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REVIEW AND PERSPECTIVES

Autopsy in adults with congenital heart disease (ACHD)

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Abstract

The adult congenital heart diseases (ACHD) population is exceeding the pediatric congenital heart diseases (CHD) population and is progressively expanding each year, representing more than 90% of patients with CHD. Of these, about 75% have undergone surgical and/or percutaneous intervention for palliation or correction. Autopsy can be a very challenging procedure in ACHD patients. The approach and protocol to be used may vary depending on whether the pathologists are facing native disease without surgical or percutaneous interventions, but with various degrees of cardiac remodeling, or previously palliated or corrected CHD. Moreover, interventions for the same condition have evolved over the last decades, as has perioperative myocardial preservations and postoperative care, with different long-term sequelae depending on the era in which patients were operated on. Careful clinicopathological correlation is, thus, required to assist the pathologist in performing the autopsy and reaching a diagnosis regarding the cause of death. Due to the heterogeneity of the structural abnormalities, and the wide variety of surgical and interventional procedures, there are no standard methods for dissecting the heart at autopsy. In this paper, we describe the most common types of CHDs that a pathologist could encounter at autopsy, including the various types of surgical and percutaneous procedures and major pathological manifestations. We also propose a practical systematic approach to the autopsy of ACHD patients.

Keywords Autopsy · Cardiovascular pathology · Congenital heart diseases · Adult congenital heart diseases · Protocol

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Introduction

Over the last 40 years, major advances have been made in the clinical diagnosis and treatment of congenital heart diseases (CHD) [1]. These developments have resulted in an increasing population of patients who survive into adulthood – the adults with congenital heart disease (ACHD). ACHD includes a large variety of congenital disorders [2]. Nowadays, the ACHD population is exceeding the pediatric CHD population and is expanding by an estimated 5% per year. More than 90% of patients with CHD are adults, and of these, about 75% have undergone palliative intervention or surgical correction [3–7].

Approximately 50% of ACHD patients face complications during their lifetime, depending on the type of defect and previous interventions, most commonly arrhythmias, ventricular dysfunction and heart failure, endocarditis, need for reoperation (e.g., due to valve or conduit dysfunction), pulmonary hypertension, and premature or sudden cardiac death (SCD) [8]. Early diagnosis and treatment has altered the natural history of CHD and has led to new and, at times, complex types and patterns of cardiovascular and lung pathology that increasingly require the attention of expert pathologists.

Autopsy can be a very challenging procedure in ACHD patients. The approach and protocol may vary depending on whether we are faced with cases of native CHD who have reached adulthood without surgical or percutaneous interventions (but with various degrees of cardiac remodeling) or cases of previously palliated or surgically/percutaneously corrected conditions.

Careful clinicopathological correlation is, thus, required to assist the pathologist in performing the autopsy and reaching a diagnosis regarding the cause of death. It is essential that the clinical history, including detailed surgical reports, is available to the pathologists at the time of the autopsy.

Clinicians and/or family members who request an autopsy may wish to obtain information on one or more of the following questions:

- Was the clinical diagnosis correct?
- Were there any associated abnormalities/comorbidities not diagnosed prior to an intervention that could have impacted on its outcome?
- Was a surgical or interventional procedure (correction or palliation) performed correctly?
- Was the timing of intervention appropriate?
- Were there any unrecognized complications contributing to the death of the patient?

For this purpose, a pathologist who performs such an autopsy must have good knowledge of the following:

- *Morphology of CHDs*: Sequential segmental analysis and knowledge of flow patterns through the morphologically abnormal heart
- *Past and contemporary surgical procedures:* For example, palliative shunts, vascular grafts, and patches; knowledge of flow patterns in the operated heart; potential complications
- *Percutaneous interventional procedures*: *For example, stents, occluder devices, percutaneous valve prostheses*
- *Postoperative pathology*: Residual lesions short- and long-term complications (e.g., valve degeneration, thrombosis, embolic events, endocarditis)
- *Patterns of heart remodeling*: *Hypertrophy, dilatation and fibrosis, associated with arrhythmia, and heart failure*
- *Related pathology in other organs*: Pulmonary edema, pulmonary vascular disease, protein loosing enteropathy, liver cirrhosis, kidney injury, cerebral abscess
- *Syndromic CHD and associated extracardiac malformations*

Due to the heterogeneity of the structural abnormalities mentioned above, and the wide variety of surgical and interventional procedures, there are no standard methods for dissecting the heart at autopsy. In this paper, we describe the most common types of CHDs that a pathologist could encounter at autopsy, including the various types of surgical or interventional procedures and major pathological manifestations. We also propose a practical systematic approach to the autopsy of ACHD patients.

The most common congenital heart defects encountered in adults

Atrial septal defects (ASDs)

Description: ASD is a direct communication between the atria allowing shunting of blood.

