Chapter 16
Aortic Coarctation

Allard T. van den Hoven and Jolien W. Roos-Hesselink

Abstract In this chapter the anatomy, epidemiology, pathogenesis, clinical aspects, and genetic associations of aortic coarctation will be discussed. Depending on the balance between the degree of flow disturbance and the compensatory mechanisms available to overcome it, the clinical presentation may vary from the critically ill neonate in heart failure to the asymptomatic child or adult with hypertension. Untreated coarctation carries a poor prognosis with average survival age of 35 years in historic cohorts.

Imaging is essential to diagnose coarctation of the aorta in time and to follow up the patient after treatment. We discuss the indication for treatment and the various treatment options and the advantages and disadvantages of percutaneous and surgical intervention. Lifelong surveillance is warranted, also after successful operative or interventional treatment, since patients remain at risk, particularly for hypertension, recoarctation, and aneurysm formation.

In the last section, we describe the myriad of syndromes that include aortic coarctation in their cardiovascular phenotype. It is important to see aortic coarctation as part of a more generalized aortopathy instead of a stand-alone defect.

Keywords Aortic coarctation • Aortic aneurysm

16.1 Background/Introduction

Aortic coarctation, a congenital stenosis usually located in juxta-ductal position [1–3], has been recognized since its first description in 1760 by Morgagni during his autopsy of a monk [4]. It was more formally recognized as a clinical entity after its description in 1928 [5]; the first surgical correction was performed in 1945 [6]. Nowadays it is generally accepted to be part of a general aortopathy, linked with other left-sided heart defects such as a bicuspid aortic valve (BAV) [7]. The coarctation can vary in severity from quite discrete to a severe long hypoplastic

A.T. van den Hoven • J.W. Roos-Hesselink (✉)
Department of Cardiology, Erasmus University Medical Center, Room Ba-583a,
P.O. Box 2040, 3000 Rotterdam, CA, The Netherlands
e-mail: j.roos@erasmusmc.nl

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aortic segment. The incidence of CoA is approximately 4 per 10,000 live births and constitutes 5–8 % of all congenital heart disease (CHD) [8]. Nowadays, aortic coarctation is preferably repaired surgically at an early age, but catheter intervention has become a valid alternative, especially in outgrown children and adults. Lifelong surveillance is warranted, also after successful repair, since patients remain at risk, particularly for hypertension, recoarctation, and aneurysm formation [9–11]. According to historic studies, when left untreated, most patients die before the age of 50 mainly due to coronary artery disease, stroke, or intracranial hemorrhage. Nowadays, 72 % of patients are alive 30 years after operation [10]. Even in patients with satisfactory repair, major complications do occur.

16.2 Anatomy, Epidemiology, and Pathogenesis

16.2.1 Anatomy

Aortic coarctation is defined as a narrowing of the aortic isthmus, often juxta-ductal in position. Three main types can be distinguished depending on the anatomical position of the infolding of the aortic wall relative to the ductus arteriosus (DA): pre-ductal, post-ductal, or at the site of the ductus [Fig. 16.1]. In 90 % of cases, the infolding is directly opposite to the DA. The pre-ductal or infant type is a cyanotic and duct-dependent lesion. After birth the closure of the DA will result in hypoperfusion of the lower extremities. Also, coarctation has been described in anecdotal cases to present in the abdominal aorta, which is however more likely to be inflammatory or autoimmune in origin. Aortic coarctation can even be traumatic when aortic dissection compromises the true lumen of the aorta.

