

Congenital absence of the pulmonary valve

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[Abstract](#)

[Keywords](#)

[Disease name and synonyms](#)

[Excluded disease](#)

[Definition](#)

[Diagnosis/anatomical variations](#)

[Differential diagnosis](#)

[Frequency](#)

[Clinical description](#)

[Diagnostic methods](#)

[Management](#)

[Etiology](#)

[Recommendations for management](#)

[Unresolved questions](#)

[References](#)

Abstract

Absent pulmonary valve (APV) is defined as total or subtotal absence of pulmonary valve leaflets. Stenosis of pulmonary artery orifice and aneurysmal dilatation of pulmonary arteries coexist in all cases. APV can be associated with simple and complex cardiovascular malformations. It occurs as an isolated anomaly in nonsyndromic patients or as part of a genetic syndrome in syndromic patients. The most common association is APV and Fallot's tetralogy with absence of ductus arteriosus (Fallot-type APV/ADA). APV with intact ventricular septum or muscular VSD with persistent ductus arteriosus (non Fallot-type APV/PDA) is less common. These phenotypic variations imply a complex pathogenesis, in particular, error in developmental pathway(s) of cephalic neural crest cells in relation to chromosome 22q11.2 deletion syndrome. The main symptoms of APV are pulmonary insufficiency and bronchial obstruction. But the clinical picture varies widely depending on the severity and onset of obstructive respiratory symptoms. Different genetic conditions in association with APV have been reported. In all its forms, APV is generally sporadic in non syndromic patients and no identifiable genetic cause has been found. By contrast, children with Fallot-type APV/ADA and clinical features of DiGeorge/Velocardiofacial syndrome (DG/VCF) frequently have 22q11.2 microdeletion. In syndromic patients with the non Fallot-type APV/PDA and persistent ductus, the association of 18q – deletion syndrome should be excluded. The overall frequency of APV is not known. But the Fallot-type – APV / ADA may be estimated to occur in 6:3000 liveborn infants with congenital heart disease. Prenatal diagnosis is imperative. Early corrective surgery with implantation of a valved conduit in right ventricular outflow tract and plication of pulmonary arteries or “LeCompte manoeuvre” to relieve bronchial compression is indicated in all patients. Persistence of respiratory symptoms require re-evaluation and if needed reintervention with the option of implantation of an intrabronchial expandable stent.

Keywords: genetic heterogeneity, chromosome 22q11.2 deletion, DiGeorge/Velocardiofacial syndrome, 18q deletion syndrome, ductus arteriosus, early prenatal development, fetal echocardiography, fluorescence

in situ hybridization, airway management, ECMO, intrabronchial expandable degradable stents, “manoeuvre de Lecompte”

Disease name and synonyms

- ❑ Congenital absence of the pulmonary valve (APV)
- ❑ Pulmonary valve agenesis
- ❑ Absent pulmonary valve syndrome

Excluded disease

- ❑ Combination of congenital absence of aortic-pulmonary valve (1,2)

Definition

Congenital APV was first described by Chevers in 1847 (3). It is defined as total or subtotal absence of the pulmonary valve leaflets.

This may be the result of error or complete failure in valve development (4). Mild stenosis of the pulmonary artery orifice and aneurysmal dilatation of the main pulmonary artery as well as of the right or left or both pulmonary artery branch(es) coexist. Compression of the major bronchi at the hilum is a secondary phenomenon and is assumed to develop in fetal life (5,6). In addition, compression of the intrapulmonary bronchi by abnormally branching pulmonary arteries may represent a serious complication (7).

Diagnosis/anatomical variations

The spectrum of malformations to which APV may be associated can be categorized into two types: APV with or without VSD (8).

APV with VSD

The most common form with VSD is the association with TOF. The similarities with TOF include:

- ❑ anterior deviation of the infundibular septum in relation to the muscular septal crest,
- ❑ malaligned VSD,
- ❑ “overriding” of the aorta (9).

The distinguishing features are:

- ❑ unobstructed right ventricular infundibulum,
- ❑ aneurysmally dilated pulmonary arteries.

Typically, absent ductus arteriosus (ADA) is reported (5,8,10-12). In the following paper, this type will be referred to as Fallot-type APV/ADA.

APV without VSD

In its less frequent form without VSD, muscular VSD may be rarely observed; the association of a patent ductus arteriosus is reported (PDA) (4,8,13-18). It will be referred to as non Fallot-type APV/PDA.

