Clin. Cardiol. 29, 439–443 (2006)

Coronary Artery Aneurysm: A Review

PAYAM S. PAHLAVAN, M.D., AND FERAYDOON NIROOMAND, M.D., PH.D.

Department of Internal Medicine, University of Heidelberg, Heidelberg, Germany

Summary: Coronary artery ectasia (CAE) is found in 0.3–5% of patients undergoing coronary angiography. Atherosclerosis is the main cause, followed by Kawasaki disease and infectious emboli. The exact pathogenesis has not been diagnosed as yet, but an inflammatory process is underlying. Symptoms, if present, are usually related to myocardial ischemia. Angiography is the mainstay for diagnosis. The prognosis is generally favorable. Thromboembolic complications are rare with antiplatelet therapy, and spontaneous rupture generally is rare but occurs more commonly in Kawasaki disease. Management varies from antithrombotic therapy to surgical ligation. Controlling coronary heart disease risk factors sharply affects the prognosis in patients with CAE.

Key words: coronary artery aneurysm, ectasia, diagnosis, management, prognosis

Introduction

Aneurysmal coronary artery disease (CAD) is an abnormal dilatation of a localized or diffuse segment of the coronary artery tree.[1] Aneurysmal coronary disease has also been termed coronary artery ectasia (CAE),[2] defined as localized or diffuse nonobstructive lesions of the epicardial coronary arteries[2, 3] that exceed the diameter of the normal adjacent segments or the patient's largest coronary vessel.[4] Based on the Coronary Artery Surgery Study (CASS) registry, definition of CAE is a dilatation with a diameter of ≥ 1.5 times the adjacent normal coronary artery.[2] Coronary artery ectasia is classified as saccular when the transverse diameter is greater than the longitudinal dimension or fusiform and when it is less than the longitudinal dimension.[5] Coronary artery ectasias are classified according to the definition of Markis *et al.* as follows: (1) diffuse ectasia with aneurysmal lesions in two vessels (type I), (2) diffuse ectasia in one vessel and discrete ectasia in another (type II), (3) diffuse ectasia in one vessel (type III), and (4) discrete ectasia in one vessel (type IV).[6]

The proximal and middle segments of the right coronary artery (RCA) are the most common sites for CAE (68%), followed by the proximal left anterior descending (LAD) (60%) and the left circumflex arteries (LCx) (50%);[1] Coronary artery ectasia of the left main stem (LMCA) is rare[1, 4] and occurs in only 0.1% of the population.[7, 8]

Coronary artery ectasia appears when the atherosclerotic process affects both the intima, forming luminal stenoses or occlusions, and the media and advantitial parts of the vessel wall resulting in arterial remodeling and dilatation.[4] The most common cause of CAE is atherosclerosis,[1] but aneurysms may also be congenital, mycotic, or part of a systemic inflammatory disease such as polyarteritis nodosa or the mucocutaneous lymph node syndrome of Kawasaki.[4] Table I summarizes the etiologies of CAE and their approximate frequencies.

Coronary artery ectasia is found during diagnostic coronary angiography in patients with different ischemic syndromes[9] with an incidence of 0.3–4.9%[10] and is seen in 1.4% postmortem examinations.[11] In addition, CAE may be associated with concomitant aneurysms in different arterial beds.[12]

Multiple CAEs in childhood and adolescence are usually late complications of Kawasaki disease,[13] which is an acute febrile illness occurring during infancy (usually before 5 years of age) and is associated with cervical lymphadeopathy, rash, and a "strawberry tongue." In survivors of Kawasaki disease, even if asymptomatic, large CAEs may be present and are frequently associated with significant CAD and even coronary occlusions.[14]

Coronary artery ectasia is associated with hyperlipidemia, systemic hypertension, and male gender.[6, 15] Significant association between aneurysm size and other cardiac risk factors has not been proven so far.[15]

Address for reprints:

Payam Samareh Pahlavan, M.D.
Department of Internal Medicine
University of Heidelberg
Im Neuenheimer Feld, 410
D-69120 Heidelberg, Germany
e-mail: P.Samareh_Pahlavan@med.uni-heidelberg.de or
payamsp@hotmail.com

