Total Anomalous Pulmonary Venous Connection: From Embryology to a Prenatal Ultrasound Diagnostic Update

Chuan-Chi Kao 1*, Ching-Chang Hsieh 2, Po-Jen Cheng 3, Chi-Hsin Chiang 2, Shih-Yin Huang 1

1 Department of Obstetrics and Gynecology, Keelung Chang Gung Memorial Hospital, Keelung, Taiwan,
2 Department of Obstetrics and Gynecology, Taipei Chang Gung Memorial Hospital, Taipei, Taiwan, and
3 Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Tao-Yuan, Taiwan

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Introduction

Prenatal investigation of the fetal venous system is becoming an increasingly important aspect of the examination of fetal circulation. This is because isolated venous anomalies can be identified not only as a lethal disease but also as a part of complex heart diseases or genetic syndromes. Among cyanotic heart diseases, total anomalous pulmonary venous connection (TAPVC) is the only condition involving a venous system malformation [1] and is easily misdiagnosed. The key characteristic of this uncommon congenital heart disease (CHD) is that all four pulmonary veins (PVs) fail to form a direct connection to the left atrium (LA); instead, they drain into the right heart through different routes of systemic venous return. The incidence of this condition is approximately 7–9 per 100,000 live births [2,3], and it accounts for 0.7–1.5% of all CHDs [4]. Patients with CHD who were born from 2000 to 2006 in Taiwan also exhibited a similar prevalence of TAPVC (0.11/1000) [5].

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* Correspondence to: Chuan-Chi Kao, Department of Obstetrics and Gynecology, Keelung Chang Gung Memorial Hospital, 222, Maijin Road, 204 Keelung, Taiwan. Fax: +886 2 24328040.
E-mail address: m7226@cgmh.org.tw (C.-C. Kao).
Over the past decades, TAPVC has been challenging for obstetricians to recognize in utero. According to a retrospective study of birth records from 1998 to 2004, only 1.9% of TAPVC (8 in 424) cases were prenatally diagnosed [6]. The diagnosis rate gradually improved through both awareness regarding the importance of assessing the venous system during routine screening and the application of new scanning technologies such as spatiotemporal image correlation (STIC) and color flow Doppler imaging. A prospective study identified 14 TAPVC fetuses before birth without missing single one (but one false positive reported) through a step-by-step, careful examination of one major and several minor sonographic features [7].

In addition to identifying echocardiographic marks related to a TAPVC diagnosis, understanding the embryonic development of the venous system is fundamental and crucial. This helps in recognizing abnormal features during anatomical screening and prenatal counseling.

Embryology

The fetal cardiovascular system is the first embryonically developed organ, which begins to develop at the gestational age of 6 weeks (fourth week of embryonic development). The embryonic formation of the pulmonary venous system is not as complicated as that of the systemic venous circulation, which involves the fusion and degeneration of dual cardinal veins, umbilical veins, and vitelline veins. However, whether the PV becomes connected to the LA directly [8] or through the tributaries of the sinus venosus remains disputed [9].

The former theory prescribes that a single embryonic common PV evaginates from the dorsal wall of the LA and develops as an outgrowth of the LA, adjacent to the septum primum. Meanwhile, the lung buds that have arisen from the lung parenchyma canalize as a vessel and gradually connect to the developing PV directly [10]. Other experts have suggested that the pulmonary bud is initially enmeshed in the splanchnic plexus, which drains into the cardinal and umbiliviscitelline veins (systemic venous system) [11]. By the gestational age of 4 weeks, the primordial common PV derived from the posterior LA connects to the pulmonary portion of the splanchnic plexus and forms the pulmonary plexus. Ultimately, the well-established pulmonary plexus loses its connection with the splanchnic plexus; in other words, the pulmonary venous system separates from the systemic veins [12]. The incorporated PV subsequently divides into four branches, two left and two right tributaries, with each having an orifice at the posterior LA.

Both theories are supported by different lines of evidence such as vascular markers or animal embryological studies [13,14]. The latter theory can offer a better understanding of the failure of PVs in emptying into the LA and for joining with the systemic venous system instead.

