Congenital Heart Disease Classification, Epidemiology, Diagnosis, Treatment, and Outcome

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Abstract

Congenital heart disease (CHD) is a problem in the structure of the heart that is present at birth. CHD is still the most common inborn defect with an approximate prevalence at birth of 5–11 per 1000 live births and incidence of 1%. The aim of this chapter is to give both a general overview on CHD and to address just a few specific issues for each type of structural disease. Congenital cardiac malformations may be classified in different ways; to highlight the underlying anatomy and pathophysiology, the diseases could be grouped as follows: (a) CHD with shunt between systemic and pulmonary circulation, (b) left heart CHD, (c) right heart CHD, (d) CHD with anomalous origin of great arteries, and (e) miscellanea.

1.1 Introduction

Congenital heart disease (CHD) is still the most common inborn defect with an approximate prevalence at birth of 5–11 per 1000 live births and incidence of 1% [1]. By definition, CHD means a disease that has been present since birth but not necessary "clinically" evident since birth: this is the case, for example, of moderate size atrial septal defect of unobstructive subaortic stenosis.

Taking into account the pathophysiology and diagnosis of CHD, it is helpful to highlight three key points: (1) the presence of shunt between arterial and venous blood, (2) the presence of cyanosis, and (3) the changes in circulation after birth [2]. A shunt consists of an abnormal communication between two cardiac chambers or vessels allowing blood to go from one side to the other. Shunting may be described

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as left-to-right, right-to-left, or bidirectional. The direction is strictly dependent on pressure gradient across the shunt; most commonly blood goes from high-pressure left-sided heart to low-pressure right-sided heart. Therefore shunt direction affects the status of pulmonary blood flow which can vary from normal, increased, or decreased. Any large left-to-right (L-R) shunt results in increased blood flow into the lungs associated with shortness of breath and prominent vascular markings on chest x-ray, volume overload of left ventricle (LV) associated with chamber dilatation, and subsequently heart failure; if untreated, it will eventually result in pulmonary artery (PA) pressure overload which, by time, will cause irreversible structural arterial wall changes ending up with pulmonary hypertension (PH), with increased pulmonary vascular resistance (PVR), and, later on, in pulmonary vascular obstructive disease (PVOD). High and fixed PVR is the feature of pulmonary vascular obstructive disease. When PVR approaches or even exceeds systemic vascular resistance, direction of the shunting becomes bidirectional or mainly right-to-left (R-L), condition known as Eisenmenger syndrome. Generally, in presence of right-to-left shunt, venous poor-oxygenated blood mixes with arterial high-oxygenated blood, causing cyanosis. Cyanosis is a bluish discoloration of the skin and mucous membranes resulting from presence of 5.0 g/dL or greater of deoxyhemoglobin in the blood.

Presence of shunts is crucial during fetal life when the placenta provides the exchange of gases and nutrients and lungs receive only about 15% of combined ventricular output. Fetal circulation is characterized by four sites of shunting: the placenta, ductus venosus through which umbilical vein drains into inferior vena cava, foramen ovale within the interatrial septum, and the arterial duct through which blood in the PA flows into descending aorta. Just after birth, placental circulation disappears and pulmonary circulation is established. Interruption of the umbilical cord results in an increase in systemic vascular resistance and closure of the ductus venosus. Concomitant lung expansion results in reduction of pulmonary artery pressure and PVR, an increase in pulmonary blood flow, functional closure of the foramen ovale, and closure of patent arterial duct due to increased arterial oxygen saturation.

With lung expansion and the resulting increase of alveolar oxygen tension, an initial significant rapid fall in PVR occurs mainly due to the vasodilating oxygen effect on pulmonary vasculature. Later on, between 4 and 8 weeks after birth, there is another slower fall in the PVR and PA pressure secondary to wall changes in pulmonary arterioles. Many neonatal conditions associated with different forms of CHD, causing inadequate oxygenation, may interfere with the normal pulmonary arteriole maturation, resulting in persistent pulmonary hypertension or delay in usual PVR fall.

Ductus arteriosus usually closes spontaneously within the first 48 h after birth, by constriction of the medial smooth muscle; after this functional closure, an anatomical closure occurs, by 2–3 weeks of age, by permanent changes in the endothelium and subintimal layers. Many factors may interfere with ductal closure such as oxygen, maturity of the newborn, prostaglandin E_2 levels, and acidosis [3].

To achieve a precise diagnosis of CHD, even in very complex cases, along with an accurate physical examination, many both noninvasive and invasive tools are currently available. Transthoracic echocardiography (TTE) is the first-line diagnostic technique in terms of anatomical and functional information in all CHD, whereas cardiac catheterization still constitutes the final definitive diagnostic test for many

of them. Over the last decade, due to the significant improvement of interventional cardiology in dealing with several forms of CHD, a new "multimodality" imaging approach has been promoted aiming at the integration rather than at the selection of the necessary details. 3D echocardiography, cardiac computed tomography (CT), and magnetic resonance (MR) have become of great interest due to their ability to generate both 3D anatomical and hemodynamic functional information.

Effective treatment of all the spectrum of CHD is currently feasible due to the amazing improvement in medical care, catheter-based interventions, and surgical procedures which have dramatically extended survival and life expectancy. Survival through childhood is now common even in the most complex and lethal malformations, such as hypoplastic left heart syndrome. As a consequence of these advances, there have been major demographic shifts, so that adult patients with CHD now outnumber children even with complex forms of CHD [4].

The aim of this chapter is to give both a general overview on CHD and to address just a few specific issues for each type of structural disease. Congenital cardiac malformations may be classified in different ways; to highlight the underlying anatomy and pathophysiology, the diseases could be grouped as follows: (a) CHD with shunt between systemic and pulmonary circulation, (b) left heart CHD, (c) right heart CHD, (d) CHD with anomalous origin of great arteries, and (e) miscellanea.

1.1.1 CHD with Shunt Between Systemic and Pulmonary Circulation

1.1.1.1 Atrial Septal Defect

Atrial septal defect (ASD) is a communication between the atrial chambers permitting left-to-right shunting (Fig. 1.1).

It is the second most common type of CHD, accounting for about 7–10% of all CHD patients, more prevalent in women (2:1), and most likely to be diagnosed in late childhood or adults. There are different types of ASD (Fig. 1.2) [5]:

- Ostium secundum ASD: The most frequent variant of ASD, 70–80% of all ASDs, results from deficiency of the flap valve of the oval fossa, ranging from incomplete development, with failed overlapping to the septum secundum, to the presence of multiple fenestrations to complete absence. Anomalous pulmonary venous return is present in about 10% of cases.
- Ostium primum ASD: Occurs in about 15% of all ASDs and is a part of atrioventricular septal defect; it is placed near the crux.
- Sinus venosus defect: 5–10%, located superiorly and posteriorly, near the entry of superior vena cava (SVC) or inferiorly and posteriorly near the entry of inferior vena cava (IVC), commonly associated with anomalous drainage of right pulmonary veins.
- Coronary sinus ASD: 1%, located in the roof of the coronary sinus which could be partially or completely missing and often associated with left SVC that drains to the left atrium.

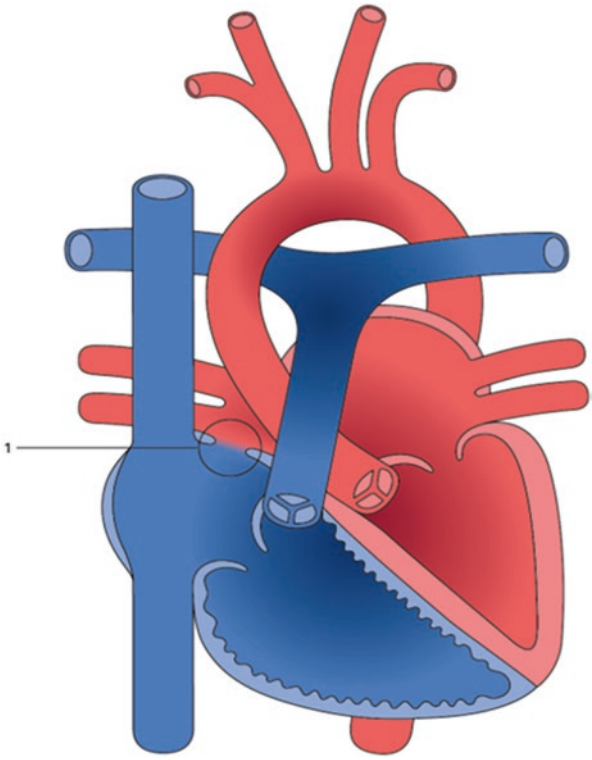

Fig. 1.1 Atrial septal defect (1)

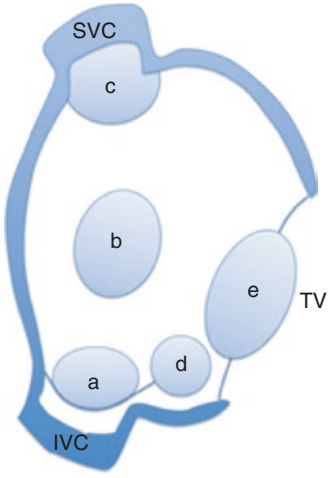

Fig. 1.2 Different types of ASD

a - Inferior sinus venosus defect,
b – ostium secundum ASD,
c – superior sinus venosus defect,
d – coronary sinus defect,
e – ostium primum ASD.
SVC: Superior vena cava.
IVC: Inferior vena cava.
TV: tricuspid valve

The L-R shunt causes volume overload of the right chambers and pulmonary circulation; the entity of shunt is related to defect size, right ventricle (RV) and LV compliance and pressure. Usually volume overload is well tolerated allowing some to go undetected until adulthood; when the shunt is significant, however, with age, symptoms can occur such as exertional dyspnea, pulmonary infections, and atrial arrhythmias [6].

Foramen ovale is an interatrial communication, during fetal life, between septum secundum (limbus of fossa ovalis) and septum primum (the valve of fossa ovalis) which allows venous return from IVC to shunt across to the left atrium. Normally it closes at birth functionally, whereas a complete anatomic closure occurs in 70–75% of adults [7]. Patent foramen ovale (PFO) refers to persistence of this normal communication postnatally; it assumes clinical importance in certain CHD and in patients with cerebral vascular accident due to paradoxical emboli [8].

Diagnosis. From childhood, the classic clinical findings include widely split and fixed second heart sound associated with a low-pitched systolic ejection murmur. TTE is the diagnostic test of choice. In case of PH, diagnostic cardiac catheterization is mandatory to calculate pulmonary vascular resistance and to assess pulmonary circulation vasoreactivity.

Treatment. The presence of hemodynamically significant L-R shunt (a ratio of pulmonary blood flow to systemic blood flow of >1.5:1.0) and/or right chamber volume overload without significant PH represents the indication for ASD closure. Closure can be accomplished by surgery or, in case of secundum ASD and adequate anatomic rims, by device implantation during interventional catheterization [9].

Outcome. Atrial arrhythmias are the most frequent late complication, and the risk increases with advancing age at repair. PH is another late complication affecting survival but is rare in patients operated before 25 years of age, and the risk increases with advancing age at repair as well [10]. If closure is performed in adolescence or childhood, life expectancy returns to normal [11].

1.1.1.2 Ventricular Septal Defect

Ventricular septal defect (VSD) is defined as a communication between the two ventricles (Fig. 1.3). It is the most common CHD, almost 20% of all defects, and may occur in isolation or as a part of a complex cardiac malformation [10]. According to the anatomical position, different types of VSD can be described (Fig. 1.3):

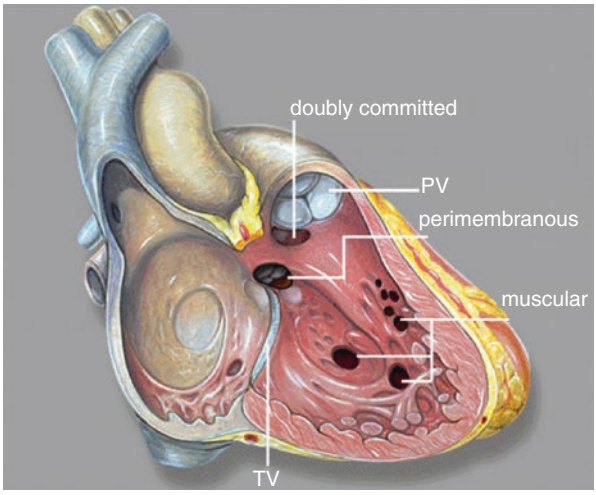

Fig. 1.3 Different types of VSD according to anatomical position within the septum viewed from RV side. *TV* tricuspid valve. *PV* pulmonary valve

- Perimembranous VSD: The most frequent variant, placed within the membranous septum with variable anatomical extension toward the other components of interventricular septum (IVS), inlet, outlet, and apical. It is in close relationship with the septal leaflet of the tricuspid valve (TV) and the his bundle of electrical conduction system. Aneurysm of membranous septum is frequently associated and may result, over time, in partial or complete closure.
- Muscular VSD: About 15–18% of all VSDs, could be placed within any muscular component of IVS, and is surrounded by complete muscular rims. Quite often small defects close spontaneously; rarely the defects can be multiple, the so-called "Swiss-cheese" septum.
- Doubly committed, juxta-arterial VSD: More frequent in Asian countries, it is localized just beneath the arterial valves which are, as a consequence, in fibrous continuity.
- Inlet defect: Located in the inlet component of the septum, immediately inferior to the atrioventricular valve apparatus; typically occurring in down syndrome.

Shunt direction and magnitude are determined by the size of the defect, ventricular systolic and diastolic function, the presence of right ventricular outflow tract obstruction (RVOT), and PVR.

The clinical spectrum of this defect is wide: large L-to-R shunt causes high pulmonary blood flow, LV volume overload presenting with heart failure, and, particularly in infancy and childhood, failure to thrive and repeated respiratory infections. Large VSD with large L-R shunt is associated with PH and, if untreated, ends up in pulmonary vascular disease as in Eisenmenger syndrome. In case of doubly committed VSD, less common perimembranous, there is a risk for prolapse of the right coronary or noncoronary cusp of the aortic valve, resulting in progressing aortic regurgitation [12]. Subaortic discrete obstruction and/or right mid-ventricular discrete stenosis (double-chambered RV) may develop, the latter being the result of a high-velocity VSD jet lesion on RV endothelium. Finally arrhythmias can occur although less frequently than other forms of CHD.

Diagnosis. The classic pansystolic murmur, which is best audible along the left mid to lower sternal border, may not be heard until a few weeks of age when the shunt becomes maximal. Generally, the smaller is the defect, the higher is the murmur intensity. A second sound physiologically split with respiration is indicative of normal pulmonary pressure. In POVD associated with VSD, varying degrees of cyanosis may be noted. On chest x-ray, the degree of cardiomegaly and the increase in pulmonary vascular markings directly relate to the magnitude of the L-R shunt. TTE is mandatory to assess all the characteristics in terms of position, size, number, association with other congenital defects or aortic valve dysfunction, direction of the shunting, relationship with tricuspid valve and its cordal apparatus, the presence of aneurysmal tissue, and the distance between VSD and aortic valve [13]. In some selected cases, a diagnostic cardiac catheterization is needed to calculate PVR and to assess pulmonary circulation vasoreactivity.

Treatment. Spontaneous closure of small, restrictive VSD may occur. Closing moderate to large VSD by open heart surgery is usually performed during infancy to

prevent complications later [14]. Although surgery remains the treatment of choice, with low operative mortality, transcatheter closure has become a valid and alternative procedure to be considered only in selected cases either in children or in adults [15].

Outcome. The long-term prognosis for a patient with a successful surgically repaired VSD is excellent with life expectancy as good as in the general population [16]. Acute and/or late-onset complete atrioventricular block (cAVB) due to conduction system injury remains a crucial issue after surgical or transcatheter closure of perimembranous VSD; the incidence of cAVB, after device closure, requiring permanent pacemaker implantation is 2.6%, and the risk is higher in children aged <6 years [17–19]. The prognosis for patients with Eisenmenger syndrome is the worst among the VSD population.

1.1.1.3 Atrioventricular Septal Defect

Atrioventricular septal defect (AVSD) refers to a spectrum of cardiac malformations characterized by abnormal development of atrioventricular junction which normally derives from endocardial cushion tissue. It is clearly associated with chromosomal abnormalities, mainly trisomy 21, Down syndrome.

The key anatomic feature is the presence of common AV junction guarded by a 5-leaflet common AV valve, associated with deficient septation. Arrangement of common AV valve leaflets differs significantly from the normal tricuspid and mitral valves. Anatomy can vary from:

- Partial AVSD, with an ostium primum ASD and two separate valve orifices and without inlet VSD
- Complete AVSD, with an ostium primum ASD, single valve orifice, and inlet VSD

The predominant hemodynamic consequence of this abnormal anatomy is the presence of intracardiac shunting between either the atriums or the ventricles or from ventricles to atriums. This will result in volume and/or pressure overload of cardiac chambers which may be exacerbated by the regurgitation of one or more components of the common AV valve. The incidence of associated lesions is high, approaching 50% of the cases. Symptoms are usually the result of intracardiac left-to-right shunting and/or regurgitation of AV valve; patients with only an atrial level shunt are rarely symptomatic, whereas signs of congestive heart failure (CHF) as tachypnea, dyspnea, diaphoresis, failure to thrive, and frequent chest infections are typical of significant ventricular level shunt and/or significant AV valve regurgitation.

Diagnosis. Due to the presence of a common AV junction, the AV conduction system is typically displaced posteriorly and inferiorly. On ECG, it results in superior and rightward QRS axis deviation frequently associated with prolonged PR interval and QRS duration.

On chest x-ray, cardiomegaly and increased pulmonary vascular markings reflect significant left-to right intracardiac shunting and/or left AV valve regurgitation; the presence of prominent central pulmonary arteries combined with peripheral “pruning” and right heart enlargement reflects Eisenmenger syndrome.

Comprehensive and sequential 2D and 3D TTE [20] should be focused on all the anatomical details and to rule out unbalanced ventricles, outflow tract obstructions, and associated lesions.

Diagnostic cardiac catheterization is usually reserved for all the cases in whom there is concern about PVR.

Treatment. Medical management with diuretics and ACE inhibitors is usually required for complete AVSD while waiting for surgical repair although the use of afterload reduction with ACE inhibitors is still controversial. In most infants, failure to thrive is an indication for repair which is usually performed within the first 3–6 months. Patients with unrepaired AVSD and Eisenmenger syndrome respond to pulmonary vasodilator therapy after diagnostic catheterization [21].

Outcome. Currently, excellent short-term survival after AVSD repair is the norm.

In the postoperative AVSD patients, the most common causes of late morbidity and mortality and consequently need of reoperation are dysfunction of the left AV valve (mainly regurgitation), subaortic stenosis, residual septal defects, and heart block [22]. Early mortality has been reported at 4% after reoperation during childhood; the highest risk is in those patients requiring left AV valve replacement [23]. Atrial arrhythmias appear to have an earlier age of onset after AVSD repair than in other atrial shunts, likely due to concomitant left AV valve dysfunction [24].

1.1.1.4 Patent Ductus Arteriosus

Patent ductus arteriosus (PDA) is a vascular structure which connects the descending aorta to the roof of pulmonary arterial trunk near the origin of left pulmonary artery. Usually it closes spontaneously within the first 48 h after birth, by constriction of the medial smooth muscle due to the acute increase in oxygen tension and reduction in prostaglandin E_2 and I_2 levels. Subsequently, during the following 2–3 weeks, muscle fibers are replaced by connective tissue resulting in formation of ligamentum arteriosum. If this does not occur, there is a patent ductus arteriosus (PDA). It accounts for 5–10% of all CHD in children, more frequent in females than in males [25]. Considering the anatomy, it can vary significantly in its shape, size, and attachment to the aorta; usually its narrowest part is the pulmonary arterial end. The most common type is a funnel-shaped duct with a localized narrowing at the pulmonary artery junction. PDA results in L-R shunt with potential left heart volume overload and pulmonary artery pressure overload. Clinical features depend on size, length, and age at presentation; especially the size should be correlated to the age and weight of the patient. Small PDA is usually not associated with either symptoms or signs of volume/pressure overload. Moderate and large PDA may present predominantly with left heart failure due to volume overload or right heart failure due to PA and RV pressure overload. Large PDA, if not closed in time, generally develops in Eisenmenger syndrome.

Diagnosis. In case of large PDA, peripheral arterial pulses are bounding with a rapid upstroke; pulse pressure is wide because of rapid runoff of the blood from the systemic circulation to the pulmonary circulation. In a patient with small to moderate PDA, only a systolic murmur may be heard, whereas, in a large shunt, a continuous machinery-type murmur is audible at the upper left sternal edge; the systolic

component sound is a crescendo, and the diastolic component sound is a decrescendo. A normal ECG or left ventricular hypertrophy (LVH) is seen with small to moderate PDA. Biventricular hypertrophy is seen with large PDA and pulmonary hypertension. Classically, chest x-ray reveals enlarged cardiac silhouette when the relative pulmonary-to-systemic flow ratio is >2:1; cardiomegaly occurs with the enlargement of left atrium (LA) and left ventricle and ascending aorta. Pulmonary vascular markings are increased. TTE evaluation gives accurate information about ductal anatomy and physiology and is practically feasible in almost all infants, in children, and in many adults.