Received: February 28, 2006
Accepted: March 28, 2006

TABLE I Etiologies of coronary artery ectasia and their approximate frequencies

Etiologies of CAE	Approximate frequency
Atherosclerosis	50%
Kawasaki disease and congenital causes	17%
Mycotic and infectious septic emboli including syphilis and borreliosis	11%
Connective tissue diseases and Marfan's syndrome	<10%
Arteritis, e.g., polyarteritis nodosa, Takayasu's disease, systemic lupus erythematosus	<10%
Ehlers Danlos syndrome	Rare
Neurofibromatosis	Rare
Tumor	Rare
Primary cardiac lymphoma	Rare
Congenital CAE	Rare
Iatrogenic, e.g., PTCA, stents, directional coronary atherectomy, angioplasty, and laser angioplasty	Rare

Abbreviations: CAE = coronary artery ectasia, PTCA = percutaneous transluminal coronary angioplasty.

Pathogenesis

Although it has been suggested that ectasia is commonly a variant of obstructive coronary artery disease, its pathogenesis remains poorly understood.[16] Systemic hypertension; inflammatory stimuli such as tobacco; hyperhomocysteinemia; acceleration of the atherosclerotic process and/or interference with the normal cross-linking of collagen and chronic Epstein-Barr virus infection; genetic factors including HLA-DR B1* 13, DR16, DQ2, and DQ5, and MMP-3 and MMP-3 gene (MMP-3 5A allele) disruption, and insertion/deletion polymorphism of angiotensin-converting enzyme (ACE DD genotype); increased inflammatory response in the vessel wall; and activation of matrix metalloproteinases are possible factors in the vessel-wall weakening that induces CAE.[2, 12, 17–20, 21]

Extensive vascular wall inflammation, involving all layers of the vascular wall, plays a major role in the development of CAE.[16] Soluble adhesion molecules including vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin, which are expressed on vascular endothelium and on immune and inflammatory cells and mediate the adhesion and transmigration of leukocytes to vascular endothelium, are increased in sera of patients with CAE.[16] Factors that may contribute to the pathogenesis of aneurysms are matrix-degrading enzymes such as collagenases, gelatinases, and stromelysins. Matrix metalloproteinases (MMPs) are enzymes that can degrade the structural proteins of connective tissue. Degradation of extracellular matrix proteins may weaken the connective tissue, thereby leading to a weakened vascular wall.[18] A key step in the regulation of MMP expression occurs at the level of transcription through a prostaglandin E2 (PGE2)-cAMP-dependent pathway. Transcription activity can be further stimulated by a variety of inflammatory cytokines, hormones, and growth factors.[18] Matrix metalloprotein activity is regulated by tissue-specific inhibitors including inhibitors of metalloproteinases (TIMP-1, -2, -3, and -4). The TIMPs are secreted by smooth muscle cells and macrophages. Their activities are increased by growth factors or decreased by different interleukins. Increased levels of MMP-2, MMP-3, MMP-9, and MMP-12, and decreased levels of TIMPs have been identified in aneurysm vessel walls.[18] A proteolytic imbalance may lead to coronary aneurysm development through degradation of matrix components, especially in the lamina elastica.[18]

Clinical Presentations and Diagnosis

Coronary artery ectasia may be detected in the absence of symptoms; however, patients sometimes present with exercise-induced angina pectoris due to myocardial ischemia without coincident significant coronary artery stenosis, myocardial infarction (MI), or sudden death. Complications such as thrombus formation, distal embolization and shunt formation and rupture can occur,[1, 4, 22, 23] but the absolute risk is not known.[4] Myocardial infarction may also occur in the absence of significant coronary artery stenosis and is usually attributed to distal microembolization or thrombotic occlusion of an ectatic segment.[24] Even though volumetric coronary blood flow is significantly higher in CAE, microcirculatory dysfunction that is reflected as depressed coronary flow reserve may be the underlying cause of myocardial ischemia, especially during exercise in patients with CAE.[24]

Coronary artery ectasia may be detected noninvasively using echocardiography, computed tomography, and magnetic resonance imaging (MRI).[1] Rare cases of giant coronary aneurysms can cause a pronounced bulge of the heart counter on chest x-rays[25] (Fig. 1). The standard of reference for diagnosis of coronary aneurysm is coronary angiography, which provides information about the size, shape, location, and number of aneurysms.[18] Even angiography may be false negative if the native vessel occludes.[4] Some aneurysms are detected calcified during angiography evaluation.[14, 26] Intravascular ultrasound (IVUS) examination allows for distinguishing true from false aneurysms. In the former, the aneurysmal wall contains the medial tissue that shows continuity with the media of the adjacent normal coronary segment; in the latter, the aneurysm is limited only by adventitial tissue or even just by the visceral