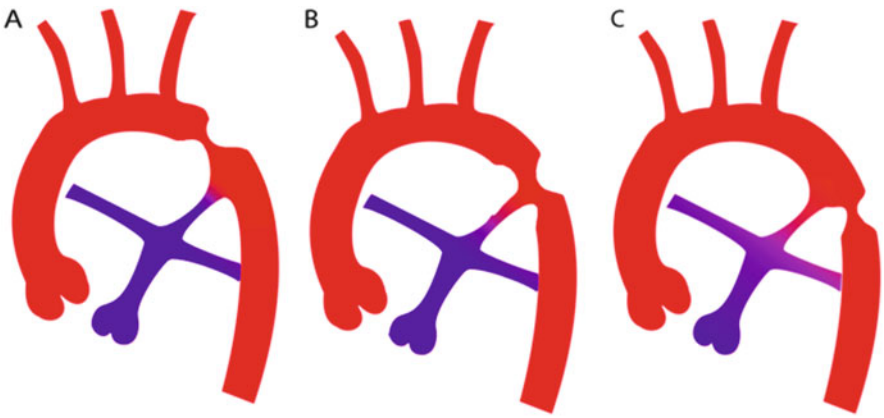

Fig. 16.1 Schematic depiction of the three possible locations of the infolding relative to the patent ductus arteriosus (PDA). (**a**) Pre-ductal coarctation. (**b**) Para-ductal coarctation. (**c**) Post-ductal coarctation

16.2.2 Epidemiology

Aortic coarctation is a relatively frequent congenital heart defect (CHD) and is found in approximately 3–4 per 10,000 live births and constitutes 5 % of all CHD [8]. It occurs more often in males than in females in a ratio between 1.27 and 1.74 and 1 [12, 13]. In most patients it is diagnosed shortly after birth, depending on the subtype and clinical symptoms.

16.2.3 Etiology

There are three possible theories explaining the development of coarctation. There is the ductal tissue theory, which suggests that ductal muscular tissue extends into the wall of the thoracic aorta, causing the aorta to constrict postnatally simultaneous with the ductus arteriosus. Several studies have confirmed the presence of ductal tissue in the aortic wall [14, 15].

Another theory is the developmental theory, which suggests coarctation formation starts with a fault in early fetal development. A part of the fetal circulation involutes to form the separate dorsal aorta and right subclavian artery. A small segment of the fetal dorsal aorta will erroneously involute and will subsequently move cranially with the left subclavian artery [16]. This would then form the coarctation.

The third theory is based on hemodynamical changes. During fetal development the aortic isthmus is a naturally occurring narrow segment because it doesn't have to conduct a large flow of blood. This segment will then later be widened to facilitate the increased blood flow. If the increase in blood flow remains absent, this narrow area will persist and a coarctation will be formed. This could also partly explain the association with BAV, as a diminished forward flow and increased postductal flow can predispose to development of CoA as well.

The etiology of CoA remains enigmatic, but it is generally assumed that coarctation is in fact part of a general aortopathy, linked with bicuspid aortic valve, aortic dissection, and even intracranial aneurysms [7]. More research is clearly needed to discern cause and effect.

16.2.4 Histology

Comparatively little attention has been directed to the prevalence, range, or degree of histological changes in the aortic wall (arterial media) of patients with CoA.

Small studies have compared pre- and post-stenotic tissue to assess the histological abnormalities and tried to account for the influence of blood pressure. There is evidence to support an inherent vessel wall weakness that occurs separately from hemodynamical changes [17]. The underlying cause of these histological abnormalities is most probably so-called cystic media necrosis [18]. More research has been conducted on the aortic vessel wall in BAV, which often coincides with CoA as discussed below. In BAV too aortic wall changes seem to take place at least partly independent from hemodynamics [19]. BAV patients have structural changes of the aortic media such as thinner elastic lamellae and greater distance between the lamellae [20]. Apoptosis of smooth muscle cells might contribute to weakness of the wall which might explain the high cardiovascular morbidity in BAV patients [21]. As BAV and CoA are two related abnormalities with both origins in the neural crest cells, they seem to be part of a broader aortopathy.

16.3 Clinical Picture

16.3.1 Pathophysiology

The main pathophysiological mechanism by which aortic coarctation causes morbidity and mortality is the afterload increase of the left ventricle (LV). This occurs when the arterial duct closes postnatally and starts a causal chain in which increased left ventricular pressures lead to compensatory hypertrophy and eventually (diastolic) dysfunction. When the coarctation is severe enough, this can be an acute process, leading to hypoperfusion distal to the coarctation, presenting in neonates with signs of shock, but also to a "backward failure," where the rapid increase in LV systolic afterload, increased wall stress, and compensatory left ventricular hypertrophy may cause increased pulmonary venous pressures with pulmonary congestion, followed by elevated pulmonary arterial pressures, right ventricular pressure overload, and subsequently heart failure. The foramen ovale might be opened by the sudden increase in pressure causing left to right shunting of blood.

