# THE COMPLETE REFERENCE FOR SCIMITAR SYNDROME

## Anatomy, Epidemiology, Diagnosis and Treatment

Edited by

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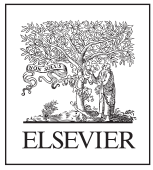


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# FOREWORD

This monograph produced by Dr. Vladimiro Vida and his coauthors on the scimitar syndrome and other pulmonary vascular anomalies focuses our attention on a syndrome which is relatively uncommon, and obviously not one of the major health problems of our era. Nevertheless the few who suffer from this syndrome equally deserve our attention.

The monograph provides important information on diagnosis and most importantly includes a detailed review of present day treatment, decision strategies, and therapeutic options. Clearly, the authors do not have all the answers, but they have accumulated a significant amount of evidence, including a review of a few multi-institutional studies, which highlights the complexity of this syndrome. We also learned that in most instances it does not present as a single lesion, but coexists with additional congenital cardiac defects, which add to the pathophysiology of the syndrome.

A variety of different surgical techniques and interventional catheterization procedures used to either correct or at least ameliorate this condition reflect remaining uncertainties. The content of this monograph fulfills an important role by stimulating continued efforts toward a better understanding of this complex congenital lesion. There is a great need to identify more precise and generally accepted guidelines to select the most effective therapeutic approaches. It is not surprising that the authors found in their review that patients with associated congenital heart defects and pulmonary hypertension fared worse and also had higher mortality. This analysis offers a large database, which will prove helpful in allowing for further important advances.

The history of the development of pediatric cardiac surgery provides us with multiple examples of similarly complex but nevertheless successfully resolved challenges. The authors deserve our thanks for their stimulating effort on a subject which has been

covered only sporadically in the literature and mostly through isolated case reports.

The patients suffering from scimitar syndrome deserve better.

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# CHAPTER 1

# Introduction and Definition

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## 1.1 INTRODUCTION

In 2006–07, I spent a period of time at the Children's Hospital, Harvard Medical School, Boston, as "senior fellow" and "chief resident" in cardiac surgery. At that time, Dr. PJ Del Nido, chief of the pediatric cardiac surgery unit called me to his office because he needed some language translation with an Italian lady, Rita Martini, who came into touch with him because of her rare congenital heart disease, the scimitar syndrome (SS).

After that, Rita told me that she was confused because in Italy she was not able to find someone who could help her in the management and treatment of her heart malformation; furthermore, she was not able to find a consistent scientific document treating the various aspects of her rare cardiac malformation. For this reason, she decided to get in touch with the chief of one of the leading pediatric and congenital heart centers in North America and she ended up coming over to Boston for her treatment. In those days I had the privilege to assist Dr. Del Nido during the operation and to take part in Rita's postoperative care till discharge.

Rita is an active and brilliant lady, and after coming back from the United States she decided to found a nonprofit association in Italy called "Amici della Scimitarra, ONLUS"

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(translated: friends of scimitar association) to create a network among patients with this rare disease and their families in order to share information, experiences, and knowledge.

Once I finished my training period in the United States, I decided to get more information on SS and I embarked on a couple of multiinstitutional studies, at a national and international basis, to evaluate surgical results and follow-up outcomes of these patients, and eventually in a multicenter study evaluating the clinical outcome of patients with SS who didn't undergo surgical correction of their anomalous pulmonary venous connection. Eventually I decided to coordinate a group of international experts about the anatomy, embryology, diagnosis, and treatment of this rare syndrome, putting together their knowledge to build up a consistent document on this topic, treating also other rare pulmonary vascular malformations such as pulmonary sequestration, horseshoe lung, anomalous arterious supply to the normal lung, and the persistent primitive hepatic venous plexus.

## 1.2 DEFINITION

A scimitar is a curved oriental sword with an edge on the convex side (from French "cimaterre," from Italian "scimitarra," from Spanish "cimitarra," and from Persian "simsir") [1] (Fig. 1.1).

SS is a rare association of congenital cardiopulmonary anomalies consisting of a partial or total anomalous pulmonary venous connection of the right lung to the inferior vena cava, right lung hypoplasia and a systemic arterial

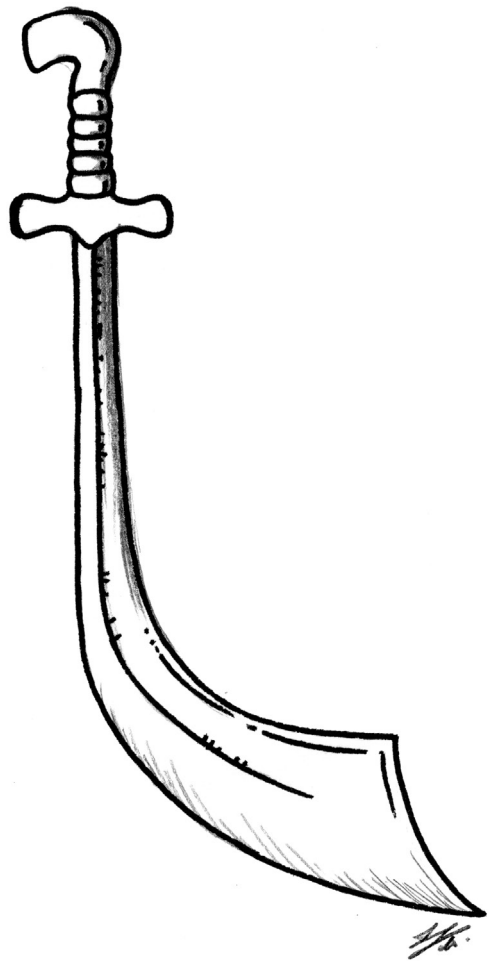

**Figure 1.1** The curved oriental sword with an edge on the convex side, named scimitar.

supply of variable hemodynamic importance to the right lung [2–5].

The origin of the name "scimitar" comes from the curvilinear shadow along the posterior-anterior chest X-ray, representing the anomalous pulmonary venous connection of the hypoplastic right lung [6,7] (Fig. 1.2).

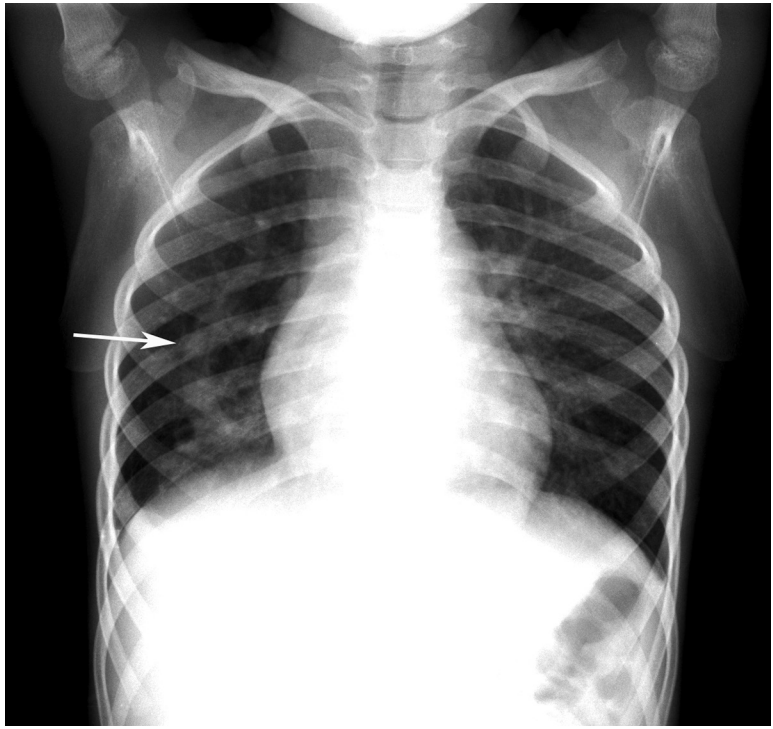

**Figure 1.2** Plain chest X-ray showing the curvilinear shadow along the posterior-anterior on the right hemithorax, representing the anomalous pulmonary venous connection of the hypoplastic right lung.

In fact, the intrathoracic course of the right anomalous pulmonary venous connection, descending toward the inferior vena cava appears as a radio-opaque waning moon gradually widening from the pulmonary hilum toward the cardiophrenic angle.

This syndrome is also known as Halasz syndrome, mirror-image lung syndrome, hypogenetic lung syndrome, epi-bronchial right pulmonary artery syndrome, vena cava bronchovascular syndrome, or congenital pulmonary venolobar syndrome [3,8,9].

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# CHAPTER 2

# Historical Notes

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The first anatomical observation of this peculiar anomalous venous connection was described by George Cooper [1] in the United Kingdom and by Raoul Chassinat in France [2], both in 1836.

George Cooper was an English pathologist who reported the autopsy findings of an "imperfect development of the right lung with malposition of the heart" in a 10-month-old girl with right pulmonary hypoplasia, systemic arterial supply from the descending aorta to the lung, and pulmonary venous drainage below the diaphragm [1] (Fig 2.1). Although both Cooper and Chassinat accurately described the anatomy of this rare congenital malformation, the term "scimitar" did not appear in their reports.

The next anatomical description of this anomaly belongs to Park [3], who 76 years later, in 1912, reported the postmortem observation of an anomalous pulmonary venous drainage of the right lung into the diaphragmatic portion of the inferior vena cava in three infant patients. Again, the word "scimitar" did not appear in his report.

