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Chapter

Pulmonary Vein: Embryology, Anatomy, Function and Disease

Chan I-Ping and Hsueh Tung

Abstract

Four pulmonary veins come from respective lung lobes drain oxygen-rich blood back to the left atrium. Failure of incorporation with the left atrium can lead to a condition, called Cor triatriatum sinister, that the left atrium is separated into two chambers by an abortive fibrous tissue. The venous system of lung and whole body communicate with each other in the earlier time and they will be disconnected in the following developmental process. Total or partial anomalous pulmonary venous connection refers to that there is/are some degree of the communication exists after birth, which can occur in different sites. In the veterinary field, retrospective studies and several case reports have been published to describe these rare congenital cardiovascular diseases in several species. More cases are need for better understanding their clinical manifestation, treatment options and outcomes.

Keywords: congenital, development, Cor triatriatum sinister, anomalous pulmonary venous connection, outcome

1. Introduction

All the vessels that drain blood out of the heart are called artery, and those that drain blood into the heart are called vein. Pulmonary veins, literally, are the vessels that transport oxygenated blood from the lungs back to the left atrium. The information of those veins is hardly found in veterinary textbooks. First of all, this chapter is focus on the development of those veins in fetus. If something wrongs during the process, different type of the abnormality leads to different results. The diagnosis, treatment and prognosis in human medicines are introduced simply in this chapter. In addition, pulmonary venous abnormalities in the veterinary medicines are reported in several species. Those case reports will also be briefly reviewed in this chapter.

2. The embryology of pulmonary veins

The development of the cardiovascular system is complicated because it involves the process from before the folding of heart tube and extend to the later stage of vascular growth. In the vertebrate embryo, most discussion start from the Carnegie stage 12, which approximately equals to 28-30 days in human [1] and 2 days in chicken [2]. At this moment, the primitive pulmonary vein originates from the venous plexus of splanchnic

mesoderm. The staining characteristic of the pulmonary vein orifices in the developing heart can prove that the pulmonary vein is not part of the heart tube: it has no atrial natriuretic factor and has connexin 40 (a transmembrane protein that responsible for electrical coupling mostly found in the nodal tissue) [3]. In addition, an observation study of chicken embryo using image analysis and three-dimensional reconstruction technique also revealed that the pulmonary vein is developing from the splanchnic plexus [4]. The venous plexus of splanchnic mesoderm is a great capillary network that spread from the heart to the liver, connecting cardinal and umbilicovitelline veins. In other words, the pulmonary vein is communicating with systemic venous system in the beginning. In the subsequent developmental process, this communication will degenerate, therefore separating the systemic and pulmonary venous systems (**Figure 1**) [5].

Figure 1.

The normal pulmonary venous development. A, the lung buds are surrounded the splanchnic plexus that communicates umbilical veins and cardinal veins. B, Common pulmonary vein is formed and connected with the sinoatrial part of the heart. C, the connection between pulmonary and splanchnic venous plexus is disappearing. D, the common pulmonary vein develops to four distinct pulmonary veins that incorporates separately with the left atrium. LA, left atrium; LCCV, left common cardinal vein; LLB, left lung bud; RA, right atrium; RCCV, right common cardinal vein; RLB, right lung bud; UV, umbilical vein.

This common pulmonary vein connects the lung buds to the dorsal heart tube, where would develop to left atrium after the outgrowth of interatrial septum. At the level of left atrium, the common pulmonary vein would usually divide into four branches and incorporate with left atrium, forming the smooth part of the left atrium wall [6]. In a study using 26 normal human embryos, the initial process of formation of the human pulmonary vein is very similar to that seen in animal models; marked temporal and morphological difference between the development process of right- and left-side pulmonary veins was found: a much longer tributary being formed on the left than on the right [7].

Various congenital abnormalities of pulmonary veins can occur if anything is wrong during these developmental processes. The cor triatriatum sinister (CTS), a condition that left atrium is separated into two chambers by a membranous tissue, is thought to be the consequence of the inappropriate incorporation of pulmonary veins with the left atrium [7]. In addition, if the atrophy of connection between pulmonary veins and systemic venous system is fail, total or partial anomalous pulmonary venous connection (TAPVC or PAPVC) occurs, depending on the degree of remanent communication between systemic and pulmonary venous system [8].