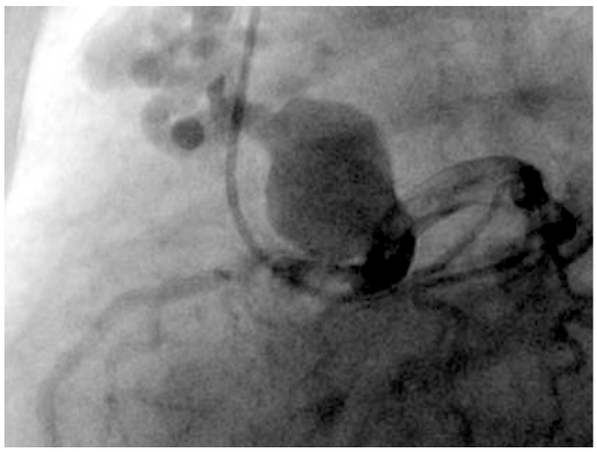

FIG. 1 Coronary angiography shows a giant aneurysm of 4.8 cm in the left anterior descending artery in a 58-year-old woman who presented to the Department of Internal Medicine, University of Heidelberg, with the chief complaint of remarkable weight loss and supine dyspnea. The patient had a concomitant pulmonary artery fistula. She underwent surgical closing of the fistula in the pulmonary arterial trunk and coronary aneurysm ligation.

pericardium.[27] False aneurysms are usually the result of trauma to the vessel wall.

Coronary artery ectasia may also break through to the right atrium, right ventricle, or coronary sinus, creating left-to-right shunts.[1, 4] If a rupture into a heart chamber occurs, a continuous murmur maybe present and cardiac decompensation may ensue.[1]

Mycotic CAE is often silent until either thrombosis results in MI or the aneurysm ruptures, producing massive hemopericardium and cardiac tamponade.[28] Rapid enlargement of coronary aneurysms has been reported.[5]

It is important to recognize that patients with coronary aneurysm may develop extracardiac aneurysm and therefore may undergo MRI of the other parts of the body to rule out this pathology.[8] Varicose veins and varicocele (dilatation of the pampiniform plexus) are significantly higher in CAE, suggesting the possible existence of a generalized defect of the vascular wall.[29,30]

Histochemical Findings

Patients with isolated CAE have significantly higher levels of plasma soluble adhesion molecules ICAM-1, VCAM-1, and E-selectin than do patients with obstructive CAD without any ectatic lesion and patients with angiographically normal coronary arteries. This finding suggests the presence of a more severe and extensive vascular inflammatory infiltration, involving all layers of the vascular wall (transmural inflammation).[16] There is also a significant positive correlation between the total length of ectatic segments and the levels of plasma soluble ICAM-1, VCAM-1, and E-selectin.[16] Furthermore, patients with isolated CAEs have higher levels of C-reactive protein (CRP) and IL-6 than do patients both with and without CAD.[31, 32]

Histologic findings in autopsy cases reveal extensive atherosclerotic changes and destruction of the media of the vessel wall.[16] In both diffuse and localized CAE, there is a thinning of the media. With increased diameter, increased wall stress causes progressive dilatation of the affected arterial segment.[1] Inflammation and excessive extracellular matrix breakdown occur as putative processes and result in expansion and aneurysm formation.[16]

Differential Diagnosis

The differential diagnosis of a cystic mass in the atrioventricular groove includes coronary aneurysm, pseudoaneurysm, pericardial cyst, dilated coronary sinus, dilated coronary fistula, cameral fistula, and echinococcal cyst.[23] Giant coronary aneurysms are an important differential diagnosis for cardiac tumors.[4] Pseudoaneurysm results from disruption of the external elastic membrane with loss of vessel wall integrity and transition from a three-layered wall to an outwardly bulging monolayer.[5] Pseudoaneurysms are often but not always a consequence of coronary perforation. They may also occur following trauma or coronary stent deployment.[27]