Treatment. PDA should be closed in patients with signs of LV volume overload even if asymptomatic and in patients with PAH but PAP < 2/3 of systemic pressure or PVR < 2/3 of systemic vascular resistance (SVR). Closure should be avoided in "silent" duct, very small with no murmur, and in PDA-Eisenmenger. Percutaneous closure can be performed in those cases who meet certain criteria concerning body weight and ductal size; it is feasible and safe in children weighing more than 5 kg with PDA diameter of 2.5–3 mm. In smaller-weight babies, this option is still under debate [26, 27], whereas larger PDAs are currently best managed with surgery (via thoracotomy).

Percutaneous closure is the first choice treatment in adults, even if cardiac surgery is indicated due to other concomitant cardiac lesions, because calcification of the duct increases surgical complications. The PDA anatomical characteristics guide the choice of proper occlusion device because different types are worldwide currently available. Small ducts can be closed using coils such as Cook detachable coil, whereas large PDAs (Fig. 1.4) can be addressed, according to the anatomy, using different devices such as an Amplatzer Duct Occluder (ADO) I device or its modification ADO II (Fig. 1.5) [28] or a mVSD Amplatzer Occluder or an ASD Amplatzer Occluder [29] or the new Occlutech(®) PDA Occluder [30].

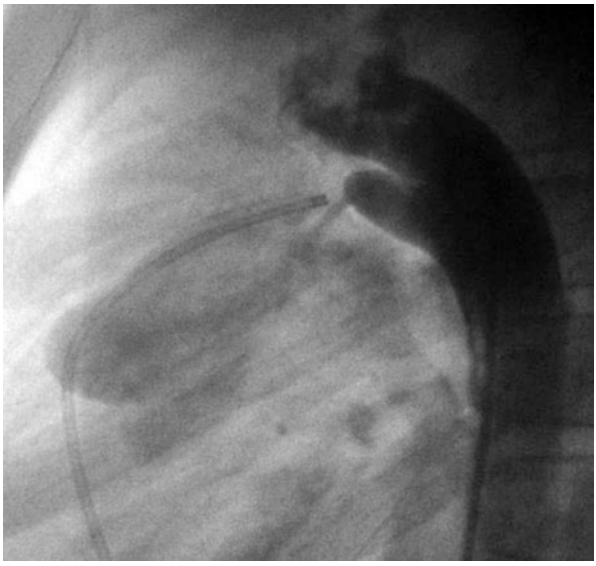

Fig. 1.4 Fluoroscopy, lateral view, aortic angiogram: PDA

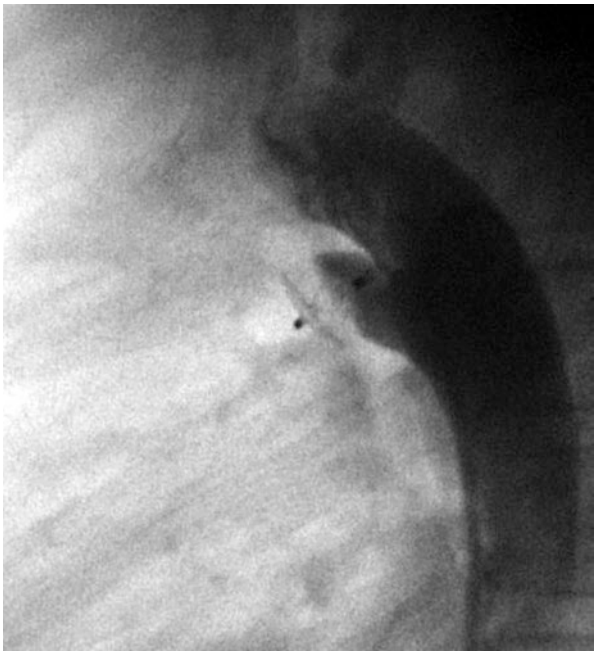

Fig. 1.5 Percutaneous closure with Amplatzer Duct Occluder II device

Outcome. Early and mid-term complications after transcatheter closure may include device embolization or dislocation. Embolization can occur more often after coil release; according to the size, coil can embolize in the pulmonary arteries or in the aorta and subsequently in all the arterial vessels as the intracranial arteries. In case of dislocation or malposition, device can cause left pulmonary artery stenosis or aortic stenosis associated, quite often, to residual shunting. Hemolysis is another rare and serious complication usually after coil PDA occlusion, related to a residual flow at the end of the procedure. If it happens, it is difficult to eliminate as long as the residual shunt is closed. At present, overall device occlusion rate is about 95%. Early complications after surgical closure may include recurrent laryngeal nerve palsy, chylothorax, pneumothorax, and immediate LV dysfunction. Untreated PDA may lead to POVD and Eisenmenger condition. Aneurysm of the ductus is a rare complication that develops gradually.

1.1.1.5 Aortopulmonary Window

Aortopulmonary window (APW) is a large defect between the ascending aorta and the main PA which results from failure of the spiral septum to completely divide the embryonic truncus arteriosus (Fig. 1.6). It represents 0.2–0.6% of all CHDs. In approximately half of the patients, there are associated cardiac abnormalities, most commonly VSD, interrupted aortic arch, aortic coarctation, and tetralogy of Fallot [31]. In isolated APW, clinical features are similar to those of large PDA.

Diagnosis. In isolated APW, peripheral pulses are bounding, but the heart murmur is of the systolic ejection type rather than continuous murmur at the base. On

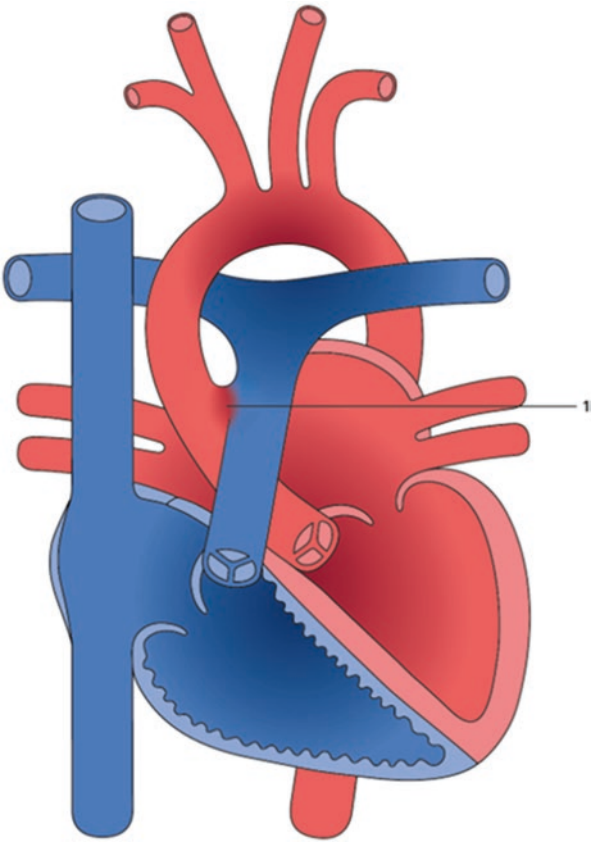

Fig. 1.6 Aortopulmonary window (1)

ECG, biventricular hypertrophy is seen. Classically, chest x-ray reveals enlarged cardiac silhouette due to the enlargement of left chambers; pulmonary vascular markings are markedly increased. TTE evaluation gives accurate information about the anatomy of APW which always should be ruled out in case of unexplained pulmonary hypertension. Diagnostic cardiac catheterization is usually reserved for all the cases in whom there is concern about PVR.

Treatment. This defect has no tendency to reduce or close spontaneously; therefore prompt surgical closure is indicated when the diagnosis is made as long as PVR is normal. In some selected cases of isolated APW with favorable anatomy, percutaneous device closure can be achieved [32].

Outcome. Without intervention, 40–50% of all patients will die due to congestive heart failure during the first year of life, and a large number of survivors will suffer from sequelae of congestive heart failure or pulmonary vascular disease later on. Outcomes of early repair of APW are excellent, including infants with complex associated cardiac lesions which should contemporarily be repaired. Cardiac reoperation can be required in complex APW, mainly with concomitant arch repair, and is usually related to aortic obstruction [33].

1.1.2 Left-Heart Congenital Heart Disease

1.1.2.1 With Inflow Obstruction

Cor Triatriatum Sinister

Cor triatriatum sinister (CTS) is a rare congenital abnormality characterized by the left atrium being divided into two chambers by a fibrous membrane, a proximal chamber that receives the pulmonary venous drainage and a distal chamber that contains the mitral valve and the left atrial appendage. CTS can occur in isolation (classic) or in association with other congenital cardiac anomalies (atypical) such as an ASD [34]. The atypical form occurs in 50–85% of all patients with CTS, although it is rare in adolescents and adults. Older patients more often have an isolated type of CTS. Symptoms are related to the size of fenestrations within the fibrous membrane and therefore to the degree of obstruction; presenting symptoms can mimic those seen in mitral stenosis and are related to both pulmonary venous and pulmonary arterial hypertension [35].

Diagnosis. Physical findings include dyspnea, a loud S2 and basal lung crackles. ECG usually shows right axis deviation and right ventricular hypertrophy (RVH). On chest x-ray, there is evidence of pulmonary venous congestion or pulmonary edema, prominent PA, and varying degree of right heart enlargement. TTE is mandatory to assess the intra-atrial membrane characteristics and the presence of associated CHD. In the differential diagnosis, a supramitral membrane is distinguished from the CTS membrane by its location below the left atrial appendage. This is an important differentiation, because, as a result of its proximity to the mitral valve and left circumflex coronary artery, the resection of a supramitral membrane is more difficult than in case of CTS membrane.

Treatment. Surgery is the definitive treatment and should be considered at any age if there are any associated symptoms or complications.

Outcome. Surgery in patients with CTS is performed with good outcomes. Mortality and reoperation rate are nearly 0% in patients with classic CTS and are determined by the repair of associated anomalies in atypical CTS [36]. The risk of recurrent intra-atrial obstruction postoperatively is low [37]. Pulmonary hypertension regresses rapidly in survivors if the correction is made early.

Congenital Mitral Valve Stenosis

Different anatomic types are described [38]:

- Congenital mitral valve (MV) stenosis: Extremely rare, it usually involves abnormalities of one or more components of the valve apparatus (Fig. 1.7).
- Supravalvar mitral ring: A thin fibrous membrane partially or completely encircles the mitral orifice and adheres to the leaflets. It is most commonly associated with “shone complex” which comprises parachute MV, subaortic stenosis, and coarctation of the aorta.
- Parachute MV: In the most typical and frequent form, all the chordal attachments are to a single papillary muscle (Fig. 1.8).

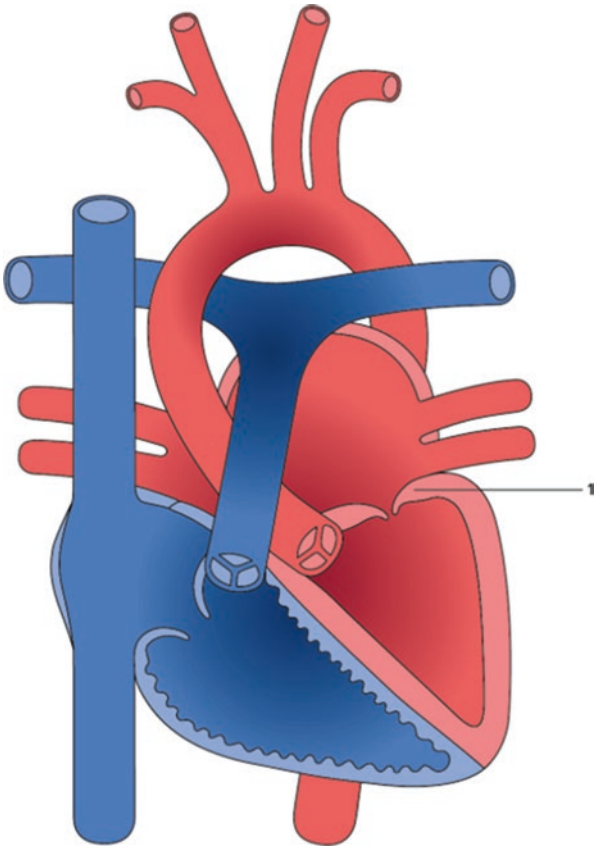

Fig. 1.7 Congenital mitral valve dysplasia and stenosis (1)

- Double-orifice MV: Two complete mitral orifices are supported by their own tension apparatus. The orifices are usually unbalanced with the smaller one directed to the anterolateral commissure. Rarely it may be associated with AVSD or VSD and coarctation.
- Arcade MV: The leaflets insert directly into the papillary muscles or the ventricular wall without chordal attachments, resulting in stenosis and regurgitation.

Symptoms and clinical signs clearly reflect the degree of pulmonary venous congestion, pulmonary hypertension, and right heart failure. The onset strictly depends on the severity of the stenosis: severe stenosis becomes evident in the neonatal period (failure to thrive, diaphoresis, cough, and recurrent respiratory infections), whereas mild or moderate disease usually presents later on in infancy, childhood, or adolescence.

Diagnosis. The typical murmur is an apical low-pitched rumbling mid-diastolic murmur. In presence of PH, a right ventricular heave is usually palpable. ECG during infancy may be normal; as the disease progresses, LA enlargement, RVH, and RA enlargement gradually appear. With ongoing atrium dilatation, atrial

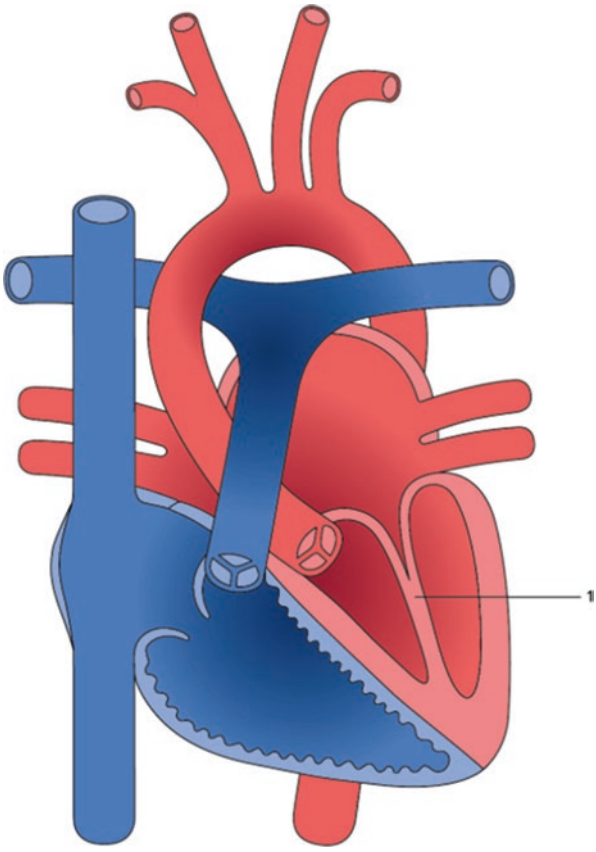

Fig. 1.8 Parachute mitral valve (1)

arrhythmias may occur. Chest x-ray shows dilatation of LA, PA, and RV; in severe disease, Kerley's B lines may be evident. TTE is diagnostic of the condition in terms of anatomic and functional MV details. Cardiac catheterization is indicated when there is discrepancy between echo measurements, hemodynamics, and clinical status or to ascertain the presence of POVD and its reversibility.

Treatment. Patients may require diuretics to alleviate pulmonary venous congestions. In case of severe obstruction, surgical valve repair or replacement with a prosthetic valve may be indicated but carries morbidity and mortality [39]. Only a few selected patients with hypoplastic annulus may benefit from balloon angioplasty which delays the need for surgical valve repair or replacement [40]. Valve choices for infants are limited: a mechanical valve is preferred with the caveat that long-term anticoagulation is necessary. For supravalvar mitral ring, early surgical repair should be considered in the presence of severe heart failure. Isolated double-orifice MV may never require intervention. MV arcade is usually repairable making the need of replacement quite rare.

Outcome. The prognosis after valve repair or replacement depends on many factors: patient age and size, the degree of annual hypoplasia, ventricular size and

performance, severity of PH, and presence of other lesions [41]. MV replacement in neonates and infants is associated with an early mortality rate of approximately 10–20% at 6 months [42]; furthermore, prosthetic valves need to be replaced within 5–10 years due to the infant's growth and prosthetic stenosis or pannus formation. Similar data are reported in children: 50% of patients require prosthesis replacement by 10 years post-valve implantation [43].

In adults following percutaneous valvuloplasty, the survival rate is 80–90% in those with favorable MV morphology. Bioprosthetic valves last approximately 5–10 years, whereas mechanical valves last a lifetime. Five-year survival rate in adults after valve replacement exceed 70% unless they have coinciding complex CHD.

1.1.2.2 Congenital Mitral Valve Regurgitation

It is most often associated with other congenital cardiac abnormalities. Mitral valve prolapse (MVP) is rare in infants and extremely rare in neonates; exceptions are cases associated with Marfan syndrome or other connective tissue disorders as Ehlers-Danlos syndrome or osteogenesis imperfecta [44]. In MVP leaflets extend beyond the annular plane during ventricular systole; any portion of MV leaflets can be affected resulting in varying degrees of regurgitation.

Along with aortic dilation, MVP is the cardiovascular abnormality typical of Marfan syndrome which is a heritable autosomal dominant connective tissue disorder causing histologic and morphologic changes in fibrillin structure. Both the anterior and posterior leaflets become elongated and redundant; chordal rupture, progressive annular dilation, and calcification may occur.

Timing of MVP presentation is variable and depends on the degree of regurgitation. Due to left atrial dilation, left main stem bronchial compression, elevated pulmonary capillary hydrostatic pressure, atrial arrhythmias, and respiratory symptoms occur. Children with severe MV regurgitation may present with orthopnea, dyspnea, chest pain, palpitations, reduced exercise tolerance, or syncope.

Diagnosis. A regurgitant holosystolic murmur is audible at the apex with radiation to the left axilla and left back. A loud S3 and an apical rumble may be present as well. In case of moderate to severe regurgitation, ECG and CXR may show hypertrophy and dilation of left chambers. The main tool used for diagnosing congenital MV regurgitation is echocardiography for both qualitative and quantitative assessment.

Treatment. Patients presenting with congestive heart failure require diuretics and ACE inhibitors to reduce afterload and to improve cardiac output [45]. Isolated MVP and cleft mitral valve rarely require intervention in infants or children unless Marfan syndrome coexists; in this case, MV replacement may be indicated depending on the severity of regurgitation. Percutaneous MV repair has been emerging as an option for the treatment of MV regurgitation in adults; current modalities include MV repair by placing metal clip on the leaflets and MV annuloplasty by placing into the coronary sinus to the great cardiac vein in order to circle three-fourths of the entire annulus [46].

MV is typically repaired prior to the need for replacement; multiple techniques are nowadays available for repair. Replacement is most commonly performed using mechanical valves, necessitating lifelong anticoagulation.

Outcome. Cleft MV and MVP, without intervention, have excellent short-term outcomes because they feature no progression of insufficiency except in the presence of connective tissue abnormalities. Short- and immediate-term outcomes after repairing a cleft MV are excellent, and most patients require no additional interventions. Patients with Marfan syndrome and MV involvement should be closely monitored keeping in mind the associated complications, in particular of the aortic valve, aorta, ventricular function, and arrhythmias; aortic aneurysm dissection or rupture is rare in childhood and more typically occurs in the third and fourth decades of life [47].

1.1.2.3 With Outflow Obstruction

Aortic Stenosis

Aortic stenosis (AS) represents 3–6% of all patients with CHD, and it occurs more often in males (male-female ratio of 4:1). Stenosis may be at the valvular (70%), subvalvular (23%), or supravalvular (7%) level.