Differential diagnosis

The malformation “absent pulmonary valve” is not a single diagnostic entity. It may occur as part of a range of cardiovascular defects either simple or

complex. However, the combination of pulmonary insufficiency and bronchial obstruction by aneurysmal pulmonary arteries is unique. It is both prenatally and postnatally pathognomonic. In addition to these key-findings, the typical features of the following associated congenital heart defects can be present:

- ❑ TOF
- ❑ VSD
- ❑ Atrial septal defect
- ❑ Coarctation of the aorta
- ❑ Tricuspid atresia

If pulmonary insufficiency and bronchial obstructive disease are considered separately, the differential diagnosis includes many congenital cardiovascular and extracardiac defects, that can lead to severe symptoms in the newborn and young.

Frequency

In all its forms, APV is a rare and severe disease, particularly in the newborn infant and the fetus (11,15,19,20-23).

The overall frequency of APV is not known, because in epidemiological studies, APV is not categorized as a malformation on its own (24). However, several reports quote a prevalence of 3% to 6% of APV in patients with TOF (17,21,25-28). Relying on the Baltimore – Washington Infant Study (BWIS) (24) with a 7% frequency of Fallot’s tetralogy of all congenital heart defects, the Fallot-type APV occurs probably in 6:3000 (0.2% – 0.4%) liveborn infants with congenital heart disease. This estimated frequency in liveborns differs from the prenatal echocardiographic study, in which the overall prevalence of APV with VSD – perimembranous or muscular – within fetuses with structural cardiac anomalies was 1.4% (15). Intrauterine death and perinatal mortality in Fallot-type APV/ADA as well as in non Fallot-type APV/PDA, with increased risk if APV is associated with genetic anomalies, may explain the discordance between prenatal and postnatal frequencies (6,11,15,22,23,29,30).

Clinical description

All variants of APV share the main clinical findings:

- ❑ pulmonary insufficiency,
- ❑ ostial stenosis,
- ❑ bronchial obstruction secondary to aneurysmally dilated pulmonary arteries.

The clinical presentation of infants with either Fallot-type or non Fallot-type APV is essentially the same:

- ❑ air trapping and CO₂ retention,

- ❑ loud “to-and-fro” murmur of pulmonary stenosis,
- ❑ insufficiency on auscultation,
- ❑ cardiac enlargement,
- ❑ aneurysmal hilar pulmonary arteries,
- ❑ hyperinflation and dystelectasis of lung lobes with shift of mediastinum on chest X-ray,
- ❑ right ventricular hypertrophy on ECG.

Diagnosis is confirmed by echocardiography: subxiphoid long-axis and short-axis views of aneurysmally dilated pulmonary arteries are almost pathognomonic for APV. Pulmonary stenosis and insufficiency are shown by Doppler color-flow mapping (20). The clinical picture, however, varies according to onset and severity of symptoms, especially those of respiratory insufficiency. Thus, previous reports divided patients with APV into two groups:

1. The adult group included children without respiratory complications who had corrective operation electively between 5 and 20 years.
2. The infantile group presented commonly as critically ill newborns with severe respiratory distress requiring mechanical ventilation (21,31). Mortality in these infants is high. Early reparative results were not promising until plication of pulmonary arteries together with implantation of a valved conduit in the right ventricular outflow tract became the standards of the initial correction (21,28,32).

More recently, the fetus with APV became another important group. During the first half of pregnancy, the diagnosis seems to be incomplete (6,11). The clinical and hemodynamic signs are predominantly those of pulmonary stenosis and insufficiency for both main variants of APV. They are shown by Doppler color-flow echocardiography as turbulent “to-and-fro” flow in systole and diastole (6,15,22,29). Enlargement of pulmonary arteries and right ventricle develop in the second half of pregnancy (6,11,15,22,29).

In the fetus with Fallot-type APV/ADA, a distinct echocardiographic feature is the right-to-left shunt during systole and diastole across the unrestricted VSD secondary to the pressure-volume overload of the right ventricle (29). Furthermore, the risk of survival for the fetus with this condition in later pregnancy may be related to cessation of the physiological flow from the pulmonary artery into the descending aorta through the ductus arteriosus prior to premature closure (6,11,15,26).