In less pronounced cases, this process will be less rapid, and collaterals can develop, bypassing the coarcted segment and delaying the onset of clinical signs.

In addition to ductal tissue in the aortic wall, other histological wall changes are present in CoA patients. Wall stiffness is increased and distensibility is decreased [22]. There is more collagen but less smooth muscle tissue in the prestenotic aortic wall when compared to post-stenotic aortic wall. Cystic medial necrosis, the depletion or disarray of elastic tissue, is also seen.

The effects of coarctation are not yet fully explained, as patients with a relieved coarctation often still suffer from hypertension, requiring pharmacological treatment. No clear association could be established between the remaining gradient over the CoA and the occurrence of hypertension. Therefore, the involvement of the

renin-angiotensin-aldosterone system is supposed, although also other mechanisms, such as baroreceptor resetting, may be involved.

16.3.2 Complications

The natural history has been described in coarctation patients before correction became imperative. These patients often suffer from left heart failure, intracranial hemorrhage, infective endocarditis, aortic dissection and rupture, and coronary artery and cerebrovascular disease [2, 10]. Nowadays, after intervention the most common complications are hypertension, recurrent coarctation, aortic aneurysm or rupture, early coronary artery disease, and cardiomyopathy. When the coarctation is relieved at a very early age, the risk of recoarctation increases, while repair at older age is associated with hypertension. Risk for complications increases with age, and BAV is an independent additional risk factor for complications as is age [23]. BAV itself is associated with ascending aortic dilatation and higher risk of aortic dissection and rupture, which possibly explains the increased risk when present in addition to CoA. Intracranial berry aneurysms are reported in patients with coarctation. It is however unclear if there is a common pathophysiological ground to this association and whether it is due to secondary modifiable risk factors, such as blood pressure.

16.3.3 Diagnosis

The clinical presentation of CoA varies greatly with age. When CoA becomes evident shortly after birth, it presents as a severe cyanotic heart defect, with poor feeding, tachypnea, lethargy, symptoms of congestive heart failure, or shock. The onset of symptoms will coincide with closure of the ductus arteriosus. When CoA presents later, during childhood or even in adulthood, the clinical symptoms will mainly be due to high blood pressure in the upper extremities and may include nosebleeds, intracranial hemorrhage, dizziness, tinnitus, and shortness of breath. Also symptoms from low blood pressure in the lower extremities may become evident including abdominal angina, claudication, leg cramps, exertional leg fatigue, and cold feet [24]. A blood pressure gradient can often be seen as a high upper body systolic hypertension, in combination with a relative lower body hypotension. However, when large collaterals exist, this may be absent.

There are different diagnostic techniques used to objectify the presence and severity of CoA.

Inspection and *patient history* might reveal some of the symptoms mentioned above. A telltale sign would be differential cyanosis, where the upper extremities are normally perfused and the lower extremities are hypoperfused.

On *palpitation* a weak or absent femoral pulse may be noted, which may have a prognostic value, especially in combination with a prominent brachial pulse [25]. Radio-femoral pulse delay and palpable collaterals on palpation are both pathognomonic for CoA. Of note is that an origin of the right subclavian artery distal to the coarctation might mask this difference, as it would also be decreased and therefore the carotid pulse should be palpated as well. In addition ventricular dysfunction may decrease pulses both in the upper and lower extremities which may have effect on the gradient.

A suprasternal thrill may be palpable, and, in isolated CoA, a vascular murmur (often systolic) at the back or a continuous vascular murmur can be heard.

An *electrocardiogram* may reveal signs of left ventricular hypertrophy with or without secondary ST-segment abnormalities.

On *chest X-ray* rib notching as a result of dilated intercostal arteries, a dilated ascending aorta, kinking or double contouring in the descending aorta, and a dilated left subclavian artery can be found. Also cardiomegaly in the infant can be a sign of a coarctation.

Echocardiography is of great value in estimating site, structure, and severity of the CoA. Especially in newborns this technique gives excellent opportunities as the entire aortic arch, isthmus, arterial duct, and descending aorta are imaged from the suprasternal notch and from the right and left infraclavicular windows. It can also provide information on the function and severity of left ventricular hypertrophy as well as associated cardiac abnormalities and vessel diameters. In adolescents and adults, echocardiography of the isthmus and descending aorta may become difficult as the distance from the transducer increases and the airways may form a more prominent barrier. High systolic velocities are generally found, but a diastolic runoff phenomenon in the descending or abdominal aorta is presumably the most reliable sign of significant coarctation. Doppler flow tracing can show a "serrated" pattern with a rapid acceleration and a high-velocity systolic peak, followed by a gradual deceleration throughout diastole [Fig. 16.2].