There are four types of ASD, depending on the location of the defect (Fig. 1a):

- *Type 1: Ostium secundum type ASD*. This is the most common type of ASD. The defect is located within the fossa ovalis (FO), which is about 1–2 cm in diameter, and often remains undiagnosed until later in life.
- *Type 2: Ostium primum defects*. These are located inferiorly close to the atrioventricular valve and are separated from the FO by its inferior muscular rim. This type of ASD is typically part of the spectrum of atrioventricular septal defects and is associated with abnormal atrioventricular valves (see also atrioventricular septal defect section)

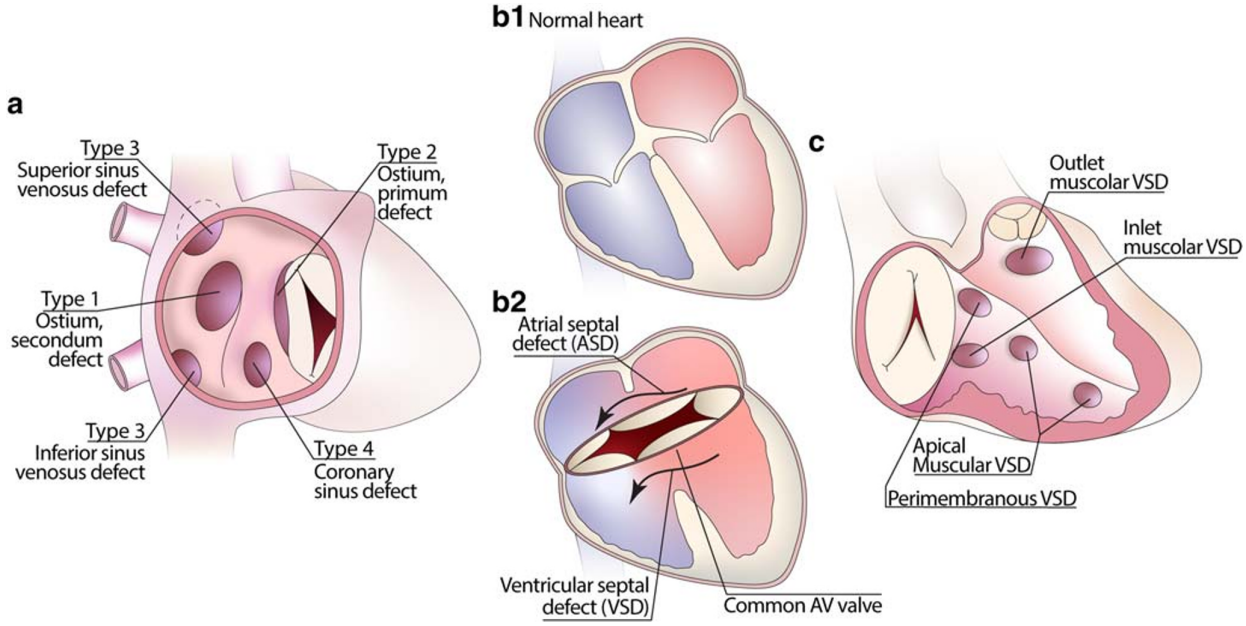

Fig. 1 Drawings of the most common types of atrial (**a**), atrioventricular (**b**) and ventricular septal defects (**c**), and their locations inside the cavities

- *Type 3: Sinus venosus ASD*. This can be a superior or an inferior sinus venosus type of ASD, being related to the orifice of either the superior or the inferior vena cava (SCV or IVC), respectively. The superior variant is commonly associated with partially anomalous pulmonary venous connection [9]. The inferior defect is positioned close to the orifice of the ICV and can be associated with an anomalous right inferior pulmonary vein.
- *Type 4: Coronary sinus defect*. It is very rare and located closely to the ostium of the coronary sinus (CS). It is due to deficiency of the walls of the coronary sinus allowing shunting with the left atrium (LA) [10].

Most ASD cases are sporadic and very few run in families in an autosomal dominant pattern [11]. Ostium primum defects are common in individuals with Down syndrome or Ellis-Van Creveld syndrome. One third of ASD occur in association with other cardiac malformations [12].

Symptoms related to ASDs depend on the size of the defect and associated lesions/comorbidity. Many patients remain asymptomatic for many years and may remain undiagnosed throughout their lives, while others present in childhood. Many ASDs are nowadays diagnosed after the age of 40 years. Symptoms include arrhythmia, paradoxical embolism, right ventricular failure, and, more rarely, cerebral abscess and pulmonary hypertension.

ASD causing significant left-to-right shunting or other complications should be repaired, unless pulmonary vascular disease has developed. Most cases of secundum ASD are nowadays closed percutaneously, using an occluder device.

Failure to align the device can result in device embolization and is likely to occur in very large defects (>/ = 35 mm), with absent or deficient posterior or inferior rim. Moreover, percutaneous closure may be challenging in cases with a multi- fenestrated and/or aneurysmal atrial septum or proximity of the FO to the venous orifices [13, 14] (Table S2 supplement). When a transcatheter approach is not feasible or a primum or sinus venosus ASD is present, open-heart surgery is required to close the defect with a graft or prosthetic patch [15, 16] (Table 1).

Autopsy recommendations

Autopsy should identify the location, type, and size of an unrepaired ASD, as well as associated lesions. Moreover, dilatation of the RA and LA, tricuspid valve annular dilatation, and dilatation (and at times hypertrophy) of the right ventricle (RV) are typically encountered. Pulmonary artery dilatation is common, while atheromatous changes in the pulmonary arteries and significant RV hypertrophy suggest pulmonary hypertension. Histology of the lungs is essential to detect vascular changes.

In repaired ASDs, the position and size of surgical patches and closure devices, as well as residual communications, should be described. Displacement or embolization of a device and dehiscence of a surgical patch should be excluded. After timely successful repair, the heart is expected to remodel toward normal. Both patches and devices become endothelialized 6–12 months after intervention and may be difficult to identify. Late complications include thrombosis of the device and embolic phenomena (stroke or coronary artery and systemic embolization), complete heart block, and infective endocarditis. Moreover, rare cases of

device erosion toward the aorta have been described [17] (Table 1, Table S2 supplement).

Atrioventricular septal defects (AVSD)

Description: AVSDs (synonyms: atrioventricular canal defects or endocardial cushion defects) are characterized by a common atrioventricular junction and a common atrioventricular valve resulting in communication between the atria and ventricles and all four cardiac chambers, depending on the anatomical severity (Fig. 1b). Down's syndrome is commonly associated with AVSDs, present in one third to one half of all patients.