Valvular AS is usually caused by bicuspid aortic valve with a fused commissure and an eccentric orifice [48] (Fig. 1.9). Less common is the unicuspid valve with

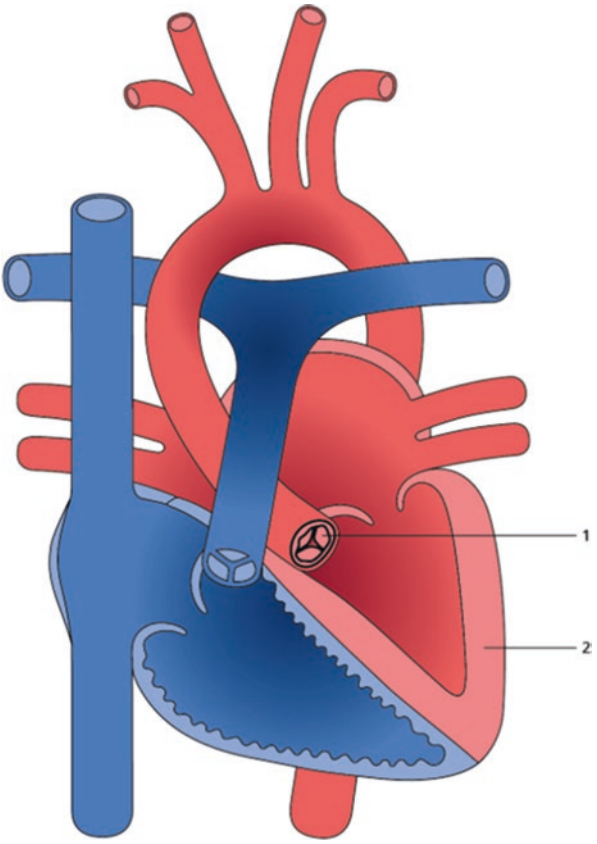

Fig. 1.9 Congenital aortic valve stenosis: (1) Valvular AS. (2) Left ventricular hypertrophy

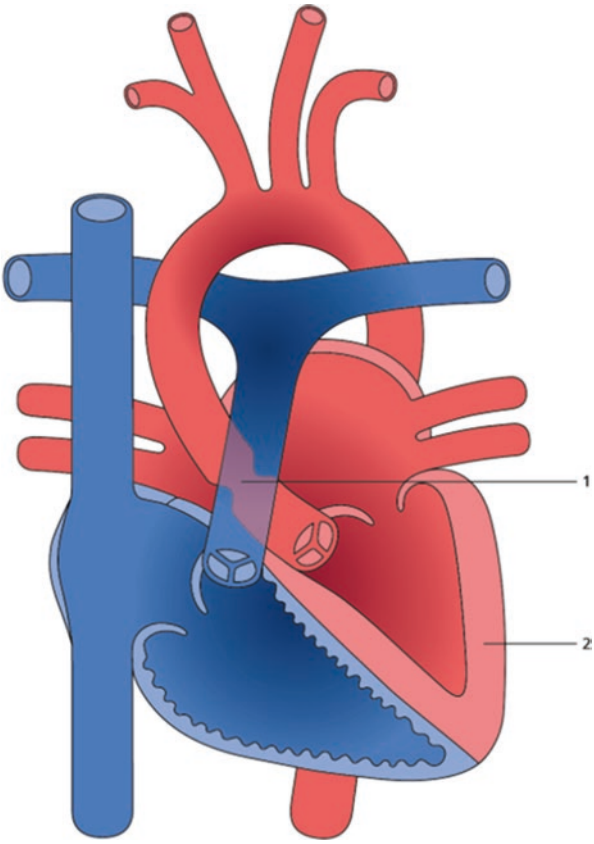

Fig. 1.10 Supravalvular aortic stenosis: (1) Supravalvular AS. (2) LV hypertrophy

one lateral attachment, while a tricuspid valve with a central stenotic orifice is the least common form.

Subvalvular stenosis may result from discrete membranous diaphragm, usually associated with other CHDs like VSD, PDA, or coarctation, or, less commonly, from tunnel-like fibromuscular narrowing of left ventricular outflow tract. The latter is usually associated with other LV anomalies including Shone complex.

In supravalvular AS the constriction occurs at the upper margin of the sinus of Valsalva, and aorta narrows in an hourglass deformity (Fig. 1.10). This is often associated with Williams-Beuren syndrome, an elastin protein gene disorder, which includes characteristic facies, mental retardation, and multiple PA stenoses.

Patients with AS are usually asymptomatic throughout childhood, even when stenosis is severe. Only 5% of children develop congestive heart failure in the neonatal period due to critical AS. Some children, as they approach adolescence, may become symptomatic for exercise intolerance; episodes of chest pain, due to myocardial ischemia; and syncope on exertion. Both chest pain and syncope are serious symptoms which may precede sudden death.

Aortic valvular stenosis is a progressive disease; two processes probably account for this: the development of myocardial fibrosis and the decrease in size of the stenotic valvar orifice by fibrosis and, later on, calcification of the valve. Bicuspid aortic valves often go undetected in early life; however, up to 70% of the cases develop some degree of stenosis or regurgitation by age 30.

Diagnosis. Infants with critical AS usually present in poor general condition, poor pulses, S3 and/or S4, and hyperdynamic precordium with a right ventricular tap. They may have either no murmur or a soft systolic ejection-type murmur due to the severe cardiac function impairment; differential oxygen saturations between the right arm (higher) and lower limbs (lower) are often detected.

In children and adolescents with severe valvular AS, a harsh grade 3–4/6, ejection systolic murmur is best heard at the second right or left intercostal space with good transmission to the neck and apex. In case of stenotic and regurgitant bicuspid valve, a high-pitched, early diastolic decrescendo murmur may be audible as well. Correlation of the severity of AS and the ECG abnormalities is relatively poor; LVH with or without strain pattern may be present in severe cases. Echocardiography is the preferred method for diagnosis and decision-making; it allows one to visualize directly the valve, to quantify the degree of stenosis, to assess cardiac function, and to detect associated CHD. In infant with severe AS, endocardial fibroelastosis can be visualized by the presence of a bright white layer in the endocardial tissue. Cardiac catheterization is rarely performed solely for diagnostic purposes; low cardiac output state can underestimate the degree of AS; therefore the aortic valve area can be calculated using the Gorlin and Hakki equations which include cardiac output and pressure gradient.

Treatment. For critical, neonatal valvular AS, inotropic agents and diuretics should be started to treat CHF; prostaglandin E_1 infusion should be given to reopen the arterial duct. Relief of the AS, either by percutaneous balloon valvuloplasty (PBV) or surgical valvotomy, should be achieved as soon as possible. Percutaneous valvuloplasty has become the preferred treatment at many centers, also in children and young adults [49]. Children who have undergone aortic valvotomy may require valve replacement later on if the valve becomes calcified or rigid or, sooner, if important regurgitation occurs; no currently available replacement valve is perfect: mechanical prostheses are long-lived but thrombogenic so anticoagulation is required; homograft valves, although free from thrombogenic complications, are often shorter-lived because of destruction by calcification at an unpredictable rate. Another option for aortic valve replacement, even in neonates and especially in small children with dysplastic and obstructed aortic valves, is the Ross operation [50] in which the patient's native pulmonary valve is excised and placed in aortic position and a homograft valve is placed in pulmonary position. The major advantages are related to the neoaortic valve which, being the patient's own tissue, degenerates very slowly, continues to grow with the patient, and does not require anticoagulation. Major disadvantages are high operative rates of acute and chronic morbidity and mortality when performed in neonates and infant, RV-PA conduit degeneration and dysfunction, and the potential dilation of the neoaorta with subsequent development of aortic regurgitation.

In subvalvar AS, surgical obstruction removal is indicated to relieve the LV pressure overload and to reduce the mechanical trauma to the aortic valve. The operative risk approaches that of operation for valvular AS; the major hazard is the possibility of damage to the mitral valve anterior leaflet since the membrane is quite often attached to that.

In supravalvular AS, surgery may be indicated for a lesser pressure gradient compared with valvular AS due to the potential concomitant disease of coronary arteries. Surgical obstruction relief is accomplished by different techniques: patch enlargement of the narrowing or slide aortoplasty techniques, according to the anatomy and the degree of ascending aorta hypoplasia.

Outcome. Mortality rate for infants and small children with valvular AS ranges from 15 to 20%. Sick neonates with poor preoperative general conditions have a mortality rate as high as 40%. The hospital mortality in older children is 1–2%.

Overall, PBV achieves a 60% reduction in the aortic valve gradient with a procedure-related mortality of 1.9% and complication rate strongly correlated with the age of the child. Repeat PBV and valve replacement occurred in 15% of patients after initial PBV [51], whereas 25% of patients require valve replacement 15–20 years after the original surgery.

Subaortic membrane has a high recurrence rate after surgical removal mainly in patients operated sooner and with high peak pressure gradients, suggesting a more severe form of disease [52].

Over the long term after supravalvular stenosis surgical relief, reobstruction and aortic valve progressive regurgitation can occur [53].

Coarctation of the Aorta

Coarctation of the aorta (CoA) is considered part of a generalized arteriopathy and not only a circumscript narrowing of the aorta. It occurs as a discrete stenosis most commonly seen in periductal region or as a long, hypoplastic segment (Fig. 1.11). It accounts for 5–8% of all CHD and may occur in isolation or in association with other anomalies: bicuspid aortic valve (up to 80%); subvalvular, valvular, or supravalvular AS; MV stenosis (as seen in Shone complex); hypoplastic left heart syndrome; and aberrant subclavian artery. CoA can be associated with Turner, Williams-Beuren [54], and congenital rubella syndromes or neurofibromatosis.

CoA causes significant increase in LV afterload resulting in increased wall stress, compensatory hypertrophy, and LV dysfunction; from the aorta a variable degree of arterial collateral circulation can develop. Elastic fiber rupture and fibrosis are typical of cystic medial necrosis which is found in the ascending and descending aorta determining an increased arterial stiffness [55]. Clinical signs and symptoms depend on the severity of CoA; when severe, closure of the arterial duct after birth will result in critical aortic obstruction, LV dilatation and dysfunction, low cardiac output state, and, if untreated, death. In less severe forms, CoA may be picked up during childhood when a murmur may be heard and femoral pulses found to be weak; in adulthood the most common sign is systemic hypertension [56]. Symptoms may include nosebleeds, dizziness, headache, shortness of breath, abdominal angina, leg cramps, claudication, exertional leg fatigue, and cold feet. Some life-threatening

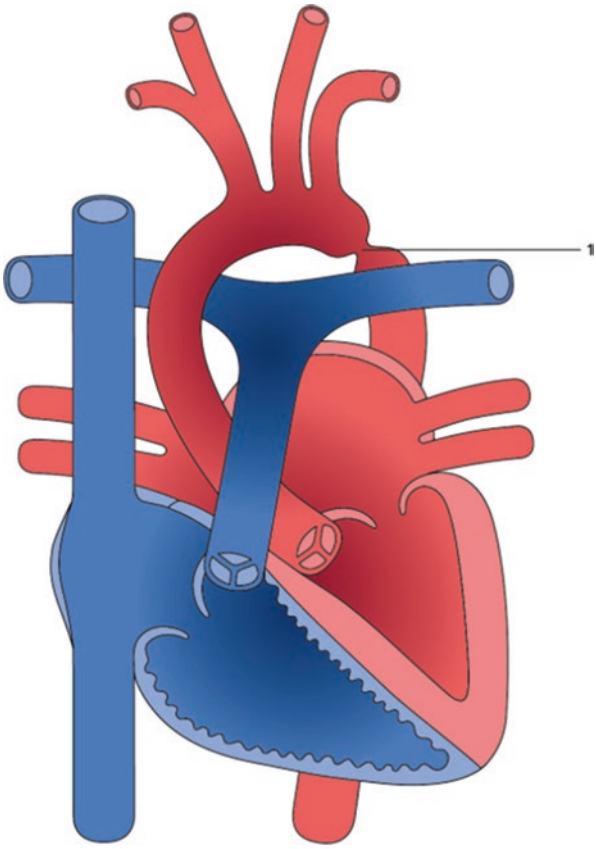

Fig. 1.11 Aortic isthmic coarctation (1)

conditions may occur during "natural history" of CoA: left heart failure, intracranial hemorrhage (from berry aneurysm of circle of Willis), aortic rupture/dissection, premature coronary and cerebral artery disease, and infective endocarditis.

Diagnosis. Neonates with severe CoA are pale and experience varying degree of respiratory distress and low cardiac output state; differential cyanosis may be present due to a right-to-left ductal shunt causing cyanosis only in the lower half of the body. Peripheral pulses may be weak and thready; the S2 is single and loud; a gallop is usually present, whereas a heart murmur is not audible in 50% of sick babies as long as the cardiac function improves. On ECG, RVH or right bundle branch block (RBBB) is often seen rather than LVH. On x-ray, marked cardiomegaly and pulmonary venous congestion are usually present.

In adolescent and adult patients, a significant CoA is diagnosed when there is a systolic blood pressure gradient between the upper and lower limb of at least 20 mmHg or less than 20 mmHg in the presence of systemic hypertension; common physical findings are weak or absent lower limb pulses. A continuous murmur in the left back near the scapula signals the presence of large collateral arteries; a systolic murmur sometimes can be heard in the left infraclavicular area or in the left upper

back. ECG generally shows LVH in patients with chronic hypertension. In some cases, chest-x-ray shows some typical findings which strongly suggest CoA: prominent ascending aorta contour, the change in aortic caliber at the coarctation site producing the "3" sign, and notching of the inferior margin of ribs 3–8 owing to erosion by large and developed collateral arteries.

Echocardiography is the definitive imaging modalities for diagnosing CoA and for identifying all associated cardiac defects; a sagittal view from the suprasternal notch should be used to visualize the posterior wedge-shaped shelf that characterizes true CoA. In neonates and infants, it is sometimes difficult to establish a proper diagnosis in the presence of PDA, and CoA may become evident once the duct closes. A typical Doppler flow pattern with persistent forward flow into diastole usually confirms a significant stenosis.

Key features, prior to any treatment, are the aortic arch morphology and the branching pattern of the head and neck vessels. If echocardiography is inconclusive, MR and CT are the preferred noninvasive techniques to evaluate the entire aorta, while cardiac catheterization is still the gold standard in case of complex CoA associated with other CHD: a peak-to-peak gradient >20 mmHg is indicative of significant CoA in the absence of well-developed collaterals.

Treatment. For sick neonates, PGE_1 infusion should be given to reopen the arterial duct; inotropic agents, diuretics, and, if necessary, mechanical ventilation should be started to treat CHF. All these measures aim at stabilizing the patient in preparation for surgery. In fact, the standard management of native CoA in neonates, infants, and young children is surgical repair [57]. Some different surgical techniques have been used: subclavian flap repair, patch aortoplasty, and, currently, resection with end to end anastomosis, via a left lateral thoracotomy or, in the presence of severely hypoplastic aortic arch, via a median sternotomy on cardiopulmonary bypass. For older children, adolescents, and adults with native CoA, in many specialized centers, balloon angioplasty (BA) with covered or non-covered stent implantation has become first choice treatment if anatomy is appropriate [57, 58] (Figs. 1.12 and 1.13). Procedure is generally performed under general anesthesia which reduces sympathetic drive and may result in a falsely low gradient across the CoA site.

Outcome. Surgical short-term complications include recurrent laryngeal or phrenic nerve damage, Horner syndrome, pleural effusion, and chylothorax. Short-term outcomes relate mostly to the clinical condition of the patient prior to surgery and the severity of associated cardiac lesions. For children and adolescents operated on, spinal cord injury with paraplegia is quite rare but is more common in patients with poor collateral circulation. Initially, long-term incidence of recurrent CoA after surgery approached 30%, whereas, nowadays, percentage has gone down to about 10% [59]. BA is mainly indicated in recoarctation in infants and young children providing excellent acute relief of obstruction but being associated with high rate of coarctation recurrence and big concerns regarding aneurysm formation and dissection. The use of covered stents has reduced significantly the incidence of dissection and aneurysm formation at the site of treated coarctation; furthermore, stents can be re-dilated later in life in case of recoarctation or residual stenosis.

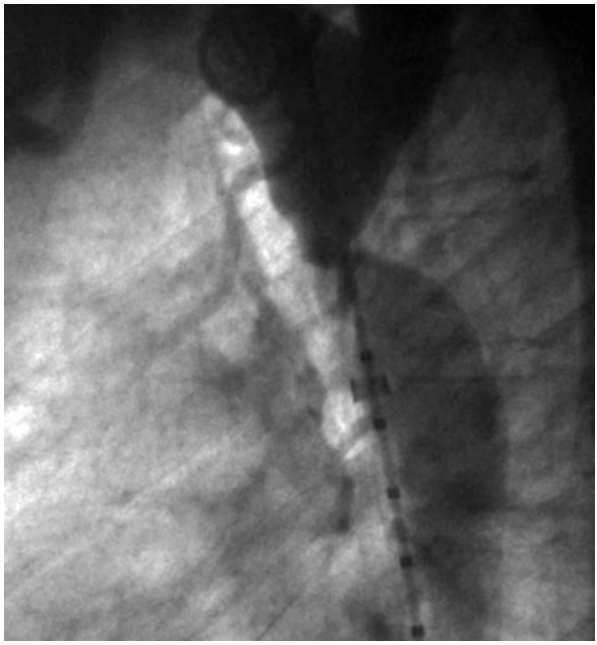

Fig. 1.12 Angiography: severe isthmic aortic coarctation

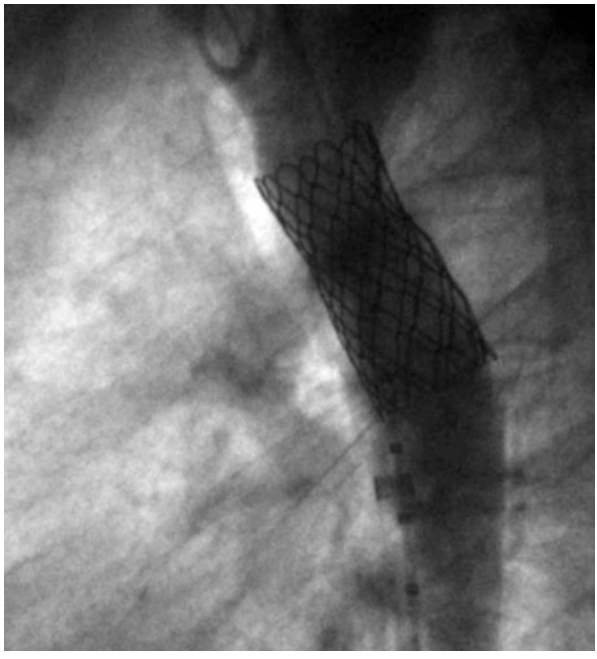

Fig. 1.13 Angiography post-covered stent implantation

After BA with stenting, acute complications may include stent migration, the most important one occurring in 5% of cases; cerebrovascular accident, seen more frequently in older patients; and femoral artery injury resulting in leg ischemia or retroperitoneal bleeding [60]. Considering delayed complications, the incidence of aortic dissection or aneurysm formation following stenting is reported at approximately 10% of cases, most commonly at the site of the narrowest segment of CoA. The vast majority of aneurysms are small and can be managed conservatively [60, 61].

Any successful CoA treatment is usually effective in lowering systemic blood pressure, but during follow-up at least one-third of patients remain hypertensive demonstrating that CoA is not purely an isolated mechanical obstruction but a complex aortic vasculopathy involving many factors such as arterial stiffness and elasticity, endothelial function, and renin-angiotensin system. Hypertension is definitely the most important long-term concern, being a key determinant of late morbidity and mortality [62, 63]. The most relevant predictor of problematic hypertension long after repair is the age at treatment; the lowest rate is seen in those repaired under 1 year of age.

Interrupted Aortic Arch

Interrupted aortic arch (IAA) accounts for approximately 1.5% of all CHD, and 15% of IAA patients have DiGeorge syndrome. The anatomical spectrum varies from an extreme form of CoA to an absence of an arch segment. According to the site of interruption, three different types are described:

(a) Type A: The interruption is distal to the origin of left subclavian artery; it occurs in 30% of cases (Fig. 1.14).
(b) Type B: The interruption is between the left carotid and left subclavian arteries (Fig. 1.15); it occurs in 43% of cases. DiGeorge syndrome is reported in about 50% of patients.
(c) Type C: The interruption is between the innominate and left carotid arteries; it occurs in 17% of cases.

VSD is the most common associated anomaly seen in approximately 73% of these cases. A PDA is invariably present with IAA, and the descending aorta is a continuation of the ductus. Bicuspid aortic valve occurs in 60% of all cases, subaortic stenosis occurs in about 20%, and truncus arteriosus and AP window occur in about 10%.