Management

The management of CAE consists of medical management, stent insertion, and surgical excision. Recently, it has been advocated that all patients with angiographic evidence of coronary aneurysms should receive aggressive modification of coronary risk factors whether or not obstructive CAD is present.[15] To avoid thromboembolism, antiplatelet and anticoagulation therapies are reasonable and probably beneficial despite lacking evidence-based medicine.[4] Based on the association of ACE gene polymorphism and CAE, ACE inhibitors could be useful in the suppression of CAE progression, but this has yet to be proven.[20] Because elevated MMP-3 levels likely contribute to the development of coronary aneurysms, this matrix-degrading enzyme may represent an important therapeutic target. Some statins could be beneficial by inhibiting MMP-3 activity and corticosteroids and IL-4, and by suppressing MMP expression.[18] Trimethazine can also improve coronary flow in CAE by increasing plasma adenosine levels;[22] dipyridamole may be used as well.[33] However, administration of nitroglycerin and nitrate derivates may induce angina pectoris in patients with CAE and should be avoided.[22]

Especially with accompanying stenosis, the use of grafted stents, for example, Jostent coronary stent graft, is advocated.[34] The Jostent® polytertafluoroethylene (PTFE)-covered, balloon-expandable stent (Abbott Vascular Instruments Deutschland GmbH, Rangendingen, Germany) has been shown to be an effective device for the percutaneous management and exclusion of coronary aneurysms.[3, 9, 10] Self-ex-

pandable PTFE stents (Symbiot®, Boston Scientific, Natick, Mass., USA) may be preferable in aneurysms of great longitude that are located in vessels with angulations or in those with larger diameters;[9] however, only limited experience is available.[9]

In the symptomatic patient not suitable for stent insertion, surgical excision or ligation of the CAE with bypass graft of the affected coronary arteries may be the procedure of choice.[11] Coronary artery ectasias that present with life-threatening complications such as heart chamber compression or fistula formation with severe shunts require prompt surgical intervention.[1] Some authors argue that CAE of at least three to four times the size of the original vessel diameter is an absolute indication for surgical intervention because of the propensity for complications such as compression, rupture, or thrombosis.[1] Discrete CAEs do not appear to rupture, and these patients seem to have a favorable long-term prognosis; therefore, elective resection in asymptomatic patients is not warranted.[1]

Because of the rarity of LMCA aneurysm, it is difficult to standardize treatment.[13] Anticoagulation with warfarin is advocated for therapy for LMCA aneurysm; however, compared with platelet adhesion inhibitor, the benefit of this therapy is not known.[14] There are also few reports of surgical treatment of LMCA aneurysms.[8] Surgical therapy is reserved for those with large thrombotic aneurysms or with myocardial ischemia and significant associated CAD. In some patients with LMCA aneurysm, ligation of the aneurysm may be difficult because it is located behind the pulmonary artery. The pulmonary artery can easily be divided and repaired, and this greatly facilitates the exposure of the LMCA and eliminates any dangerous dissection posteriorly with traction on the pulmonary artery. If the main pulmonary artery can be satisfactorily mobilized, it should not be divided. Coronary bypass graft with ligation of the aneurysm is an alternative surgical treatment for aneurysms of the LMCA.[13] Intracoronary thrombolytic agents for angiographically evident thrombi have also been used, but the long-term result is unclear.[14]

In Kawasaki disease, the U.S. multicenter study observed a reduced incidence of aneurysms and ectasia from 23 to 5% and giant aneurysms from 5 to 1% when intravenous immunoglobulin (IVIG) is given within 10 days of occurrence.[35]

Survival and Prognosis

The CAE prognosis is controversial. Some believe that the presence of CAE has an independent adverse effect on long-term mortality rate,[15] and some mention that the prognosis is based on the coronary atherosclerosis per se and not on the presence of the aneurysms.[4] However, it is generally believed that the strongest predictors of long-term mortality in patients with CAE are concomitant diabetes followed by hyperlipidemia, presence of coronary aneurysm (nonmanaged ones), and obstructive CAD.[1, 15] It has been estimated that CAE as an independent predictor of mortality has an overall 5-year survival of only 71%.[15]

Conclusion

Regardless of the causes and the predisposing factors, CAE is an independent cause of morbidity and mortality in patients with CAE. Giant CAEs are not common. The management varies from medical management to stent insertion and surgical ligation. In symptomatic patients, surgical excision and ligation is the procedure of choice. Risk factors for CAD should be controlled and antithrombotics should be started to decrease the effect of parallel factors. Long-term prognosis is still controversial and uncertain.