In 1949, Dotter et al. [4], reported the first diagnosis of an infra-diaphragmatic anomalous pulmonary venous connection on a living patient. Dotter, in fact, included the use of angiocardiography and cardiac catheterization, describing as "a newly developed technique of venous angiography to

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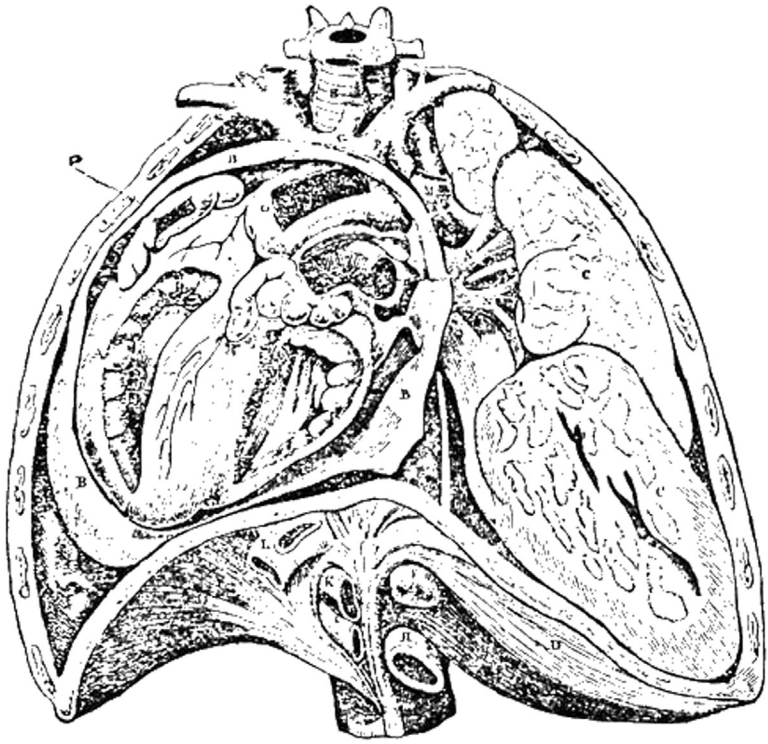

**Figure 2.1** Cooper's paper in the *London Medical Gazette* (1836) describing findings of scimitar syndrome. *From "Scimitar vein draining to the left atrium and a historical review of the scimitar syndrome" [Holt PD, et al. Pediatr Radiol (2004) 34: 409–413], with permission.*

follow the vessel course." He also described the pathological entity as "a crescent-like shadow curving downward through the right lower lung field" creating "a band-like shadow which widened gradually as it descended, paralleling the right cardiac border." This was the first published report of the radiologic description of this still "un-named syndrome."

The following year, Drake E. H. and colleagues performed a right lower lobe lobectomy on a patient with this peculiar anomalous pulmonary venous connection who presented also with recurrent pneumonias [5].

**Figure 2.2** Dr. Nicholas A. Halasz as a young man when he did his pioneering dissection studies at Yale in 1956. *From "Scimitar vein draining to the left atrium and a historical review of the scimitar syndrome" [Holt PD, et al. Pediatr Radiol (2004) 34: 409–413], with permission.*

The word "scimitar" first appeared in 1956 in a paper by Halasz and colleagues [6] which included also the famed pulmonary pathologist Averill Liebow. Halasz (Fig. 2.2), a surgical resident at Yale University who performed anatomic cast injections in three resected lungs from children with congestive heart failure, reported an intra-cardiac

defect and anomalous right pulmonary venous return. He demonstrated a "scimitar-shaped" vein that drained the entire right lung into the inferior vena cava. The word scimitar was used in the text of the paper to describe the shape of this anomalous pulmonary venous connection, but they still didn't name the syndrome.

Eventually, in 1960, the syndrome was christened by Catherine Neill (Fig. 2.3) in her landmark paper "The familial occurrence of hypoplastic right lung with systemic arterial supply and venous drainage: 'Scimitar Syndrome' [7]. The article elucidated the pathophysiology of the syndrome, correlated it with previously reported cases of similar anomalies and labeled them all as "scimitar syndrome." It also made the distinction between two clinical presentations: a more severe and early symptomatic "infantile" form, complicated by pulmonary hypertension, and an usually milder "adult" form, often diagnosed in asymptomatic adults.

Catherine Neill was an English pediatric cardiologist working as the first assistant of Dr. Helen B. Taussig at the Harriet Lane Home of Johns Hopkins Hospital in Baltimore, MD, United States. She was motivated by an early interest in the pulmonary venous system of patients with congenital heart disease and in 1956 she had already published a paper about the normal and various abnormal development of the pulmonary veins [8].

Catherine and colleagues, as they named the "scimitar syndrome" with a certain literary flair, hoped that the curvilinear shadow in a posterior-anterior chest X-ray would provide accurately the diagnosis of an anomalous pulmonary

**Figure 2.3** Dr. Catherine A. Neill, when she first reported a parent and child with scimitar syndrome at Johns Hopkins Hospital in 1960. *From "Scimitar vein draining to the left atrium and a historical review of the scimitar syndrome" [Holt PD, et al. Pediatr Radiol (2004) 34: 409–413], with permission.*

venous connection of a hypoplastic right lung to the inferior vena cava. Following these thoughts and interest for this rare syndrome, two radiologists and their colleagues, Roehm et al. [9] and Kiely et al. [10], exhaustively described the syndrome from an anatomical, clinical, and radiological point of

view. Over the years the wide spectrum of anatomical anomalies associated with the syndrome led to new nomenclature proposals, including the "congenital pulmonary veno-lobar syndrome," coined by Felson in 1973 [11]. However, "scimitar syndrome" remains the most common name for this rare anomalous pulmonary venous connection.

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# CHAPTER 3

# Embryology

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## 3.1 INTRODUCTION

Scimitar syndrome (SS) is diagnostically characterized by the scimitar-like profile of the right lower pulmonary vein draining preferentially into the inferior caval vein. However, as described in Chapter 4, this syndrome comprises more than an abnormal right-sided pulmonary venous drainage (Fig. 3.1) [1,2]. The combination of abnormally connecting inferior pulmonary vein(s), atresia/stenosis of the pulmonary artery, systemic-to-pulmonary arterial connections, diaphragmatic abnormalities, and abnormal lung anatomy does not give a direct clue about the primary cause of the syndrome that may also be related to disturbed right/left signaling, given the predispositioned right-sidedness of the problem. In addition, associated congenital heart disease occurs in 19%–31% of cases [3], with atrial septal defect (ASD) being the most common [3,4]. Other reported anomalies include tetralogy of Fallot, ventricular septal defect, aortic coarctation, hypoplastic left heart syndrome, total anomalous pulmonary venous return, patent ductus arteriosus, cor triatriatum, bicuspid aortic valve, and subaortic stenosis [3].

From a developmental point of view, several considerations apply. To understand the developmental background of SS and its associated malformations, first the relevant

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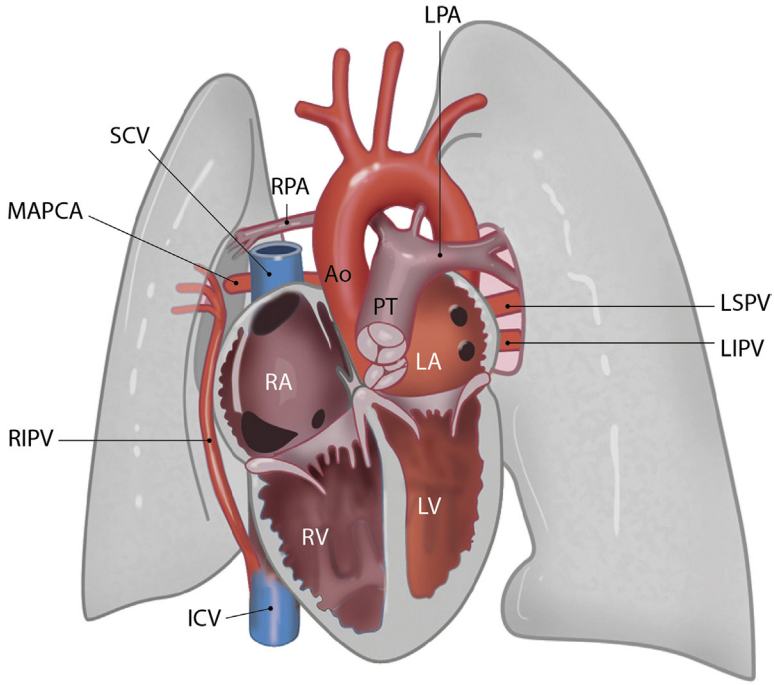


**Figure 3.1** ***Scimitar syndrome.*** The right inferior pulmonary vein (RIPV) drains in the inferior caval vein (ICV). The right lung is hypoplastic, as well as the right pulmonary artery (RPA). An aortopulmonary arterial connection (MAPCA) can be seen. *Ao*, aorta; *LA*, left atrium; *LIPV*, left inferior pulmonary vein; *LSPV*, left superior pulmonary vein; *LV*, left ventricle; *PT*, pulmonary trunk; *RA*, right atrium; *RV*, right ventricle; *SCV*, superior caval vein.

processes in embryonic development will be described. These comprise the formation of the embryonic germ layers, including the splanchnic mesoderm with the cardiac, lung, and early vascular plexus formation. The morphogenesis of these components is intricately linked to all aspects of the SS. After a summary of normal development, morphogenetic considerations on the developmental abnormalities encountered in the SS will be described.

## 3.2 EARLY EMBRYOGENESIS

During early embryonic development, a three-layered embryonic disk is formed, consisting initially of the endodermal and ectodermal germ layers. The primitive streak provides the somatic mesoderm, situated in between the endoderm and ectoderm, as well as two plates of lateral mesoderm, the somatic and splanchnic layers enveloping the coelomic cavity. The splanchnic mesoderm is the layer contributing to the anatomical structures most related to the malformations encountered in SS.