Diagnosis. Neonates present with signs of CHF, variable degrees of cyanosis, and respiratory distress. Due to the frequent association of VSD, differential cyanosis is uncommon. Peripheral pulses may be weak and thready; a gallop rhythm is usually present. On ECG, RVH is often seen in uncomplicated cases. On x-ray, cardiomegaly, increased pulmonary vascular markings, and pulmonary venous

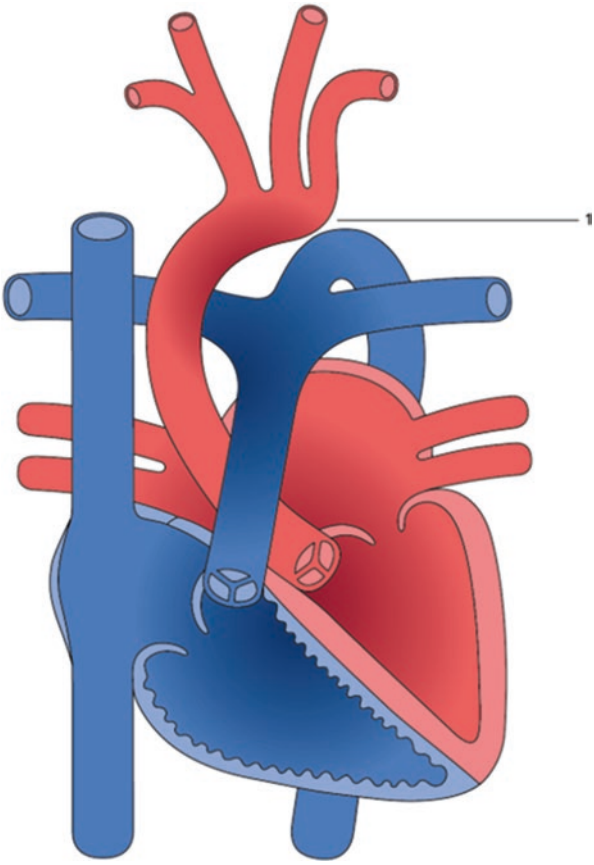

Fig. 1.14 Type A aortic arch interruption (1)

congestion are usually present; the upper mediastinum may be narrow in case of absence of thymus as in DiGeorge syndrome. Echocardiography is the preferred method for diagnosis and decision-making; it allows one to evaluate the type of interruption, the aortic valve, the cardiac function, and the associated CHD. Cardiac catheterization is rarely performed, in complex cases, just for diagnostic purposes.

Treatment. For sick neonates, PGE_1 infusion should be given to keep the arterial duct open; inotropic agents, diuretics, and, if necessary, mechanical ventilation should be started to treat CHF. All these measures aim at stabilizing the patient in preparation for surgery. In fact, the standard management of IAA and simple VSD is a single-step surgical repair [64]. If primary repair is not feasible, PA banding and interruption repair should be the initial operation followed by, at a later date, debanding and repair of other cardiac anomalies.

Outcome. Perioperative mortality can be as low as 10% for initial surgery [64]. Surgical short-term complications include recurrent laryngeal or phrenic nerve damage, ischemic cerebral accident, pleural effusion, and chylothorax. The long-term outcomes after conventional repair of IAA and VSD are acceptable; bicuspid

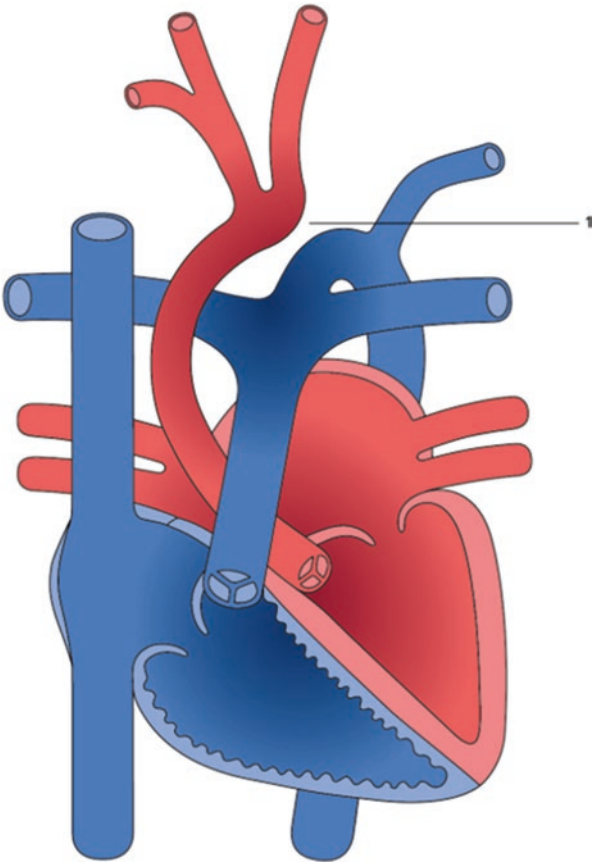

Fig. 1.15 Type B aortic arch interruption (1)

aortic valve is a significant risk factor for valve-related reinterventions [65]. Mortality rate is estimated in 3.6% at 2 years and about 39% at 21 years. Main causes of reintervention are left ventricular outflow tract obstruction (LVOTO) and recurrent aortic arch obstruction. Subjects with IAA demonstrate a significant burden of operative and transcatheter intervention and large magnitude deficits in exercise performance, health status, and health-related quality of life [66].

1.1.3 Right-Heart Congenital Heart Disease

1.1.3.1 Ebstein Anomaly

Ebstein anomaly (EA) accounts for <1% of all CHD with an equal distribution between the sexes. It is a malformation which involves both the tricuspid valve (TV) and the right ventricle (RV). Embryologically, TV leaflets arise from the myocardium through a process known as delamination which appears apically and proceeds to the atrioventricular junction. An incomplete and variable delamination,

involving the septal and posterior leaflet, results in an apically displaced and anteriorly rotated, toward the RVOT, zone of leaflet coaptation which can be considered as the "functional" TV orifice [67]. Due to the variable degree of delamination, leaflets can be very limited in excursion resulting in variable degree of regurgitation or, less frequently, stenosis. Also the anterior leaflet can have some myocardial attachments along its entire length and because the hinge point usually remains at the atrioventricular junction level, it shows a "sail-like" aspect which compensates for the abnormal septal and inferior leaflets. As a consequence of this apical and anterior displacement of the TV functional orifice, functionally RV is variably hypoplastic; the myocardium above the orifice becomes "atrialized" and, thus, thin and dysfunctional; the myocardium below the orifice typically possesses a more normal ventricular wall thickness but is still dysfunctional (Fig. 1.16). The RV impairment and the TV regurgitation decrease forward flow across the pulmonary valve reducing systemic cardiac output and increase right atrial dimensions and pressure thus favoring a right-to-left shunt through the interatrial communication; cyanosis depends upon the right-to-left shunting. Associated lesions include an ASD and less commonly a VSD or PDA; in complex forms of EA, pulmonary valve stenosis or atresia, tetralogy of Fallot, or left-sided abnormalities such as MV stenosis or regurgitation can be seen. Quite often, conduction system abnormalities coexist.

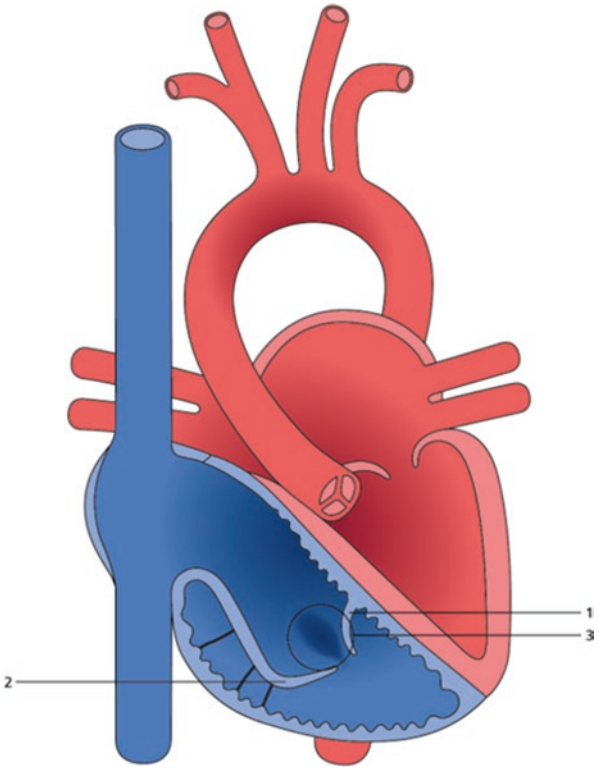

Fig. 1.16 Ebstein anomaly: (1) septal leaflet delamination abnormality. (2) Sail-like anterior leaflet. (3) Tricuspid valve regurgitation

Due to the large spectrum of anatomical features, clinical presentation and age at presentation can vary widely ranging from overt cardiac failure (dyspnea, poor feeding, and failure to thrive) or low pulmonary blood flow in neonates and infants with complex forms to almost normal findings in patients able to survive into adulthood. Approximately two-thirds of patients will present before 1 year of age and 10% will present prenatally [68]. A history of exertional dyspnea and palpitations is common in children, adolescents, and adults.

Diagnosis. Physical examination is extremely variable. Mild to severe cyanosis is usually observed as well as clubbing in older infants and children. Jugular venous distension is not common because the large RA and the atrialized RV dissipate the V wave; however it could be seen in case of severe TV regurgitation without interatrial communication. The heart examination may reveal split first and second heart sounds and/or third and fourth sounds resulting in a triple or quadruple rhythm; a soft holosystolic murmur is usually audible at the lower left sternal border. The lungs typically are normal on auscultation. Hepatomegaly is usually present.

Characteristic ECG findings of RA enlargement and RBBB are detected in most of the patients; 20–30% will display features of Wolff-Parkinson-White preexcitation with occasional episodes of supraventricular tachycardia (SVT). First-degree AV block occurs in about 40% of cases.

Due to the variability of the malformation, chest x-ray findings can range from normal to severe cardiomegaly (mainly involving the RA) with balloon-shaped heart and significantly reduced pulmonary vascular markings.

Echocardiography is the gold standard technique for morphologic and functional assessment of EA. One of the most diagnostic features is the apical displacement of the TV septal leaflet hinge point which is, in normal heart, slightly apical to mitral valve leaflet hinge point; the "displacement index" is measured in systole from the hinge point of anterior MV leaflet to the hinge point of tricuspid septal leaflet, where it begins to delaminate; if it is greater than 8 mm/m^2, a diagnosis of EA is made. Echo assessment should include TV regurgitation, RVOT obstruction, intracardiac shunts, and ventricular dimensions and function. Right heart morphology and function may alter LV geometry and subsequently function which can also be compromised by the presence of increased fibrosis within the LV myocardium since birth [69].

Cardiac MRI provides more accurate evaluation of ventricular size and function, whereas CT can help assess the coronary arteries in the adults. Cardiac catheterization can be useful only in selected and complex cases to evaluate intracardiac and intrapulmonary pressure before surgical intervention especially prior to a bidirectional cavopulmonary connection.

Treatment. Individual patient characteristics dictate how EA is managed. Patients with mild Ebstein require only regular observation. In severely cyanotic newborns, the RV is not able to generate enough pressure to open the pulmonary valve, and the R-L interatrial shunt is significant, resulting in functional pulmonary atresia and low pulmonary blood flow (PBF); PGE_1 should be given to keep the ductus arteriosus open as long as the PVR drops and antegrade flow across pulmonary valve increases. Subsequently patient's cyanosis will improve as a result of both TV regurgitation and R-L atrial shunt reduction.

Acute episodes of SVT may be treated effectively with adenosine, whereas beta blockers are commonly used as first-line preventive therapy for SVT of undetermined mechanism. In children with refractory arrhythmias, electrophysiology (EP) study and ablation should be considered; if preexcitation exists on baseline ECG, EP study and ablation should be performed before the first surgical intervention.

Only neonates with most severe forms of EA with significant TV regurgitation and/or severe RVOT obstruction will need palliative surgery consistent with a systemic-to-pulmonary arterial shunt (modified Blalock-Taussig shunt) which enables the patient to grow [70]. Indications for surgery in children, adolescents, and adults include worsening cyanosis, reduced exercise tolerance, progressive RV dilatation, and onset or progression of atrial arrhythmias. TV repair is preferred than replacement in patients less the 50 years of age; different surgical techniques have been reported, but currently, the Carpentier technique and the so-called cone reconstruction are the most effective. For patients older than 50, TV replacement with a bioprosthesis is the preferred procedure. In all patients undergoing surgery, intercardiac shunts are closed at the same time, whereas a bidirectional cavopulmonary shunt is performed in presence of markedly dysfunctional RV in order to reduce ventricle preload [71]. For patients experiencing recurrent atrial arrhythmias prior surgery, intraoperative ablation (maze procedure) is usually done. Cardiac transplantation is reserved only for the most severe, worst cases.

Outcome. Early mortality in neonates is related to right heart enlargement, severe tethering of all TV leaflets, pulmonary atresia, and LV dysfunction. Due to the medical management and surgical technique improvement over the last decades, mortality and morbidity for children with EA have been significantly reduced; consequently most children will live well into adulthood. Surgical mortality in adult patients is low, less than 3% in the current era [72]. The reoperation rate at 20 years postoperative is about 50%; the most recent procedure which has been developed for patients already operated for bioprosthesis is percutaneous valve-in-valve implantation; at the moment it is feasible in carefully selected cases [73]. Atrial arrhythmias (flutter and/or fibrillation) are the most frequent long-term complication occurring in up to one-third of operated patients [74]; even after maze procedure, recurrence rate is as high as 50% and may be the result of RA progressive enlargement secondary to worsening TV regurgitation and/or RV dysfunction. Recurrent hospitalizations are frequent with arrhythmias being, once again, the most common indications for readmission [74].

1.1.3.2 With Outflow Obstruction

Pulmonary Valve Stenosis

Pulmonary valve stenosis (PVS) with normal cardiac connections accounts for 8–12% of all CHDs. From an anatomical point of view, two forms are described: a tricuspid valve with thin leaflets, fusion of the cusps, and underdeveloped or absent commissures resulting in a dome-shaped valve, the so-called "doming," and narrow effective orifice; frequently this type of valve shows some degree of tethering to the sinotubular junction which can be mistaken for supravalvular pulmonary stenosis

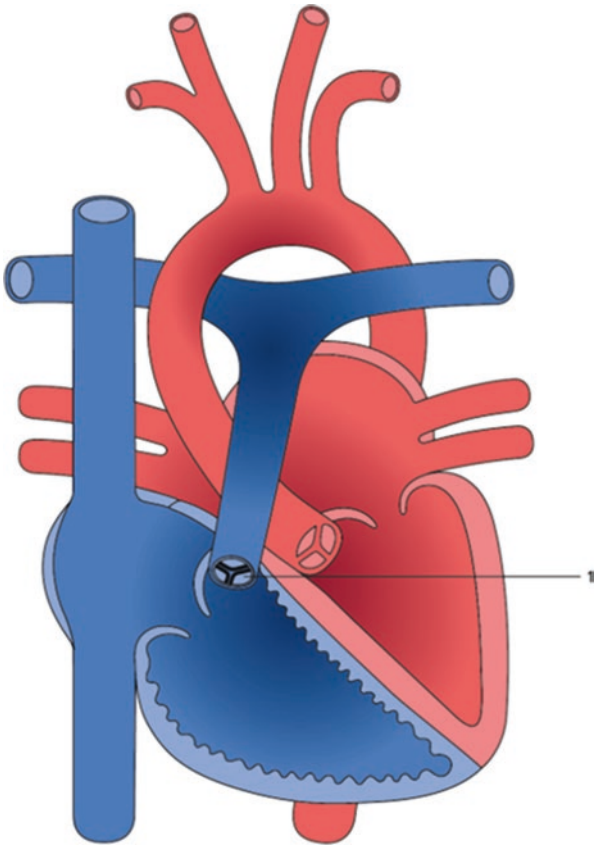

Fig. 1.17 Congenital pulmonary valve stenosis: (1) dysplastic valve

[75]; post-stenotic PA dilation is another common feature. The second form is the dysplastic one, characterized by thickened and irregular leaflets with variably hypoplastic annulus in the absence of cusp fusion (Fig. 1.17); it is typically associated with genetic syndromes such as Noonan, Williams, or Alagille syndrome.

Clinical presentation is determined by the severity of the stenosis varying from tachypnea and cyanosis in critical PVS with ductal-dependent PA circulation (due to RV hypertension, decreased output, and R-L shunt at the atrial level) to exertional dyspnea and easy fatigability in moderate to severe stenosis (due to RV inability to increase cardiac output to face the increasing demands of activity) or no symptoms as in mild obstruction; typically, these asymptomatic infants or children present with a systolic murmur at a routine pediatrician's visit.

Diagnosis. Clinical assessment is variable and correlates with severity and associated genetic syndromes. In newborns with critical stenosis, cyanosis is usually detected, and signs of CHF with hepatomegaly and peripheral vasoconstriction may be found. In children with at least moderate stenosis, a right ventricular tap and a systolic thrill may be present at the upper left sternal border; the S2 may split widely, and an ejection systolic murmur is best audible at the upper left sternal border, and

it transmits well to the back too; the louder and longer the murmur, the more severe the stenosis is.

ECG usually shows right axis deviation and RVH, with strain pattern in case of severe stenosis; the degree of RVH correlates with the severity of the disease.

On chest x-ray of neonates with critical stenosis, lungs are oligemic, and varying degrees of cardiomegaly are present. In most of the children with moderate to severe PVS, cardiac silhouette is normal and will remain normal for a long time; as they get older, main PA enlargement may become prominent consistent with post-stenotic dilation.

TTE is the primary diagnostic modality, able to assess the features of the valve, the annulus size, the RV hypertrophy and dimensions, and the presence of interatrial shunt; Doppler study estimates pressure gradient across the stenotic valve; a gradient >70 mmHg is severe. Limited utility remains for CT and MRI for diagnostic purpose in this age group as well as cardiac catheterization whose role is strictly interventional.

Treatment. Newborns with critical PVS need emergency treatment to reduce mortality; PGE_1 infusion should be started as soon as possible in order to increase the size of PDA and thereby improve the pulmonary blood flow (PBF); once stabilized, neonates should undergo cardiac catheterization for percutaneous pulmonary valve balloon dilation which is the procedure of choice. Subsequently, PGE_1 may be discontinued keeping in mind that some neonates will still temporary require an additional source of PBF even after successful balloon dilation; this situation may occur when RV stiffness prevents appropriate diastolic ventricular filling or when infundibular muscular hypertrophy becomes more evident after the procedure, obstructing antegrade PV flow. This additional source can be either a PDA stent or a surgical mBTS.

If percutaneous balloon dilation is unsuccessful, surgical pulmonary valvotomy is urgently indicated in critically ill patients [76].

Infants, children, and adolescents with PVS are referred to PPV dilation when stenosis is diagnosed as severe or should become severe during a conservative follow-up. Surgical approach is required in case of resistant PVS which did not respond to previous balloon dilation. Dysplastic valves with annular hypoplasia are less likely to have a satisfying relief of obstruction.

Outcome. Short- and medium-term results for infants undergoing balloon dilation or surgical valvotomy are excellent [77]. As anesthesia, technology, and experience have improved, mortality and annular tear associated with percutaneous procedure are extremely low [78]; about 15% of all children undergoing percutaneous PV dilation will have residual subvalvular gradient of 10 mmHg or more which will typically regress by time. A significant immediate residual RV-to-PA gradient is considered one determinant of a suboptimal long-term outcome; infants with a smaller indexed pulmonary annulus are reported to have higher incidence of reintervention, ≤30%, due to restenosis [79]. Other causes for reintervention in the long term are as follows: congestive heart failure and RV dilation/dysfunction related to pulmonary valve regurgitation (PR). Operated patients have a lower transvalvular gradient during follow-up but greater valvar regurgitation. PR may be progressive;

approximately 25% of children with at least moderate PR initially increase to more than 50% with time. Estimated freedom from reintervention rate after surgery is 93.5% at 10 years and 87.7% at 20 years whereas, after percutaneous dilation, is 87.5% at 10 years and 84.4% at 20 years [80]. The most common reintervention consists of surgical PV replacement or transcatheter PV implantation.

Pulmonary Atresia with Intact Ventricular Septum

Pulmonary atresia with intact ventricular septum (PAIVS) is a rare form of cyanotic heart disease which accounts for fewer than 1% of all CHD and for approximately 3% of the critically ill newborns affected by CHD. Anatomical key features are as follows: complete obstruction at the PV level; intact interventricular septum; wide range of TV and RV abnormalities, ranging from severe hypoplasia to severe dilation; and possibility of communications between the RV cavity and epicardial coronary artery circulation (sinusoids) (Fig. 1.18).

Cyanosis is the typical neonatal presentation due to obligatory interatrial R-to-L shunting; the severity of cyanosis also depends on the amount of pulmonary blood flow (PBF), provided through the PDA, and the pulmonary vascular resistance.