Definition and classification system

The normal pulmonary venous system consists of right and left pairs of PVs delivering the blood from both lungs to the LA. In patients with TAPVC, the anomalous veins either directly empty into the right atrium (RA) of the heart or empty through other routes of systemic venous return. Several classification systems based on anatomy, physiology, or perinatal outcomes exist.

Darling’s classification

Darling’s classification, first introduced in 1957, is the most commonly used system. TAPVC is classified into four categories according to the sites where the abnormal connection occurs [15] (Fig. 1).

Type I: Supracardiac type, which is the most common type. The entrance of the pulmonary blood flow into the systemic venous system is cranial to the RA. This accounts for 45–55% of TAPVC cases, in which the confluent vessel usually empties into the innominate vein or the right or left superior vena cava (SVC) [16,17]. Type II: Cardiac type, which is diagnosed when the PVs converge on a confluent vessel and then horizontally connect to the RA through the coronary sinus (CS) or at the posterior wall of the RA. Approximately 20–30% of TAPVC patients exhibit the cardiac type. Type III: Infracardiac type. The PVs conjoin and form a vertical vessel that travels caudally into the portal vein or its branches such as the ductus venosus, hepatic vein, and inferior vena cava (IVC). This type accounts for 13–25% of cases. Type IV: Mixed type. Less than 10% of patients belong to this subtype, in which the right and left pulmonary tributaries drain at two or more different levels. In Taiwan, the frequency of these four types are 42.3% (Type I), 39.8% (Type II), 12.8% (Type III), and 5.1% (Type IV), according to a 15-year cohort study [18].

Smith classification

TAPVC cases are simply subdivided into two groups, supradiaphragmatic without pulmonary venous obstruction and infradiaphragmatic with pulmonary venous obstruction. The distinct features of these two groups are how the abnormal drainage Anastomosis is related to the diaphragm and the presence of venous obstruction [19]. Although supradiaphragmatic TAPVC is mainly non-obstructive, obstructions have been noted in some cases [20]. Nevertheless, the infradiaphragmatic type is almost always obstructive.

Another classification system

Herlong and colleagues announced a more detailed classification system. This system is fundamentally related to the anatomical and physiological changes in TAPVC, which involve the following parameters: (1) the level of connections: supracardiac, cardiac, infracardiac, and mixed; (2) presence or absence of obstruction; and (3) cause of obstruction: extrinsic, intrinsic, or obstructive atrial septal communication [21].

Pathophysiology and presentation

The hemodynamic changes in TAPVC primarily result from the mixing of oxygen-rich blood from the pulmonary system and deoxygenated blood from the systemic venous
circulation. This leads to cyanosis and hypoxia in neonates. Hence, TAPVC is the fifth common cause of cyanotic heart disease.

Several essential factors have a considerable effect on the pathophysiology and presentation of TAPVC. The presence or absence of obstruction at any level of the venous route is the most critical factor. Obstructions may occur in different situations: (1) the confluent vein passing through tissue, which causes extrinsic compression, similar to that by intrathoracic structures (supracardiac type) or at the entry of the diaphragm (infracardiac type); (2) intrinsic compression resulting from narrowing of the lumen; and (3) at the site where the confluent blood enters the route of systemic venous return.

The infracardiac type is almost always associated with obstruction, which usually occurs when the confluent vein vertically enters the diaphragm through the esophageal orifice. The intracardiac type is rarely associated with obstruction. However, obstruction still can be detected at the CS or at the entry to the RA. Half of the supracardiac TAPVC cases are associated with venous obstruction.

Furthermore, the lumen narrowing of the left innominate vein, SVC, or azygos vein can lead to obstructive TAPVC. In addition, passing of the vertical vein between the
left pulmonary artery and left bronchus, leading to external compression, is a possible cause of obstruction [17].