## 3.3 CARDIAC DEVELOPMENT

Between 17 and 23 days of development, the rostrally located bilateral cardiogenic plates of splanchnic mesoderm will fuse, thus forming the cardiac crescent. In the cardiac crescent, endocardial tubes coalesce in the midline forming the lumen of the primary heart tube, which is surrounded by cardiac jelly and a thin layer of myocardium [5]. The primary heart tube is embedded in the primitive pericardial cavity which is part of the coelomic cavity and becomes positioned more ventrally, in front of the foregut during the cranial to caudal bending of the head of the embryo. The primary heart tube shows a rightward looping and expansion, and remains connected to the splanchnic mesoderm by an arterial and a venous pole (Fig. 3.2). Already at 3 weeks of development the tube will show peristaltic contractions propelling the blood from the venous to the arterial pole. From a subpopulation of the splanchnic mesoderm, referred to as *second heart field* (indicated in yellow in Fig. 3.2), cells

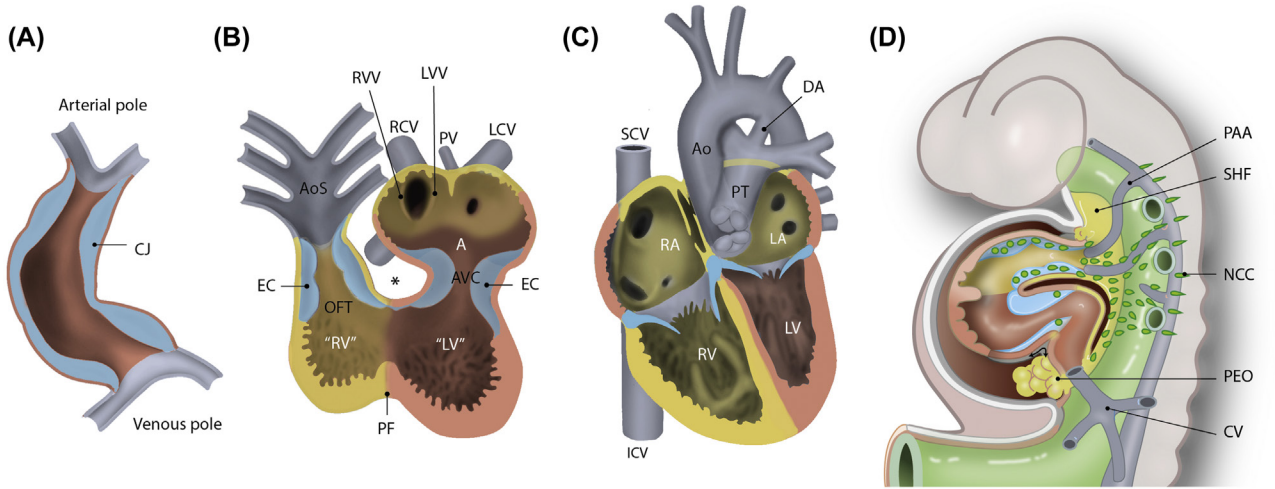


**Figure 3.2** ***Cardiac development.*** (A) Primary heart tube, consisting of an inner layer of endocardial cells and an outer layer of myocardial cells, with cardiac jelly (CJ) interposed. Second heart field (SHF)-derived parts are shown in yellow. (B) After looping, the primary heart tube has remodeled into a U-shaped form. Atrial and ventricular septation have not been established, yet. The anlage of the pulmonary vein (PV) can be observed. The asterisk indicates the inner curvature. (C) The four-chambered heart after septation. After incorporation of the PVs and its first tributaries, usually four pulmonary venous ostia can be observed, draining into the left atrium (only left pulmonary venous ostia seen in this view). (D) Lateral view of the developing heart, showing the spatial relationship of the heart tube in the coelomic space, and the position of the mesodermal SHF, depicted as the yellow area behind the heart. SHF derived cardiac areas are also depicted in yellow. The green cells indicate neural crest cells (NCC) that enter the heart at the arterial (numerous) and venous (rare) poles from the crest of the neural tube. *A*, common atrium; *Ao*, aorta; *AoS*, aortic sac; *AVC*, atrioventricular canal; *CV*, cardinal vein; *DA*, ductus arteriosus; *EC*, endocardial cushion; *ICV*, inferior caval vein; *LA*, left atrium; *LCV*, left cardinal vein; *LV*, (primitive) left ventricle; *PAA*, pharyngeal arch artery; *PT*, pulmonary trunk; *OFT*, outflow tract; *PEO*, pro-epicardial organ; *RA*, right atrium; *RCV*, right cardinal vein; *RV*, (primitive) right ventricle; *SCV*, superior caval vein. *Modified after Gittenberger-de Groot AC, Calkoen EE, Poelmann RE, Bartelings MM, Jongbloed MRM. Morphogenesis and molecular considerations on congenital cardiac septal defects. Ann Med 2014;46:640–52.*

will be added to the cardiac tube at both poles. In the splanchnic mesoderm, a plexus of endothelial cells and capillaries (further referred to as the *splanchnic plexus*) (Fig. 3.3) is formed through induction by factors secreted from the endoderm of the foregut. At the arterial pole, this splanchnic plexus will contribute to the formation of the pharyngeal arch arteries (1–6, lacking number 5) that connect the outflow tract of the heart to the concurrently developing bilateral dorsal aorta [5,6]. This splanchnic plexus is also initially contributing to the umbilical, vitelline, and cardinal veins that merge in the sinus venosus at the venous pole of the heart.

The primary heart tube initially consists of (1) a small atrial part, (2) the atrioventricular canal in which the cardiac jelly has been remodeled into atrioventricular cushions (putative atrioventricular valves), and (3) a primitive ventricle separated from the myocardial outflow tract (that is also lined by endocardial cushions; putative ventriculoarterial valves), by the primary fold and inner curvature (Fig. 3.2). During rightward looping, supported by growth and addition of second heart field-derived mesoderm, the heart tube attains all components for subsequent maturation into a four-chambered heart, which is essentially completed by 8 weeks of development. Second heart field-derived cells at the arterial pole of the heart are the source of the myocardium of the bulk of the right ventricle and the outflow tract. At the venous pole the second heart field contributes to the walls of the atria, the primary and secondary atrial septal components, as well as the wall of the sinus venosus that becomes incorporated into the atria [7,8]. Major remodeling processes take part during septation of the right and left ventricle [9]. During looping and

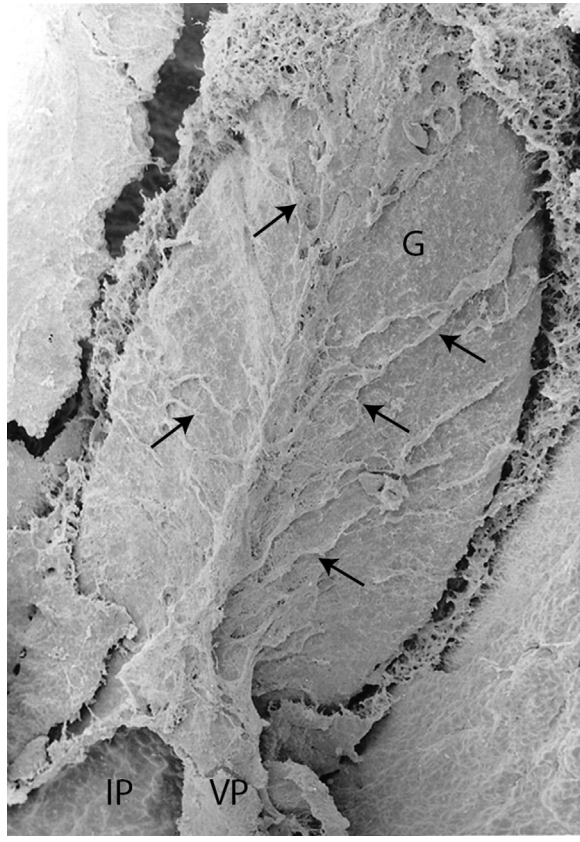


**Figure 3.3** ***The splanchnic plexus.*** Scanning electronic microscopic picture of a fetal chick heart, showing the endothelial strands (*arrows*) of the splanchnic vascular plexus on the foregut (G), after removal of the heart tube. The venous pole (VP) borders the intestinal portal (IP).

ventricular septation, the atrioventricular canal moves to the right, bringing the tricuspid orifice above the right ventricle [10] while at the same time there is a leftward and frontal translation of the outflow tract. In this process, the pulmonary trunk and orifices, separated from the ascending aorta by an aortopulmonary septum (neural crest induced) [11], is rotated frontally and elevated with regard

to the aortic orifice. This occurs by an asymmetric addition of anterior second heart field-derived mesoderm and myocardium, a modeling process referred to as the pulmonary push [12]. The connections of the pharyngeal arch arteries and the venous tributaries to the splanchnic plexus and the developing lungs will be described in separate paragraphs.

## 3.4 PULMONARY DEVELOPMENT

The lungs derive from the embryonic foregut (endoderm), and also receive contributions from the splanchnic mesoderm. At about 3 weeks of development, the division of the foregut in an esophageal and tracheal part is initiated by formation of the laryngotracheal groove that arises from the ventral part of the foregut. The tracheal part of the foregut branches into left and right lung buds at about 4 weeks of development. This endodermal foregut contribution is essential for the formation of the bronchial system, whereas the surrounding pulmonary mesenchyme derives from the splanchnic mesoderm (giving rise to cartilage, connective tissues, and muscular components of the bronchial system). The bronchial system expands its dichotomous branching until at least 16 weeks of development where after maturation the lung continues with formation of alveoli (airspaces) extending into the interstitial lung tissue. Around the developing lung buds a vascular plexus, derived from the splanchnic mesoderm, develops that connects on one side to the systemic dorsal aortae, as well as on the other side to the confluence of the venous tributaries that merge into the sinus venosus. This means that during early development, both pulmonary venous-to-systemic as well as

pulmonary arterial-to-systemic connections are present. These connections are related to the pulmonary-to-systemic connections as observed in SS which will be discussed in subsequent paragraphs. During these early developmental stages, no functional (open) connection between pulmonary veins and arteries to the heart has been achieved yet. This final development of the arterial (pulmonary arteries) and venous (pulmonary veins) connections to the heart are relative late events occurring at about 6–7 weeks of development.

## 3.5 THE EMBRYONIC SPLANCHNIC VASCULAR PLEXUS

The early endothelial plexus in the anterior splanchnic mesoderm differentiates into cells with arterial characteristics of the pharyngeal arch arteries during formation of the dorsal aorta [13]. At the venous pole, the cells of the endothelial plexus will develop into cells with venous characteristics of the pulmonary veins [14]. Systemic superior venous drainage of the embryo/fetus occurs via the superior cardinal veins, that on the right side will persist as the right superior caval vein, whereas the left-sided cardinal vein will become the vein/ligament of Marshall connected to the coronary sinus (Fig. 3.4). The inferior systemic drainage occurs via the umbilico-vitelline veins that feed bilaterally into the sinus venosus part of the right atrium (Fig. 3.4). Pulmonary venous drainage occurs initially via the venous splanchnic network into the systemic veins, whereas the normal drainage into the left atrium occurs only later during development, as will be discussed in the following section.