3. The anatomy of the pulmonary veins

The pulmonary veins, in contrast to systemic veins that collect deoxygenated blood from all organs except lungs, deliver oxygen-rich blood from the lungs to the left atrium. Generally, there are four tributaries of pulmonary vein that would form four ostia on the left atrial wall, two from the right cranial and caudal pulmonary vein and the other two from the left cranial and caudal pulmonary vein (**Figure 2**).

Figure 2.
Normal anatomy of pulmonary veins. The blue (deoxygenated) marks pulmonary arteries, and the red (oxygenated) marks the pulmonary veins.

The right cranial pulmonary vein collects blood from the right cranial and middle lung lobe, and the right caudal pulmonary vein receives blood from the right caudal and accessory lung lobe. The rest pulmonary veins serve for the corresponded lung lobes that they are named after [9].

In atypical but not rare situations in human, pulmonary veins that both originate from right (4%) or left (17.8%) may fuse into a common trunk before entering the left atrium [10]. Additional pulmonary veins derive from individual lung lobes can also happen. Generally, these variations of the number of pulmonary veins are not always problematic, but it may interfere with clinical decisions especially in surgical procedures.

4. The physiology and function of pulmonary veins

In the species that have two atriums, two ventricles, and execute oxygen exchange via the lungs, the oxygenated blood is pumped from the aorta and sent into tissues. The oxygen, nutrients and metabolic products diffuse and exchange in the capillaries that converge and form the vein. Vena cava collect all the venous blood and return to right atrium, right ventricle and lungs. After oxygenation in the lung, these fresh, oxygen-rich blood is returned into left atrium via pulmonary veins, therefore complete the cycle of blood circulation.

Before we go deeper into more understanding of the pulmonary veins, there is an important concept that should be explained first. The cardiovascular system has several functions that are all indispensable to keep the body works normally. Maintaining the systemic arterial pressure is the first priority of the cardiovascular system, it means that the systemic arterial pressure is the last one that the decompensation occurs. The second one is to keep the cardiac output at an adequate level that can provide enough blood flow to the peripheral tissues. Maintaining the normal capillary pressure is the last priority, and therefore it is the reason that the first sign of heart failure is commonly those that associate with congestion [11]. In the cases of pulmonary vein abnormalities, although the pathophysiological mechanisms are different among diagnosis, the loss of normal capillary and venous pressure is often the end result of the developmental disorders. Patient is commonly presented to the clinic because of signs related to congestion. Therefore, we will discuss the pulmonary venous pressure in the next paragraph.

In the fetus, the pressure of the pulmonary system is higher compared to after birth because of very high pulmonary vascular resistance and resultant low pulmonary blood flow (only account for 10 to 15% of right heart stroke volume). The pulmonary vascular resistance falls after birth, and the pressure of pulmonary system drops to a lower level than the systemic circulation in normal setting [12]. In an experiment that studying normal dogs with light sedation, the mean pulmonary venous pressure (17.1 ± 6.5 mm Hg) is consistently slightly higher than mean left atrial pressure (13.4 ± 6.3 mm Hg), which is almost the same with mean pulmonary wedge pressure (13.3 ± 6.2 mm Hg). Considering that the lungs are a large organ that occupy the thorax cavity, the pulmonary venous pressure between locations that differ from altitude (distance from left atrium) is vary [13]. Generally, the pulmonary veins share the similar intravascular pressure with left atrium because there is no valve between them.

During ventricular systole and early diastole, the blood in the pulmonary veins flow into left atrium, and part of blood in the left atrium would regurgitates back into

pulmonary veins when the atrial active pumping that corresponds to the ventricular late filling phase. The changes of pulmonary venous profile among different cardiac cycle can be record by the echocardiographic Doppler examination [14]. It is therefore reasonable that any reason that elevates pressure of the left atrium has the potential to increase the pulmonary venous pressure, because of the higher impedance of draining blood forward and larger regurgitated volume from the high-pressured left atrium.