There are several types of AVSDs

The *ostium primum defect (or incomplete AVSD)* (see also ASD section) has a common atrioventricular junction. The bridging leaflets of the atrioventricular valve are joined together and are adherent to the crest of the ventricular septum forming two separate valve orifices that are often regurgitant. As a result, shunting across the defect occurs only at atrial level [18]. Surgery abolishes the shunt and associated overload to the RV while repairing or, more rarely, replacing the atrioventricular valves [19].

The *complete form of AVSD* is characterized by having a communication allowing both interatrial and interventricular shunting, a common atrioventricular valve orifice and a five-leaflet valve, most often dysplastic, but with the bridging leaflets not adherent to the atrial septum or the crest of the ventricular septum. Surgical correction with closure of interatrial and interventricular components, along with repair and reconstruction of atrioventricular valves, is done. After repair of an AVSD, a re-intervention may be needed for left-sided valve insufficiency or stenosis, often years after repair, with rate of re-intervention of about 10% [20].

Complete AVSDs can be classified into balanced and unbalanced according to the relative dimensions of the ventricles. In unbalanced AVSDs, one of ventricles is too small/hypoplastic and may be deemed unsuitable for a biventricular repair. These cases require a staged single-ventricle palliation with a Fontan or Fontan-like procedure [20] (Table 1).

Autopsy recommendations

Unoperated cases are almost never seen in the adult population and are usually partial AVSDs (primum ASDs). Adults with unrepaired complete AVSDs typically present with severe pulmonary vascular diseases (Eisenmenger syndrome).

In repaired cases, patches and sutures are usually re-endothelialized and calcified for months or years following surgery. The presence of residual VSD and ASD, left-sided valve pathology (stenosis or regurgitation, surgery, endocarditis), subaortic or pulmonary stenosis, and myocardial remodeling of atria and ventricles with histologic examination of fibrosis (risk of arrhythmia) all needs to be evaluated at autopsy. Finally, pulmonary vascular disease and endocarditis should be excluded. In palliated cases, the presence of banding of the pulmonary trunk or a Fontan-type circulation (see later) should be described (Table 1).

Ventricular septal defects (VSDs)

Description: A group of common congenital heart defects characterized by holes in the ventricular septum.

There are several types of VSD (Fig. 1c): A *perimembranous* has the membranous septum incorporated into its postero-inferior border. *Muscular VSDs* are completely surrounded by muscle and can be located anywhere in the muscular ventricular septum. *Subarterial VSDs* (synonyms: supracristal, doubly committed or juxta arterial defects) are immediately adjacent to both the aortic and pulmonary valves and may have perimembranous or muscular border.

Patients with certain genetic abnormalities, e.g., Down syndrome, have a high incidence of associated VSDs: VSD is an integral part of tetralogy of Fallot, and VSDs are present in most patients with univentricular circulation or transposition of the great arteries.

VSDs with a maximal size of 2 mm or less are likely to close prenatally, while others may close within the first 10 years of life [21]. Residual scarring in the septum or scarring with aneurysmal dilatation of the membranous septum with redundant tricuspid valve tissue may be seen at autopsy at the site of spontaneously closed defect.

Persistent VSDs are often restrictive but may be larger. Large or multiple VSDs can lead to pulmonary hypertension and right ventricular hypertrophy, eventually with the development of Eisenmenger syndrome characterized by shunt reversal and cyanosis. Patients with a VSD and significant, irreversible pulmonary vascular disease are deemed inoperable.

For this reason, timely surgical closure is recommended for all large perimembranous VSDs, supracristal VSDs, and VSDs with aortic valve prolapse [22]. Muscular VSDs may be closed by percutaneous techniques. A large number of devices have been used for VSD occlusion, the Amplatzer VSD occlude device being the most popular (Table 1).

Autopsy recommendations

Surgical patches can be calcified and fibrosed, or largely incorporated into the ventricular septum many years after surgery, and can be difficult to identify. Postoperative complications that should be searched for are the following: dehiscence of the patch, heart block in perimembranous septal defects (due to surgical damage of left bundle branch), infective endocarditis (operated and non-operated cases), and patch-related thrombus or embolization. In case of supracristal defects, accompanying aortic regurgitation is common,

Table 1 Major congenital cardiac defects and autopsy considerations after surgical procedures