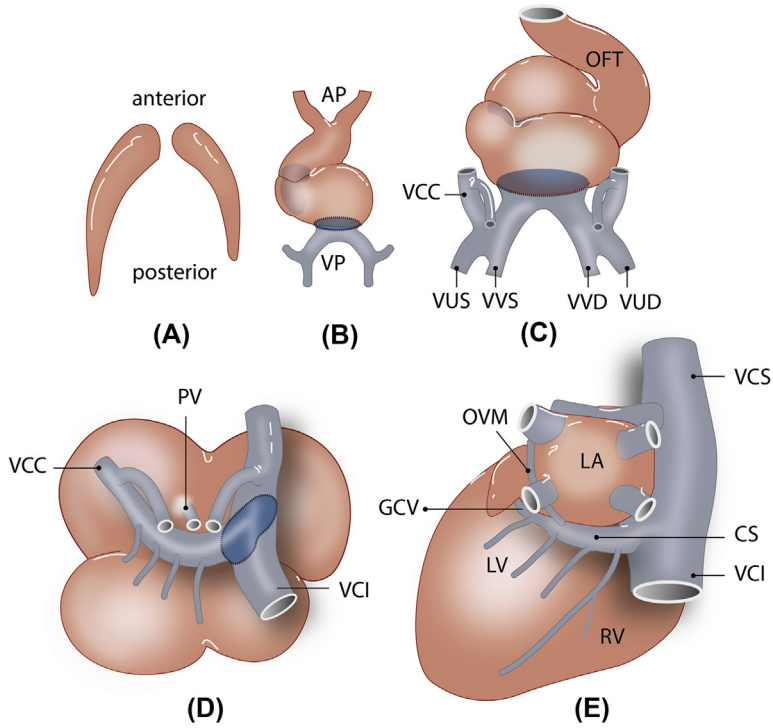


**Figure 3.4** ***Development of the venous system.*** (A–E): Schematic representation of sequential stages of cardiac development, dorsal views. (A) Bilateral field of splanchnic mesoderm that will fuse to form the cardiogenic plate and the primary heart tube (B), consisting of an arterial pole (AP) and a venous pole (VP). (C) Heart tube after looping, showing the veins draining bilateral into the venous pole, being the venae cardinales communes (VCC), the venae umbilicales dextra (VUD) and sinistra (VUS), the vena vitellinae dextra (VVD) and sinistra (VVS) and their tributaries. (D,E) During further development, remodeling in favor of the right side will occur, eventually resulting in persistence of a right-sided superior caval vein (VCS), derived from the right-sided cardinal vein, whereas the left-sided system will form the coronary sinus (CS) and its tributaries. The left cardinal vein will regress and can be recognized as the (oblique) vein of Marshall (Marshall vein or ligament, OVM). The initially single pulmonary vein (PV) will after incorporation drain into the left atrium, usually via four ostia. *GCV*, great cardiac vein; *LA*, left atrium; *LV*, left ventricle; *OFT*, outflow tract; *RV*, right ventricle; *VCI*, inferior caval vein. *Modified after Jongbloed M, Schalij M, Gittenberger-de Groot A. In: St. John Sutton M, Bax JJ, Jessup M, Brugada J, Schalij M, editors. Cardiac resynchronisation therapy. CRC Press; 2007. p. 93–108; Poelmann RE, Gittenberger-de Groot AC, Jongbloed MR, DeRuiter MC. In: Rickert-Sperling S, Kelly RG, Driscoll DJ, editors. Congenital heart diseases: the broken heart. Springer-Verlag; 2016. p. 379–96. http://dx.doi.org/10.1007/978-3-7091-1883-2. [Chapter 30]: Molecular Pathways and Animal Models*.

## 3.6 DEVELOPMENT OF THE PULMONARY VEINS

The anlage of the pulmonary veins is in continuity with the so-called *midpharyngeal endothelial strand (MPES)*. The MPES is part of the endothelial/capillary splanchnic plexus that extends from the arterial toward the venous pole in the mesoderm dorsal to the heart. The MPES gives rise to a small endothelial strand at the venous pole, which is the precursor of the pulmonary vein [14,15] (Fig. 3.5). This pulmonary venous strand is from the onset in contact with the venous pole of the heart, connecting to the atrial wall by incorporation of the sinus venosus into the atrium (Fig. 3.5). With regard to the development of the lung vasculature, this implies that there are primarily no small vessels growing out toward the lung buds but initially a primitive venous network inside the lung bud contacts the cardiac system by recruiting endothelial cells from the splanchnic plexus. The pulmonary venous endothelial

from the pulmonary venous plexus to the systemic veins via pulmonary-to-systemic venous connections. (C) *Intermediate draining period*. The endothelial anlage of the pulmonary veins has lumenized to become the common pulmonary vein (CPV), allowing drainage of the splanchnic plexus not only to the systemic veins but also into heart. The pulmonary-to-systemic venous connections are also still functional at this stage. (D) The CPV grows and dilates, and becomes the main route of drainage of the pulmonary venous blood. The primitive pulmonary-to-systemic connections gradually regress. (E) *Central drainage period*. At this stage, the primitive pulmonary-to-venous connections have regressed entirely. The route of drainage of the pulmonary venous blood is now directly into the heart. (F, G) Bifurcations of the CPV will be incorporated into the left atrium (LA), contributing to the body of the LA. Usually four separate pulmonary venous ostia can be recognized, although variations occur. *CS*, coronary sinus; *IAS*, interatrial septum; *LCV*, left cardinal vein; *LL*, left lung; *LUVV*, left umbilical and vitelline veins; *RA*, right atrium; *RCV*, right cardinal vein; *RL*, right lung; *RUVV*, right umbilical and vitelline veins; *SCV*, superior caval vein. *Modified after Poelmann RE, Gittenberger-de Groot AC, Jongbloed MR, DeRuiter MC. In: Rickert-Sperling S, Kelly RG, Driscoll DJ, editors. Congenital heart diseases: the broken heart. Springer-Verlag; 2016. p. 379–96. http://dx.doi.org/10.1007/978-3-7091-1883-2. [Chapter 30]: Molecular Pathways and Animal Models.*

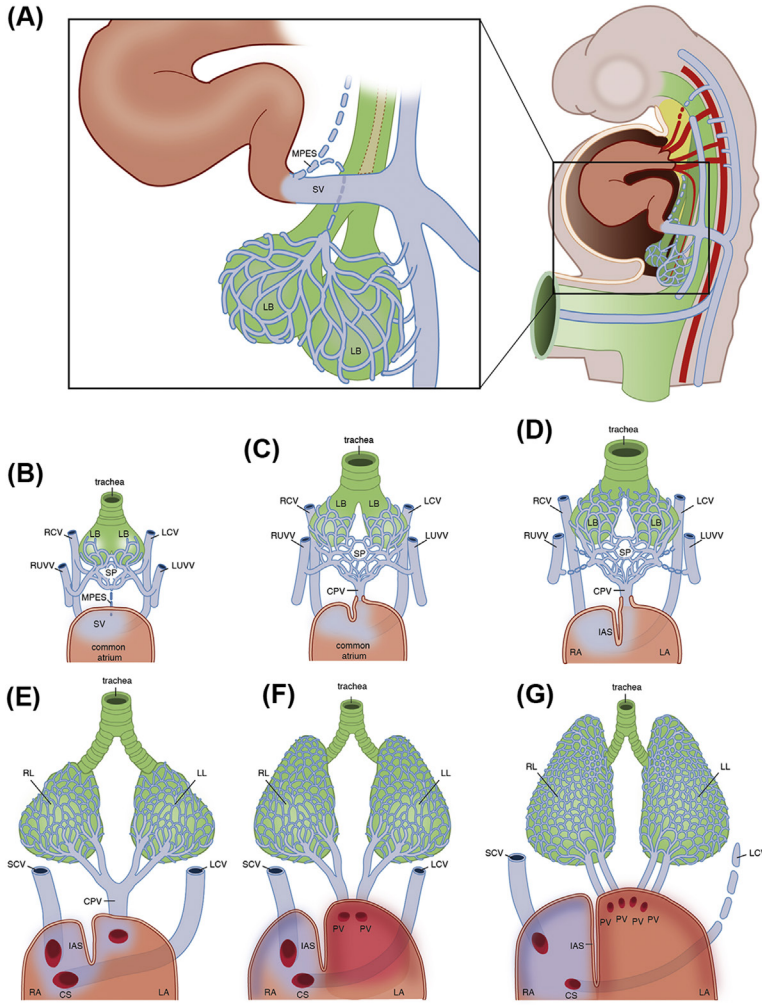


**Figure 3.5** ***Development of the pulmonary veins.*** Schematic overview of pulmonary vein development, frontal views. (A) Lateral view of the embryo. The boxed area is magnified. The foregut (green) gives rise to two lung buds (LB, putative lungs). A splanchnic vascular network (pale blue) can be observed surrounding the LBs. The venous tributaries drain into the sinus venosus (SV) to which is connected the non-lumenized pulmonary vein and the midpharyngeal endothelial strand (MPES) that runs in front of the gut from the venous to the arterial pole. (B) *Peripheral draining period*. The splanchnic plexus (indicated as the pale blue network covering the foregut including the LB) is already connected to the endocardium of the primitive heart tube, by means of the MPES. As this strand is initially not lumenized, during these early developmental stages the route of drainage is

strand, however, is initially not lumenized. Therefore, the drainage of the lung mesenchyme takes place into the systemic venous tributaries. After lumenization of the pulmonary endothelial strand, atrial septation and development of the dorsal mesenchymal protrusion (DMP) in this area are required to bring the pulmonary vein anlage to the future left atrium. During further developmental stages, the initially single pulmonary vein, will progressively become incorporated into the left atrium, contributing to the body of the left atrium (Fig. 3.5). After incorporation, no histological border can be detected between the pulmonary veins and the left atrial wall [16]. Usually, the amount of incorporation is such that four pulmonary venous ostia (two right and two left) can be recognized from the left atrium, representing the drainage of the upper and lower right and left pulmonary lobes. Dependent on the degree of incorporation, variability in the number of ostia seen from the left atrium may occur. Most commonly observed are additional right-sided pulmonary veins, as well as common ostia of the left pulmonary veins [17].