Among patients with unobstructed TAPVC, the size of interatrial communication plays an important role. After birth, pulmonary resistance decreases and an adequate amount of blood enters the pulmonary bed for adequate oxygen exchange. The mixture of saturated and desaturated blood occurs at the RA. In cases of nonrestrictive interatrial communication (such as a large atrial septal defect [ASD]), the blood enters the left heart and supplies the systemic circulation of infants. In spite of the right-to-left shunt, 3–5 times more blood enters the pulmonary bed and increases the pulmonary artery pressure gradually. Overcirculation leads to right ventricular hypertrophy, right heart failure, and subsequent desaturation in neonates.

In the obstructed types, high pulmonary venous pressure leads to an increase of hydrostatic pressure in the capillaries, leading to the development of pulmonary edema. Simultaneously, the elevated pulmonary artery pressure results in insufficient pulmonary flow. Severe desaturation occurs without immediate relief of the obstructed vessel.

The presentation of TAPVC varies widely and depends on the severity of the obstruction and the resistance of the pulmonary vessels. If severe obstruction is present, acute illness with tachypnea, tachycardia, dyspnea, hypoxemia, and metabolic acidosis manifests as early as within the first 12 h of life. Early death occurs within the first few days if surgical correction cannot be performed. At the other end of the spectrum, patients without venous obstruction are usually asymptomatic at birth, followed by the development of tachypnea, mild cyanosis, and feeding difficulties in the first few weeks. Profound failure to thrive and recurrent respiratory tract infection are noticed gradually, and only a small number of patients can survive up to late childhood or adolescence without treatment [22].

Associated anomalies and genetic mechanism

Approximately 30% TAPVC cases are associated with heterotaxy syndrome, according to an analysis of patients receiving postnatal surgical repair at a hospital [23]. This is commonly observed in cases of right atrial isomerism (RAI), owing to the lack of a functional LA for PV connection. In non-heterotaxy cases, TAPVC can be detected as an isolated anomaly or with other complex heart/great vessel lesions such as atrioventricular septal defect, transposition of the great arteries, pulmonary stenosis, double outlet right ventricle, and coarctation of the aorta. When TAPVC is diagnosed through prenatal echocardiography, a trend of more fetuses accompanied with heterotaxy syndrome or complex CHD and less fetuses with isolated TAPVC has been noted [24]. TAPVC genetic etiology is remaining vague and previous study reported some possible disease-driven genes (e.g., ACVRL1, SGCD, 4p13-q12, ANKRD1, etc.) by whole-exome sequencing and linkage mapping with polymorphic microsatellite markers [25].

Perinatal outcomes

An increasing trend in TAPVC research has been observed in the last decade, and most of these studies are related to the postnatal management, radiological diagnosis, and surgical outcomes of TAPVC [26–28]. The surgical outcomes have considerably improved from a mortality rate of 42.1% in 1970 to 7.4% after 2010 [29]. Despite the advances in perioperative cardiovascular care, TAPVC remains one of the true surgical emergencies after diagnosis. The goal of surgical repair is to establish the normal anastomosis of the PVs to the LA. Patients with heterotaxy syndrome and a single functional ventricle have a poorer prognosis [30]. Other nonpreferable factors are obstructed PVs, coexistent complex cardiac defects [2], pulmonary atresia [23], and younger age at surgery [26].

Pearls in prenatal sonographic diagnosis

Postnatal ultrasound diagnosis has a sensitivity and specificity of >97% [28], whereas prenatal diagnosis is more challenging. In a large (n = 424) TAPVC case series implemented from 1998 to 2004, only 1.9% cases were identified in utero [6]. France reported a 10% prenatal diagnosis rate for 95 isolated TAPVC neonates born between 2001 and 2011 [31].

The prenatal diagnosis rate is believed to be increased through a systemic, step-by-step ultrasound examination [7]. Here we describe the characteristics of TAPVC in prenatal ultrasonography based on the International Society of Ultrasound in Obstetrics and Gynecology guideline for cardiac screening in midgestation [32].

Step 1: Identifying the normal connection of the PV to the LA and inspecting for indirect signs (Table 1).

A. General aspects: Situs

TAPVC is part of the heterotaxy syndrome in both RAI and left atrial isomerism (LAI) subtypes. This abnormal venous return can be observed in 50% of fetuses with RAI and 5% of those with LAI. Therefore, careful attention should be paid to the examination of PV connections when the situs is ambiguous.