Type of defects	Considerations after surgical procedures
ASD	Residual defect after patch or device closure Size of the right and left atria Size of the right and left ventricular chambers Pulmonary vascular disease
AVSD	Relative size of the ventricles: unbalanced type, with one dominant and one hypoplastic ventricle Left and right atrioventricular valve incompetence Left and right atrioventricular valve dysplasia Subaortic or subpulmonary obstruction due to left atrioventricular valve replacement or ventricular patch Residual VSD or ASD Pulmonary vascular disease Complete heart block Sudden death Endocarditis
VSD	Residual defect after patch or device closure AV node/conduction tissue damage/dysfunction Remodeling of the right or left ventricle Aortic or tricuspid valve incompetence Endocarditis
Truncus arteriosus	RV-PA conduit stenosis, incompetence or infection Truncal valve regurgitation, stenosis or infection Prosthetic valve dysfunction or endocarditis Coronary arteries anomalies leading to myocardial damage Residual VSD Truncal root dilatation Pulmonary artery stenosis Pulmonary vascular disease
Tetralogy of Fallot	Pulmonary valve regurgitation Residual VSD Residual pulmonary/ right ventricular outflow tract stenosis Ventricular or atrial tachyarrhythmias Endocarditis RV-PA conduit dysfunction Aortic root dilatation (± aortic valve regurgitation) Right and/or left ventricular dysfunction Congestive heart failure
Congenital aortic valve disease	Aortic valve stenosis or incompetence LV hypertrophy, dilatation, and/or dysfunction Aortic dilatation Ross procedure: pulmonary valve prosthesis, coronary artery re-implantation, dilatation of the neo-aorta Bentall procedure: coronary artery re-implantation Conduction abnormalities Endocarditis
Aortic coarctation	Re-coarctation (most common with end-to-end or percutaneous repair) Associated defects: bicuspid aortic valve, subaortic stenosis, mitral valve disease, ascending aortic dilatation. (Pseudo) aneurysms at the site of previous repair Infective endocarditis or arteritis Cerebral berry aneurysm rupture Aortic dissection Premature coronary artery disease Left ventricular hypertrophy/remodeling
(D-)TGA	*After Mustard or Senning procedure*: systemic ventricular morphology, scarring, tricuspid valve abnormalities, pathway obstruction, baffle leaks, pulmonary stenosis, pulmonary vascular disease, subpulmonary LV size and function *After arterial switch procedure*: Coronary artery abnormalities/distortion, neo-aortic root dilatation, neo-aortic valve regurgitation, right ventricular outflow tract obstruction, ventricular remodeling
Pulmonary valve disease	Pulmonary/ prosthetic valve stenosis or incompetence Right ventricular remodeling Right ventricular scarring Aneurysmal dilatation of the pulmonary artery Endocarditis

produced by prolapse of the anterior aortic leaflet. Residual VSDs should be identified and described (e.g., suture dehiscence). Muscular VSDs may be more difficult to identify. Remodeling of the LV and RV should be described, and lung histology is required to identify and grade pulmonary vascular disease. The presence of pacemakers for permanent pacing may indicate manifestations of complete heart block during life (Table 1, Table S2 supplement).

Truncus arteriosus or common arterial trunk

Description: The *common arterial trunk (CAT)*, also known as *truncus arteriosus*, is a rare type of CHD (1–3% of cases) and therefore mentioned only briefly here.

The anomaly is characterized by a single (common) arterial trunk overriding a large VSD, supplying the coronary, systemic, and pulmonary arterial system. The latter arises from the common trunk either as separate right and left pulmonary arteries or as a single pulmonary trunk that subsequently bifurcates. This common trunk is guarded by a truncal valve, which is always in continuity with the mitral valve. In most cases, there is usual atrial arrangement (situs solitus) and concordant atrioventricular connections. In majority of cases, the truncal valve has three leaflets and is grossly dysplastic and incompetent, but it may also be stenotic. Approximately 30% of truncus arteriosus cases are associated with a genetic syndrome, frequently DiGeorge syndrome with 22q11deletion. The most significant variation in the aortic pathways associated with CAT is severe coarctation or complete interruption of the aortic

arch, with the proximal aorta arising directly from the common trunk and the distal aorta fed through a patent arterial duct.

Without surgical repair, most truncus arteriosus patients die in early life, most frequently due to severe pulmonary arterial hypertension (PAH) or from heart failure and associated low flow conditions such as myocardial ischemia and necrotizing enterocolitis.

Surgical repair is indicated in the neonatal period, or by 2–3 months of age due to the rapid progression of pulmonary vascular disease. Repaired cases achieve an 80% long-term survival [23]. The aim of surgical repair is to restore a normal physiologic circulation. The pulmonary arterial trunk (or branches) is detached from the truncus and attached to the right ventricle (RV) via a homograft (a valve conduit). The VSD is closed with a patch. The truncal valve becomes the neo-aortic valve, and, if necessary, it is repaired or replaced by an aortic homograft with coronary artery re-implantation (Table 1).

Autopsy recommendations

In surgically repaired CAT adult patients, the pathologist has to look for a possible residual VSD in relation to the patch, truncal valve regurgitation or stenosis due to dysplastic leaflets, or prosthetic valve dysfunction, aortic (truncal) root dilatation, coronary artery abnormalities, stenosis or incompetence of the valved conduit right ventricular outflow or pulmonary artery stenosis, and, importantly, endocarditis. Histological examination of the myocardium and lungs is required to evaluate early and late scaring and the presence of pulmonary vascular disease (Table 1, Table S2 supplement).

Pulmonary stenosis

Description: Pulmonary stenosis is a common type of CHD and is frequently isolated but can also be associated with simple or complex congenital cardiac defects.

The stenosis can be *valvular*, localized at the site of pulmonary valve or its annulus, or, more rarely, in the *subvalvular* (muscular) infundibulum of the RV, or *supravalvular* in the pulmonary trunk or its branches. In *pulmonary valvular stenosis*, the valve is typically a dome-shaped diaphragm with a central perforation without recognizable leaflets. *Isolated infundibular stenosis* is frequently associated with a VSD. Restrictive VSDs can be associated with hypertrophic muscular bundles within the RV causing mid-ventricular obstruction (double-chambered RV).

Supravalvular stenosis is a circumferential fibrous ring that obstructs the pulmonary trunk, the main pulmonary branches, or even the distal branches with multiple stenoses typical of Williams syndrome.

The stenosis can be relieved by percutaneous dilatation with balloon (angioplasty) or by surgical maneuvers such as pulmonary commissurotomy, complete or partial removal of the malformed leaflets with or without enlargement of the annulus with a transannular patch. The presence of infundibular obstruction can be addressed through the pulmonary valve annulus if not too hypoplastic, or through the tricuspid valve ventriculotomy, which is rarely required nowadays for the resection of the hypertrophic muscle bands, as it is associated with long-term complication (RV dysfunction, ventricular tachycardia). In supravalvular stenosis, it is necessary to enlarge the pulmonary trunk with autologous or heterologous pericardium or with Gore-Tex (Table 1).