This development of primitive to mature pulmonary venous drainage patterns has been elegantly described in detail by Rammos et al. [18] for a series of human and murine embryos recognizing three stages (Fig. 3.5):

1. A *peripheral period* [crown-rump-length (CRL) 4.4–7 mm, approx. 6–6.5 weeks] with no open connection between the lung vascular network and the developing atrium. The pulmonary strand of the MPES has not lumenized yet and the lung drains by way of the splanchnic network into the systemic venous circulation (Figs. 3.5A,B).

2. An *intermediate period* (CRL 7–11 mm, approx. 6.5–7.5 weeks) in which the now lumenized common

pulmonary vein is connected to the left atrium, but with the pulmonary tot systemic connections still persisting (Fig. 3.5D).

3. A *central period* (CRL>11 mm, >7.5 weeks) with the only drainage through the pulmonary veins into the left atrium. The systemic connections have regressed at these stages (Figs. 3.5E–G).

## 3.7 DEVELOPMENT OF THE PULMONARY ARTERIAL SYSTEM

The endothelial plexus covering the foregut gives rise to the pulmonary arteries. However, similar to the situation at the venous pole before the pulmonary arteries develop within the plexus in this way, the plexus is connected to the systemic circulation, i.e., the dorsal aortae. After establishment of a blood flow from the heart through the pulmonary arteries, these connections disappear except for the distal part of the sixth pharyngeal arch artery that will become the ductus arteriosus. More specifically, at the arterial pole the pharyngeal arch arteries 1–4 and 6 (the fifth is missing in mammals) develop in subsequent order from cranial to caudal [13–19]. During this process the first and second pharyngeal arch arteries are incorporated in the facial vasculature, the third develops into the carotid arteries, the left fourth forms the major component of the aortic arch (B segment) while the right fourth is incorporated in the right subclavian artery (Fig. 3.6). The left and right pulmonary arteries grow from the lung buds into the side of the sixth pharyngeal arch arteries, of which the distal part on the left persists as the ductus arteriosus until its closure after birth. The distal part of the right sixth artery regresses already early in development leaving only the right

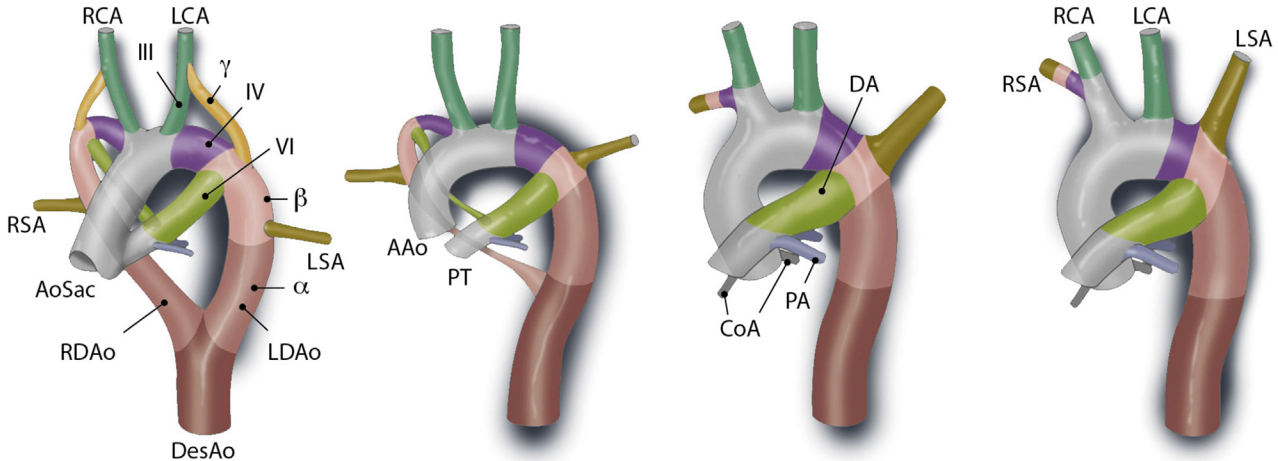


**Figure 3.6** ***Remodeling of the pharyngeal arch arteries.*** The vascular system evolves from an initially symmetrical bilateral system into an asymmetrical system. In the development of the definitive cardiovascular system, the IIIrd, IVth, and VIth pharyngeal arch arteries (PAA) are involved. The left and right IIIrd PAAs (indicated in green) will form the right (RCA) and left (LCA) common carotid arteries. The left IVth PAA (purple) will form part of the aortic arch (the so-called B segment), whereas the right IVth PAA will form the proximal part of the right subclavian artery (RSA). The left VIth PAA (light green) will form the ductus arteriosus (DA), whereas the right VIth PAA will regress. *AoSac*, aortic sac; *CoA*, coronary arteries; *DesAo*, descending aorta; *LDAo*, left dorsal aorta; *LSA*, left subclavian artery; *PA*, pulmonary arteries, *RDAo*, right dorsal aorta. *Modified after Molin DGM, et al. Altered apoptosis pattern during pharyngeal arch artery remodelling is associated with aortic arch malformations in Tgf-beta2 knock-out mice. Cardiovasc Res 2002;56:312–22.*

pulmonary artery to connect to the pulmonary trunk [19]. In human embryos the pulmonary artery ingrowth occurs directly into the developing pulmonary trunk next to the sixth pharyngeal arch artery [20]. Furthermore, in the pulmonary arterial system a transient period exists in which the developing lung arterial system changes from a system initially connected to the dorsal aorta, into the mature system containing a cardiac pulmonary trunk and pulmonary arteries connecting to the lungs. This implies that, similar to the situation at the venous pole during early development, pulmonary arterial-to-systemic connections are present.

## 3.8 DEVELOPMENT OF THE DIAPHRAGM

As (mostly right-sided) diaphragmatic abnormalities have incidentally been reported in SS [21,22], the development of the diaphragm will therefore briefly be mentioned here. Of interest, this muscular structure receives contributions from the so-called posthepatic mesenchymal plate [23], and is related to the transcription factor Tbx18, expressed in sinus venosus myocardium [24], thus potentially fitting into the spectrum of anomalies described above. In addition, several other tissues, including the transverse septum and the pleuroperitoneal folds, contribute [23]. Considerations with regard to the concurrence in SS will be discussed in the following section.

## 3.9 INTRATHORACIC ASYMMETRY

The last aspects that need attention are the clues guiding right and left developmental pathways. The right-sided predisposition of SS indicates a potential contribution of

laterality genes. Sporadic cases of left-sided scimitar drainage have been reported [25,26]. During normal cardiac development, asymmetry is required for proper looping, positioning of cardiac segments, and connecting of vasculature. Left- and right-sided signaling cascades are active already in early developmental stages. Normally, the heart with its rightward looping and its left aortic arch becomes positioned on the left side of the sternum. This asymmetry is also reflected in the lungs, which possess a different right (3 lobes) and left (2 lobes) morphology, also visible in the bronchial tree that branches in the lungs. The right and left atria with their venous tributaries are strongly linked to this left/right patterning. Many genes are essential in this left/right designation [27] with a major role in heart and lung development for Pitx2, which dominates left-sided development [28,29]. Indeed, SS has been associated with situs anomalies in some cases [30].

## 3.10 UNDERSTANDING DEVELOPMENTAL ERRORS IN THE SCIMITAR SYNDROME

As has been described earlier, the combination of anomalies observed in SS likely has its origin in early vascular, pulmonary, as well as cardiac, developmental events. The main question is whether SS is primarily related to defects in the developing foregut (giving rise to the lung epithelium), the splanchnic vascular plexus (giving rise to both the arterial and venous vascular system), or the splanchnic mesoderm (giving rise to the heart and the mesenchymal part of the lungs). All systems involved have a temporospatial connection through the intervening splanchnic mesoderm during the embryonic time window, between 3 and 6 weeks of development.

### 3.10.1 Abnormal Pulmonary Venous Drainage, Pulmonary Arterial-to-Systemic Connections

From cardiac morphology (see Chapter 4) we know that abnormal drainage can be supracardiac, cardiac, and infracardiac and can be complete (total abnormal pulmonary venous connection: TAPVC) or partial (partial abnormal pulmonary venous connection: PAPVC) [31]. SS is in general an example of PAPVC in which the lower lobe of the right lung does not drain into the left atrium but rather into the superior part of the inferior caval vein either in an infra- or supradiaphragmatic way [32]. Variations exist with drainage patterns into the subdiaphragmatic portal or hepatic veins [33].

This anomaly can be explained to originate during the *intermediate period* [18] of pulmonary vein development, in which the transition from a systemic venous to a cardiac drainage develops. Interestingly, also the arterial supply (following the expanding bronchial system) is abnormal, while the middle and upper left lung lobe can be normally structured and perfused. This might provide us with some clues as to developmental sequence and or origin, favoring primarily the abnormal right lower lung lobe development with persistent drainage to the systemic venous system (i.e., inferior caval vein) with subsequent abnormal lung artery branching. A molecular-biology-related explanation, involving the patterning of the splanchnic plexus, comes by the way of semaphorin3 expression. In a mutant mouse lack of expression acted directly on the splanchnic plexus system by disturbance of boundaries with the eventual resultant TAPVC [15]. TAPVC and PAPVC have also been reported in PDGFR-alpha mutant mice [34,35]; however, these all refer to the

cardiac type or supracardiac types of abnormal venous drainage. In a human embryo of CRL 18 mm (approx. 8 weeks gestational age) and several mouse embryos of comparable developmental stages, we have seen that a diminished or absent development of a pulmonary vein can lead to persistence and even expansion of the splanchnic plexus maintaining the connection between the lungs and the large venous tributaries [18] (Fig. 3.7). This hypothesis can also apply to TAPVC and PAPVC at the cardiac and supracardiac level. Although several familial cases of SS have been described [36–41], there are as yet no explanations either from mouse genetic or human family studies that reveal a specific gene pathway that can lead to SS.

In a number of patients with SS major aortopulmonary connections (MAPCAs) coexist, which probably develop during the *intermediate period* in which the splanchnic plexus remains connected to the dorsal aortae [14].