B. Four-chamber view

(a) Demonstrate normal PV connections into the LA

The PVs can often be seen entering the LA in the axial four-chamber view (Fig. 2). An inability to demonstrate this normal connection is an important sign for suspecting TAPVC. Recent studies have described this as the first clue to suspect the disease [7,24]. A smooth posterior wall of the LA can be viewed as an accessory feature to this abnormal connection of PVs and is observed in some cases.

(b) Ventricular disproportion: RV > LV

The discrepancy in bilateral ventricles is not always observed and tends to be recognized after the gestational age of 7 months [24]. This is because the flow of pulmonary circulation increases in the latter stage of fetal life. Therefore, the extra abnormal flow from the PV appears to affect the size of the heart chambers in the late second trimester. Furthermore, dilatation of the right ventricle is not obvious among cases of prominent ASD or obstructive TAPVC [33]. A recent study recommended that this feature
should not be enrolled into the diagnostic criteria because routine second trimester obstetric ultrasonography is executed at the gestational age of 18–22 weeks [7].

(c) Retrocardiac space examination: wide space behind the heart

Evaluation of the area behind the heart offers important information for diagnosing a fetal CHD, including TAPVC [34]. The diagnostic marker is a longer-than-usual distance between the LA and aorta [7]. A Japanese group introduced a post-LA space index to objectively examine this area. This index, defined as the ratio of the LA-descending aorta distance to the descending aorta diameter, was significantly higher in eight TAPVC fetuses than in 101 non-TAPVC fetuses (mean, 1.51 versus 0.71±0.23) [35].

C. Three-vessel view

(a) A fourth vessel adjacent to the pulmonary trunk (supracardiac type)

The three-vessel view is a section for surveying the alignment, position, and size of the pulmonary artery, aorta, and SVC. In supracardiac TAPVC, the PV empties into a common vertical vein, which then connects to the RA. In this view, the vertical vein can be observed as a fourth vessel to the left or posterior left of the pulmonary artery [36].

(b) SVC dilatation (supracardiac type)

In the three-vessel view, the SVC usually appears smaller than both the pulmonary artery and aorta. In some cases of

Table 1  Indirect imaging features of prenatal echocardiography for TAPVC.

| View                  | Description of the abnormal image                                      | Comment                                                                 | Sensitivity (from small case series) |
|-----------------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------|--------------------------------------|
| Situs                 | Situs ambiguous                                                          | TAPVC is associated with heterotaxy syndrome, especially RAI            | –                                    |
| Four-chamber view     |                                                                           |                                                                         |                                      |
| Atrium               | Failure to visualize the normal PV connection to the LA                  | - First clue to suspect TAPVC                                          | 60–100% [7,24,31]                    |
|                      | Smooth posterior wall of the LA                                          | - diagnostic triad                                                     |                                      |
| Ventricle             | Ventricular disproportion or asymmetry (RV > LV)                         | Additional feature                                                     | 79% [7]                              |
|                      |                                                                           | Inconsistent feature for fetuses before 28 weeks of gestation; observed in a large VSD and obstructive type of TAPVC | 19–60% [24,31]                      |
| Retrocardiac space    | Increased space between the LA and DAo                                   | Post-LA space index cut-off of 1.27                                     | 50–100% [7,35]                       |
| Three-vessel view     | A fourth vessel adjacent to the pulmonary trunk                          | Supracardiac type                                                      | 33% a [24]                           |
| Abdominal view        | An extra vessel between the IVC and aorta                                 | Supracardiac type                                                      | 72–100% b a [7,24,31]                |
|                       |                                                                           | Infracardiac type                                                      | 100% b [24]                          |

TAPVC, total anomalous pulmonary venous connection; RAI, right atrium isomerism; PV, pulmonary vein; LA, left atrium; RV, right ventricle; LV, left ventricle; VSD, ventricular septal defect; Dao, descending aorta; SVC, superior vena cava; IVC, inferior vena cava.

a The sensitivity is solely calculated for the supracardiac type.
b The sensitivity is solely calculated for the infracardiac type.