Autopsy recommendations

In adult patients with unoperated pulmonary stenosis, the pathologist has to evaluate the level at which obstruction occurs. Secondary changes due to the pulmonary valve anomaly are RV hypertrophy, tricuspid valve insufficiency, and RA dilatation. Poststenotic dilatation affects the pulmonary trunk or its left branch. Surgically treated cases should be examined for pulmonary valve incompetence, RV dilatation, and ventricular scarring. After percutaneous or surgical valve implantation, evaluate the position of the valve, residual stenosis, and valve complications such as paravalvular leak, endocarditis, and calcification of the leaflets (Table 1, Table S2 supplement).

Tetralogy of Fallot

Description: The defining anatomical abnormalities of the tetralogy, as described by Étienne Fallot in 1888, are VSD with overriding aorta, pulmonary stenosis, and right ventricular hypertrophy (RVH).

TOF is the most common cyanotic CHD accounting for up to 9% of CHD [24]. It can be associated with trisomy 21, trisomy 18, trisomy 13, and DiGeorge syndrome, but in most patients, no genetic association can be found. Congenital abnormalities associated with ToF include bicuspid pulmonary valve, left pulmonary artery stenosis, coronary artery anomalies, right-sided aortic arch, anomalous pulmonary venous return, and skeletal abnormalities of the vertebrae and ribs [25–27].

The severity of right ventricular outflow tract obstruction is variable, but when severe, there is right-to-left shunting through the VSD and systemic cyanosis. Most adult cases encountered nowadays in developed countries will have had reparative surgery early in life, with takedown of any previous palliative shunt (Table 1).

Definitive repair consists of patch closure of the VSD, with the overriding aorta supplied only by the LV and relief of pulmonary and subpulmonary stenosis by infundibular remodeling and/or a transannular patch. Surgical closure of the VSD may be done through a right ventriculotomy (more traditional approach) or with a transatrial approach through the tricuspid valve (more recent technique) (Fig. 2). Recently, a surgical technique with pulmonary valve reconstruction has been proposed by several authors to avoid or minimize the long-term pulmonary valve regurgitation that is inevitable with the traditional techniques [28–30] (Table 1).

Nowadays, the life expectancy of patients with repaired ToF is felt to be similar to the general population [31], even though there persists a small risk of sudden cardiac death at all ages [32], and pulmonary regurgitation is common which frequently requires further intervention.

Early complications after repair include residual VSD, right ventricular outflow tract obstruction or pulmonary stenosis, and ventricular tachyarrhythmias (Table 1). Later complications include pulmonary regurgitation, progressive dilatation of the aorta with secondary aortic valve incompetence, progressive right ventricular dilatation, or aneurysm, following extensive ventriculotomy, infundibular remodeling, or transannular patching, and tricuspid valve incompetence. Patients with pulmonary atresia, at the extreme end of the spectrum of ToF, require an RV to PA conduits at repair, which typically becomes stenotic or regurgitant over time; a synthetic conduits may develop neointimal hyperplasia, while homograft conduits and valves tend to calcify.

Previous palliative shunts, right ventricular hypertrophy with fibrosis (Fig. 3), a prolonged QRS duration, ventricular dysfunction, and atrial arrhythmias have been shown to be predictors of death and sustained VT [33]. Patients felt to be at significant risk of sudden death may be offered an ICD as a primary prevention [34].

During adult life, reoperation for pulmonary valve regurgitation is often required in the presence of severe RV dilatation, RV dysfunction, and associated symptoms or progressive tricuspid regurgitation, with very low surgical risk [35]. Several types of bioprosthetic valves, homografts, and, more recently, percutaneous pulmonary valves are used in these patients, depending on availability and anatomical features [36] (Fig. 4) (Table 1, Tables S2 and S3 supplement).

Autopsy recommendations

On external examination, there are typically the scars of previous operations, sternotomy or thoracotomy. In patients dying of heart failure, there may be systemic signs of right or biventricular failure, while internally, there may be pleural effusions, pulmonary edema, ascites, and hepatic congestion. Fibrosis and calcification of operation sites, patches, and conduits may be present, with possible stenosis or infection of conduits. Pulmonary and tricuspid valve competence should be assessed, and ventricular size should be measured. Right ventricular hypertrophy and fibrosis may be the substrate for fatal arrhythmia. Endocarditis may be an early or late complication of the original surgery (Fig. 2) or later valve replacements and is often associated with septic emboli in the lung. Percutaneous pulmonary valve implants appear to be prone to infective endocarditis, which is often obstructive. Older patients may have developed superimposed atheroma of native coronary vessels (Table 1, Tables S2 and S3 supplement).