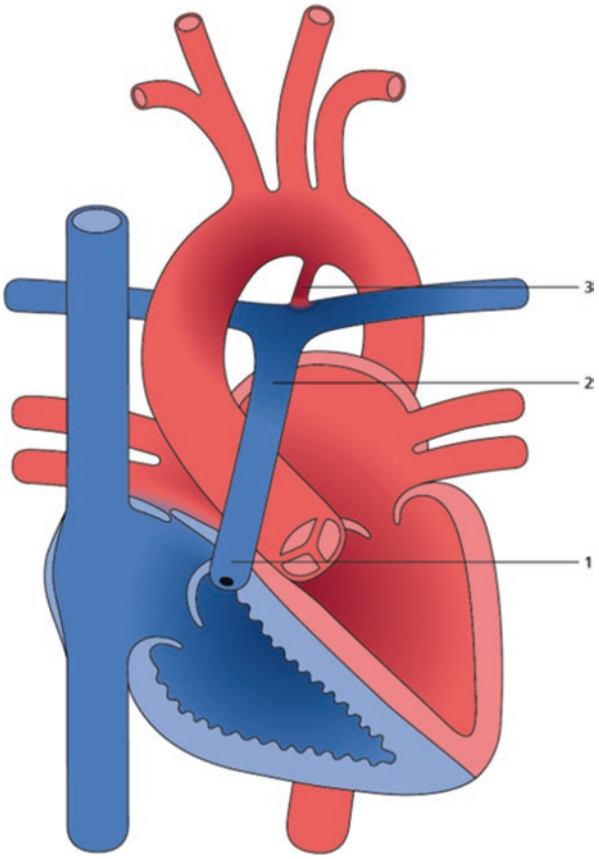

Fig. 1.18 Pulmonary atresia with intact septum: (1) Valvular atresia. (2) Main pulmonary artery. (3) PDA

Diagnosis. Variable degrees of cyanosis are detected; sometimes, in the presence of large PDA, neonates may have systemic oxygen saturation in the 90s, rendering the finding of cyanosis very subtle. Arterial pulses are generally well palpable. Auscultation reveals a single S2 with or without a murmur; generally the murmur is caused by TV regurgitation, rarely by coronary artery fistulae or markedly constricted ductus arteriosus.

On ECG, right atrial enlargement is common, occurring in about 70% of cases; the QRS axis is normal; LVH is usually present, whereas RV forces will depend on the degree of RV hypoplasia.

The cardiac silhouette on chest x-ray frontal projection can vary from normal to large, resulting from right atrial enlargement secondary to TV regurgitation; in case of severe regurgitation, cardiomegaly may resemble that observed in Ebstein anomaly. Pulmonary vascular markings are usually decreased with dark lung fields.

TTE is the definitive imaging modality for diagnosing and for addressing all the specific issues: a large PFO is present in most of the cases associated with R-L obligatory shunting. TV abnormalities are common and can vary from annular hypoplasia to Ebstein-like features or subvalvular leaflet tethering. Indeed, TV annular dimension is strongly correlated with the RV cavity size ranging from normal to severely hypoplastic, in case of small RV, or severely dilated in case of significant valvar regurgitation. Through the regurgitation jet, systolic RV pressure should be measured by Doppler and compared with systemic arterial blood pressure; most children with PAIVS have suprasystemic pressure secondary to complete obstruction at the PV level and the presence of a reasonably competent TV. Based on the presence or absence of the three portions, inlet, trabecular, and infundibular, RV cavity should be classified as tripartite, bipartite if only inlet and infundibular portions are present, or unipartite if the inlet portion is the only one developed [81]. RV systolic dysfunction is common at presentation due to extremely high afterload and not to a proper contractility impairment. PV atresia in most of the cases is functional rather than anatomical: in fact, three well-formed sinuses in the PA, thin valve leaflets, and normal or mildly hypoplastic annulus are usually found in this condition. Pulmonary arteries are commonly confluent and of normal size, whereas major aortopulmonary collateral arteries are quite unusual. Presence of right ventriculocoronary communications, also known as RV-to-coronary fistulae or coronary sinusoids, is directly related to the degree of TV hypoplasia: the smaller the TV, the more likely the existence of sinusoids which may involve both the right and the left coronary system. Furthermore, variable degree of coronary artery stenosis can be detected within the coronary circulation at any level, both proximal and distal; if proximal significant obstruction is present, coronary perfusion depends mainly on RV cavity desaturated blood through the sinusoids; this is the typical feature of a condition known as RV-dependent coronary circulation which occurs, more likely, if the coronary stenosis is severe and proximal and varies from partially to totally dependent according to the extension of coronary system disease.

Cardiac catheterization with angiography is currently recommended in almost all the cases with PAIVS in order to assess the coronary circulation and, consequently, to evaluate the suitability for RV decompression.

Treatment. In the neonatal period, PGE_1 infusion should be started as soon as the diagnosis is suspected or confirmed to maintain the arterial duct open. Subsequently, the aims of treatment should be to decompress the RV if appropriate, to achieve an adequate PBF, and to have an unrestrictive flow across the ASD. Cardiac catheterization with RV angiography and aortogram is fundamental for decision-making: if RV dependence of a major portion of coronary circulation is confidently ruled out, RV decompression can be performed. Catheter-based radiofrequency perforation of pulmonary valve followed by valvar balloon dilation is nowadays the first-line procedure worldwide [82, 83]. Due to the frequently associated RV diastolic dysfunction secondary to the compliance impairment, hypertrophy, and/or hypoplasia, RV decompression quite often does not immediately result in adequate pulmonary and systemic blood flow and adequate oxygen saturation level (>75%). Therefore, an additional source of PBF may be required, consisting of either a surgical modified Blalock-Taussig shunt (mBTS) or transcatheter arterial duct stent implantation performed at the time of the initial catheterization or some days later in case of persisting inadequate systemic oxygen saturation once the arterial duct closes [84]. Modified BTS or PDA stent implantation is the procedure performed in all the neonates judged not suitable for RV decompression at the initial cardiac catheterization. A restrictive interatrial shunt is extremely rare in PAIVS and may require balloon atrial septostomy, at the time of cardiac catheterization, only in case of concomitant rudimentary RV and/or when RV decompression is contraindicated.

Outcome. After neonatal period, infants with PAIVS may follow two possible treatment strategies according to whether or not RV decompression has been performed:

(a) If unsuitable for decompression, patients will be managed along a univentricular pathway consisting of bidirectional cavopulmonary anastomosis (Glenn) at about 3–6 months of age, followed by total cavopulmonary anastomosis (Fontan) at about 2–5 years of age.
(b) If suitable for decompression, patients will follow different possible pathways:
   – Patients who continue to have hypoplasia of the RV and TV annulus will be directed to univentricular circulation.
   – Patients who show substantial growth of the RV cavity and TV annulus will be directed to biventricular circulation consisting of additional PBF source occlusion (if present) and ASD occlusion; all these procedures should be preceded by a complete cardiac catheterization including an ASD balloon occlusion test as well, in order to assess the RV capacity to handle all the systemic venous return.
   – Patients who show some growth of the RV cavity and TV annulus but not enough to support the entire PBF and to maintain adequate systemic oxygen saturation. These patients will be directed to a bidirectional cavopulmonary anastomosis with or without ASD closure. If the ASD is closed, patient will achieve a so-called one and a half ventricle circulation: the RV will accept the systemic venous return only from IVC while SVC blood reaches directly the pulmonary arteries via the cavopulmonary anastomosis [85]. If the ASD

cannot be closed because of the insufficient RV cavity growth, variable degrees of cyanosis will persist lifelong due to the right-to-left shunting across the defect. Regardless of ASD closure, in both anatomical situations, SVC will be exposed directly to the pulmonary vascular resistance via cavo-pulmonary anastomosis, whereas IVC will maintain normal or near-normal pressure regime avoiding long-term complications of venous hypertension such as protein losing enteropathy (PLE), ascites, and liver cirrhosis.

Later on, in adolescence and adulthood, the management of patients with PAIVS varies greatly depending on type of circulation achieved in early childhood. Those with coronary sinusoids and not suitable for decompression are at risk of developing chronic myocardial ischemia and infarction, ventricular dysfunction, and sudden death [86]; cardiac transplantation may become the only therapeutic option. Those who achieved a univentricular-Fontan circulation will be exposed to the risks commonly associated to this circulation: ventricular dysfunction, gastrointestinal complications such as cirrhosis and PLE, and pulmonary complications such as plastic bronchitis. Those who managed to reach biventricular or a one and a half ventricle circulation will likely experience pulmonary valve regurgitation as a result of transcatheter or surgical RV decompression; therefore, percutaneous or surgical pulmonary valve replacement might become necessary, at some point, to stop RV dilation and to prevent long-term complications as much as possible.

Tetralogy of Fallot

Tetralogy of Fallot (TOF) occurs in 10% of all CHD and is the most common cyanotic defect seen in children beyond infancy. It involves the following four anatomic abnormalities of the heart: large malaligned VSD, anterior shift of the aorta over the VSD (overriding aorta), right ventricular outflow tract (RVOT) obstruction, and right ventricular hypertrophy (Fig. 1.19). All these anatomic findings are the result of one developmental anomaly: the anterocephalad deviation of the outlet septum which inserts, in the normal anatomy, into the central portion of the Y-shaped septo-marginal trabeculation of the RVOT. The obstruction is most frequently in the form of infundibular stenosis (45%) although it may be present at different levels at the same time: subvalvar, valvar, and supravalvar [87]. PA branches are usually small but confluent; stenosis at the origin of LPA is very common while systemic collateral arteries feeding into the lungs are occasionally detected, especially in severe forms of RVOT obstruction. The VSD is typically a perimembranous, unrestrictive defect which allows pressure equalization between RV and LV and, consequently, contributes in determining RVH. Approximately 25% have a right-sided aortic arch, and about 5% have coronary artery anomalies, some of which may change the surgical approach such as the anterior descending artery arising from the right coronary artery (RCA) and passing over the RVOT; this is the most common anomaly which prohibits any surgical incision in infundibular area. Atrioventricular septal defects occur in about 2% of the cases and should be considered in TOF patients with trisomy 21.

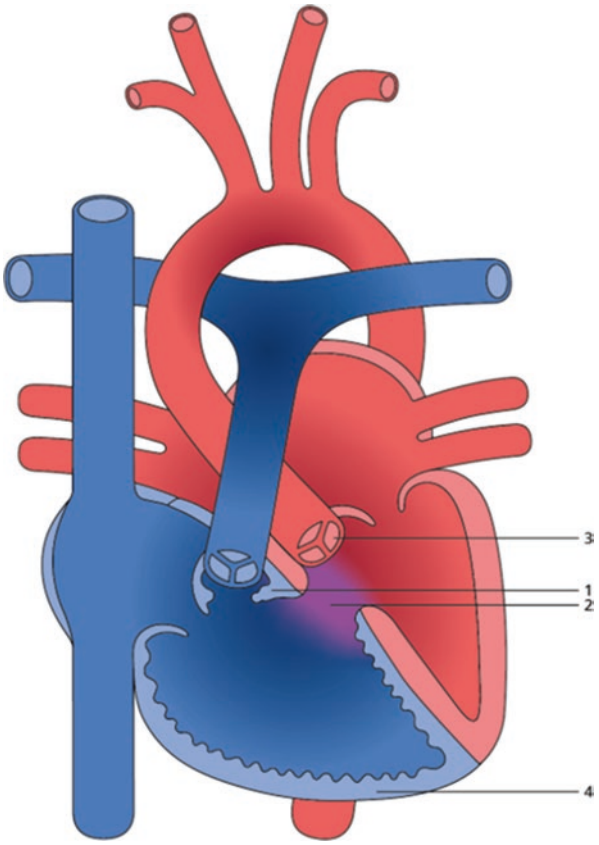

Fig. 1.19 Tetralogy of Fallot: (1) infundibular stenosis. (2) Malaligned VSD. (3) Overriding aorta. (4) RV hypertrophy

Within TOF, there is a wide spectrum of presentation: the degree of cyanosis depends on the degree of RVOT obstruction. This is quite variable, from a slight obstruction to the extreme variant of TOF with pulmonary atresia. With mild pulmonary stenosis, also known as "pink TOF," it behaves as a VSD with high PBF, normal oxygen saturation, and potential CHF symptoms early in life. Progression in RVOT obstruction may occur later on, as a result of hypertrophy of the RV and the septomarginal trabeculation, resulting in increasing cyanosis. Apart from pink TOF, all the other forms may experience the so-called hypoxic or hypercyanotic spells which occur in infants with a peak incidence between 2 and 4 months of age and manifest as a paroxysm of hyperpnoea, worsening cyanosis, irritability, and decreasing intensity of the heart murmur. They are often associated with prolonged crying or exercise, and they require immediate recognition and treatment because they can lead to serious complications such as limpness, convulsion, cerebrovascular accident, or even death. Some believe that spells may be explained by a catecholamine-induced spasm of the muscularized infundibulum resulting in acute worsening of RVOT obstruction, in acute increased amount of blood shunting R to L across the

VSD, and, eventually, in worsening cyanosis and acidosis. Some believe that SVR plays a primary role in the hypoxic spell etiology.

Another rare and unique clinical presentation is represented by TOF infants with absent pulmonary valve syndrome characterized by the presence of a rudimentary pulmonary valve apparatus and abnormal pulmonary artery development, resulting in mildly–moderately reduced PBF and markedly dilated pulmonary arteries which can cause compression of the main bronchi and gas exchange limitations.

Diagnosis. Variable degrees of cyanosis are detected at birth or shortly thereafter. Arterial pulses are generally well palpable. Auscultation reveals a normal S1, a single S2, and a long, loud ejection systolic murmur at the mid and upper left sternal border radiating to the back; the more severe the RVOT obstruction, the softer and shorter the systolic murmur. Furthermore, during hypoxic spell, murmur may disappear as less blood flows across the RVOT and more flows through the large VSD. On ECG, right QRS axis deviation is common in the cyanotic forms; the axis is normal in pink TOF, whereas it is superior or leftward in TOF with AVSD. RVH is common, but the strain pattern is unusual. Combined ventricular hypertrophy may be found in the acyanotic forms.

In cyanotic forms, the cardiac silhouette on chest x-ray frontal projection is characteristic: a concave main PA segment (secondary to reduced PBF) with an upturned apex (secondary to RVH), the so-called "boot-shaped" heart. In acyanotic forms, x-ray findings are almost indistinguishable from those of a small to moderate VSD.

TTE is the definitive diagnostic imaging modality for addressing all the four components that classify the disease, evaluating the total PBF including PDA and aortopulmonary collateral arteries, and ruling out any associated anomalies such as AVSD, right aortic arch, coronary anomalies, and pulmonary or systemic venous return abnormalities. Further investigations and imaging techniques such as CT, MR, or cardiac catheterization are rarely requested after an accurate and complete echocardiographic evaluation.

Treatment. PGE_1 infusion should be started in all TOF cases with arterial duct-dependent pulmonary circulation or in case of nonconfluent pulmonary arteries (PAs) with one branch supplied by the PDA; infusion should be maintained until a more definitive intervention can be performed either percutaneously or surgically. After neonatal period, it is important to recognize and treat hypoxic spells: the infant should be picked up and held in a knee-chest position in order to raise SVR and increase PBF. Supplemental oxygen is usually provided, but it has little demonstrable effect on arterial saturation. When noninvasive treatment fails, analgesic therapy, such as morphine sulfate, should be given subcutaneously or intramuscularly or intravenously if an access is obtained. Fluid volume can increase RV preload, whereas beta blocker, propranolol, can lower heart rate, improve RV filling, and stop catecholamine surge. Acidosis should be promptly treated with intravenous sodium bicarbonate in order to prevent PVR rise. If the spell does not respond to these measures, intubation and mechanical ventilation should be considered as well as intravenous peripheral vasoconstrictor, such as norepinephrine, to raise SVR and promote PBF.

Oral propranolol is often used to prevent hypoxic spells while waiting for an optimal time for surgery. Recurrent spells are an indication for intervention.

Surgical management includes both palliative and repair procedures:

(a) Palliative procedures. In order to achieve an adequate PBF and enable the infant to grow properly till the age of repair, a Gore-Tex interposition shunt, modified Blalock-Taussig shunt (mBTS), placed between the subclavian artery and the ipsilateral pulmonary artery, is the procedure of choice. Indications for mBTS vary from institution to institution, but it usually is performed in children with hypoplastic PAs.
(b) Repair procedure. It consists of patch closure of the VSD and relief of RVOT obstruction with patch augmentation under cardiopulmonary bypass and circulatory arrest; if the stenosis involves PV annulus, transannular patch augmentation is performed at the expanse of creation of free pulmonary regurgitation (PR). Over time, surgical strategy for VSD closure has shifted from a transventricular approach to a transatrial plus transpulmonary approach with the aim of reducing ventriculotomy scar with its potential arrhythmogenic effect. Patients with extreme hypoplasia or atresia of RVOT/PV, or those with left coronary artery crossing the infundibulum, are not good candidates for patch augmentation, but they will benefit from RV-to-PA valved conduit implantation. Optimal timing of repair is still under debate; although several strategies have been developed, almost all the institutions perform repair by 12 months of age [88, 89]. A worldwide accepted strategy is to delay the repair until the patient is older than 3–4 months of age unless cyanosis dictates palliative shunt implantation; this way seems to reduce, as much as possible, the need of transannular patch and hence of consequent PR [90]. Many other institutions have been promoting an early TOF repair in neonatal period to avoid RVH, to lower the risk of hypoxic spells, and to improve PA growth and development [91].

Over the last few decades, interventional cardiac catheterization has become a valid option for some selected patients, as premature TOF neonates, as an effective initial palliation: procedure consists of stent implantation in the RVOT [92].

Outcome. mBTS has a surgical mortality rate of about 1%. Generally, for surgical repair, mortality rate is about 2%. After repair, the majority of patients have normal oxygen saturation and no residual shunt. Symptom-free survival in children after TOF repair is excellent with 30-year survival rates approaching 90%; however, survival is less than expected for the general population at all times [93]. The most common late complication is chronic PR, whereas residual RVOT obstruction and PA stenosis are less frequent but significant late sequelae [94]. Chronic PR is the major contributor to long-term morbidity and mortality: it leads to progressive RV dilation and dysfunction, arrhythmias, and functional tricuspid valve regurgitation. PV replacement with a biological valve is the treatment of choice for patients with severe PR and RV dysfunction and/or symptoms related to arrhythmias, both atrial and ventricular. Surgical replacement has been for a long time the only technique

available; nowadays percutaneous pulmonary valve implantation (PPVI) is a valid and effective alternative either in native RVOT, in selected patients, or in dysfunctioning RV-PA conduit [95]. Cardiac MR [96] and cardiopulmonary exercise test provide a lot of information used in clinical decision-making to establish the right timing for PV replacement. Atrial flutter and fibrillation are the most frequent arrhythmias encountered in the late follow-up, whereas prevalence of ventricular arrhythmias increases with age and is associated with LV dysfunction [97]. Atrial arrhythmias can be treated with a surgical ablation, maze procedure, at the time of PV replacement, whereas sustained ventricular tachycardia (VT) or aborted sudden cardiac death (SCD) should be addressed with ICD implantation for secondary prevention. SCD due to ventricular arrhythmias is the most common cause of death after TOF repair with a risk of about 3–6% over the 30-year follow-up period. Progressive aortic valve regurgitation along with aortic root dilation may be seen in 15–18% of patients after repair as a long-term complication as well [98].

Tetralogy of Fallot and Pulmonary Atresia with Ventricular Septal Defect

TOF and pulmonary atresia with VSD occurs in approximately 15–20% of all tetralogy cases. Chromosome 22q11 deletion and infants of diabetic mothers have a strong association with this pathology. Intracardiac anatomy resembles that of TOF in all features except for the presence of pulmonary atresia which is the extreme form of RVOT obstruction and may be at the infundibular and/or at valvar level. Typical of this CHD is the disposition of the pulmonary arteries and their relationship to additional sources of PBF; the pulmonary supply is most commonly mediated through a PDA (70%) and less commonly through major aortopulmonary collateral arteries (MAPCAs) (30%). PDA is usually small and long and arises from the aortic arch with an acute angle and courses downward. PAs anomalies can widely vary in terms of degree of hypoplasia, nonconfluence, and abnormal distribution:

- In general, the more hypoplastic are central PAs, the more developed is the MAPCA circulation pulmonary supply.
- Central PAs are nonconfluent in about 15% of patients. Usually, in the presence of PDA, central PAs are confluent in 70% of cases. If the PAs are nonconfluent, the PDA may supply just one of the pulmonary branches, whereas the contralateral lung will be supplied by MAPCAs.
- Incomplete distribution of one or both PAs to all lung segments occurs in about 80% of patients with nonconfluent PAs compared to 50% with confluent PAs.

Also MAPCAs can widely vary in terms of origin, caliber, course, and pattern of anastomosis with the pulmonary circulation. Some of them derive from bronchial arteries which originate from ascending aorta and make an intrapulmonary anastomosis, being the sole suppliers to the target lung segments. Other collaterals originate from aortic vessels, such as subclavian, intercostal or internal mammary arteries, and usually anastomose with the central PAs. Another type of MAPCAs, the most common one occurring in about two-thirds of patients, is represented by

collaterals that arise from descending aorta and usually anastomose with PAs at the hilum level, resulting in so-called dual blood supply for that specific corresponding lung segment [99]; these vessels are often stenotic at some point of their course or tend to become stenotic over time.

Cyanosis is the common clinical presentation which may become evident early after birth or later on, according to the patency of arterial duct and how extensive the collateral artery supply is. In case of increased PBF, infant may present with signs of CHF within the first weeks of life.