CMR and CCT are the preferred noninvasive imaging techniques because these allow assessment of the entire aorta. It allows for the precise location and collateral anatomy to be imaged. In addition, the diameter of the ascending aorta, in case of a bicuspid valve, and the presence of aneurysms can be detected. 3D (or even 4D) reconstructions can provide insightful visual aid to the surgeon when planning reconstruction [Fig. 16.3].

Angiography. Also cardiac catheterization and manometry or angiography are important diagnostic modalities. Especially when the severity of the coarctation and gradient are not clear, the invasive measurement will be helpful in deciding on the indication for treatment.

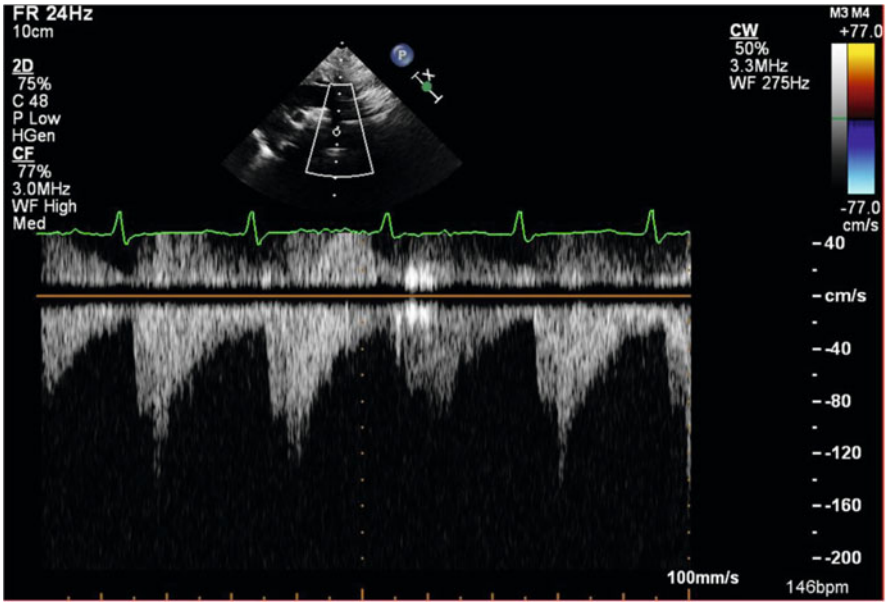

Fig. 16.2 Serrated diastolic runoff pattern in the aorta

16.3.4 Treatment

In case of severe coarctation, there is clear evidence that treatment of CoA will reduce left ventricular afterload and will improve the long-term outcome of the patient. There are however different treatment options with pros and cons for all techniques, and there is no clear superior technique.

16.3.4.1 Indication for Intervention

The decision to intervene should preferably be taken in a multidisciplinary setting where careful evaluation on the level of the individual patient is possible. According to the most recent guidelines, a pressure gradient between the upper and lower body extremities of >20 mmHg in combination with an upper body hypertension (>140/90 mmHg in adults), an abnormal blood pressure response during exercise, and a significant left ventricular hypertrophy are class I, level C indications for intervention [24]. When there is hypertension in combination with a 50 % narrowing of the aorta compared to the aortic diameter at the level of the diagram as measured on CT, MR, or invasive angiography, an intervention should be considered (class IIa, level C). And finally, in case of an anatomical narrowing (>50 %) in the absence of hypertension or a significant pressure gradient, an