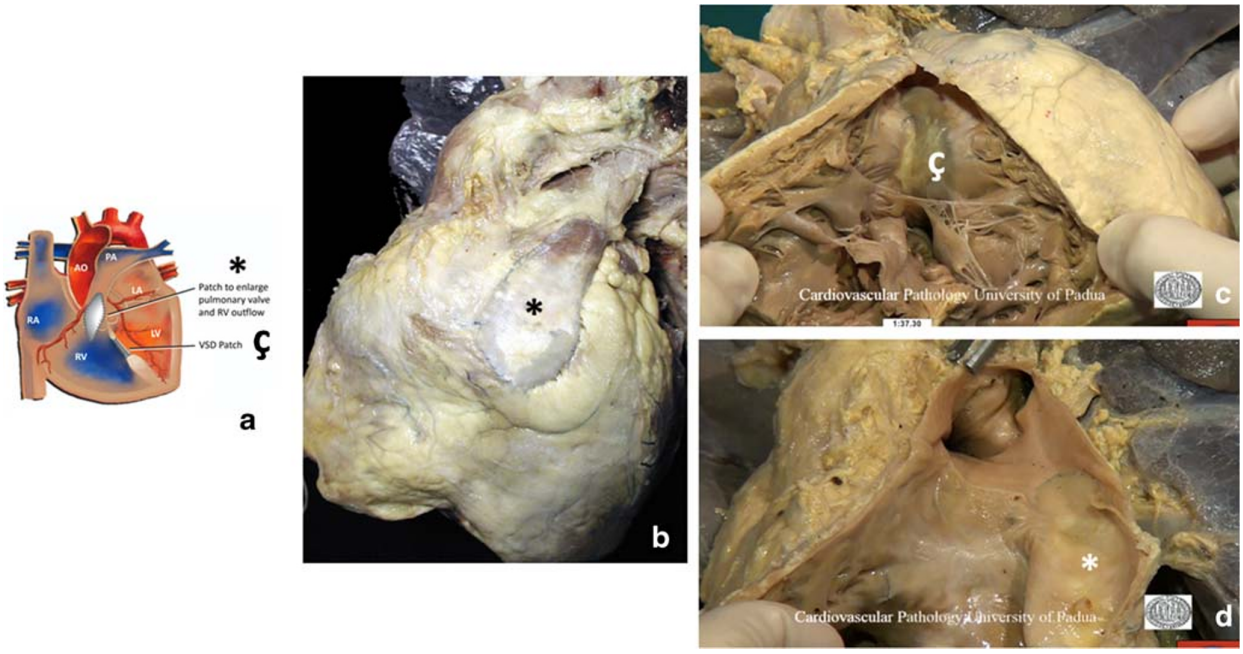

Fig. 2 Diagram of ToF after surgical repair, with a patch inserted to enlarge the pulmonary valve and the RV outflow tract (*) and closure of the interventricular defect with a patch (ç) **(a)**. Operated TOF at adult age; the patient died of heart failure **(b, c, d)**. Anterior view of the heart with transannular patch (*) and dilatation of the right ventricle with enlargement of the right heart silhouette **(b)**; internal view of the RV outlet showing the site of the ventricular septal defect closed by an endothelialized patch (ç) and dilatation of the RV **(c)**; close view of the calcified RV outflow patch (*) **(d)**

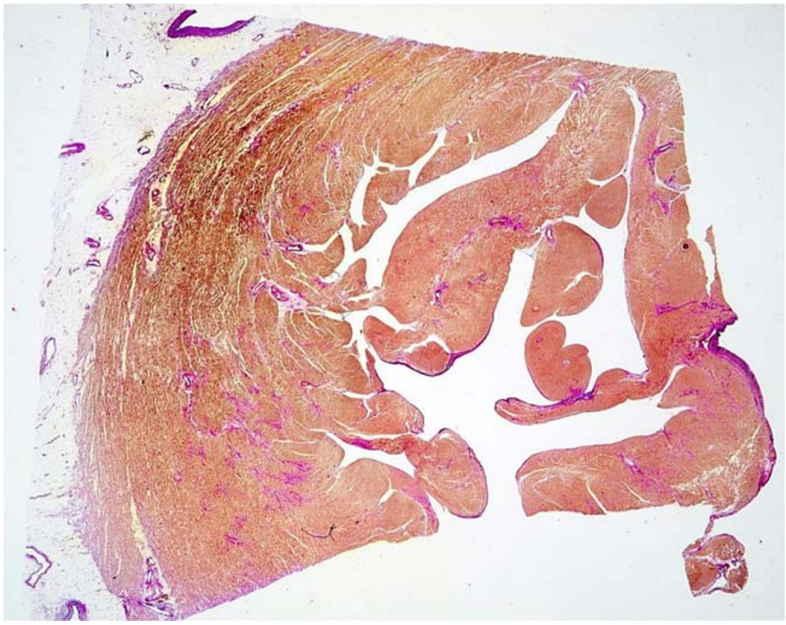

Fig. 3 Histology of RV wall of an adult patient with operated ToF. Transmural section showing hypertrophic myocardium and fibrosis of interstitial reactive and replacement type. Elastic van Gieson stain

Left ventricular outflow tract obstruction (LVOTO)

Description: LVOTO in adults includes a series of stenotic lesions which can be single or at multiple sites along the tract. Obstruction can be subvalvular, valvular, and/or supravalvular.

Valvular AS is the most frequent form, accounting for 75% of LVOTO cases, while subvalvular and supravalvular account for 20–25% and 5–7%, respectively. AS can occur in isolation or in association with other forms of CHD such as VSD, mitral valve disease, or aortic coarctation (Shone complex).