Conversely, in the fetus with non Fallot-type and large ductus, there is an anomalous left-to-right shunt from the aorta across the ductus into the pulmonary artery, and together with the pulmonary regurgitant flow into the right ventricle. In this condition, the fetal circulation is compromised in two ways: “run-off” from the aorta

and volume overload of the right ventricle. The severe negative effect on right ventricular function resembles that of severe aortic insufficiency on left ventricular function (4,15). In all types, the full clinical picture may be complicated in the prenatal period by nonimmune hydrops fetalis and polyhydramnios secondary to cardiac failure with the risk of fetal or perinatal death or birth of a critically ill newborn (6,11,15,29). Thus, prenatal diagnosis of APV is essential. Antenatal evolution and progression of the disease require sequential follow-up studies and postnatal evaluation and treatment in specialized centers. Immediate respiratory support and earlier corrective operation will improve outcome (21-23,28,29,31).

Diagnostic methods

As indicated above, the primary diagnostic method is echocardiography, Doppler color-flow mapping in the fetus and newborn infant (6,11,15,20,23,29).

The following findings are pathognomonic for the Fallot-type APV/ADA and non Fallot-type APV/PDA:

on echocardiography:

- ❑ rudimentary pulmonary valve tissue,
- ❑ aneurysmal dilatation of the main pulmonary artery and branch pulmonary arteries,
- ❑ enlargement of the right ventricle.

on color flow Doppler (continuous wave and pulsed wave) mapping:

- ❑ antegrade and retrograde flow at site of absent pulmonary valve (“to-and-fro” flow pattern),
- ❑ systolic pressure gradient across the narrowed pulmonary orifice.

In patients with the common variant of Fallot-type, however, the distinguishing echocardiographic features are:

- ❑ subaortic VSD with right-to-left shunt during systole and diastole on Doppler color-flow image.
- ❑ “overriding” of the aorta.
- ❑ typical absence of the ductus arteriosus. By contrast, in patients with the rare variant of non Fallot-type, no VSD is observed or only a muscular VSD, and the ductus is widely patent.

Potential for intrauterine evolution from an incomplete diagnosis to the full clinical picture makes close follow-up studies necessary in every fetus with suspected APV. Findings detected during routine antenatal ultrasonography, that led to referral for evaluation of cardiac abnormality of the fetus included: polyhydramnios, large echo-free spaces at the base of the heart (“intrathoracic mass”), right-sided heart enlargement, “overriding” of the aorta, fetal nuchal thickening,

and ascites, fetal growth retardation, history of familial congenital heart disease (15,22,29).

Cardiac catheterization may be necessary to specify additional hemodynamic and anatomic details.

Magnetic resonance imaging (MRI) and tracheobronchoscopy are supplementary tools, especially in the evaluation of postoperative complications and persistent respiratory symptoms by reoccurrence of pulmonary artery dilatation and bronchial compression or underlying tracheobronchial malacia (17,21,28,31).

Management

Respiratory distress in the newborn infant is the most serious symptomatology. It occurs predominantly in the Fallot-type APV/ADA. Airway management as a primary procedure involves intubation, mechanical ventilation, and extracorporeal membrane oxygenation (ECMO) in some infants. It is usually performed under emergency circumstances (21,31). Urgent complete surgical repair should, in the first place, relieve the compression of the tracheobronchial tree. This is achieved by combined anterior and posterior plication of the pulmonary arteries (21,32) or by translocation of the pulmonary artery anterior to the aorta and away from the airways ("manoeuvre de Lecompte" (33))(28).

Repair of pulmonary insufficiency and stenosis requires placement of a valved conduit (homograft or heterograft) in the right ventricular outflow tract. Repair in the Fallot type APV/ADA includes additional closure of the VSD with a patch. In infants with non Fallot APV/PDA, the ductus arteriosus must be closed. Asymptomatic infants can undergo pulmonary-cardio repair within the first 6 to 12 months. Repair should, however, not be delayed for too long in order to avoid the harmful effect of the dilated pulmonary arteries on tracheobronchial tree (28). Apart from conduit replacement in children as they grow, other reinterventions may be required, mainly for persistent respiratory symptoms. Mid-term outcome for patients with Fallot type APV/ADA who survive the initial repair is favorable. Repeat plication of pulmonary arteries and/or utilization of intrabronchial expandable stents may improve outcome in patients with persistent airway compression and in those who cannot be weaned from respirator because of severe tracheobronchial malacia (21).