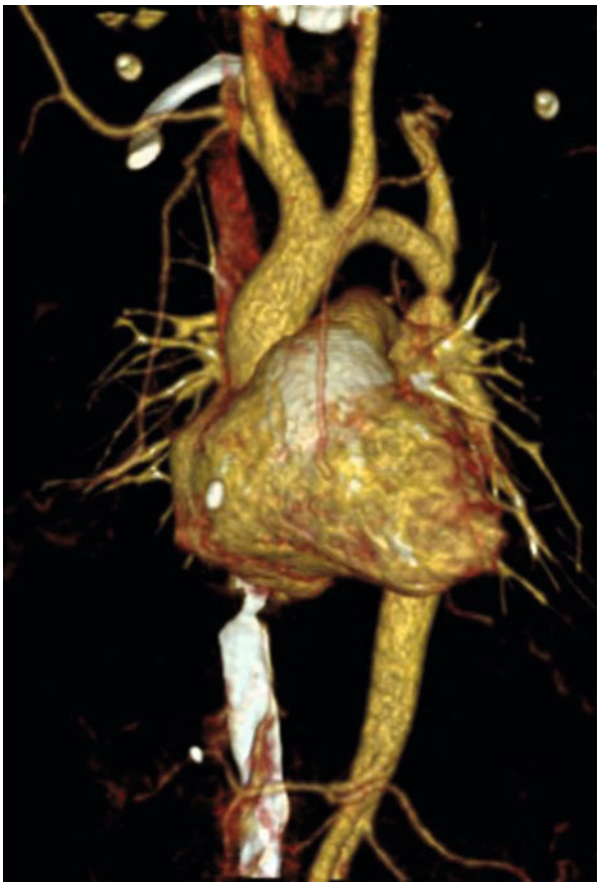

Fig. 16.3 3D reconstruction (CT) of aortic coarctation in a 6-month-old child. Very prominent *A. anonyma* and late branching a. subclavia sinistra

intervention may be considered (class IIb, level C). After intervention, endocarditis prophylaxis is advised for 6 months.

16.3.4.2 Choice of Intervention

There are two main therapies for the relief of CoA: surgical and percutaneous intervention. Surgery is the preferred treatment of infants with coarctation with an overall survival rate of 98 % at a median follow-up of 4.8 years of age. When considering surgery, there are several operative techniques to choose from: (extended) end-to-end anastomosis, patch aortoplasty, subclavian flap aortoplasty and resection with interposition of a graft, or others. All techniques have different advantages and disadvantages. With Dacron patch angioplasty, for example, there is a higher incidence of aneurysm formation, while in subclavian flap aortoplasty, a higher incidence of recoarctation has been found. The incidence of dissection is approximately equal among all modalities [26]. The (extended) end-to-end

anastomosis is the most widely used technique and generally regarded as the safest and most effective method. However, this technique is not feasible in every situation.

The other option for gradient relief, percutaneous intervention, is used more often in full-grown children and adults. Catheter intervention is a safe and effective alternative to surgery, with good gradient relief for both native and recurrent coarctation. A balloon is used to disrupt the intimal and medial layers of the narrowed segment. Compared to surgery, balloon angioplasty is equally effective in reducing pressure gradient early after intervention; however, the risks of recoarctation and aneurysm formation are greater [27]. Generally a covered stent is deployed to prevent recoarctation and aneurysm formation. Stent placement after balloon angioplasty or surgery reduces the complications, improves luminal diameter, results in minimal residual gradient, and sustains hemodynamic benefit. Stent placement is not generally recommended in patients less than 25 kg due to the small aortic size and the potential injury to the femoral artery from the large sheath required for stent delivery. There is however little evidence regarding the long-term outcome of the effectiveness of the blood pressure reduction and late complications after stenting. No randomized trials have compared stenting to surgery [28], and it is therefore hard to objectively compare the two modalities.

16.3.4.3 Conservative Treatment

The acute medical treatment of CoA in the neonate is focused on maintaining patency of the ductus arteriosus. This is mainly done by administering a prostaglandin E1 inhibitor and diuretics can be given to alleviate symptoms of heart failure. In the adult patient, treatment is mainly focused on blood pressure control. This is normally achieved using beta-blockers, ACE inhibitors, and angiotensin-receptor blockers [29]. The use of ACE inhibitors has been associated with renal failure, especially when renal perfusion cannot be sustained [30].

In case of a less severe coarctation or increased intervention risk, the choice between intervention and conservative treatment is especially important. For example, in patients with Turner syndrome, more complications may be encountered after intervention than in the normal population, and the balance may shift toward a more conservative approach.