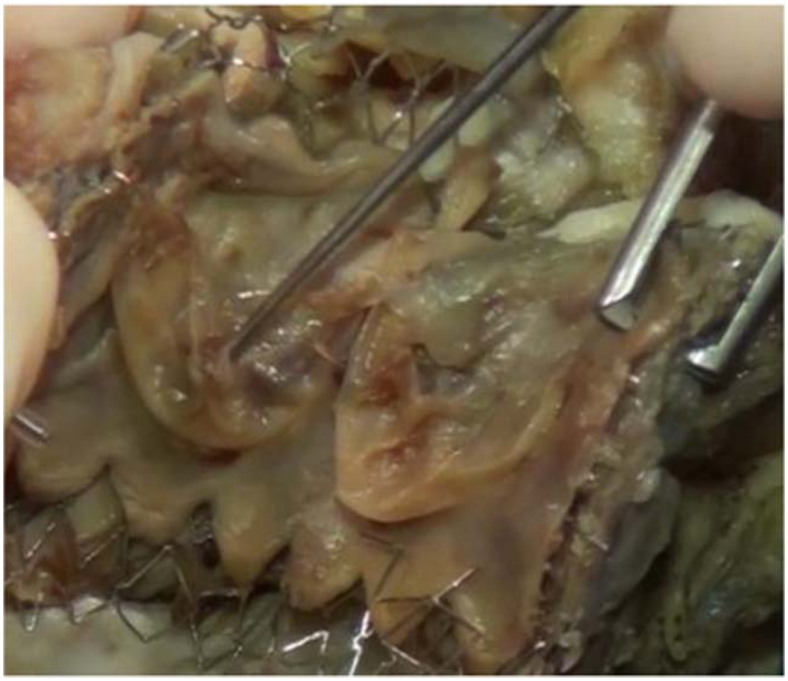

Fig. 4 Hybrid procedures in a case of ToF with previous surgery and stenting of the pulmonary valve with a percutaneous intervention, using a *Melody* valve

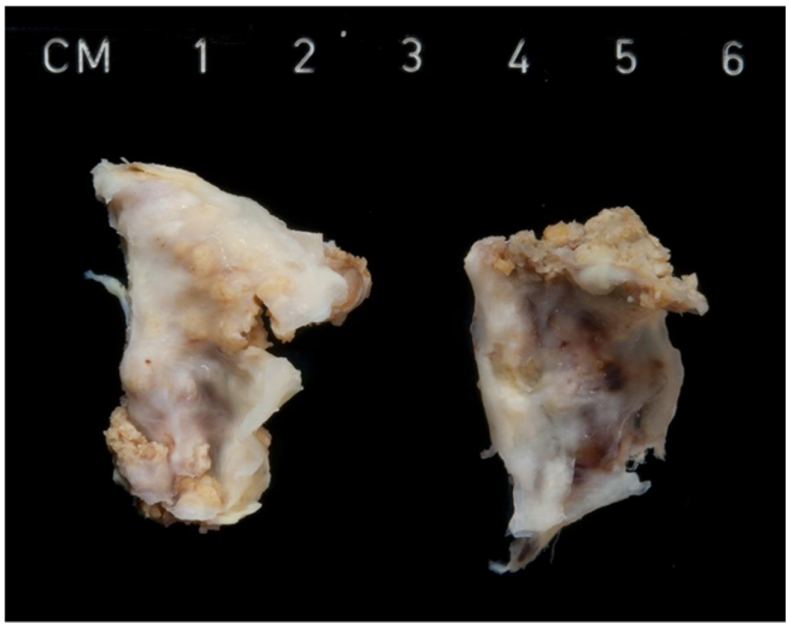

Fig. 5 Bicuspid aortic valve in a 50-year-old man, with dystrophic calcification causing aortic valve stenosis

Valvular stenosis is the most common cause of bicuspid aortic valve (BAV), with an estimated prevalence of 1–2% in the general population [37]. BAV represents the most common cause of aortic valve replacement or implantation in adult population < 70 years, due to leaflet calcification (Fig. 5). There is complete absence of one of the commissures or presence of a, often heavily calcified, ridge ("raphe") between two cusps, resulting in a functionally bi-leaflet valve. It is recommended to describe the orientation of commissural anomaly of these valves: absent commissure (or raphe) between the left and the non-coronary (LC-NC) or between the right and the non-coronary leaflets (RC-NC, more frequently associated with aortic coarctation) or between the left and right cusps (LC-RC, more frequently associated with dysfunction and aortic root dilatation). Dilatation of the ascending aorta bears a related risk, albeit still rare, of aortic dissection and rupture with hemopericardium due to medial degeneration. One half of aortic dissections in the youth are associated with BAV.

BAV may be hereditary, and cardiological screening of the family, including echo, is advisable. Much rarer valve abnormalities are the tricuspid aortic valve due to dysplastic leaflets, with thickening or partial commissural fusions or annular hypoplasia; the quadricuspid valve (four normal-looking leaflets or with a double "raphe"); and the unicuspid aortic valve (single cusp with an eccentric "keyhole" or a dome-like appearance) and can be associated with a hypoplastic aortic annulus and ascending aorta. *Subvalvular stenosis* includes a wide range of anomalies from a discrete fibroelastic membrane/ring to a tunnel-like fibromuscular band. It can be complicated by valvular stenosis or with other abnormalities of the subaortic region, such as anomalous accessory mitral leaflet or accessory muscular band. *Supravalvular stenosis* is characterized either by a discrete focal stenosis at the sinotubular junction due to thickening of the aortic wall (seen in Williams Syndrome) [38], or an isolated fibrous membrane, or diffuse tubular hypoplasia of the ascending aorta and brachiocephalic vessels.

Patients may present very early in life or remain asymptomatic for many years. Progression of AS depends on the anatomical features of the valve and the degree of superimposed degenerative calcification or atherosclerosis. Symptomatic lesions in adults are surgically treated, with valves sent to the pathologist as a surgical specimen, but sometimes be found at autopsy, the cause of a severely hypertrophied left ventricle (or dilatation when the valve is severely regurgitant) (Table 1, Tables S2 and S3 supplement).

Autopsy recommendation

At autopsy, the pathologist should identify the type and location of LVOT stenosis or obstruction, including accessory fibrous tissue, aortic valve anatomy, and extent of calcifications and signs of endocarditis. The ascending aortic diameter/circumference and aortic wall thickness should be measured to evaluate stenosis, ectasia/aneurism, and atherosclerosis.