Figure 2  On an apical four-chamber view, right and left inferior pulmonary vein enters left antrum posteriorly and forms a “horn-like” insertion. Note the posterior wall of left antrum is not as round and smooth as right antrum.
supracardiac TAPVC, the SVC is either as large as or more prominent than the aorta [37]. In supracardiac TAPVC, SVC dilatation is more frequently identified than is the extra vertical vein [24].

D. Abdominal view

(a) An extra vessel between the IVC and aorta (infra-cardiac type)

Similar to the fourth vessel in the supracardiac type, the descending vertical vein in infracardiac TAPVC can be seen between the IVC and aorta in the transverse view of abdominal images [36].

Step 2: Actively looking for the confluent vessel and vertical vein and identifying the TAPVC type.

A. Confluent vein

When the four PVs fail to develop a normal connection with the LA, they usually drain into a confluent vein before emptying into the RA. Carefully searching for the confluent vein is important when a normal PV connection is not identified, and this can be achieved in most cases [38]. This tubular vessel is usually located between the LA and aorta in types I, II, and III TAPVC [24]. Among those with highly suspected TAPVC but without a visible confluent vein, focus on the CS or mixed-type TAPVC should be emphasized [36,24] (see description below).

B. Dilatation of the CS (intracardiac type)

The diameter of the CS is usually <3 mm in a normal fetal heart, and an enlarged CS is associated with CHD, including left SVC and coarctation [39]. In intracardiac TAPVC, the PV empties into the CS through PV confluence or direct drainage. Therefore, dilatation of the CS raises the suspicion of this type of TAPVC [31].

C. Vertical vein (infracardiac and supracardiac types)

Following the recognition of the confluence vein, the sonographer can sweep the transducer along the transverse axis or change to the coronal/sagittal view to identify the site of PV confluence joining the vertical vein [38]. The ascending or descending vertical vein can usually be visualized in both infracardiac and supracardiac cases through two-dimensional ultrasound or Doppler flow examination [24] (see below).

D. Color flow Doppler and spectra Doppler

The application of color Doppler imaging is very useful to detect the aforementioned direct and indirect signs, especially the (1) normal connection of the PVs to the LA,
(2) confluent vein, and (3) vertical vein [24, 36]. The fetal heart should be placed apically or transversely, and then the color box should be narrowed to the LA for depiction of the PV entry. Using low pulse-repetition frequency and high sensitivity settings, the PV can be rapidly identified in most pregnant women [7] (Fig. 3). A careful survey of the vertical vein through color flow mapping is essential for both the diagnosis and outcomes. Color Doppler shows flow turbulence if an obstruction is present at the connection site, which leads to a poor prognosis [38].

The normal PV Doppler waveform is pulsatile and biphasic, with distinct systolic and diastolic peaks, followed by little or no forward flow at the end of diastole [36] (Fig. 4). Abnormal PV spectral Doppler findings include a continuous monophasic pattern or abnormal pulsatility [24]. A low velocity monophasic waveform in the vertical vein with a high velocity (>0.5 m/s) flow over the connection site indicates the presence of obstruction [24, 38].

E. Four-dimensional ultrasound

One study applied four-dimensional ultrasound with B-flow imaging and STIC to obtain more information regarding abnormal venous connections. The advantage of this technique is the demonstration of the entire route and anatomic correlation of the PV confluence, vertical vein, and anomalous venous connection site, which sometimes cannot be clearly identified through two-dimensional examination [37].

Conclusion

Over the past few years, an increasing number of studies on the prenatal diagnosis and postnatal management of TAPVC have been published. Through awareness of this rare disease and a good understanding of the embryology/anatomy of the venous system, the recognition of anomalous venous return can be achieved in mid-trimester anatomical screening examinations or through echocardiography. Failure to identify a normal PV connection and a demonstration of the vertical vein and confluent vessel are essential for a confirmation of the diagnosis. Advanced sonographic techniques offer further detailed information for postnatal care and surgical preparation.

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