References

1. Chia HM, Tan KH, Jackson G: Non-atherosclerotic coronary artery aneurysms: Two case reports. *Heart* 1997;78(6):613–616
2. Swaye PS, Fisher LD, Litwin P, Vignola PA, Judkins MP, Kemp HG, Mudd JG, Gosselin AJ: Aneurysmal coronary artery disease. *Circulation* 1983;67 (1):134–138
3. Fineschi M, Gori T, Sinicropi G, Bravi A: Polytetrafluoroethylene (PTFE) covered stents for the treatment of coronary artery aneurysms. *Heart* 2004; 90(5):490
4. Anfinsen OG, Aaberge L, Geiran O, Smith HJ, Aakhaus S: Coronary artery aneurysms mimicking cardiac tumor. *Eur J Echocardiogr* 2004;5(4): 308–312
5. Aqel RA, Zoghbi GJ, Iskandrian A: Spontaneous coronary artery dissection, aneurysms, and pseudoaneurysms: A review. *Echocardiography* 2004;21 (2):175–182
6. Markis JE, Joffe CD, Cohn PF, Feen DJ, Herman MV, Gorlin R: Clinical significance of coronary arterial ectasia. *Am J Cardiol* 1976;37(2):217–222
7. D'Eri A, Cassin M, Burelli C, Zardo F, Dametto E, Nicolosi GL: Left main coronary artery aneurysm (congenital?). *Ital Heart J* 2005;6(5):428–429
8. Elahi MM, Dhannapuneni RV, Keal R: Giant left main coronary artery aneurysm with mitral regurgitation. *Heart* 2004;90(12):1430
9. Burzotta F, Trani C, Romagnoli E, Mazzari MA, Savino M, Schiavoni G, Crea F: Percutaneous treatment of a large coronary aneurysm using the self-expandable Symbiot PTFE-covered stent. *Chest* 2004;126(2):644–645
10. Briguori C, Sarais C, Sivieri G, Takagi T, DiMario C, Colombo A: Polytetrafluoroethylene-covered stent and coronary artery aneurysms. *Cathet Cardiovasc Interv* 2002;55(3):326–330
11. Badmanaban B, Mallon P, Campbell N, Sarsam MA: Repair of left coronary artery aneurysm, recurrent ascending aortic aneurysm, and mitral valve prolapse 19 years after Bentall's procedure in a patient with Marfan syndrome. *J Card Surg* 2004;19(1):59–61
12. Rigatelli G, Gemelli M, Franco G, Menini A, Rigatelli G: Unusual combination of coronary artery, abdominal aortic and iliac artery inflammatory aneurysmal disease. *Int J Cardiol* 2004;96(1):105–107
13. Turkay C, Golbasi I, Sahin N, Kabukcu M, Bayezid O. Surgical management of an atherosclerotic aneurysm of the left main coronary artery. *J Thorac Cardiovasc Surg* 2001;122(3):626–627
14. Abbate A, Patti G, Dambrosio A, Di Sciascio G: Left main coronary artery aneurysm: A case report and review of the literature. *Ital Heart J* 2001;2(9): 711–714
15. Baman TS, Cole JH, Devireddy CM, Sperling LS: Risk factors and outcomes in patients with coronary artery aneurysms. *Am J Cardiol* 2004;93: 1549–1551
16. Turhan H, Erbay AR, Yasar AS, Aksoy Y, Bicer A, Yetkin G, Yetkin E: Plasma soluble adhesion molecules; intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and E-selectin levels in patients with isolated coronary artery ectasia. *Coron Artery Dis* 2005;16(1):45–50
17. Kikuta H, Sakiyama Y, Matsumoto S, Hamada I, Yazaki M, Iwaki T, Nakano M: Detection of Epstein-Barr virus DNA in cardiac and aortic tissues from chronic, active Epstein-Barr virus infection associated with Kawasaki disease-like coronary artery aneurysms. *J Pediatr* 1993;123(1):90–92
18. Tengiz I, Ercan E, Aliyev E, Sekuri C, Duman C, Altuglu I: Elevated levels of matrix metalloprotein-3 in patients with coronary aneurysm: A case control study. *Curr Control Trials Cardiovasc Med* 2004;5(1):doi:10.1186/1468-6708-5-10
19. Akdemir R, Ozhan H, Gunduz H, Erbilen E, Yazici M, Duran S, Orkunoglu F, Albayrak S, Imirzalioglu N, Uyan C: HLA-DR B1 and DQ B1 polymor-