Diagnosis. Some degree of cyanosis is obligatory, ranging from mild to severe, and may be detected at birth or thereafter. Arterial pulses are generally well palpable. Auscultation reveals a normal S1 and a single S2; a systolic or a continuous murmur may be audible in the presence of PDA or collaterals. ECG usually shows RVH and right QRS axis deviation. On chest x-ray, quite often the heart appears as a "boot-shaped" silhouette whose size varies according to the amount of PBF: the higher is the PBF, the larger will be the cardiac size. A combination of areas of increased and decreased pulmonary vascular marking is characteristic of patients with MAPCAs. TTE is very useful and accurate for addressing all the anatomic components that classify the disease, providing many details about RVOT variable anatomy which ranges from well-developed tract to an imperforate pulmonary valve to a complete muscular atresia without a demonstrable infundibulum, the total PBF including PDA and aortopulmonary collateral arteries, and the presence of associated anomalies such as AVSD, right aortic arch, coronary anomalies, and pulmonary or systemic venous return abnormalities. Although MAPCAs can be detected on echocardiogram, further imaging modalities are usually required in order to better define the PBF and to plan treatment strategy. CT and three-dimensional CT or MR are able to clearly delineate the origin and distribution of systemic-to-pulmonary collaterals and the anatomy of native PAs in most of the patients with some limitations such as in case of severe central PA hypoplasia. Therefore, cardiac catheterization still remains the most accurate technique used to assess all the sources of PBF and their arborization and to measure hemodynamics within native PAs and MAPCAs.

Treatment. PGE_1 infusion should be started in all cases with duct-dependent pulmonary circulation or nonconfluent PAs with one branch supplied by the PDA; infusion should be maintained until a more definitive intervention can be performed either surgically or percutaneously. According to the anatomy and hemodynamics, surgical management may differ as follows:

(a) Single-stage repair. Complete, primary surgical repair is feasible when adequate size central PAs exist and the central PA connects without obstruction to sufficient areas of both lungs; it consists of closing the VSD and creating a continuity between RV and central PA via a patch or conduit implantation.
(b) Staged repair. When criteria for single-stage repair are not met, surgical strategy should both promote maximal central PA growth and improve the PA distribution in order to supply as many lung segments as possible. To promote central PA growth, different techniques have been used: mBTS has been performed

extensively but with the disadvantage of iatrogenic stenosis of the PA at the level of the anastomosis; for very hypoplastic but confluent central PAs, a "central shunt" is a valid option which consists of anastomosis of the small main PA to the side of the ascending aorta but with the disadvantage of risk of excessive PBF and CHF [100] and RVOT reconstruction with a patch, leaving the VSD open or partially closed with fenestrated patch.

To improve PA arborization, for patients with multiple MAPCAs, so-called unifocalization procedure is performed: It consists of connecting those collateral arteries, being the sole suppliers of some lung segments, to native PAs in order to achieve a single source of perfusion.

Alternative percutaneous interventional procedures exist and have been performed routinely in some centers and in some selected patients: PDA stenting to palliate neonates or infants pending later surgical repair, RVOT perforation, and stenting to create a continuity between the RV and the main PA, delaying surgical intervention for weeks or even months [101].

Outcome. Surgical repair can be performed, even at neonatal age, with a relatively low mortality rate albeit higher than that associated with repair of TOF and pulmonary stenosis. In terms of morbidity, early postoperative period can be complicated by the onset of RV restrictive physiology secondary to RV compliance impairment and consequent low cardiac output state; this condition may be worsened by arrhythmias, such as junctional ectopic tachycardia, and severe PR resulting from transannular patch implantation.

Long-term outcome for repaired patients is similar, in many cases, to that observed for patients with TOF and PS. Children who had RV-PA conduit implantation commonly required recurrent conduit changes throughout childhood due to body growth and throughout adolescence and adulthood due to conduit dysfunction (stenosis and/or regurgitation); at present, if the original conduit is larger than 16 mm and can be dilated and stented to that size or above, PPVI can be done successfully and has become the percutaneous procedure most performed in TOF patients with pulmonary atresia. Mid- and long-term outcome of patients who have undergone unifocalization is affected by many factors: the type of RVOT reconstruction, the number of lung segments recruited, the development of native PAs, the presence of collateral and/or PA stenosis in combination of pulmonary regurgitation, and the degree of RV dysfunction. Interventional cardiac catheterization plays a major role in treating pulmonary vascular bed stenosis with balloon dilation and stent implantation and in closing residual VSD with device. Another group of patients who requires careful and regular follow-up includes both survivors of early attempts at palliation in the early era of congenital surgery and unoperated adult patients; cyanosis can be improved by stenting the shunt connections or stenotic MAPCAs [102].

1.1.4 CHD with Anomalous Origin of Great Arteries

1.1.4.1 Transposition of the Great Arteries

Transposition of great arteries (TGA) accounts for 2–5% of all CHD with a prevalence of about 0.2–0.3 of 1000 births; it is more common in males than in females with a ratio of 2–3:1. It derives from truncal ridge and infundibulum normal spiraling rotation failure during fetal life which results in discordant ventriculo-arterial connection: aorta arises from the morphologically RV and is located anteriorly and to the right of PA (D-transposition), whereas the PA arises from morphologically LV (Fig. 1.20).

Consequently pulmonary and systemic circulations flow in parallel instead of in series, having oxygenated blood pumped by the LV into the lungs via the PA and back to the LV and deoxygenated blood pumped by the RV to the body via the aorta and back to the RV. This hemodynamic condition is incompatible with life unless a communication exists between the two circulations which allows a mixing between

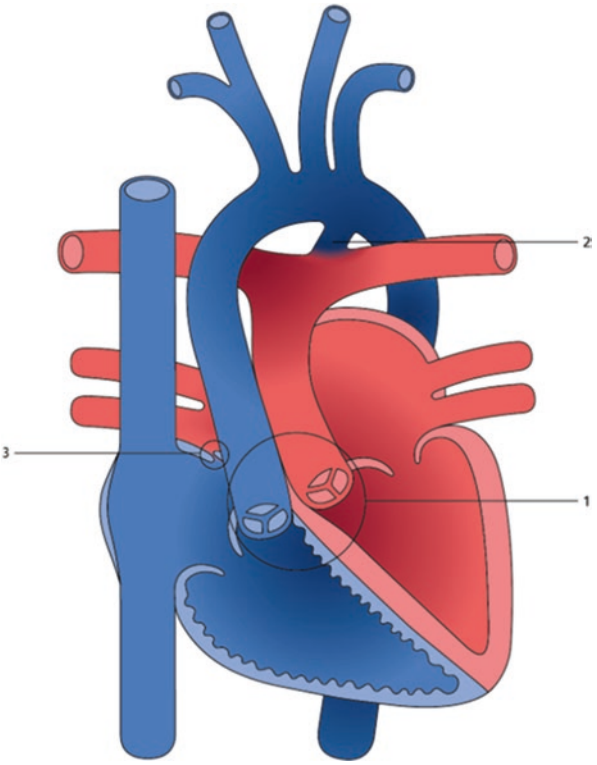

Fig. 1.20 Transposition of the great arteries: (1) discordant ventricular-arterial connection. (2) PDA. (3) PFO

oxygenated and deoxygenated blood. Effective systemic blood flow is the amount of oxygenated blood coming from the lungs which reaches systemic circulation through the anatomic shunts; effective PBF is the amount of deoxygenated blood coming from the body which reaches the pulmonary circulation through the anatomic shunts.

During neonatal period, PDA and mainly PFO usually maintain an adequate mixing because they ensure the effective systemic/pulmonary blood flow going respectively into the aorta and the PA; as the PDA starts to close and PFO by itself is restrictive in size, infant develops severe cyanosis.

Approximately one-half of patients with TGA have an intact interventricular septum (IVS). VSD is present in 30–40% of D-transposition cases and may be located anywhere within the septum (Fig. 1.21).

Associated lesions with TGA-VSD are left ventricular outflow tract (LVOT) obstruction in 30% of cases, at valvar (Fig. 1.22) and subvalvar level, coarctation of the aorta, interrupted aortic arch, overriding and straddling of the atrioventricular valve, and coronary anomalies.

Coronary arteries usually arise from the two facing sinuses which are opposed directly to the pulmonary valve; their origin, course, and branching pattern may vary significantly affecting surgical mortality at the time of the repair, the so-called

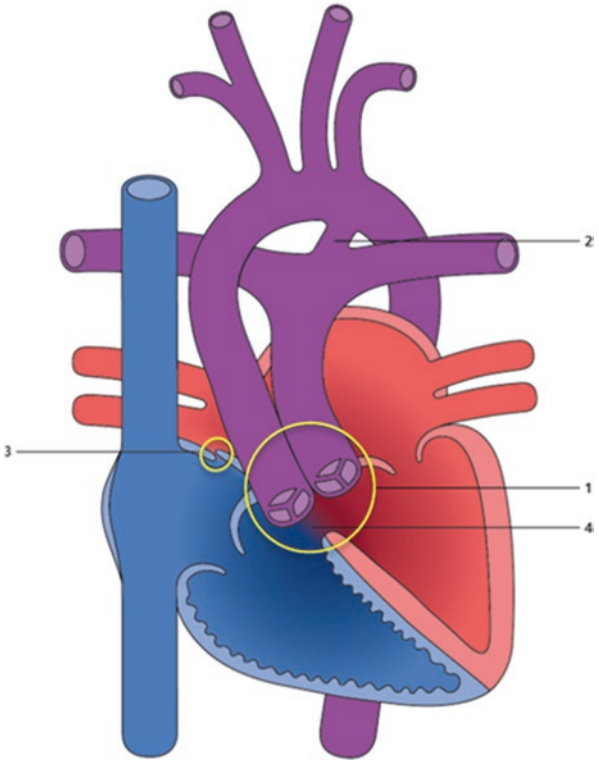

Fig. 1.21 Transposition of the great arteries: (1) Discordant ventriculo-arterial connection. (2) PDA. (3) PFO. (4) Subaortic VSD

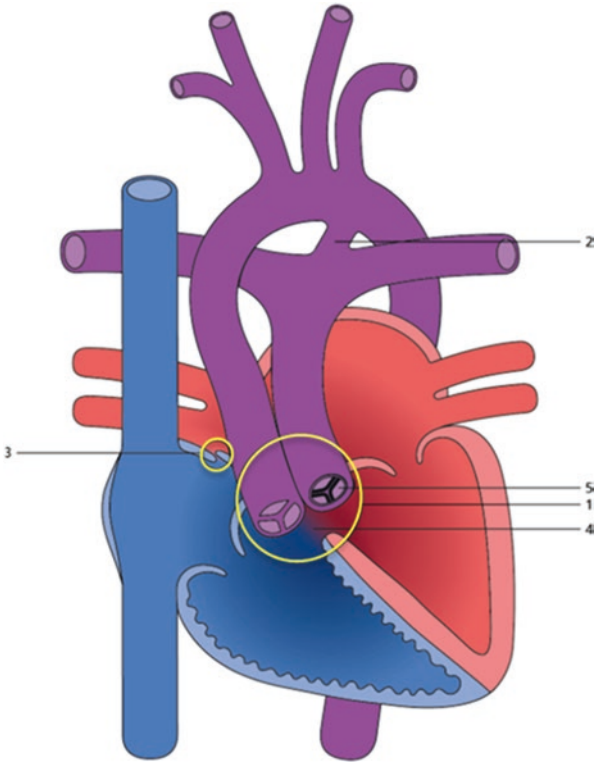

Fig. 1.22 Transposition of the great arteries: (1) discordant ventriculo-arterial connection. (2) PDA. (3) PFO. (4) Ventricular septal defect. (5) Pulmonary valve stenosis

arterial switch operation (ASO). Yacoub surgical classification, currently used worldwide, describes all the coronary anomalies encountered, including the origin of left coronary from the right facing sinus, a single coronary artery, and intramural course [103].

Unoperated children with TGA-IVS have a tendency to develop POVD within months to years, whereas babies with TGA and large VSD without pulmonary stenosis may develop POVD earlier, within 6–12 months.

Diagnosis. Cyanosis from birth is always present as well as arterial hypoxemia with or without acidosis; hypoxemia does not respond to oxygen. Neonatal reversed differential cyanosis is a typical finding, resulting from blood circulations in parallel: arterial oxygen saturation is higher in the postductal extremities than in the preductal ones due to the amount of oxygenated blood which reaches the descending aorta from the PA through the PDA. Signs of CHF, with tachypnea, dyspnea, and failure to thrive, develop during the newborn period as PVR decreases. On auscultation S2 is single and loud. No murmur is audible in infants with TGA-IVS, whereas a systolic ejection murmur will be detected in TGA-VSD due to increased blood flow across the LVOT and pulmonary valve.

On ECG, RVH is usually present and persists thereafter. In case of associated large VSD or PDA or POVD, combined ventricular hypertrophy may be seen.

The cardiac silhouette on chest x-ray frontal projection is characteristic: a narrow superior mediastinum, secondary to anterior position of the aorta which obscures PA, the so-called egg on a string. Vascular markings and cardiac size depend on the amount of PBF and tend to increase in the presence of large VSD and/or PDA.

TTE is the modality of choice for addressing all the components that classify the disease and to achieve all the information required for planning the management: the origin and course of the great arteries which run parallel, in their proximal portion, in parasternal long axis view; both arterial valves can be seen in parasternal short-axis view as double circles; PA is identified by observing bifurcation of the artery; presence and size of PFO/ASD and PDA, being the sites of blood mixing; any associated anomalies such as VSD, PS, LVOT obstruction, and CoA; and the origins and courses of coronary arteries by using parasternal and apical views.

Treatment. Oxygen is given in case of severe hypoxia in order to lower PVR and increase PBF. Metabolic acidosis should be corrected, and, depending on the degree of mixing, PGE1 infusion should be started to maintain ductal patency. All infants with TGA-IVS and restrictive atrial communication should undergo emergency percutaneous balloon atrial septostomy (BAS), the Rashkind procedure: a balloon-tipped catheter is advanced into the LA through the PFO and then, after having inflated the balloon, is abruptly withdrawn to the RA in order to enlarge the interatrial communication; if effective, the oxygen saturation will rise to 10% or more due to the improvement of intracardiac mixing [104]. After successful BAS, neonates can wait for surgical repair even without prostaglandin infusion if oxygen saturation does not drop too much, below 70%, as the PDA closes. For TGA-IVS patients, ASO is the procedure of choice since the late 1980s and is usually performed by the first 3–4 weeks of life before PVR drops to normal level, and, consequently, morphologic LV systolic pressure decreases making the LV "deconditioned"; in fact, morphological LV should be able to support systemic circulation after surgery. It consists of anatomic correction by transecting the great arteries above the level of sinotubular junction, relocating the aorta over the morphological LV and the PA over the morphological RV; moving PA bifurcation anteriorly to the ascending aorta, according to the so-called Lecompte maneuver; and, finally, transferring the coronary artery buttons to the "neoaorta"; the latter is a critical part of the operation especially in case of coronary pattern abnormalities.

Prior the ASO introduction, before the early 1980s, physiological correction used to be performed by switching the right- and left-sided blood at the atrial level, using either the Mustard or the Senning technique. Atrial switch consists of creating intra-atrial baffles to redirect the blood, using, respectively, prosthetic material in Mustard operation or right atrial and atrial septal tissue in Senning operation. These techniques are still performed in rare cases such as "double-switch" operation (combined with arterial switch or Rastelli operation), palliative atrial switch, or isolated ventricular inversion.

For patients with TGA-VSD and/or CoA, associated lesions are usually repaired at the same time as ASO. For patients with significant pulmonary valve stenosis which contraindicates ASO, Rastelli or Nikaidoh operation is used. In Rastelli technique, the pulmonary and systemic venous blood are switched at the ventricular level

by creating an intraventricular tunnel between the VSD and the aortic valve which connects LV to the aorta and by placing a conduit between the RV and main PA.

In Nikaidoh technique, there is reconstruction of both ventricular outflow tracts by patch augmentation, but there are variations on it which are currently used as well.

Outcome. Survival without surgery is unlikely. The early surgical mortality rate for ASO is between 2–5%, whereas the overall 5-year survival exceeds 90% [105]. PA stenosis is the most frequent complication after ASO: possible causes include scarring and retraction of the tissue used to fill the coronary artery button sites, tension at the anastomotic site in case of inadequate mobilization of the distal PAs, and abnormal growth of the suture lines. Balloon dilation and stent implantation are usually effective to treat stenosis. Dilation of the aortic root and consequent neoaortic valve regurgitation are common, especially in patients who had VSD closure, but not significant or progressive. Coronary artery complications, stenosis or occlusion, have been reported in 5–7% after ASO and have been associated with ventricular dysfunction and sudden death [106]; usually these lesions can be treated percutaneously, during cardiac catheterization. Cardiac catheterization used to be performed, later in childhood, even in asymptomatic patients after ASO, in order to assess coronary artery circulation.

Following the Rastelli repair, often the RV-to-PA conduit will become stenotic and/or regurgitant with the need of replacement during adolescence or adulthood; if the original conduit is larger than 16 mm and can be dilated and stented to that size or above, PPVI can be done effectively. Subaortic stenosis may develop at the level of LV to aortic valve tunnel and may require reintervention. After atrial switch operation, some mid- and long-term complications may occur: sinus node dysfunction and atrial arrhythmias (mainly intra-atrial reentry tachycardia) are the most frequent and progressive; by 20 years, only 40% of patients remain in sinus rhythm [107]; pacemaker implantation is required for symptomatic sinus node dysfunction and arrhythmias. Because the morphological RV remains the systemic ventricle, progressive ventricular dysfunction is usually observed in long-term follow-up; symptoms are relatively uncommon until the systemic RV failure is advanced. Intra-atrial baffle leakage and/or obstruction occurs in about 10% of patients and may be addressed by interventional techniques or surgical revision. Sudden death may occur in up to 10%–12% of these patients, mainly related to arrhythmias.

1.1.4.2 Congenitally Corrected Transposition of the Great Arteries

Congenitally corrected transposition of the great arteries (ccTGA) accounts for about 0.05% of all CHD. There is an increased incidence among families who have had a previous child with ccTGA with a recurrence risk in siblings approximately 2–5%. It is characterized by discordant atrioventricular (A-V) and ventriculo-arterial (V-A) connections, resulting in functionally corrected circulation because the oxygenated blood comes into the LA, goes into the morphologically RV, and then flows out into the aorta, whereas deoxygenated blood comes into the RA, goes into the morphologically LV, and then flows out into the pulmonary artery (Fig. 1.23). This abnormal configuration is secondary to impaired cardiac looping during embryologic development. In 90% of ccTGA patients [108], there are associated

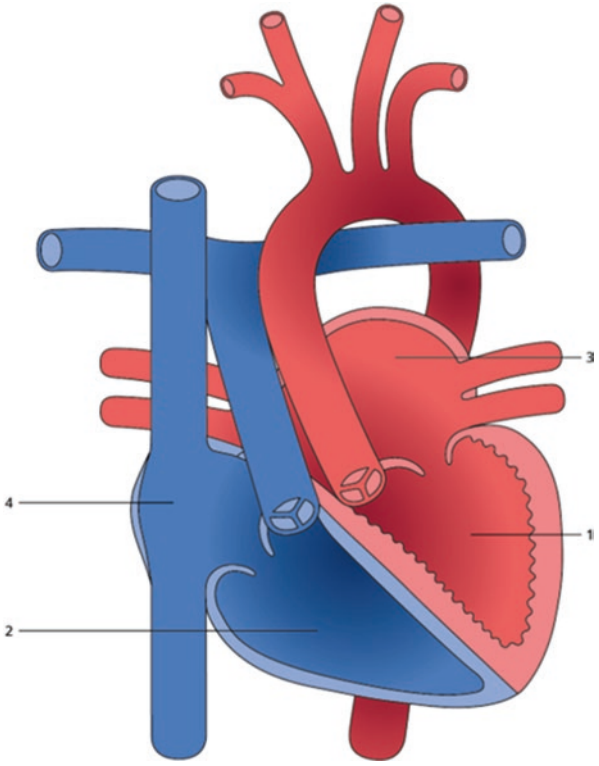

Fig. 1.23 Congenitally corrected transposition of the great arteries: (1) morphologically RV. (2) Morphologically LV. (3) Morphologically LA. (4) Morphologically RA

CHDs as follows: a VSD in 60–80%, mainly perimembranous; LVOT obstruction/PVS in 30–50%; tricuspid valve anomalies, in about 90% of autopsy cases, which can vary from mild valvar dysplasia to Ebstein-like features with variable degree of regurgitation; and heart position abnormalities such as dextrocardia (heart placed mainly in right-sided chest) in about 30% of cases. Because the pulmonary valve is wedged between the atrial septum and the mitral valve, there is a malalignment between the interatrial and interventricular septum causing an abnormal arrangement of the conduction system; instead of the normal position, at the apex of triangle of Koch, AV node is located just beneath the opening of right atrial appendage, at the lateral margin of the area of PV-to-MV continuity. This anatomic condition predisposes to AV conduction disturbance which can occur in fetal life as well. A complete AV block is present in 10% of ccTGA neonates at birth, whereas the risk of AV block occurrence is about 2–3%/year.