16.3.4.4 Long-Term Outcome

Patients with CoA historically have a reduced long-term survival, mainly influenced by early interventional and late hypertensive complications. Until the 1980s patients still only had an average life expectancy of 38 years [10], and patients often died before the age of 50 due to cardiovascular causes. Nowadays patients, who have been operated successfully, using the most recent techniques, have a good medium- to long-term survival with actuarial survival of 98 % at

40, 98 % at 50, and 89 % at 60 years of age [31]. Still atherosclerotic cardiovascular disease and cerebrovascular events contribute significantly to late morbidity and mortality. An important risk factor is late repair which is associated with hypertension, but even patients with repair at young age have a 30 % 10-year prevalence of hypertension [32]. Vigilant blood pressure control is therefore indicated, also in patients with good results after repair. Recoarctation requiring reintervention and descending aortic aneurysms occur in 34 % and 18 %, respectively. The lowest occurrence is found in patients treated with an end-to-end repair [31]. Higher rates of recoarctation tend to occur in smaller patient size, in younger age at repair, and in the presence of associated transverse arch hypoplasia. Indications for reintervention are similar to those for native coarctation. Aneurysms of the ascending aorta or in the region of the aortic isthmus are the most dangerous complications because they carry the risk of life-threatening rupture. Bicuspid aortic valve, aortic wall changes, and systemic hypertension may together be responsible for aneurysmal formation of the ascending aorta. Because the incidence of aneurysm formation after surgery or balloon angioplasty appears to increase with longer follow-up periods, all patients need careful periodic surveillance. Generally, aortic aneurysms are treated surgically. Alternatively, endovascular stent grafts have been used to repair aortic aneurysms successfully without major complications.

16.3.4.5 Pregnancy

Cardiac output increases by almost 50 % during pregnancy and rises even further during labor. There are cases of aortic dissection described during pregnancy in women with CoA [33, 34], but in general pregnancy is well tolerated. There might be a mildly elevated risk of miscarriage. Some studies show an increased rate of miscarriage [35], where others show a risk that is comparable to the general population [33]. Hypertensive disorders are more frequently found. In the normal population, these hypertensive disorders of pregnancy occur in approximately 8 % of all pregnancies, whereas in CoA patients, hypertension and (pre)eclampsia probabilities are estimated in some studies to be 0.183 (SE 0.285) and 0.061 (SE 0.211), respectively [35]. Women with CoA are in principal advised to deliver vaginally [36].

16.3.4.6 Quality of Life

No specific research on the psychological function of CoA patients has been published so far, but there are studies on other types of CHD. These studies show that although patients score significantly better on most scales of subjective health being compared to normative data [37, 38], patients do show signs of reduced sexual functioning. Sexuality has received not so much attention by physicians despite a clear need for information by patients. In addition, not much information is available on sports participation in these patients. Patients often grow up in a

protective environment where sports participation is discouraged, while even for complex CHD patients, participating in sports can have a positive influence on exercise capacity and subjective physical function without a clear increased risk of sudden death or cardiac arrhythmias. Topics such as contraceptives, sexuality, pregnancy, and sports participation need more attention from medical specialists and caregivers.

16.4 Associations

In this paragraph we will discuss a number of syndromes and other congenital cardiovascular defects that are seen in combination with CoA.

There is no known single causal genetic defect for CoA, but it often occurs together with several other left-sided defects such as BAV. It is seldom associated with right-sided defects. There is a myriad of genetic syndromes which are known to have a relatively frequent occurrence of CoA and genetic abnormalities occur in 6.2 % of patients with a CoA. They have however different genetic origins and therefore a single genetic cause for CoA is improbable. Almost all syndromes described below have a frequent occurrence of several congenital heart defects and therefore it seems plausible that there is a common developmental pathway. A patent arterial duct is found in almost half (43 %) of CoA patients, and also septal defects are very common (39 % ventricular defects, 20 % atrial septal defects, and 4.4 % atrioventricular septal defects). We will discuss the aortic valve separately, but also the mitral, tricuspid, and pulmonary valves are found to be abnormal in, respectively, 4.9 %, 2.4 %, and 1 % of CoA patients.