Another important characteristic of vessel that we cannot forget when we are discussing the hemodynamic is the vascular distensibility and compliance. Distensibility is an ability of vessel whose volume can increase or decrease for every increase or decrease intravascular pressure, and the compliance is equal to distensibility times the volume of blood in the given portion of the circulation. Because of the different wall constitution between veins and arteries, the distensibility of veins is about eight times larger than that of arteries. That is, the venous system can conserve more blood and only has slightly elevation of the intravascular pressure [15]. The pulmonary veins have similar distensibility to the systemic veins, meaning that the pulmonary venous pressure would not exceed the normal range before large amount of blood is congested in the pulmonary capillary and veins.

Various congenital and acquired cardiovascular diseases that affecting pulmonary veins themselves and the left atrium could lead to the congestion of pulmonary veins. They can be simply classified into conditions that cause obstruction or pulmonary overcirculation. Occlusions of one or more pulmonary veins, and the divided left atrium (like the CTS) are examples that pulmonary venous blood flow has difficulties to get through obstacles in its normal pathway and therefore causing high pressure to the rest part of pulmonary veins. In addition, pulmonary overcirculation caused by intra- or extra-cardiac left to right shunting (atrial and ventricular septal defects, patent foramen ovale, patent ductus arteriosus, and anomalous pulmonary venous connection and so on) also has the potential to causes pulmonary congestion because of larger than normal volume that circulates the pulmonary vasculature. Among them, CTS, TAPVC and PAPVC are three of the good examples that is closely related to the development of pulmonary veins. We will discuss these diseases in the following sections.

5. Cor triatriatum sinister

The CTS is a relatively rare congenital cardiovascular disease that has been first reported in 1868 [16]. In an autopsy research, it was accounted for 0.1% to 0.4% in human patients with congenital heart disease [17]. In veterinary medicine, the true prevalence is hard to know because this abnormality is not always producing heart murmur and develops clinical signs that can be observed by the owner and the veterinarian at the general practice. By reviewing case reports, naturally-occurred CTS is identified more frequently in cats [18–23] than in dogs [24–26].

The embryonic cause of CTS is still controversial, but the theory of pulmonary venous abnormality is the most popular. In the development of pulmonary veins, they should incorporate with left atrium and form four ostia on the smooth part of the dorsal left atrial wall. If certain degree of failure in this process occurs, the left atrium could be separated by the remains of the pulmonary veins, most of the time is a fibromuscular membrane. The left atrium is therefore divided to a proximal chamber that locates between the atriopulmonary junction and the fibromuscular membrane, and a distal chamber that extends from the fibromuscular membrane to the mitral valve

annulus. The molecular cause of CTS was first reported in experimental mice without hyaluronidase 2, which is an enzyme required for the degradation of hyaluronan that is the major extracellular matrix component of the heart [27]. Later, the similar result was obtained by genetic studies in affected human families and mice [28].

Anatomic variation of the membrane exists and whether or how much of the blood flow would be impeded depends on the three-dimensional relative position between the membrane and left atrium. This intra-atrial septum can be complete, incomplete or fenestrated, and its size, shape, thickness and location can be varied among affected patients. Types of diaphragmatic, hourglass and tubular has been used to describe the variations [29]. In a retrospective study, the histopathology of the membranous tissue was investigated. Elastin fibers were found to be presence in the top and bottom side and was absent in the middle layer of the diaphragm. Cardiomyocytes with positive staining of cardiac troponin C were located in the peripheral region, more on the side that near the diaphragm and atrial septum than on the side that near the diaphragm and the atrial free wall. The remanent area was mostly made up by the fibrous collagen and other mesenchymal cells. These specimens were collected from human patients that undergo surgical repair of the Cor triatriatum sinister, without surgical death in this cohort [30].