Coronary arteries usually arise from aortic sinuses adjacent to the PA and show an epicardial distribution which follows their respective ventricle; coronary anomalies can occur as well.

Clinical presentation is widely variable according to the underlying anatomy: patients are usually asymptomatic when ccTGA is not associated with other defects and the disease is found incidentally later on in life. In case of VSD and PVS, variable degree of cyanosis may be detected. Signs of CHF may appear during first

weeks of life in case of large VSD or severe bradycardia. Exertional dyspnea and reduced exercise tolerance may develop with worsening tricuspid valve, the systemic AV valve, regurgitation.

Diagnosis. Cyanosis is detected in case of associated VSD and PVS. Bradycardia, tachycardia, or irregular rhythm may be the reason for cardiology referral. S2 is loud and single at the upper left sternal border. A pansystolic murmur can be audible at the lower sternal border in case of VSD or tricuspid regurgitation; an ejection systolic murmur at the upper sternal border is typical of LVOT obstruction/PVS.

In usual atrial arrangement and levocardia, ECG usually shows Q waves in the right precordial leads (V1) and absent Q wave in the left precordial leads (V5–V6); this is the result of abnormal initial ventricular depolarization which occurs from right to left in a superior and anterior direction, according to the abnormal ventricular arrangement [109]. On chest x-ray, a straight left upper cardiac border is a characteristic finding in case of normal atrial arrangement and levocardia; other cardiac position abnormalities are easily detected. Cardiomegaly and increased vascular markings are associated with large VSD, whereas pulmonary venous congestion and left atrial enlargement are seen in significant systemic, tricuspid valve regurgitation.

TTE is extremely useful and accurate for addressing all the anatomic components, following a segmental approach, and for taking many details about the associated lesions. The aorta is no longer in fibrous continuity with the AV valve and is usually anterior and to the left of the PA. TV anatomy and function require careful examination.

CT and MRI can provide a complete, noninvasive evaluation of the cardiac morphology and hemodynamics but require anesthesia for children.

Treatment. In neonates with severe PVS or severe coarctation or aortic arch interruption, PGE1 infusion should be given to keep arterial duct patency until surgical intervention. Infants born with complete AV block may require a pacemaker soon after birth.

Repair strategies for ccTGA associated with other CHDs are multiple and include the "physiological"-classic repair, single or 1.5-ventricle repair, and the "double-switch" operation, so-called "anatomic" repair.

The "physiological" biventricular repair aims at restoring normal circulatory patterns and hemodynamics by closing VSD, relieving LVOT obstruction, repairing or replacing the TV, or, when needed, LV-to-PA conduit implantation; the key point is that the patient remains with a systemic morphologically RV which tends, over time, to deteriorate in function along with TV regurgitation worsening. In patients with straddling AV valves or unbalanced ventricles, a univentricular-Fontan circulation is the final target. Double-switch operation is an alternative biventricular repair which aims at restoring the normal anatomy leaving the morphologically LV as the systemic ventricle; it consists of an atrial switch (Mustard or Senning) combined with an arterial switch or Rastelli procedure [110].

Outcome. Infants with significant TV regurgitation and progressive AV block are at higher risk of morbidity and mortality. Most patients with ccTGA do well during childhood and adolescence and survive into adulthood; outcome determinants are

systemic RV function, TV regurgitation, and progressive conduction disturbances. In adulthood, most ccTGA patients start to experience morbidity and mortality in their 30s and 40s; those with associated lesions are at higher risk of developing RV dysfunction and CHF than those without associated defects [111].

Surgical mortality rates have improved significantly over the last decades, and a gradual shift from physiological to anatomic repair has been observed worldwide; systemic RV function and TV function are still the most important outcome determinants in long-term prognosis. Regardless of type of operation, 10-year survival has been estimated between 70 and 75% [112].

1.1.4.3 Double Outlet Right Ventricle

Double outlet right ventricle (DORV) accounts for 1–2% of CHD with an incidence of about 0.1/1000 births. It could be associated with chromosome 22q11 deletion, as the other conotruncal anomalies, with polymalformative syndromes and a heterotaxy syndrome, the right isomerism.

DORV is not a single entity but refers to that group of CHD in which both outflow tracts arise entirely or predominantly from the RV and which physiologically may behave like VSD, TGA, TOF, or single ventricle. Associated anomalies include ASD, VSD, AVSD, AV valve abnormalities, PDA, PVS, CoA, and coronary anomalies. Different DORV classifications exist, based on great artery relationship or the position of the VSD in relation to the great arteries. The great vessels can lay side by side, or aorta rightward and anterior to PA, or aorta rightward and posterior to PA, or aorta leftward and anterior to the PA. VSD position can vary: subaortic, closer to the aortic valve (Fig. 1.24); subpulmonary, closer to the pulmonary valve, the so-called Taussig-Bing anomaly; doubly committed, equally committed to both arterial valves; and, then, noncommitted, far from both arterial valves. The most frequent position is subaortic, 58–68%, followed by subpulmonary one in about 60% of cases [113].

Because more than 60% of infants with DORV with subaortic VSD have some degree of pulmonary stenosis, they will present, clinically, like infants with TOF: mild stenosis will not protect from high PBF and, consequently, from CHF; severe stenosis will determine low PBF and severe cyanosis. Neonates and infants with DORV and subpulmonary VSD will present like those with TGA and VSD, therefore with variable degree of cyanosis and possibly CHF. In this setting, there is a frequent association with subaortic obstruction and aortic coarctation which should be suspected in case of cardiogenic shock at presentation, as the PDA closes.

Diagnosis. As mentioned before, variable degree of cyanosis may be detected in both forms of DORV. S2 is loud. An ejection systolic murmur may be audible at the upper sternal border. ECG shows right axis deviation, RVH. LVH may be seen during infancy in Taussig-Bing anomaly, whereas first-degree AV block is more common in Fallot-type DORV.

Chest x-ray shows normal heart size with an upturned apex in the Fallot type, whereas cardiomegaly and increased vascular markings are characteristic of TGA-type DORV.

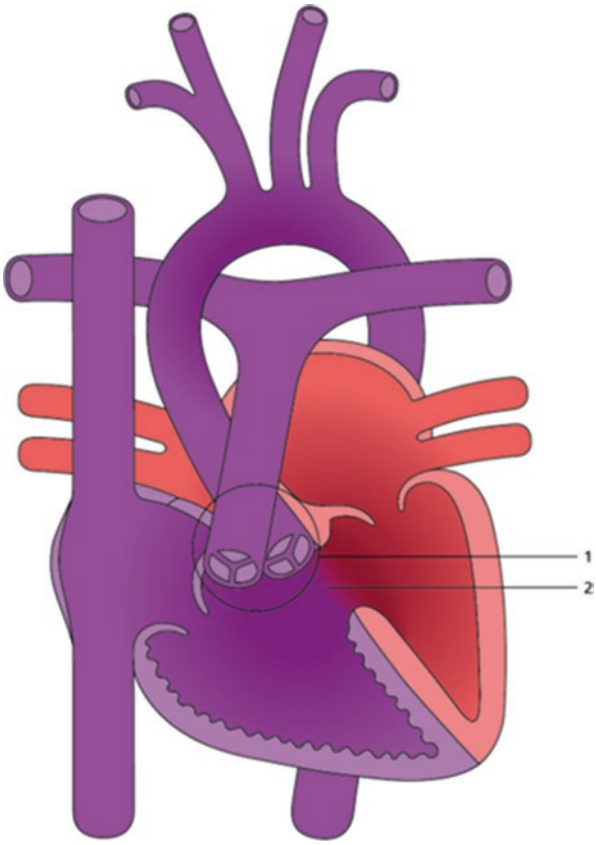

Fig. 1.24 Double outlet RV: (1) normally related great arteries. (2) Subaortic VSD

TTE is diagnostic in almost all cases and should be based on accurate sequential, segmental approach for addressing all the components that classify the disease and to achieve all the information required for planning the management: VSD position, great artery relationship, associated anomalies, coronary artery origins, and proximal course should be investigated.

Treatment. In neonates with Fallot-type DORV, the PBF is often well balanced, so they do not require any medical treatment. In case of Taussig-Bing anomaly, severe cyanosis should be treated with PGE1 infusion; if cyanosis does not meliorate despite the presence of PDA, a Rashkind balloon atrial septostomy may be necessary to improve blood mixing and oxygen saturation. Diuretics may be helpful to treat CHF.

Fallot-type DORV surgical management is similar to that for TOF patients: repair can be performed either in neonatal period or within the first 4–6 months of life by VSD closure with patch, directing LV into the aorta, and by relieving RVOT obstruction with infundibular and/or transannular patch or with RV-to-PA conduit implantation in case of coronary anomaly at the level of infundibulum. Some

neonates with severe PS may require an mBTS as a first surgical procedure, followed by complete repair and takedown of the shunt later on.

TGA-type DORV surgical management is similar to that for TGA patients: repair can be performed within the first 3–4 weeks of life by VSD closure with patch along with an arterial switch operation. Coa, if present, can be treated at the same time of the repair.

Outcome. Within the DORV group, the Fallot type is the anatomic variation with the lowest surgical mortality; best overall survival, about 96% at 15 years [114]; lowest ongoing complication rate; and best freedom from reoperation, estimated about 87% at 15 years. Pulmonary valve regurgitation and/or stenosis and RV-PA conduit dysfunction are the most common complications during long-term follow-up. TGA-type DORV patients have a 15-year survival rate of approximately 90% with an estimated 15-year freedom from reoperation of 72% [114]. Survival is lower for those who underwent CoA repair as well. Cardiac catheterization used to be performed, later in childhood, even in asymptomatic patients after ASO, in order to assess coronary artery circulation.

1.1.4.4 Truncus Arteriosus

Truncus arteriosus (TA) occurs in 1–4% of all CHDs. Of the other conotruncal anomalies (TOF, TGA, and DORV), TA may be associated with chromosome 22q11 deletion typical of DiGeorge syndrome, in about 35% of the cases [115], and with another polymalformative syndrome such as CHARGE association which comprises coloboma, heart disease, choanal atresia, retardation of growth, genitourinary abnormalities, and esophageal atresia. It consists of a single great artery arising from the cardiac ventricles through a single arterial valve which is most often placed over a large VSD, in 70–90% of cases; rarely, the common trunk arises entirely from the RV. TA gives rise to the pulmonary, systemic, and coronary circulation. It is the result of abnormal embryological great artery septation and is frequently associated with a large variety of other CHDs which includes partial or total anomalous pulmonary venous drainage, CoA, or type B aortic arch interruption. Coronary anomalies are detected in more than half of the patients. The truncal valve is most commonly tricommissural, followed by bicommissural and then by quadricommissural; valvar leaflets can be thickened and redundant with stenosis, regurgitation, or both [116]. Four types of TA are described according to Collett and Edwards classification, based on the origin of PAs from the common arterial trunk.

- Type I: The main PA arises from the common arterial trunk and the divides into the RPA and LPA (Fig. 1.25).
- Type II: Both PAs arise independently from the posterior aspect of the arterial trunk.
- Type III: Both PAs arise independently from the lateral aspect of the arterial trunk.
- Type IV: No PAs but arteries, supplying the lungs, arise from the anterolateral aspect of the descending aorta.

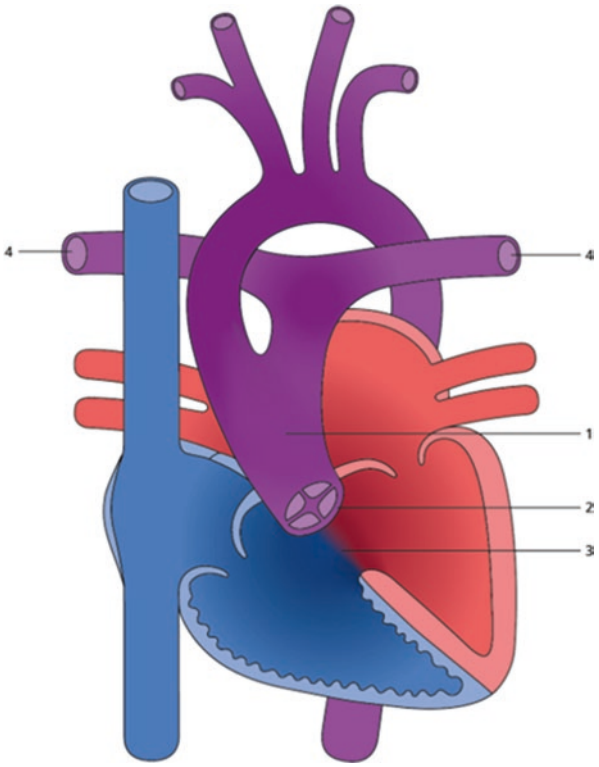

Fig. 1.25 Truncus arteriosus type I: (1) common arterial trunk. (2) Common arterial valve. (3) VSD. (4) Pulmonary arteries

Clinical presentation is dependent on the amount of PBF: in case of mild obstruction to PBF, patients will present with signs of CHF, tachypnea, failure to thrive, and mild degree of cyanosis; situation can be worsened by truncal valve dysfunction and/or by the physiological decrease of PVR within 6–8 weeks of age. Poor development is often associated with DiGeorge syndrome. If not repaired, the condition will lead to POVD as early as 6 months of age, leading to poor results with late surgical correction. Later presentation is often associated with pulmonary hypertension and possible Eisenmenger syndrome. In case of significant impediment to PBF, patients will present with at least moderate cyanosis and hypoxemia and less signs of CHF.

Diagnosis. Variable degrees of cyanosis are usually present. Peripheral pulses are bounding with a wide pulse pressure. On auscultation, S2 is single and loud; a pansystolic murmur may be detected at the left sternal border, whereas a diastolic decrescendo murmur is audible in presence of truncal valve regurgitation. In case of TA type IV, a continuous murmur may be heard over either side of the chest or at the interscapular area. ECG may show RVH or LVH or combined ventricular hypertrophy in more than 70% of the patients. Chest x-ray may reveal cardiomegaly and increased pulmonary vascular markings according to the amount of PBF. A right aortic arch is seen in 25–30% of cases. TTE is diagnostic in almost all cases and

should be based on accurate sequential, segmental approach for addressing all the components that classify the disease and to achieve all the information required for planning the management: VSD dimension, truncal valve anatomy and function, coronary artery origins, PA origin and dimension, aortic arch, and any associated CHD.

If TTE is inadequate for preoperative assessment, CT and MR are very helpful especially for extracardiac anatomy but require general anesthesia.

Treatment. Medical management should stabilize neonates or infants in preparation for surgical repair. In case of CHF, anticongestive treatment should be commenced.

Surgical repair is usually carried out within the first 6 months of life by VSD patch closure, directing the LV blood to the truncal valve, and by PA separation from the arterial trunk and connection to RV with the interposition, in Rastelli procedure, of a RV-to-PA conduit; in this way, the truncal valve will become the "neo-aortic" valve [117].

Outcome. Currently, surgical repair, even at an early age, is performed with low mortality rate and excellent chance of survival with good quality of life well into adulthood. Severe truncal valve regurgitation, type B interrupted aortic arch, coronary anomalies, and genetic anomalies are considered significant risk factors for perioperative morbidity and mortality. In general reoperation later on in life is required for truncal valve replacement and/or RV-to-PA conduit replacement; both can be performed with low morbidity and mortality rates. Some of the mid- and long-term complications, such as residual shunts at atrial, ventricular, or pulmonary levels, or discrete pulmonary branches stenosis or RV-to-PA conduit dysfunction, may be addressed with transcatheter interventions. Unoperated patients who have developed Eisenmenger syndrome have the poorest long-term prognosis [118].

1.1.5 The "Functional-Univentricular Heart"

Hearts with functional single ventricle are rare, comprising 1–2% of all CHDs. This group includes a large variety of CHD with single atrioventricular connection (tricuspid atresia, mitral valve atresia, double-inlet LV) and/or severe hypoplasia of one ventricle and its own atrioventricular valve (hypoplastic left heart syndrome, unbalanced complete AVSD) (Fig. 1.26). Although, from anatomic and physiological aspects, these lesions can vary widely, they can be considered collectively taking into account the management pathway, the so-called single ventricle pathway.

Clinical presentation may differ a lot, according to the underlying anatomy: neonates with well-balanced circulation may show mild cyanosis and normal growth with no signs of CHF; if one of the outflow tracts is significantly obstructed, neonates may present with variable degrees of cyanosis and low PBF or low cardiac output state, requiring emergency care; if both outflow tracts are unobstructed, neonates may present with signs of CHF.

Diagnosis. Physical findings depend on the amount of PBF. With high PBF, mild cyanosis and CHF signs are present; single S2 and a systolic murmur are audible

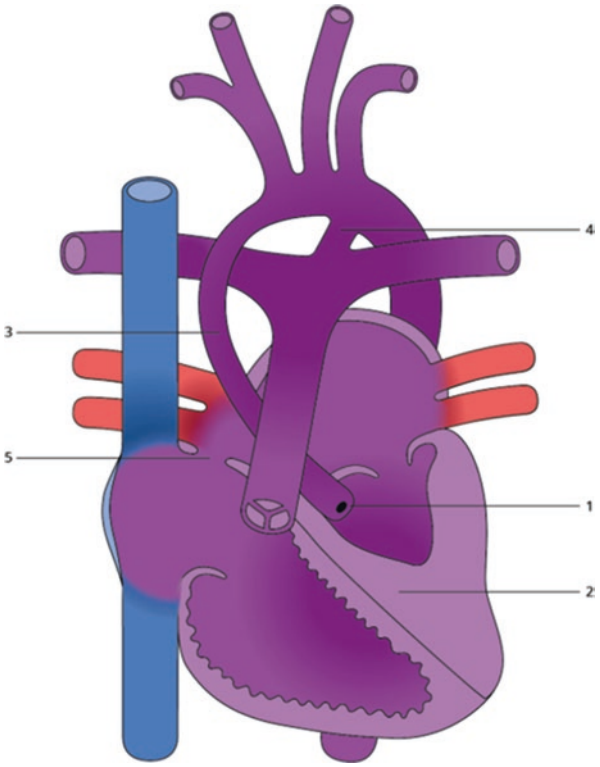

Fig. 1.26 Functional univentricular heart: (1) aortic valve atresia. (2) LV hypoplasia. (3) Ascending aorta hypoplasia. (4) PDA. (5) ASD

along the upper sternal border. With low PBF, moderate to severe cyanosis is present; S2 is single and loud; an ejection systolic murmur may be audible at the upper sternal border. On ECG, ventricular hypertrophy pattern may be seen in most or all precordial leads. Chest x-ray may reveal cardiomegaly and increased pulmonary vascular markings according to the amount of PBF.

TTE is the modality of choice for assessing all the anatomic details, considering the complexity of this group of CHD. It should be performed using a through sequential, segmental approach, including atrial and visceral situs, A-V and V-A connections, cardiac valves, outflow tracts, and great artery anatomy and their relationship.

Treatment. Affected neonates often require PGE1 infusion for pulmonary or systemic outflow tract obstruction. Surgical management consists of a staged approach: in the neonatal period, a palliative procedure may be necessary to increase the PBF via an mBTS or to reduce PBF via a PA banding or to optimize the systemic cardiac output via a Damus-Kaye-Stansel or Norwood procedure. Subsequently patients will be managed along a univentricular pathway consisting of bidirectional cavopulmonary anastomosis and Glenn procedure, followed later on by total cavopulmonary anastomosis (TCPC) and Fontan operation. Glenn procedure consists of superior vena cava-ipsilateral pulmonary artery anastomosis and is routinely

performed at about 3–6 months of age [119]. The TCPC or Fontan operation aims to separate completely systemic and pulmonary venous circulations by directing inferior vena cava deoxygenated blood into the PA via an intracardiac or extracardiac conduit. The original procedure described by Kreutzer and Fontan was a right atrial to main PA anastomosis; then, over time, different modifications had been used; currently it is performed using an extracardiac conduit between the IVC and ipsilateral PA, at about 18 months to 5 years of age [120]. Because of its preload dependency, any Fontan circulation requires the following elements to work properly: good ventricular function, both systolic and diastolic, and low PVR and normal pulmonary vascular bed, both arterial and venous. If any concern arises about one of these elements, a fenestration can be created in the Fontan conduit at the time of the operation, in order to allow systemic venous blood to enter into the atrium and to lower systemic venous pressure at the expense of some degree of oxygen desaturation and hypoxemia. Fenestration was thought to reduce Fontan pressure and the duration of pleural drainage and to maintain a reasonable cardiac output in the immediate postoperative period [121].

Outcome. Interstage morbidity and mortality are mainly related to the onset of some complications such as ventricular dysfunction, AV valve regurgitation, PA stenosis, and PVR rise. To note that after Glenn procedure and takedown systemic-to-pulmonary shunt, coronary circulation is no longer exposed to a diastolic runoff caused by the shunt. Conversely, if some degree of PA hypoplasia persists after the Glenn, it will be challenging to treat because venous flow is a less potent stimulator of arterial growth than pulsatile arterial flow.