Etiology

Background

Malformations that are the consequences of abnormal development of the embryonic conotruncus, aortico-pulmonary sac and aortic arches have been categorized as conotruncal

defects (CTD) (20,34). These include, among others, Fallot's tetralogy (9) with different abnormalities of the pulmonary valve: stenosis (classic Fallot), atresia and aplasia (Fallot-type APV/ADA).

Role of neural crest cells

The involvement of "cardiac" (cephalic) neural crest cells in normal and abnormal cardiovascular development, including that of the semilunar valves, has been documented in animal studies. Surgical ablation of the cephalic neural crest in the chick embryo resulted in different types of CTD (35-40). In rats, the teratogen bis-diamine administered during pregnancy caused distinctly Fallot's tetralogy with absent pulmonary valve and absent ductus arteriosus (Fallot-type APV/ADA). In some fetal rats, it was associated with partial or complete absence of the thymus and craniofacial anomalies, such as medial facial cleft and cleft palate (41).

Role of the *Tbx1* gene in the etiology of DiGeorge and velocardiofacial syndrome

In recent studies in mice, the *Tbx1* gene was found to be responsible for developmental anomalies – especially defects of structures with contribution of cephalic neural crest cells, such as pharyngeal pouches, arches and arteries, and outflow tract of the heart. Thus, mice mutant for *Tbx1* gene exhibited a high incidence of malformations of the cardiac outflow tract and of the aortic arch arteries in association with hypoplasia of thymus and parathyroid glands, facial dysmorphisms, cleft palate and abnormal vertebrae (42,43). This combination of specific cardiovascular and extracardiac anomalies in the *Tbx1* – mutant mice models the typical malformations of the thymus, face and cardiovascular system of the DiGeorge (DG), Conotruncal Anomaly Face (CTAF), - and Velocardiofacial (VCF) syndromes in humans, referred to as DG/VCFS (44-49). Sporadic and familial DG/VCFS are usually associated with deletion of chromosome 22q11.2 (50-63). The acronym CATCH 22 stands for the most important clinical findings in patients with DG/VCFS and 22q11.2 deletion syndrome: C = cardiac defect, A = abnormal face, T = thymus hypoplasia, C = cleft palate, and H = hypocalcaemia (64,65). The diagnosis of associated chromosome 22q11.2 deletion is made prenatally and postnatally at a high detection rate by routine fluorescence *in situ* hybridization (FISH) or molecular analysis of DNA by means of the polymerase chain reaction with polymorphic markers, which map to the DiGeorge critical region within 22q11.2 (18,27,56,57,66-68). The evidence of significant psychiatric disorders in adults with VCFS, and the observation of cognitive - behavioural and psychiatric complications in children with the chromosome

22q11.2 deletion syndrome are the urgent indications for early diagnosis, close follow-up, guidance and therapy in specialized centers (69-72). But so far, it has not been possible to correlate the range or severity of clinical features in deletion 22q11.2 patients with the loss of one or more specific gene(s) (73). On the basis of the DG/VCFS phenotype in the *Tbx1* - mutant mice, it was proposed, that *TBX1* in humans is a key gene in the etiology of DG/VCFS (42,43).

Morphogenetic and genetic aspects of APV

As noted, APV is a complex anomaly which consists basically of two components:

1. Hypoplasia or aplasia of the pulmonary valve,
2. Absence or persistence of the ductus arteriosus.

In most cases, an additional intracardiac defect is observed, usually Fallot's tetralogy with absence of the ductus arteriosus (Fallot-type APV/ADA). Patients with this pathology may have hypoplasia of the thymus and parathyroid glands and typical features of DG/VCFS (18,45,74). Thus, the anomalies of semilunar valves, and ductus arteriosus, conotruncal defects and DG/VCFS may appear to be morphogenetically related on the basis of failure of neural crest cell contribution (35-40,49,75-77).

In most patients, APV occurs without any associated genetic syndrome, and is "sporadic" in pattern with no identifiable genetic cause (18). A small number of familial cases of Fallot-type APV/ADA has been reported. All had a normal karyotype and no 22q11.2 deletion (6,78,79). The incidence of chromosome 22q11.2-deletion in APV with Fallot's tetralogy, studied in prenatal and postnatal patients, ranged between 10% and 75% (23,27,68,80).