### 3.10.2 Pulmonary Hypoplasia, Diaphragmatic Abnormalities

The pulmonary hypoplasia that occurs in SS can either be related to the abnormal drainage patterns or be a result of diaphragmatic abnormalities. Scimitar drainage may occur at both the supra- and infradiaphragmatic level [3,42]. Drainage to the inferior caval vein is present in a substantial number of cases. In cases with infradiaphragmatic drainage, the abnormal draining pulmonary vein needs to pass the diaphragm. Whether this relates to the diaphragmatic abnormalities that are observed in some cases of SS is as yet undetermined. An association with hernia diaphragmatica seems unlikely given

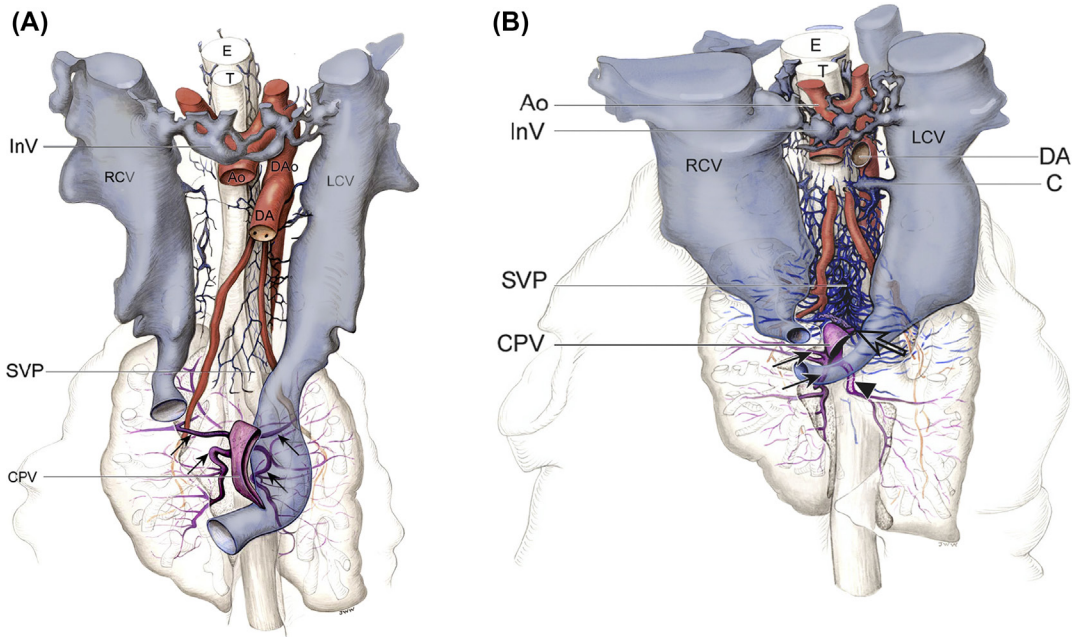


**Figure 3.7** ***Human normal and abnormal development.*** Frontal views of 3D reconstruction of human embryos of approximately 8-weeks gestational age (crown rump length 18 m). The heart and part of the left atrial dorsal wall have been removed for clarity. (A) Normal embryo. Four pulmonary veins (*arrows*) drain the lung toward the common pulmonary vein (CPV). No pulmonary-to-systemic connections are present any more via the splanchnic venous plexus (SVP), although small communications of this plexus into the right and left cardinal veins (RCV and LCV) can still be observed. (B) Abnormal pulmonary venous connection. Two right-sided pulmonary veins (*black arrows*) have normal drainage patterns toward a hypoplastic CPV. The left superior pulmonary vein is lacking (*open arrow*), and the left inferior pulmonary vein is devoid of blood (*black arrowhead*). There are extensive systemic to venous connections, with a high number of connections to both lungs. In addition, a large additional connection (C) can be observed between the systemic-to-pulmonary connections and the left cardinal vein (LCV). *Ao*, aorta; *DA*, ductus arteriosus; *DAo*, descending aorta; *E*, esophagus; *InV*, innominate vein; *T*: trachea. *Modified after Rammos S, Gittenberger-de Grott AC, Oppenheimer-Dekker A. The abnormal pulmonary venous connexion: a developmental approach. Int J Cardiol 1990;29:285–95; Poelmann RE, Jongbloed MR, DeRuiter MC, Gittenberger-de Groot AC. In: Rickert-Sperling S, Kelly RG, Driscoll DJ, editors. Congenital heart diseases: the broken heart. Springer-Verlag; 2016. p. 373–8. http://dx.doi.org/10.1007/978-3-7091-1883-2. [Chapter 29]: Human Genetics.*

the left-sided predisposition of this disorder [23]. Remarkably, cases of accessory hemidiaphragm, occurring most often on the right side, have been reported in SS [22,43].

### 3.10.3 Lateralization Defects

Lateralization defects as a primary cause should also be considered because of the prevalence of the anomaly at the right side. Heterotaxia syndromes and situs anomalies have been reported as associated anomalies [30]. The observed dextroposition does not need to be essentially a lateralization problem as the right side of the thoracic cavity is less filled by lung tissue, which can result in a rightward shift of the heart.

### 3.10.4 Associated Congenital Anomalies

As reported earlier, associated congenital heart disease occurs in a 19%–31% of SS patients [3], with ASD being the most common [4]. ASD may be considered developmentally as being part of the splanchnic mesoderm-second heart field spectrum. Mouse models with deficient second heart field contributions display a variety of congenital heart diseases, including ASDs (reviewed in reference [44]).

## 3.11 CLOSING REMARKS

Although the above considerations provide several developmental clues relating to the complex spectrum of malformations observed in SS, it remains challenging to distinguish causal relationships of all anomalies encountered, and determine whether certain anomalies are either the cause or results

of other defects. For example, pulmonary hypoplasia can either result from the abnormal drainage itself, or from associated diaphragmatic defects [23]. Likewise, dextroposition can either be the result of pulmonary hypoplasia or of lateralization defects. Animal models specifically demonstrating SS are not available to date, thus hampering developmental studies.

Although many questions still need to be resolved, from a developmental point of view SS seems to be related to early events during embryology, which encompass involvement of the splanchnic (second heart field) mesoderm, giving rise to the heart and splanchnic plexus, in interaction with endodermal tissues of the foregut, giving rise to the epithelial parts of the lungs. Detailed phenotyping of drainage patterns and associated anomalies will extend developmental clues and contribute to progression of insight into the developmental background of this variable anomaly.

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# CHAPTER 4

# Anatomy and Histology

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The syndrome is anatomically characterized by:

- partial or complete anomalous venous communication of the right lung into the inferior vena cava (Figs. 4.1–4.3);
- hypoplasia of the right pulmonary artery and lung;
- dextroposition of the heart;
- presence of a systemic artery which commonly originates from the aorta and connects to the right lower lobe of the right middle lobe of the right lung (Fig. 4.2C).

The right pulmonary vein connects with the inferior vena cava, either above or below the diaphragm. Usually the veins of the lower and sometimes the middle lobe of the right lung are involved but less commonly the whole right lung drains into the inferior vena cava [1–4].

The scimitar vein may be stenotic, just distal or at its junction, with the inferior vena cava in 10%–20% of cases [1,4–6].

Some rare variants have been observed in the literature such as: a scimitar vein draining to the left atrium (less than a dozen documented cases) [7,8], bilateral partial anomalous pulmonary venous connection [9], anomalous connection

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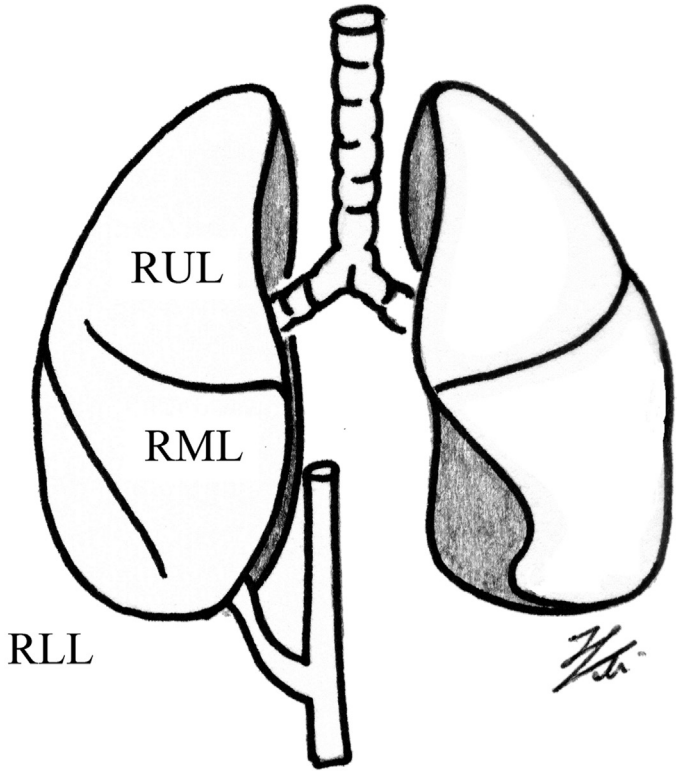


**Figure 4.1** Scimitar syndrome. Image showing the percentage of right lung drained by the scimitar vein collector. 100% of cases originated from the right lower lobe (RLL), 83% right middle lobe (RML), and 67% right upper lobe (RUL).

of the left superior pulmonary vein to the left innominate vein, the most common variant [10].

Hypoplasia of a various degree of the right lung with abnormal lobation and bronchial distribution is common and occurs in more than 50% of cases.