Patients with TCPC are at risk for multiple long-term complications which involve multiple apparatus; cardiac, pulmonary, hepatic, gastrointestinal, and neurological problems may occur starting from 5 to 10 years after the operation. Intra-atrial arrhythmias [122], especially for people who had atrio-pulmonary anastomosis, such as atrial flutter, atrial tachycardia, or atrial fibrillation, are difficult to treat either medically or interventionally and tend to have high rate of recurrency. Sinus node dysfunction is common, occurring in about 45% of patients after 5–7 years; it may require pacemaker implantation. Liver dysfunction due to chronically elevated central venous pressure can lead to fibrosis, cirrhosis (30%), and hepatic tumors (2.9%) mainly hepatocellular carcinoma [123]. The occurrence of plastic bronchitis and protein losing enteropathy, whose etiology is still partially unknown, may be the alarming feature of a failing Fontan circulation. Moderately reduced exercise tolerance is observed in the majority of these patients due to poor conditioning, elevated systemic vascular resistance, lack of a subpulmonary ventricle, and sinus node dysfunction. Heart failure and sudden cardiac death are the leading causes of mortality; the incidence of heart failure increases with age. At some point, heart transplantation may become the only effective option in Fontan patients with untreatable arrhythmias and/or protein losing enteropathy and/or overt cardiac failure; survival after transplantation is similar to that observed in patients without complex CHD [124].

1.1.6 Miscellanea

1.1.6.1 Partial Anomalous Pulmonary Venous Connection

Partial anomalous pulmonary venous connection (PAPVC) occurs in <1% of all CHD and is found commonly in Noonan and Turner syndromes, up to 18%. There is a frequent association with left isomerism, the polysplenia form of heterotaxy. In PAPVC, one or more, but not all, pulmonary veins drain into the systemic venous circulation instead of entering the left atrium. Multiple combinations are possible; the right pulmonary veins (RPVs) are involved twice as often as the left pulmonary veins (LPVs). The following forms are the most frequent:

– RPVs may drain into the SVC (Fig. 1.27), at any level even in the azygos vein, or directly into RA; there is a common association with sinus venosus defect ASD.

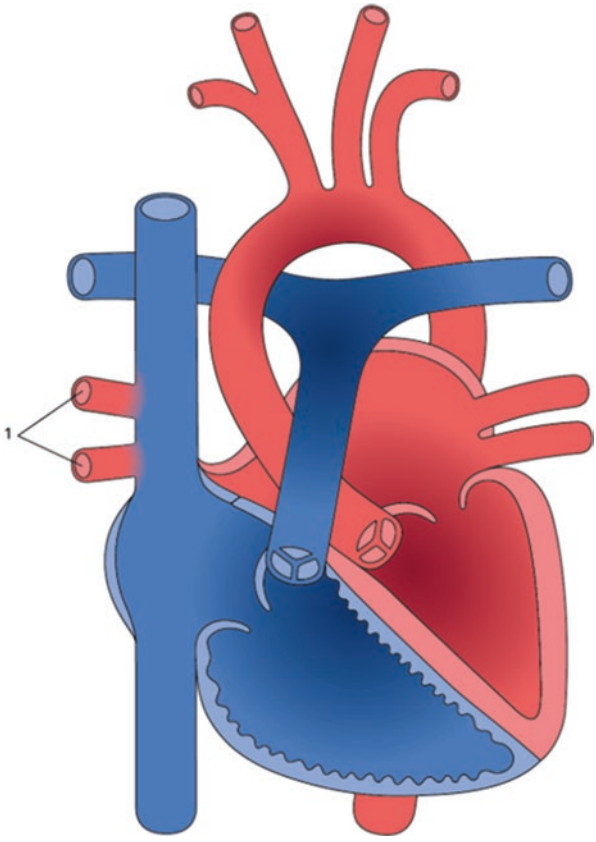

Fig. 1.27 Partial anomalous pulmonary venous connection. (1) Two right pulmonary veins into SVC

– RPVs may drain into the IVC at any level; it is typical of the so-called scimitar syndrome in which the affected part of the right lung has the characteristics of a sequestration: hypoplastic, with abnormal bronchi and abnormal arterial supply which comes directly from the descending aorta. The right PA is usually hypoplastic as well and the atrial septum is typically intact.
– Left upper pulmonary vein may drain into the left innominate vein via an anomalous vertical vein; an ASD is typically present.

Clinical presentation of PAPVC is quite similar to that of an ASD: being an acyanotic defect, symptoms depend on the amount of L-to-R shunting. If a single vein drains anomalously, it carries less than 25% of the pulmonary venous return, resulting in a hemodynamically insignificant shunt; however, patients may become symptomatic later on in life due to LV diastolic dysfunction or worsening LA capacitance. When all but one of the pulmonary veins are involved, patients may present in infancy or early childhood with dyspnea on exertion, repeated respiratory tract infection, and asthma. Rarely older patients present with PH and PAPVC should be considered in the differential diagnosis. Two forms of scimitar syndrome exist with two different presentations: the infantile form and the adult one. Infants may present with some degree of cyanosis, recurrent pneumonia, PH, poor feeding, and failure to thrive. In adults, symptoms and PH are quite rare, and often the syndrome is discovered incidentally when a chest x-ray shows dextrocardia and/or lung hypoplasia.

Diagnosis. When associated with ASD, S2 is split widely and fixed; without ASD, S2 is normal. A 2–3 ejection systolic murmur may be audible at the upper left sternal border as well as a mid-diastolic tricuspid rumble. ECG may reveal RA enlargement, incomplete RBBB, and RVH. On chest x-ray, RA, RV, and PA dilation may be seen in case of large L-to-R shunt, along with increased pulmonary vascular markings. Occasionally, a dilated SVC, a crescent-shaped vertical shadow in the right lower lung (the "scimitar sign"), or a widened superior mediastinum may suggest the site of the anomalous connection. In scimitar syndrome, lung hypoplasia and dextrocardia are easily detected. On TTE, the diagnosis of PAPVC requires a high index of suspicion: dilation of RA and RV in the absence of a large ASD should raise the suspicion as well as a large coronary sinus in the absence of a left SVC. In scimitar syndrome, subcostal views may be helpful to detect the anomalous connection to IVC and, sometimes, the aortopulmonary collateral supplying the affected lung; usually the RPA is small in caliber. If TTE is not conclusive for the diagnosis, CT and MR are excellent imaging modalities. Cardiac catheterization is required whenever PH is suspected or, in older adults, to rule out coronary artery disease.

Treatment. Symptomatic infants or children may require diuretics in case of high PBF. Definitive therapy is surgery that is recommended with a significant L-to-R shunt (> 2:1) or when more than one vein is involved or in case of recurrent pneumonia. In asymptomatic children, repair is delayed until early school age. The surgical approach may vary greatly, according to the anomalous anatomy: in case of RPVs into SVC with ASD, repair is performed by rerouting the anomalous veins into the LA via a patch through the ASD. For scimitar syndrome, resection of the abnormal lung may be necessary [125]; interventional cardiac catheterization may

play a role in closing aortopulmonary collateral artery with device. Nowadays, surgical mortality rate is very low. The major long-term concerns are pulmonary vein stenosis, at the level of surgical reimplantation or within the baffles created for rerouting the anomalous vein. After scimitar syndrome repair, a 13-year freedom from pulmonary venous drainage obstruction is approximately 85%, regardless of the surgical technique used [126].

1.1.6.2 Total Anomalous Pulmonary Venous Connection

Total anomalous pulmonary venous connection (TAPVC) is a cyanotic disease which accounts for 1% of all CHDs. Occurrence is typically sporadic. It could be associated with both forms of heterotaxy. There is a marked male preponderance for the infracardiac type with a 4:1 ratio. It is the result of an abnormal incorporation of the common pulmonary vein into the posterior LA which may lead to persistency of fetal connections to the fetal venous systems. In TAPVC all the pulmonary veins drain directly or indirectly into the systemic venous circulation. A R-to-L shunt at the atrial level is necessary for life, to allow blood to enter into left-sided circulation to maintain systemic cardiac output. Based on the anatomic site of the connection, TAPVC can be classified into the following four types: supracardiac 49%, cardiac 16%, infracardiac 26%, and mixed 9% [127].

- Supracardiac: The pulmonary venous confluence drains superiorly into the left cardinal system via a vertical vein which is not a persistent left SVC because its position is more posterior; vertical vein usually runs anterior to the LPA and then enters the left innominate vein; rarely it courses between LPA and the left mainstem bronchus and may become obstructed.
- Cardiac: The pulmonary venous confluence drains into the coronary sinus or directly into RA; obstruction is uncommon (Fig. 1.28).

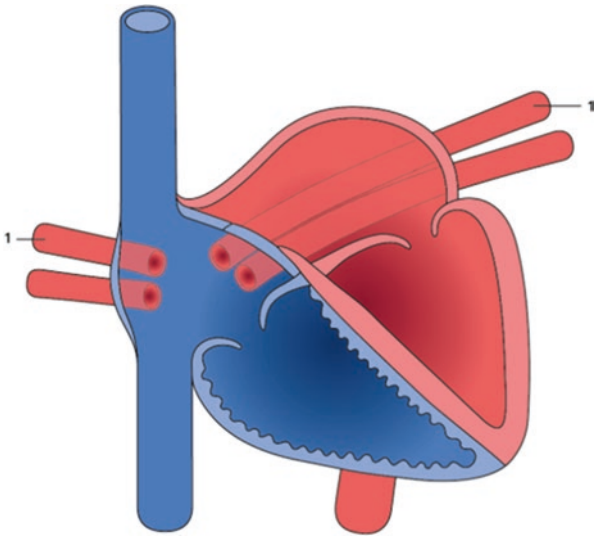

Fig. 1.28 Cardiac total anomalous pulmonary venous connection. (1) Pulmonary veins

– Infracardiac/infradiaphragmatic: The pulmonary venous confluence, via a vertical vein, courses through the esophageal hiatus anterior to the esophagus and then enters into the portal vein or, more rarely, the ductus venosus or hepatic vein or IVC. Obstruction is typical of this form and can occur at different levels: at the esophageal hiatus, at the hepatic sinusoids, or at the ductus venosus as the duct closes postnatally.
– Mixed: The veins drain to at least two different levels; most frequently three veins drain together into the coronary sinus, while the left upper vein drains into the left innominate vein.

For all the forms described, obstruction can rarely occur at the atrial level, should the ASD/PFO become restrictive.

Clinical presentation depends on whether the pulmonary venous return is obstructed. Neonates with unobstructed TAPVC are usually asymptomatic at birth with minimal degree of cyanosis; as the PVR decreases during the first weeks of life, PBF increases and patients gradually develop symptoms of pulmonary overcirculation: tachypnea, feeding difficulties, recurrent respiratory infections, and failure to thrive. Without treatment, 75–85% of cases will die by 1 year of age.

Neonates with obstructed TAPC typically present early after birth and develop symptoms within the first few days: moderate to severe cyanosis, tachypnea with retraction, and signs of respiratory distress. Cyanosis worsens with feeding in the infracardiac type due to the compression of the pulmonary vein confluence by the food-filled esophagus.

Diagnosis

– Unobstructed TAPVC: Hyperactive RV impulse is present. S2 is widely split and fixed; a 2–3/6 ejection systolic murmur is usually audible along with a mid-diastolic tricuspid rumble. ECG shows RA dilation and RVH. On chest x-ray, cardiomegaly is present with increased vascular markings. In supracardiac form, the "snowman" sign, due to enlarged superior mediastinum (vertical vein, dilated innominate vein, and dilated SVC), may be seen but rarely before 4 months of age.
– Obstructed TAPVC: Moderate to severe cyanosis is present. A loud and single S2, indicative of severe PH, along with a gallop rhythm is audible. Typically, heart murmur is absent. Pulmonary crackles and hepatomegaly are present. ECG is not particularly helpful and shows RVH but not RA dilation. On chest x-ray there is no cardiomegaly, and the lung parenchyma is markedly abnormal with pulmonary venous congestion and edema; in severe obstruction, diffuse ground glass appearance becomes evident and could be misdiagnosed as respiratory distress syndrome.

TTE is the modality of choice for assessing all the anatomic details and should be performed using a thorough sequential, segmental approach. The intracardiac anatomy, the pulmonary veins, the pulmonary venous confluence, the entire route of drainage, and the level of the obstruction should be identified quite clearly.

Treatment. In older infants with unobstructed TAPVC and presenting with signs of pulmonary overcirculation, diuretics may be helpful until surgical correction. Because obstruction can develop late, close follow-up is mandatory. Surgical repair is the definitive therapy and is usually carried out shortly after the diagnosis.

Infants with obstructed TAPVC are critically ill and require aggressive medical stabilization, mechanical ventilation, and inotropic support prior to surgical repair which should be performed as soon as possible after the diagnosis as an emergency procedure. Surgical techniques depend on the anatomy of TAPVC and aim at rerouting the pulmonary venous drainage back to the LA via an unobstructed course.

Outcome. Surgical mortality rate is about 5% [128]. Immediate postoperative period can be tough especially in case of significant residual PH which can affect early prognosis and survival. Mid and long term are mainly related to residual or progressive pulmonary venous obstruction which can occur in 10% of cases; some risk factors for significant postoperative venous obstruction have been identified and include hypoplastic or stenotic pulmonary veins and the absence of a common venous confluence at the time of operation. Atrial arrhythmias may occur along with sinus node dysfunction.

1.1.6.3 Anomalous Origin of Left Coronary Artery from the Pulmonary Artery

Anomalous origin of left coronary artery from the pulmonary artery (ALCAPA) occurs in about 0.2% of all CHD with an incidence of 1/300,000 infants. It can cause myocardial ischemia, infarction, and congestive heart failure within the first few months of life and carries a risk of sudden cardiac death in all age groups. The anomalous coronary artery usually arises from the main PA (Fig. 1.29); because coronary perfusion depends on the diastolic pressure gradient existing between the PA and the myocardium supplied by that left coronary artery (LCA), when diastolic PA pressure decreases, LV myocardial ischemia and/or infarction can occur. These critical events may happen as PVR decreases after birth, before coronary collaterals from the right coronary artery (RCA) are well developed. Gradually, over time, after collaterals have enlarged, there will be high flow in the enlarged RCA and in the coronary collaterals supplying the LCA and significant retrograde flow into the PA.

The timing of presentation depends on the development of coronary collateral circulation supplying the LCA from the RCA. Symptoms usually appear at 2–3 months of life and consist of recurrent acute episodes of distress (anginal pain) and CHF such as feeding difficulties and failure to thrive.

Occasionally, children, adolescents and even adults may present with exercise intolerance, fatigue, palpitations, chest pain, or arrhythmias. Late presentation is associated with significant collateral coronary circulation that has been preserving LV function.

Diagnosis. Tachypnea, diaphoresis, tachycardia, and poor peripheral perfusion are commonly present. On auscultation gallop rhythm may be audible, whereas significant murmur is usually absent. ECG usually shows an anterolateral myocardium infarction pattern consisting of deep (>3 mm) and wide (>30 ms) Q waves, inverted T waves, and ST segment elevation in leads I, aVL, and V3–V6. On chest

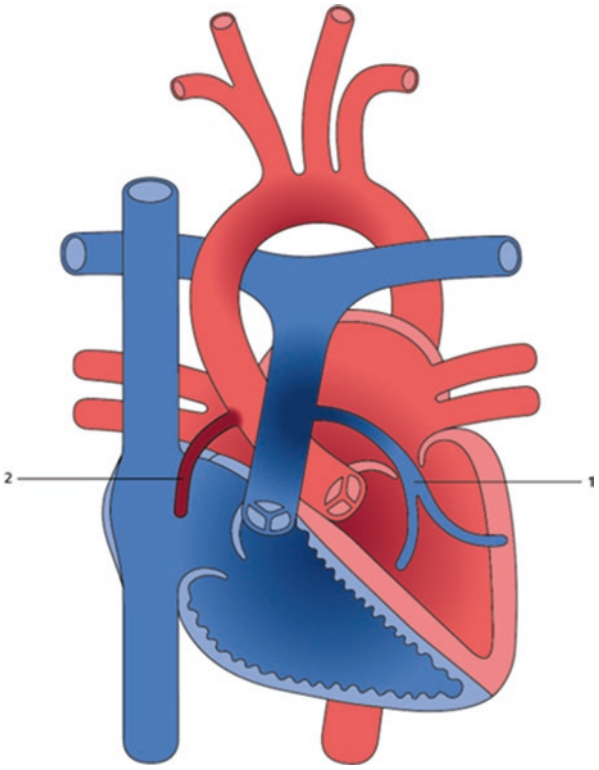

Fig. 1.29 Anomalous origin of left coronary artery from the pulmonary artery. (1) LCA from the PA. (2) RCA from the aorta

x-ray, cardiomegaly and pulmonary edema are common. TTE shows a markedly dilated LV with poor systolic function with variable degree of MV regurgitation due to papillary muscle ischemia. The coronary artery origins should be fully interrogated, in parasternal short-axis view, by 2D imaging and then by color Doppler flow in order to study the flow direction within the coronaries as well [129]. The endocardium and MV papillary muscles may appear echo-bright, indicating prior infarction. Cardiac catheterization has been the gold standard for diagnosing ALCAPA; however, over the last decade, CT but mainly MR has often replaced cardiac catheterization as the preferred diagnostic modality.

Treatment. All the medical treatments are a bridge to surgical treatment; inotropic support and/or diuretics may be helpful to stabilize the patient. Surgical correction is the definitive treatment and is usually carried out shortly after the diagnosis. Surgical technique may vary; the most common approach consists of translocation of the anomalous artery from PA to the aorta. Another procedure termed the Takeuchi repair allows in situ rerouting of the LCA by creating an intrapulmonary baffle; unfortunately it may result in supravalvar pulmonary stenosis later on.

Also in adolescents and adults, surgical techniques are multiple: reimplantation of LCA from PA to the aorta, coronary arterial bypass grafting from the aorta to the left anterior descending artery with closure of the anomalous coronary from inside

the PA, and closure of the anomalous coronary from inside the PA only. Regardless of the technique used, the aim is to remove the L-to-R shunt from the LCA to the PA in order to stop any coronary steal.

Outcome. Although LV function may remain significantly impaired immediately after surgery, usually, in most of the cases, it gradually improves, often going back to normal value. Also functional outcomes in the long-term follow-up are very good for children operated on, despite the severe initial LV dysfunction at presentation. An important issue is the residual, significant MV regurgitation which could be seen in about one-third of the patients.

In patients operated on in adolescence or in adulthood, the RCA tends to decrease to normal size, and the collaterals appear to involute within 3 or more years after surgery. LV function may not recover as much as in infants or children. LV function and LV myocardial damage are the most relevant determining factors in the long-term survivals.

1.1.7 Heterotaxy

Heterotaxy does not define a single specific condition but includes many cardiac and systemic anomalies characterized by an abnormal arrangement across the left-right axis of the body of the internal thoracic and abdominal organs secondary to an embryological failure in differentiation. The key feature of heterotaxy is the mirror-image duplication of normally unilateral structures; some patients appear to have bilateral right-sidedness, so-called right isomerism, and others bilateral left-sidedness, so-called left isomerism. This abnormality becomes evident in the lungs, each of which may show either three lobes and a short bronchus (right isomerism) or two lobes and a long undivided bronchus (left isomerism). At cardiac level, atrial appendages may exhibit isomerism of the pectinate muscles, and a strong association is seen between bronchial morphology, lungs, and atrial appendages. Within the atrium, it is the appendages that are the most constant components; their shape and the particular morphology of their junction with the rest of the atrium permit them to be distinguished as morphologically right or left. Furthermore, a strong association, up to 85%, exists between pulmonary, bronchial, and atrial isomerism and abdominal visceral arrangement; right atrial isomerism is usually associated with absence of the spleen, so-called asplenia syndrome, whereas left atrial isomerism is commonly associated with multiple spleens, so-called polysplenia syndrome. CHDs are usually present in heterotaxy, and they can vary from mild to severe complexity; some CHDs can be seen in both forms of isomerism, such as AVSD, although more prevalent in the right one, about two-thirds of cases, compared to half in left isomerism. Other CHDs occur much more commonly in right isomerism such as pulmonary stenosis, TGA, and TAPVC.

Two extracardiac conditions are frequently seen in patients with heterotaxy: impaired immune system secondary to asplenia or malfunctioning spleen or dysfunctional cilia and bowel obstruction secondary to gut malrotation.

Because of the complexity of heterotaxy, patients should be evaluated following a sequential, segmental approach to properly describe systemic and cardiac anatomy: evaluation should address the thoracoabdominal situs, cardiac position, atrial situs, A-V and V-A connections, cardiac looping, great artery relationship, and systemic and pulmonary vein connections.

Focusing on atrial and abdominal situs, the following arrangements are described: solitus, inversus, right-sided isomerism, and left-sided isomerism.

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