Impendence of the blood flow in the left atrium could cause turbulence, but the pressure gradient between two chambers may be not large enough for the heart murmur to be heard. Elevated pressure in the proximal chamber of the left atrium could raise the intravascular pressure of the pulmonary veins, and signs of left-side congestive heart failure may occur. However, the natural progression of the CTS in human patients is generally stable, with more than half patients were diagnosed in adulthood. In patients that need surgical correction using cardiopulmonary bypass, the surgery is safe and effective [31].

Transthoracic echocardiography is usually helpful in making diagnosis [32]. Except for detecting Cor triatriatum sinister, the echocardiography can also identify concurrent lesions. High proportion (58%) of affected human patients had associated abnormalities, and atrial septal defect and anomalous pulmonary venous connection were the most common and should be always keep in mind [30, 31, 33]. Two feline cases had been published that one kitten had CTS combined with persistent left cranial vena cava [20], and the other was diagnosed CTS with incomplete atrioventricular septal defect [21]. Some conditions can mimic the CTS under two-dimensional imaging mode, including supramitral ring or pulmonary stenosis [34]. In cases that the echocardiographic result alone is controversial or is suspicious of having multiple cardiovascular developmental diseases, additional imaging tools should be considered. A special case that was diagnosed as CTS with TAPVC by echocardiography combined with saline contrast technique was report in 2020 [35]. In some conditions especially when our target area is located near the heart base, the transesophageal echocardiography can provide better image resolution and details than the transthoracic echocardiography. Cardiac catheterization angiography has its advantages that it can measure the true intra-lumen pressure, which is always an estimated value if only echocardiography is performed. However, its clinical utility is limited in the veterinary field because deep sedation to generalized anesthesia is usually required in veterinary patients. Other imaging tools like computed tomography angiography and magnetic resonance imaging can provide multiplaner image reconstruction and assist with the diagnosis process [29].

Early in the 1998, a kitten presented signs of respiratory distress and diagnosed with CTS was successfully surgically managed. The membrane was torn by a dilator

introduced from an opened left atrium [18]. Procedure that combining thoracotomy and cardiac catheter guided cutting balloon was performed in a cat that signs of congestive heart failure resolved completely after the hybrid technique [22]. Surgical correction under cardiopulmonary bypass was also feasible in feline patient with appropriate body size and weight [23]. In canine, the first case was published in 2012, and the patient was doing well only by internal medical treatment for the congestive heart failure [25]. A poodle case was presented with acute dyspnea and cyanosis, and was unfortunately made its definite diagnosis in postmortem examination [26]. Recently, Toaldo et al. reported a 6-year-old intact male French bulldog was accidentally diagnosed as CTS [24].

By reviewing veterinary literature, we can find that cats are more frequently presented, and their age at diagnosis is generally younger (8 weeks old to 4 years old, mostly <1 year old) than dogs (3, 5 and 6 years old). Although most of affected cats had congestive heart failure at admission (this result can be biased in veterinary patients), the surgery is usually tolerable and the patient can be free of heart failure after procedure. Medicine for controlling congestive heart failure is an alternative option if surgery is not performed. Whether the surgery is also benefit and recommended in patient without heart failure is not conclusive.

6. Anomalous pulmonary venous connection

Another important developmental abnormality of pulmonary vein is the anomalous pulmonary venous connection. In human medicine, the TAPVC was comprised of 1–5% congenital heart diseases cases [36] and 0.6 to 1.2 per 10,000 live births [37]. The PAPVC was found 0.4% to 0.7% in the routine autopsies [38, 39]. A retrospective study that reviewed 290 dogs with cardiovascular malformations from 1953 to 1965 revealed that only 1 case was diagnosed PAPVC with secundum atrial septal defect [40]. For the published case reports, there are only 3 dogs [41–43] and each 1 of chicken [44] and foal [45] that are diagnosed as TAPVC; only 4 dogs [46–48] and 2 cats [49, 50] are PAPVC. One canine case reported in 1975 did not describe its detail (TAPVC or PAPVC) [51].