The right pulmonary artery is usually hypoplastic or can be absent. The association of right lung hypoplasia and

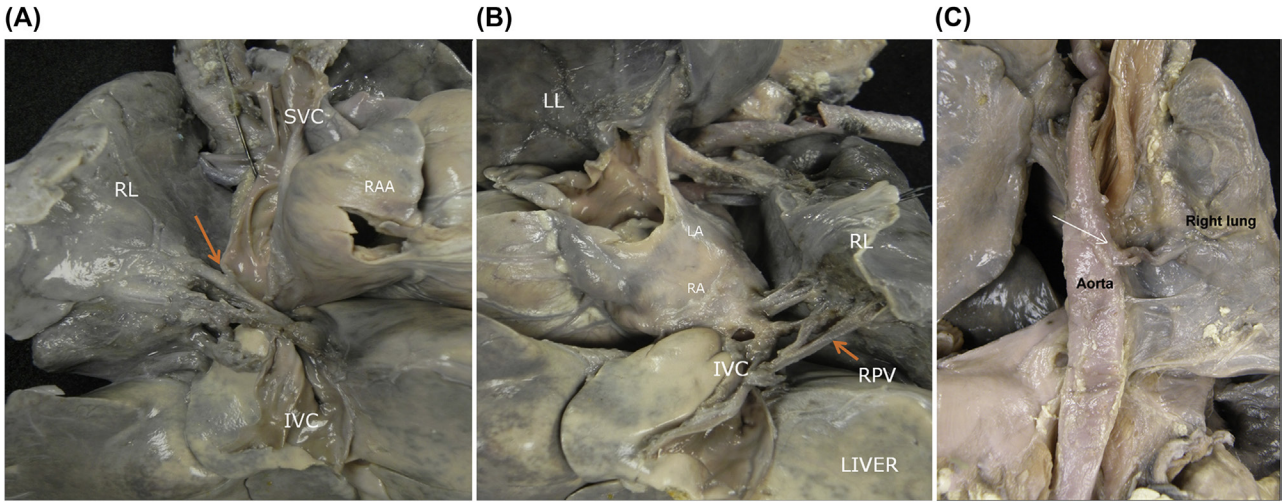


**Figure 4.2** Scimitar syndrome in a five-month-old female. (A) Antero-lateral view of the lung and the heart showing the anomalous pulmonary venous return of the medium-inferior lobe of the right lung to the inferior vena cava. (B) Posterior view of the heart and lungs showing the anomalous drainage to the inferior vena cava. *IVC*, inferior vena cava; *LA*, left atrium; *LL*, left lung; *RA*, right atrium; *RAA*, right atrial appendage; *RL*, right lung; *RPV*, right inferior pulmonary veins; *SVC*, superior vena cava. (C) Posterior view showing the hypoplastic right lung and the systemic vessel (*white arrow*) which arises from the aorta and supplies the pulmonary circulation in the inferior lobe.

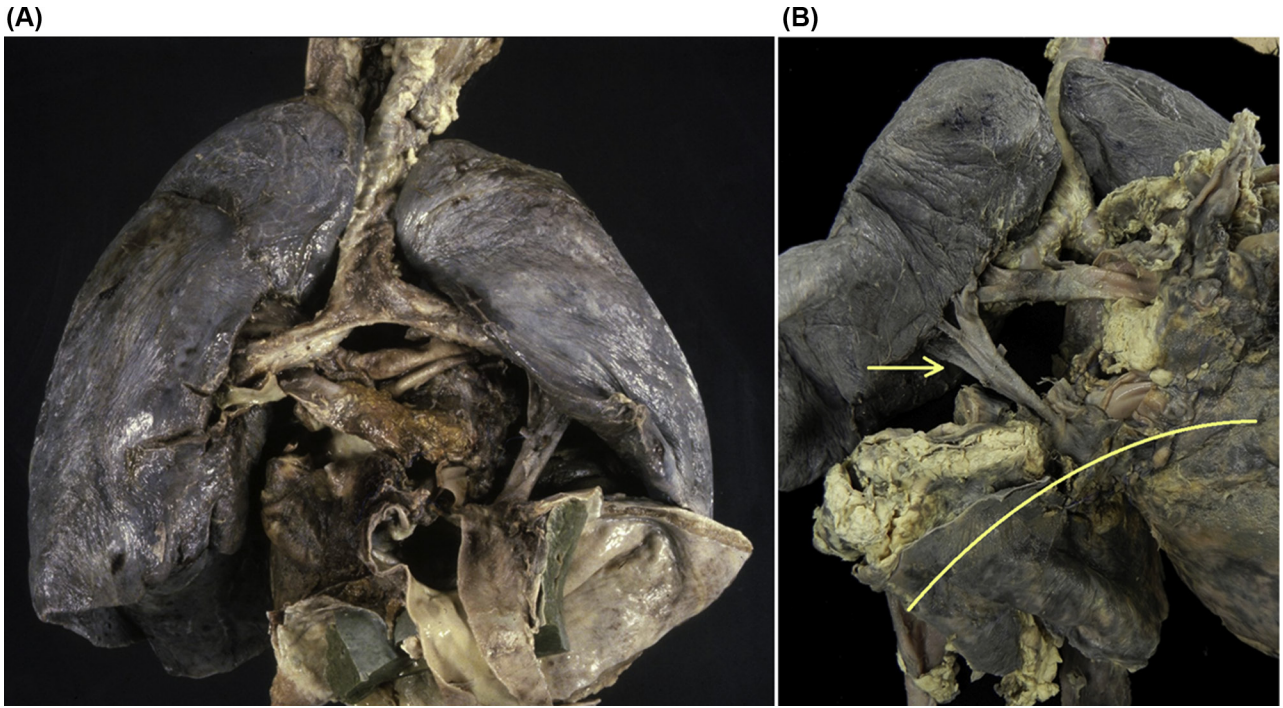


**Figure 4.3** Scimitar syndrome in a 53-year-old woman, who has been operated on. (A) Posterior view of the lungs and heart with the typical features of the anomalous venous return of the inferior right lung to the IVC. (B) Antero-lateral view of the right lung with the anomalous venous drainage of the inferior lobe to the IVC. The superior lobe is draining toward the left atrium. *IVC*, inferior vena cava; *LL*, left lung; *RA*, right atrium; *RL*, right lung; *RPV*, right inferior pulmonary veins; *SVC*, superior vena cava. A *yellow curved line* identifies diaphragm level.

pulmonary artery hypoplasia is also responsible for the rotation of the heart into the right hemithorax, i.e., dextroposition of the heart.

In some cases, the whole mediastinum is shifted to the right and the scimitar vein may be difficult to visualize or can even be completely obscured. Other airway anomalies, such as diverticuli of the right bronchus, hypoplastic or absent bronchi, are quite common [11,12].

The hypoplastic right lung, mostly the basal segment of the lower lobe, receives blood supply from an anomalous systemic artery arising from the thoracic or abdominal aorta (Fig. 4.2C). These vessels course superiorly, pass through the diaphragm and reach the lung lobe where they branch. The rate of flow of these collaterals is variable, ranging from insignificant to almost complete arterial supply to the right lung [13].

The bronchi of the right lung are usually abnormal and a sequestration of the right lower lobe of the right lung may be present. This part of the lung is separated from the bronchial tree and contains nonfunctioning lung tissue and is usually supplied by an anomalous systemic artery. It is of note that the majority of the pulmonary sequestrations are not associated with anomalous pulmonary venous connection. In scimitar syndrome the rest of the lung is usually normally connected to the airways and to the pulmonary artery vascular tree [13]. There are no data available on extensive histological evaluation of the lungs in scimitar syndrome. We have evaluated the lungs in two cases of scimitar syndrome: one in a pediatric case, a five-month-old female, un-operated, affected by scimitar syndrome who died and one in an adult case, a 53-year-old woman who had been operated on

and died immediately after surgery for a hemorrhagic complication. In the pediatric case, the histology of the unaffected lobes showed the parenchyma with normal arterial distribution with peri-adventitial fibrosis and thickened media suggestive of persistent fetal circulation. The scimitar lobe showed a normal aerated parenchyma with arterial and venous normal distributions with increased peri-adventitial fibrosis and thickened media, similar to the unaffected lobes. No differences could be detected for bronchial distributions (Fig. 4.4). In the adult case the arteries of the unaffected lobe appeared dilated, tortuous, and with thin walls. The adventitia is prominent with severe fibrosis. The veins appeared dilated with thinning of the wall. The alveoli are squashed without bronco-dysplasia but with diffuse interstitial fibrosis. The scimitar lobe showed tortuous dilated veins, artery with hyalinization of the parietal wall and intimal hyperplasia, and marked interstitial fibrosis (Fig. 4.5).

About 70% of patients with scimitar syndrome have an associated atrial septal defect (ASD) [14–16], with the ostium secundum type being the most common. The syndrome has also less commonly been described in association with other cardiac malformations such as tetralogy of Fallot [17,18], ventricular septal defect [14,15], coarctation of the aorta [3,19–21], hypoplastic left heart syndrome [6], total anomalous pulmonary venous connection [21], patent ductus arteriosus [1,3,17,21–23], cor triatriatum [2], bicuspid aortic valve [17,19], and subaortic stenosis [21]. Overall, 19%–31% of patients with scimitar syndrome have associated cardiac anomalies [6,17,18,23].

The presence of associated cardiac lesions characterizes the "infantile" form [1] leading to symptoms early in infancy with poorer prognosis as compared with the "adult" form.

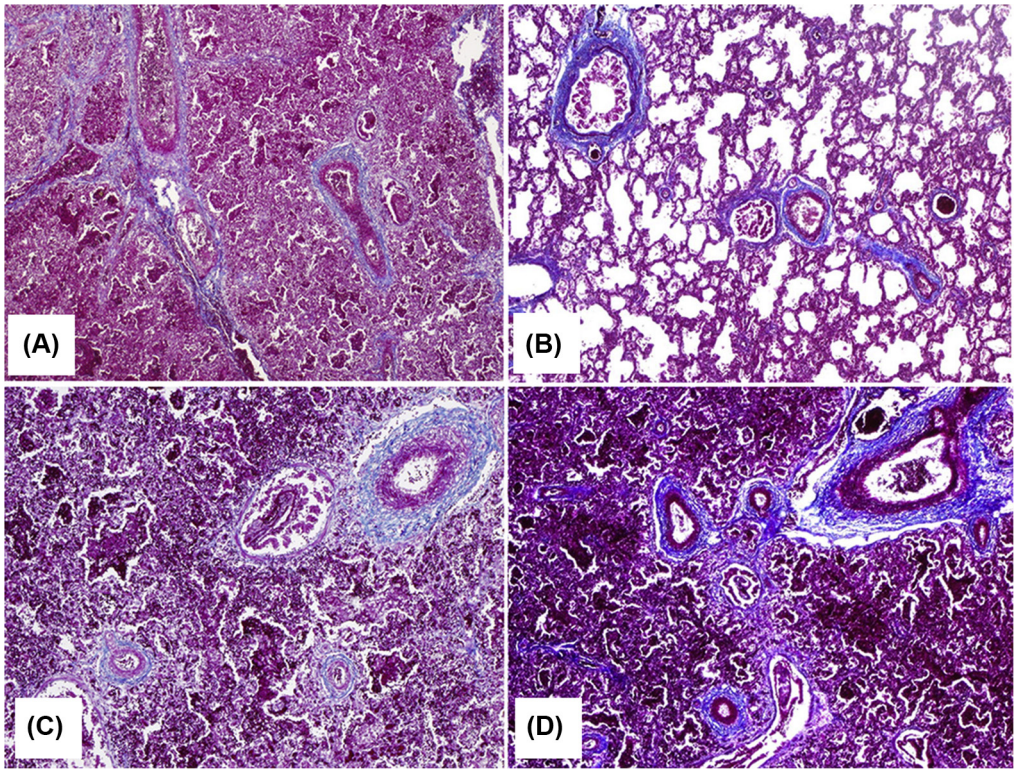


**Figure 4.4** Histology of the lungs of case of Figure 4.2. (A) Superior lobe of right lung showing the parenchyma with normal arterial distribution with increased peri-adventitia fibrosis and thickened media suggestive of perinatal circulation. The alveoli with normal pattern are hemorrhagic. (B) Scimitar lobe with normal aerated parenchyma with arterial and venous normal distributions with increased peri-adventitial fibrosis and thickened media similar to the superior lobe. No differences could be detected for bronchial distributions. (C) Superior lobe of left lung showing the parenchyma with normal arterial distribution with increased peri-adventitia fibrosis and thickened media suggestive of perinatal circulation. The alveoli with normal pattern are hemorrhagic. (D) Inferior lobe of the left lung similar to the superior lobe.