In all cases, native valve anatomy should be evaluated. In patients with aortic dissection spontaneous or procedure related, the presence of a BAV should be recorded (see above). In cases of transcatheter aortic valve replacement (TAVR), the valve bearing stent should be removed carefully.

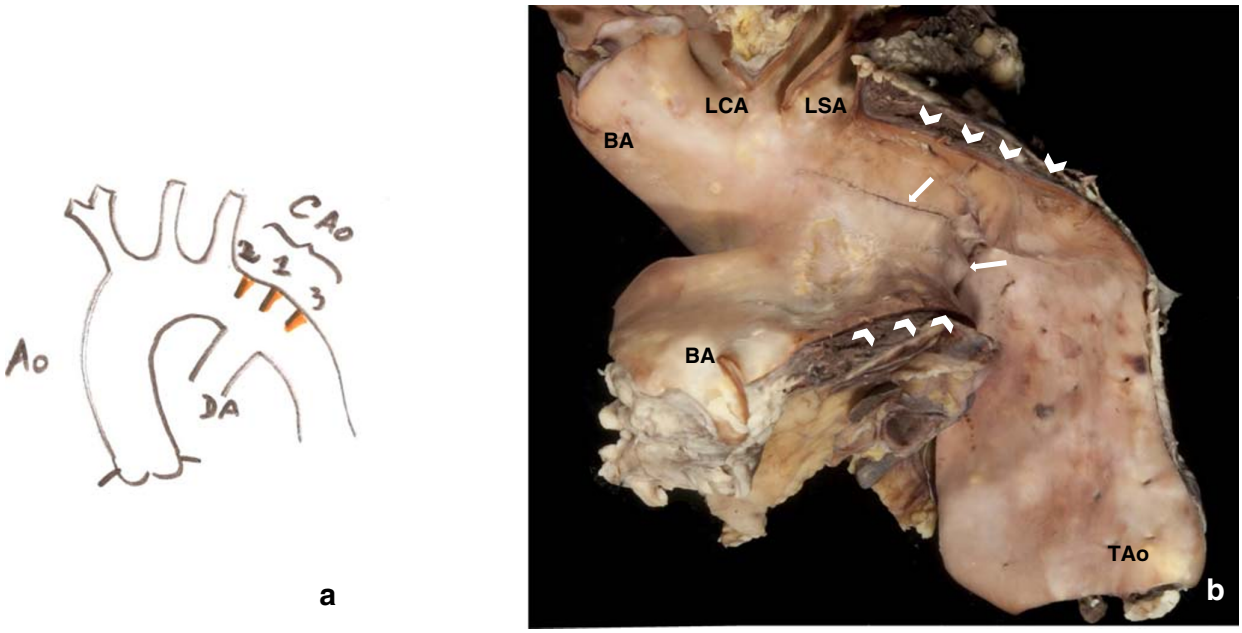

Fig. 6 Diagram of the different types of CoA **(a)**. A case of an adult patient with asymptomatic aortic coarctation (arrows without tail), who died because of iatrogenic laceration and dissection (white arrows) of the aorta during percutaneous aortic valve implantation. (TA, thoracic aorta). The patient also had bicuspid aortic valve **(b)**

Histological examination of the aortic wall is recommended, with hematoxylin-eosin and elastic van Gieson stains, to establish type and severity of aortopathy (medial degeneration). The aortic arch should be inspected, to rule out isthmic coarctation.

In all cases, left ventricular size and parietal wall thickness should be assessed (hypertrophy, dilatation, scars) also in relation to the RV dimensions. The diameter of the aorta at the aortic annulus (at the level of ventriculo-arterial junction), sinotubular junction, and tubular portion of the ascending aorta should be recorded.

The results of percutaneous valvuloplasty, surgical valvulotomy, and percutaneous or surgical replacement should be evaluated:

1. Acute or short-term procedure-related complications: Hemorrhages (paravalvar), hematomas (check topographic relation with conductive tissues); aortic root lacerations, dissection, thrombosis, and endocarditis; correct position of implant, patency, and (paravalvar) leakage; and thromboembolic complications.
2. Long-term complications (> 6 weeks): Correct position of implant, patency/stenosis, paravalvar leakage (probe), and ingrowth/encapsulation; endocarditis and thromboembolic complications; and excessive fibrosis and calcifications. Always check entire LVOT and mitral valve (specifically anterior leaflet).

A cerebral autopsy is recommended to evaluate potential thromboembolic complications. Eventual associated syndromic pathology should be recorded.

Cardiogenetic consultation should be advised or recommended, both in the proband and relatives, when hereditary disease is suspected (Table 1, Tables S2 and S3 supplement).

Coarctation of the aorta (CoA)

Description: CoA is a focal or segmental congenital narrowing of the aorta [22].

It usually occurs near the *ductus/ligamentum arteriosum*, in a para-, pre- or postductal location, causing a discrete aortic lumen narrowing or a hypoplastic segment of the aorta [22, 39, 40] (Fig. 6a). Often, discrete CoA and tubular hypoplasia can co-exist. CoA can occur as an isolated form or be associated with other vascular malformations or syndromes [41]. About 15–20% of affected individuals are asymptomatic until adulthood (Fig. 6b). Without repair, adult CoA has a high mortality rate (75% by the fifth decade of life). Therapeutic approach includes balloon dilatation, stent implantation, or surgery (end-to-end anastomosis, prosthetic patch or subclavian flap aortoplasty, or interposition of graft). All the methods may fail leading to re-coarctation and/or have complications [42–45] (Table 1, Tables S2 and S3 supplement).