In a study of the whole spectrum of congenital APV, we examined 24 patients for associated cardiovascular anomalies, features of DG/VCF syndrome, chromosomal aberrations and 22q11.2 deletion. Twenty-one patients had a Fallot-type APV, and 3 patients had a non-Fallot type with large persistent ductus arteriosus. In 2 of these, the ductus originated abnormally from the aortic arch. A remnant of the ductus arteriosus was also found in 5 patients with a Fallot-type APV. Again, it connected abnormally to the aortic arch in 2 cases.

Four patients (17%) with Fallot-type APV had a 22q11.2 deletion. All of them were severely affected by DG/VCF syndrome. However, a correlation between the size of the deletion within the q11.2 region on chromosome 22 and the severity of the disease could not be established.

None of the 16 patients (67%) of the whole APV study group, who did not have DG/VCFS, had the deletion 22q11.2. Of special note was still another group of 4 patients (17%), also with the Fallot-type APV and the typical DG/VCFS phenotype,

but these did not have this deletion detected by standard FISH N 25 (D22S75), and genotyping at loci D22S:427, 941, 944, 264, 311, 539. Previously, it has been suspected that comparable nondeleted DG/VCFS patients with CTD may have a smaller deletion, a different genetic rearrangement, or a point mutation in one of the genes mapping to the DiGeorge critical region (DGCR), that is not deleted by standard FISH assay (60). Whether this implies also that our group of 13 nondeleted patients (54%) with isolated Fallot-type APV, *i.e.* without DG/VCFS, may have an equivalent or partial deletion within DGCR is uncertain.

The possibility of another etiologic basis, such as the interstitial deletion of the long arm of chromosome 6 should also be taken into consideration (81).

Finally, among our 3 patients with non Fallot APV/PDA, 2 patients (8%) had the severe form of 18q - deletion syndrome, caused by terminal deletion of the long arm of chromosome 18. To date, these are the first cases described with the combination of the 18q deletion syndrome with congenital absence of the pulmonary valve *i.e.* non Fallot-type APV with persistent ductus arteriosus (18,82-88).

Thus, apart from the two structural anomalies with a presumable contribution of neural crest cells, namely absent pulmonary valve leaflets and absence (regression) or persistence of the ductus arteriosus, our patients presented with a great variability in phenotype and genetic heterogeneity. But in most cases of APV, the etiology is still unknown, and a complex pathogenesis with disruption of a complexity of developmental pathways may be suspected.

Recommendations for management

Optimal treatment of the newborn infant with APV closely depends on early recognition, ideally by prenatal echocardiography and sequential follow-up and delivery in a specialized center with an interdisciplinary team approach of management planning by the gynecologist, neonatologist and intensivist, pediatric cardiologist-surgeon and geneticist.

APV is known to show variable cardiovascular, bronchopulmonary and clinical manifestations. This variability may be explained by an heterogeneous morphogenesis and certainly by genetic heterogeneity. The incidence of chromosomal, karyotypic abnormalities, as well as the frequent association of deletion 22q11.2 in patients with normal karyotype, requires prenatal or postnatal karyotyping and fluorescence *in situ* hybridization (FISH) in each patient with suspected APV. In APV patients with typical DG/VCFS and therefore high risk of deletion 22q11.2, and in whom routine FISH and

genotyping with standard markers mapping to the commonly deleted region q11.2 failed to make the diagnosis, special cyto - molecular analyses are indicated.

Identification of deletions supported – if indicated – by genetic and echocardiographic examination of parents and siblings, enables accurate assessment of the recurrence risk for the family and the patient.

The question mark and important limitation for counseling and decision-making is the fact that, so far, it has not been possible to correlate the manifestation and severity of features of the associated 22q11.2 deletion syndrome (DG/VCFS) with the size of deletion or the loss of one or more specific gene(s). The risk of mental retardation in APV patients with the 22q11.2 - deletion or 18q – deletion syndrome, influences counseling (6, 15, 18, 22, 23, 29, 60, 68-72, 83, 84, 87).

Unresolved questions

- What are the developmental pathways and molecular mechanisms affected by deletion 22q11.2 and 18 – deletion in APV?
- What is the basis of the phenotype variability?
- What is the role of the ductus arteriosus in the etiology of APV?
- Is there a potential for influencing the prenatal formation of intimal cushions of the ductus arteriosus – which is fibronectin – dependent – by gene transfer – biological engineering (89)?

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