16.4.1 Bicuspid Aortic Valve

The aortic valve is normally made up of three cusps; however, in 1–2 % of the general population, abnormal cusp formation during valvulogenesis leads adjacent cusps to fail to segregate and form one single cusp. BAV can cause significant morbidity as the valve is prone to leakage or stenosis and is often accompanied by ascending aortic dilatation. Histopathological changes of the aortic media such as loss of smooth muscle and medial layer elastic fibers can be seen in the ascending aorta of BAV patients, and it has been argued that BAV and CoA are part of the same aortopathy. BAV is, as CoA, more often seen in males than in females (2:1, male/female). In 50–75% of the patients with a coarctation, also BAV is present [39]. The prevalence of CoA in BAV patients is less well studied but is approximately 7 % [40]. Aortic dilatation seems more severe in patients with both BAV and CoA than in patients with an isolated CoA [41]. The dilatation varies from patient to patient, and clear associations with age and hypertension could not be proven. A current parameter in BAV research is the cusp anatomy; different valve

types are discerned [42], based on their morphological cusp phenotype, of which the type with fusion of the left and right coronary cusp is associated with CoA [7].

16.4.2 Hypoplastic Left Heart Syndrome

Hypoplastic left heart syndrome (HLHS) occurs in 0.016–0.036 % of live births and occurs more often in males [43]. It is the clinical presentation in 11 % of CoA patients. It entails severe left-sided outflow obstruction due to an abnormal development of the left-sided cardiac structures, a predominant underdevelopment of the left ventricle and aorta, and sometimes also mitral atresia or stenosis. The degree of left ventricular outflow obstruction can vary from patient to patient [43], and the right heart may also be enlarged and hypertrophic. Coarctation of the aorta in juxta position is commonly present [44–46]. HLHS is a duct-dependent lesion, and it needs a series of univentricular surgical palliations to correct the situation or heart transplantation may be considered. The coarctation of patients with HLHS is histologically similar to isolated coarctation as ductal tissue has been found at the coarctation site [47].

16.4.3 Taussig-Bing Anomaly and Transposition Complexes

In 1949 Helen Taussig and Richard Bing described the first case of what is now known as the Taussig-Bing anomaly (TBA), an uncommon form of double outlet right ventricle (DORV) in which both the aorta and pulmonary artery arise from the right ventricle [48]. The pulmonary artery overrides a subpulmonary ventricular defect. It is associated with additional aortic arch obstruction in 39–52 % of patients, substantially complicating the surgical management [49, 50]. Approximately 6.7 % of coarctation patients have this anomaly. Also a complete transposition of the great arteries and transposition complexes are found to be associated with an aortic obstruction at subaortic level or in the aortic arch [51, 52].

16.4.4 Kabuki Syndrome

This syndrome with an estimated prevalence of 1 in 32,000 received its name from the supposed resemblance of its typical facial features to makeup worn by the artists in a traditional Japanese dance drama called “Kabuki.” In Kabuki syndrome, 69–91 % of patients have a congenital heart defect; most of these lesions are left-sided obstructions of which 29 % an aortic coarctation [53, 54]. It is caused by a mutation of two genes located on the short arm (or p-arm) of the X chromosome KMT2D or KDM6A (or MLL2) and inherits in an autosomal dominant fashion. In a

study describing the KMDA6A knocked-down zebrafish, prominent defects in heart development were found [55].

16.4.5 Shone's Syndrome

Shone's complex or Shone's syndrome, first described in eight cases in 1963, includes a supravalvular mitral valve membrane, a "parachute mitral valve," a subaortic stenosis, and a coarctation of the aorta (CoA) [56]. In addition BAV was also present in 30–83 % of these patients [56–58]. CoA is seen in approximately 96 % of patients; however, only 63 % patients exhibit all four symptoms. It is managed surgically, where the level of involvement of the mitral valve and presence of secondary pulmonary hypertension are the main determinant of clinical outcome in these patients.

16.4.6 Myhre Syndrome

Myhre syndrome is a very rare syndrome (prevalence <1/1.000.000), caused by a heterozygous mutation in the SMAD4 gene on chromosome 18q21 [59]. A study of 32 patients describes congenital heart defects in 17 patients, including patent ductus arteriosus, aortic coarctation (12.5 %), mild-to-moderate valvular aortic stenosis (12.5 %), and membranous ventricular septal defect (3.3 %).