As previous discussed, the primitive pulmonary veins from the lung buds develop from the splanchnic plexus, which communicates with the systemic venous system, and connects to the left atrium. As development proceeds, the connection between pulmonary veins and the systemic venous system disappears. If the communication between pulmonary veins and the systemic venous system persists, TAPVC or PAPVC would be diagnosed depending on the degree of persistent connections [8].

The TAPVC is that all pulmonary veins being abnormally connected to the systemic venous circulation, that is, the right atrium would receive both systemic and pulmonary venous return. Researchers had described four types of TAPVC depending on the connection level (**Figure 3**). Type I, or supra-cardiac type, is the most common type that consist 40–55% of cases. The pulmonary veins empty through left innominate vein, superior vena cava or azygos veins. Type II, or cardiac type, is the second common type that consist 15–30% of cases. The pulmonary veins drain into the right atrium through the coronary sinus or in the posterior wall of the right atrium. Type III, or infra-cardiac type, is accounting approximately 15–26% of cases. The pulmonary veins run to the portal venous system or inferior vena cava. And type IV, or mixed type, is representing 2–10% cases that there are at least two different drainage sites [52, 53].

Figure 3.
The classification of TAPVR. Type I, the Supra-cardiac type; Type II, the cardiac type; Type III, the infra-cardiac type, and the Type IV, the mixed type. CaVC, caudal vena cava; CrVC, cranial vena cava; PA, pulmonary artery; PV, pulmonary vein; RA, right atrium.

In the setting of TAPVC, a right-to left shunt via an atrial septal defect (ASD), patent foramen ovale (PFO) or to a lesser extent of patent ductus arteriosus is required for completing circulation and maintaining life [54]. The presence of right (pulmonary) to left (systemic) shunting permits mixture of oxygenated and deoxygenated blood to enter the systemic circulation. Signs of dyspnea with exertion, cyanosis and exercise intolerance could be observed, and the patient is at risk of developing to pulmonary hypertension and congestive heart failure. Three veterinary cases were found to have concurrent ASD (secundum type in 1 dog [41] and 1 chicken [44]; sinus venous type in another dog [42]) and the case of foal [45] had concurrent PFO. A special child case had been recognized recently that all of his pulmonary veins

were anatomically connected to the left atrium but the blood inside actually was drained into superior vena cava via an innominate vein, therefore corresponded to the definition of supra-cardiac type of anomaly [35].

Thoracic radiography is commonly the first imaging exam, it can be normal or some classic changes may exist depending on the types of abnormal connections. A snowman sign has been described in patients with supra-cardiac TAPVC. The head is formed by superior vena cava, vertical vein (common vein that formed by the four anomalous pulmonary veins) and innominate vein, and the body is formed by enlarged right atrium. Another famous radiographic characteristic is the scimitar signs in the PAPVC. It describes the anomalous pulmonary veins like a sword with a curved blade that mostly affect the right-side lung lobes [5, 55].

In addition, the clinical utility of echocardiography in diagnosing abnormalities of pulmonary venous connection is somewhat difficult because of limited echo window, but it can provide the information of the concurrent congenital cardiac anomalies and hemodynamic consequences like the dilated right heart or possible pulmonary hypertension. Transesophageal echocardiography has the advantage that it can access from the heart base aspect, therefore providing more clear images of the structures near the heart base. Right heart catheterization can opacify the right heart chambers and venous vasculature but is limited that some small accessory and anomalous vessels may be missed.

For obtaining the full picture of abnormal development of pulmonary veins, multidetector computed tomography and magnetic resonance imaging both can provide good images. The importance of advanced imaging modules in diagnosing these complex cardiovascular developmental diseases had been emphasized in these years [49, 50]. Both of multidetector computed tomography and magnetic resonance imaging are non-invasive, and they can offer multiplanar and three-dimensional reconstructive model. Small lesions and details can be further illustrated by contrast median. Lack of ionizing radiation is the advantage of magnetic resonance imaging, but this procedure needs longer time and sedation which may be risky in some patients [53].