phisms in patients with coronary artery ectasia. *Acta Cardiol* 2004;59(5): 499–502
20. Gulec S, Aras O, Atmaca Y, Akyurek O, Hanson NQ, Sayin T, Tsai MY, Akar N, Oral D: Deletion polymorphism of the angiotensin I converting enzyme gene is a potent risk factor for coronary artery ectasia. *Heart* 2003; 89(2):213–214
21. Sorrell VL, Davis MJ, Bove AA: Origins of coronary artery ectasia. *Lancet* 1996;347(8995):136–137
22. Dogan A, Ozaydin M, Gedikli O, Altinbas A, Ergene O: Effect of trimetazidine on exercise performance in patients with coronary artery ectasia. *Jpn Heart J* 2003;44(4):463–470
23. Desai MY, Biederman RW, Mankad S: Incidental echocardiographic detection of coronary artery aneurysm in a patient with multiple vascular aneurysms. *Echocardiography* 2004;21(3):265–267
24. Akyurek O, Berkalp B, Sayin T, Kumbasar D, Kervancioglu C, Oral D: Altered coronary flow properties in diffuse coronary artery ectasia. *Am Heart J* 2003;145(1):66–72
25. Tanabe M, Onishi K, Hiraoka N, Kitamura T, Okinaka T, Ito M, Isaka N, Nakano T: Bilateral giant coronary aneurysms diagnosed non-invasively by dynamic magnetic resonance imaging. *Int J Cardiol* 2004;94(2-3):341–342
26. Sarkar DA, Smith EE, Brecker SJ: Giant coronary aneurysms. *Lancet* 2004;363(9402):37
27. Rubartelli P, Terzi G, Borgo L, Giachero C: Coronary artery aneurysm after stent implantation: Acute and long-term results after percutaneous treatment with a stent graft. *Ital Heart J* 2002;3(3):202–205
28. Oe H, Ehara S, Yoshikawa J: Crab claw-like appearance on coronary angiography. *Heart* 2005;91(4):437
29. Androulakis AE, Katsaros AA, Kartalis AN, Stougiannos PN, Andrikopoulos GK, Triantafyllidi EI, Pantazis AA, Stefanadis CI, Kallikazaros IE: Varicose veins are common in patients with coronary artery ectasia. Just a coincidence or a systemic deficit of the vascular wall? *Eur J Vasc Endovasc Surg* 2004;27(5):519–524
30. Yetkin E, Kilic S, Acikgoz N, Ergin H, Aksoy Y, Sincer I, Akturk E, Beytur A, Sivri N, Turhan H: Increased prevalence of varicocele in patients with coronary artery ectasia. *Coron Artery Dis* 2005;16(5):261–264
31. Turhan H, Erbay AR, Yasar AS, Balci M, Bicer A, Yetkin E: Comparison of C-reactive protein levels in patients with coronary artery ectasia versus patients with obstructive coronary artery disease. *Am J Cardiol* 2004;94 (10):1303–1306
32. Tokgozoglu L, Ergene O, Kinay O, Nazli C, Hascelik G, Hoscan Y: Plasma interleukin-6 levels are increased in coronary artery ectasia. *Acta Cardiol* 2004;59(5):515–519
33. Kobayashi T, Sone K: Effect of dipyridamole on the blood flow in coronary aneurysms resulting from Kawasaki disease. *Pediatr Cardiol* 1994;15(6): 263–267
34. Erol MK, Bozkurt E, Arslan S: Percutaneous sealing of coronary aneurysm by grafted stent implantation. *Heart* 2004;90(11):1309
35. Wilson N, Heaton P, Calder L, Nicholson R, Stables S, Gavin R: Kawasaki disease with severe cardiac sequelae: Lessons from recent New Zealand experience. *J Paediatr Child Health* 2004;40(9-10):524–529