16.4.7 Williams-Beuren Syndrome

Williams-Beuren syndrome is caused by a deletion on chromosome 7q11.23 and occurs in approximately 1 in 10,000 live births [60]. One of the deleted genes is the ELN gene which codes for the protein elastin [61]. The syndrome was first described by Williams et al. in 1961 in four patients and then in the following year also by Beuren et al. in an additional five patients. Congenital cardiovascular defects occur in about 80 % of all patients where some form of arterial stenosis is the predominant form occurring in 40–75 % of patients [62]. It differs however from the typical juxta-ductal CoA in that its preferred location is at the sinotubular junction (supravalvular aortic stenosis) and is also often seen as an elongated hypoplastic segment [61], of which the first is the most common, occurring in approximately 75 % of the children.

16.4.8 Noonan Syndrome

Noonan syndrome (NS) occurs in approximately 1/1000 to 1/2000 live births [63], and it is one of the most common syndromic causes of congenital heart disease second only to Down syndrome [64]. It inherited in an autosomal dominant manner, although many individuals have a de novo mutation. Mutations recognized to cause the syndrome include mutations in the *PTPN11*, *SOS1*, *RAF1*, *KRAS*, *NRAS*, and *BRAF* genes. The congenital heart disease occurs in between 50 and 80 % of patients, with pulmonary valve stenosis and hypertrophic cardiomyopathy being the most common (50–60 % and 20 % of patients, respectively). However, other structural defects such as atrial septal defect, patent ductus arteriosus, and tetralogy of Fallot have also been described [64]. The left-sided outflow obstructions can occur at the valvular or supravalvular level or as classic aortic coarctation [65, 66]. CoA itself is seen in approximately 8.8 % of patients [65] and is more often seen in patients with a PTPN11 mutation [64].

16.4.9 Alagille Syndrome

Alagille syndrome (AGS) is a multisystem disorder affecting the liver, heart, eyes, face, skeleton, and other systems occurring in 1 in 70,000 newborns. Up to 70 % of patients have a mutation in the Jagged1 gene, which fulfills a function in the Notch signaling pathway. The remaining 30 % is probably also caused by a mutation in this large gene, but not yet found due to testing limitations [67]. The cardiovascular defects are predominantly of the pulmonary arteries (67 %) [68]. In a study describing 268 individuals with AGS, aortic coarctation was only found in three cases (1.1 %), still substantially higher than in the normal population.

16.4.10 The 22q11.2 Deletion Syndrome

The 22q11.2 deletion syndrome is the most common microdeletion syndrome and is known for its wide variety of signs and symptoms. It has been described under many different names of which some well-known include the Shprintzen syndrome, the DiGeorge syndrome, and the velo-cardiofacial anomaly. Its incidence is approximately 1 in 3000 persons and 75 % of patients have a form of CHD. A common 3 Mb hemizygous deletion of 22q11.2 is detected in the majority of patients. Smaller deletions within this 3 Mb region together with rare deletions outside of the region account for the other 30 % [69]. This syndrome occurs in 0.9 % of patients with a CoA. Other CHDs are tetralogy of Fallot, pulmonary stenosis, pulmonary stenosis, and septal defects.

16.4.11 Turner Syndrome

Of the aforementioned syndromes, Turner syndrome (TS) is probably the most well-known, with a prevalence of approximately 1 in 2500 live-born girls [70]. It has a broad variety of features, among which short stature, infertility, and a webbed neck. Aortic pathology is seen quite frequently in TS. Aortic dilatation and especially aortic dissection are seen more often, probably associated with BAV and CoA [1, 70]. In up to 17 % of patients, a CoA is found. The presence of CoA in TS patients is often associated with BAV (RR, 4.6) [71, 72]. More recently Ho et al. found that in 50 % of Turner patients, aortic coarctation appeared to be associated with an elongated transverse aortic arch [1]. Supposedly other abnormalities such as an aberrant right subclavian artery (8 %) and common origin of the innominate and left carotid artery (8 %) belong to the same cardiovascular phenotype [70].

16.4.12 Miscellaneous

In addition to the syndromes and associations mentioned above, there are other associations with CoA; congenital rubella syndromes are known to cause cardiac and cardiovascular disease especially pulmonary artery stenosis and patent ductus arteriosus in 50 % of patients [73]. But also aortic coarctation has been reported in these children.

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