Generally, surgical repair is recommended at the time that TAPVC is diagnosed [56]. The surgical outcome is acceptable with the 6.6% of intraoperative and late death and 15% of recurrent pulmonary venous obstruction in the survivors. Risk factors for both undesired consequences including preoperative pulmonary venous obstruction, infra-cardiac type and mixed type [57]. This result emphasizes the importance of pre- and intra-operative assessment.

Partial anomalous pulmonary venous connection refers to equal to or more than 1, but not all, pulmonary veins being connected to the systemic venous circulation rather than the left atrium. Affected animals can exhibit no clinical signs or have symptoms associates with congestive heart failure and pulmonary hypertension. In the total of 6 veterinary cases, half of them were asymptomatic (2 miniature schnauzers [46] and 1 Devon Rex cat [49]) and the other half were presented with signs of decompensation (exercise intolerance in 1 Belgian Malinois dog [47], pulmonary edema in 1 toy poodle [48] and 1 American shorthair kitten [50]). The severity of symptoms depends on the number of affected pulmonary veins, that is, the degree of left-to-right shunt. A ratio of pulmonary to systemic blood flow ($Q_p:Q_s$) can be used to estimate the magnitude of left-to-right shunt, and the ratio greater than 1.5 to 2 is generally considered hemodynamic significant because the patient is at risk of pulmonary hypertension and heart failure, and surgical treatment is usually recommended in these cases [58].

According to the affected pulmonary veins, as many as 27 different anatomic variations had been proposed [59]. The characteristic of partial APVR in pediatric and adult populations varies significantly. In a prospective survey of pediatric patients, mostly (90%) were right-sided and in association of sinus venosus atrial septal defect [60]. In other two retrospective study that focused on adult (>18 years old), abnormal development of pulmonary vein from the left upper lobe was the most (ranging from 47–79%), followed by the right upper pulmonary vein (ranging from 17–38%) [61, 62]. The human patients that were diagnosed in childhood were mostly symptomatic, and those that diagnosed until adulthood were usually an incidental finding. Related signs including dyspnea, orthopnea, fatigue, chest pain, palpitations, tachycardia, and peripheral edema [53].

Surgical repair of the PAPVC with different strategies (intracardiac baffle, pulmonary vein implantation, or superior vena cava division with reimplantation on the right atrial appendage) in children showed excellent outcomes [60]. In a case series that only contain adult patients (20 to 66 years old), conservative management with close monitoring is recommended in asymptomatic patients, and the surgical outcomes in symptomatic patients are usually excellent with low complication rate [63]. Sinus node dysfunction and postoperative venous stenosis are the possible consequences followed surgery [64]. In a recent canine case, his PAPVC and sinus venosus ASD were successfully repaired by single-patch method under cardiopulmonary bypass. The patient remained stable and free of clinical signs in the following one year, suggesting that this is a valid treatment option for other similar case [48].

We can find that the terms of “connection”, “drainage” and “return” are all used in the literature to describe the abnormality. The “connection” indicates an anomalous venoatrial connection, whereas the word “drainage” or “return” describe the concept of abnormal pulmonary venous return despite normal anatomical connection [65]. Appropriate wording should be applied depending on the individual case. By reviewing veterinary literature, the clinical manifestation of TAPVC or PAPVC can vary depending on the individual. Owing to the scarcity of these diseases, we still know little about them. Future reports, including studies before and after death, treatment options and related outcome, are warrant.

7. Conclusions

In this chapter, we describe the embryology, physiological function and congenital diseases associated with pulmonary veins. The developmental process of the cardiovascular system is complicated, and every step is crucial. The CTS, TAPVC and PAPVC are rare congenital cardiovascular diseases in human and other animals, and can be asymptomatic or life-threatening. The improvement of advance imaging modules helps in diagnosing these abnormalities, particularly those have multiple concurrent developmental diseases. Knowledges regarding to the treatment intervention in the veterinary medicine is much less than the human medicine, further studies are welcome to provide more information.

Acknowledgements

We really appreciate of Dong-Hua, Liu, who provided these wonderful drawings for our chapter.

Conflict of interest

The authors declare no conflict of interest.

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