa K, Siu SC, Webb GD, et al. Progressive aortic root dilatation in adults late after repair of tetralogy of Fallot. Circulation 2002; 106: 1374–1378.
24. Losay J, Touchot A, Capderou A, et al. Aortic valve regurgitation after arterial switch operation for transposition of the great arteries: incidence, risk factors, and outcome. J Am Coll Cardiol 2006; 47: 2057–2062.
25. Marino BS, Wernovsky G, McElhinney DB, et al. Neo-aortic valvar function after the arterial switch. Cardiol Young 2006; 16: 481–489.
26. Takeuchi T, Imai Y, Takanashi Y, et al. Histological study of the great arteries in patients with arterial switch operation. Act Ped Cardiol Jpn 1996; 12: 506–512.
27. Schwartz ML, Gauvreau K, del Nido P, et al. Long-term predictors of aortic root dilation and aortic regurgitation after arterial switch operation. Circulation 2004; 110: II128–132.
28. Cohen MS, Marino BS, McElhinney DB, et al. Neo-aortic root dilation and valve regurgitation up to 21 years after staged reconstruction for hypoplastic left heart syndrome. J Am Coll Cardiol 2003; 42: 533–540.
29. Carlo WF, McKenzie ED, Slesnick TC. Root dilation in patients with truncus arteriosus. Congenit Heart Dis 2011; 6: 228–233.
30. Egan M, Phillips A, Cook SC. Aortic dissection in the adult Fontan with aortic root enlargement. Pediatr Cardiol 2009; 30: 562–563.
31. Carlson RG, Lillehei CW, Edwards JE. Cystic medial necrosis of the ascending aorta in relation to age and hypertension. Am J Cardiol 1970; 25: 411–415.
32. Schlatmann TJ, Becker AE. Histologic changes in the normal aging aorta: implications for dissecting aortic aneurysm. Am J Cardiol 1977; 39: 13–20.
33. Monalo-Estrell P, Barker AE. Histopathologic findings in human aortic media associated with pregnancy. Arch Pathol 1967; 83: 336–341.
34. Dietz HC, Pyeritz RE. Mutations in the human gene for fibrillin-1 (FBN1) in the Marfan syndrome and related disorders. Hum Mol Genet 1995; 4: 1799–1809.
35. Bonderman D, Gharehbaghi-Schnell E, Walleneck G, et al. Mechanisms underlying aortic dilatation in congenital aortic valve malformations. Circulation 1999; 99: 2138–2143.
36. Wang J, Nagy A, Larsson J, et al. Defective ALK5 signaling in the neural crest leads to increased postmigratory neural crest cell apoptosis and severe outflow tract defects. BMC Dev Biol 2006; 6: 51–64.
37. Schaefer BM, Lewin MB, Stout KK, et al. The bicuspid aortic valve: an integrated phenotypic classification of leaflet morphology and aortic root shape. Heart 2008; 94: 1634–1638.
38. Jackson V, Petrini J, Caidahl K, et al. Bicuspid aortic valve leaflet morphology in relation to aortic root morphology: a study of 300 patients undergoing open-heart surgery. Eur J Cardiothorac Surg 2011; 40: e118–124.
39. Chowdhury UK, Mishra AK, Balakrishnan P, et al. Role of fibrillin-1 genetic mutations and polymorphism in aortic dilatation in patients undergoing intracardiac repair of tetralogy of Fallot. J Thorac Cardiovasc Surg 2008; 136: 757–766.
40. John AS, McDonald-McGinn DM, Zackai EH, et al. Aortic root dilation in patients with 22q11.2 deletion syndrome. Am J Med Genet A 2009; 149A: 939–942.

41. Cheung YF, Ou X, Wong SJ. Central and peripheral arterial stiffness in patients after surgical repair of tetralogy of Fallot: implications for aortic root dilatation. Heart 2006; 92: 1827–1830.
42. Murakami T, Nakazawa M, Momma K, et al. Impaired distensibility of neoaorta after arterial switch procedure. Ann Thorac Surg 2000; 70: 1907–1910.
43. Sievers HH, Lange PE, Arensman FW, et al. Influence of two-stage anatomic correction on size and distensibility of the anatomic pulmonary/functional aortic root in patients with simple transposition of the great arteries. Circulation 1984; 70: 202–208.
44. Niwa K. Aortopathy in congenital heart disease in adults: aortic dilatation with decreased aortic elasticity that impacts negatively on left ventricular function. Korean Circ J 2013; 43: 215–220.

https://doi.org/10.1017/S1047951117002116 Published online by Cambridge University Press