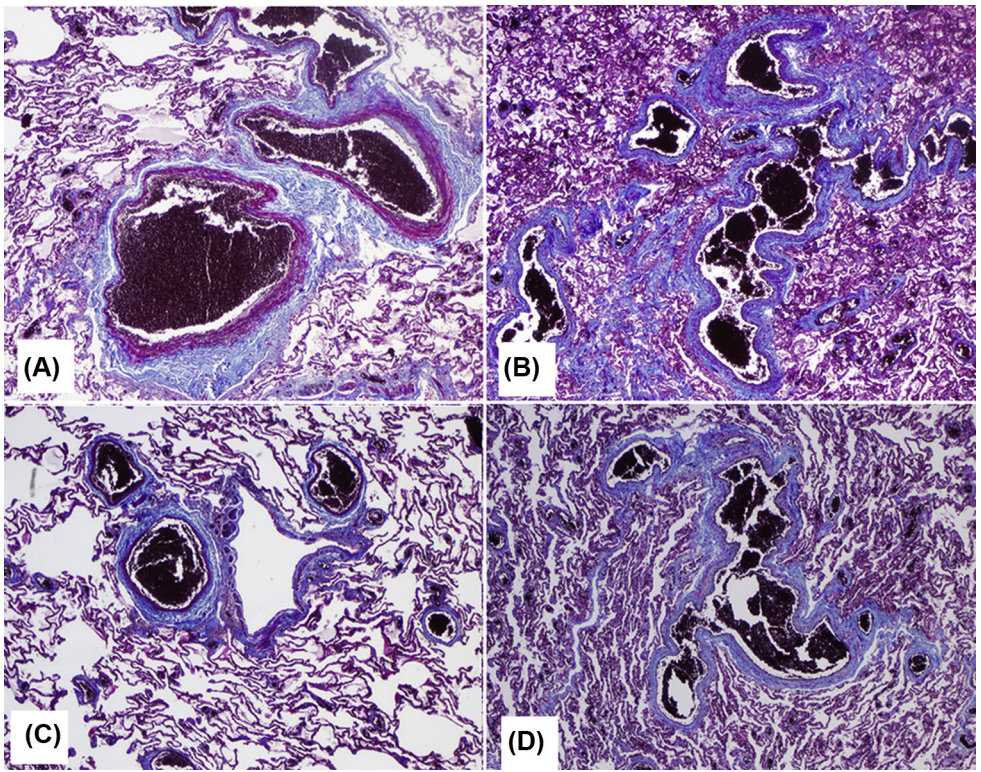


**Figure 4.5** Histology of the lungs of case of Figure 4.3. (A) Right superior lobe with two arteries which appear dilated and with thin wall. The adventitia is prominent with fibrosis. In the upper part is evident a vein. The alveoli are squashed but appear normal with mild interstitial fibrosis. (B) Scimitar lobe with tortuous veins and marked interstitial fibrosis. Note an artery with hyalinization of the parietal wall and intimal hyperplasia. (C) Left superior lobe with artery, vein, and bronchus. (D) Left inferior lobe with similar pattern as in the scimitar contralateral wall.

Other visceral anomalies associated to the scimitar include: a horseshoe lung (parenchymal continuity between the right and the left lung behind the heart and anterior to the esophagus), an accessory diaphragm, eventration or partial absence of the diaphragm, phrenic cyst, absence of pericardium, or rarely an absent inferior vena cava [24].

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CHAPTER 5

# Epidemiology and Physiopathology of Scimitar Syndrome

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## 5.1 EPIDEMIOLOGY

Scimitar syndrome (SS) is a rare congenital heart malformation occurring in one to three per 100,000 live births with a 2:1 female predominance and accounts for the 3%–6% of partial anomalous pulmonary venous connection (PAPVR) [1,2]. The true incidence may be higher because many patients are asymptomatic. Familiar cases have been described [3–7]. In the experience of the Pediatric Department of Padova University, sibling cases occurred for four patients, and for two patients in the experience of the Department of Pediatric Cardiology in Lyon University. However no genetic mutation specifically linked to SS has been yet reported.

## 5.2 PHYSIOPATHOLOGICAL MECHANISMS

The physiopathological mechanisms of SS are supported by the complex anatomical components of the disease.

1. The abnormal return of one or more right pulmonary vein(s) results in a left-to-right shunt and increased

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Qp:Qs (significant if > 2:1). The amount of blood drained through the scimitar collector varies according to one or more subsequent factors, which are as follows:

**a.** The pulmonary lobes or segments from which the anomalous vein originates. In fact, in an upright position, blood flow to the lungs is primarily directed to the lower and middle lobes. Therefore, more blood returns to the systemic venous circulation when the anomalous connection drains from the right middle and lower lobes of the lung, than from the upper lobe.

**b.** The number of pulmonary veins involved in the scimitar vein drainage.

**c.** The relative resistances of the normally and anomalously draining pulmonary vascular beds.

**2.** The left-to-right shunt induces volumetric overload of the right atrium and the right ventricle (RV), as well as dilation of the pulmonary artery (PA). Over the years it may result in increased risk of arrhythmias and right-sided heart failure [4,8,9]. Initially, increased volume causes RV diastolic overload but, as pulmonary arterial resistance and pressure rise, an increase in systolic overload also does occur [10] and signs of right heart dilatation may be present.

**3.** The presence of aortopulmonary vessels is frequent. Intralobar lung sequestration is formed by aberrant systemic arteries (ASAs) connecting to the inferior right pulmonary lobe and draining to the scimitar vein. ASAs deliver high-pressure hyperoxygenated blood to the inferior lobe and distal lung tissue. The additional

presence of a large systemic arterial blood supply to the lower lobe of the right lung may lead to an early onset of congestive heart failure. It has been estimated that when the dimension of the systemic aortopulmonary fistula is in diameter 40% of that of the infra-diaphragmatic aorta, it leads to a significant increase of the pulmonary blood flow (increasing Qp:Qs) [11].

4. Right lung and/or right pulmonary artery (RPA) hypoplasia contributes to modulate the left-to-right shunt and pulmonary flow. The more hypoplasia, the less left-to-right shunt from right pulmonary veins return. Patients with severe right lung hypoplasia and/or a reduced amount of anomalous pulmonary venous drainage develop a consequently little volume overload to the right heart and often, therefore, have no symptoms.

5. Stenosis of the scimitar vein is an important factor of poor prognosis and clinical severity. The obstructed right lung venous return induces subsequent post-capillary increasing pulmonary pressure and pulmonary edema.

6. Associated lesions: multiple associated lesions may be present and contribute to aggravate the deleterious physiopathological mechanisms of SS.

    a. Cardiac lesions:

        i. Left-to-right shunts, i.e., atrial septal defect, ventricular septal defect, or persistent ductus arteriosus enhance pulmonary overflow. Patients with other coexisting congenital left-to-right shunts develop symptoms earlier due to the increased

volume overload to the right heart chambers usually in association with pulmonary arterial hypertension. Patients with a Qp:Qs smaller that 1.5:1 are unlikely to present symptoms during infancy.

**ii.** Left heart obstruction (left heart hypoplasia, coarctation of the aorta) contributes to decreased systemic flow and increased pulmonary flow and/or to post-capillary congestion. Coarctation of the aorta, anomalous drainage of the left pulmonary veins, left ventricular hypoplasia, and other associated congenital left heart malformations tend to worsen symptoms and outcome [12].

**b.** Extracardiac, and mostly lung, abnormalities like bronchial lesions (horseshoe lung, bronchiectasis, right diaphragmatic Bochdalek hernia) aggravate right lung dysfunction and respiratory symptoms.

**7.** Hypoxemia: another important feature to consider is the presence of a significantly smaller right lung, with the left lung frequently undergoing compensatory growth [13]. Pulmonary hypoplasia presents with dyspnea upon exertion, cyanosis, respiratory failure, and occasionally scoliosis. When accompanied by intralobar lung sequestration it may cause recurrent pneumonia; bronchitis; acute, chronic, or recurrent lower lobe infection; chronic cough; sputum production; bronchospasm; and hemoptysis [14].

**8.** Pulmonary arterial hypertension (PAH) is probably the main factor of poor prognosis. PAH is often recognized as the cause of severe symptoms and poor outcome of SS during infancy [4,15–18]. Multiple entangled factors

may be responsible for the PAH [4,12,15] including the following:

**a.** Left-to-right shunt, modulated by RPA and/or right lung various degree of hypoplasia, and presence/number of ASA;

**b.** Post-capillary pressure elevation due to scimitar vein stenosis and/or left heat obstruction;

**c.** Right lung hypoplasia and/or bronchial anomalies;

**d.** Supply of hyperoxygenated blood to the inferior lobe [similar to major aortopulmonary collateral arteries (MAPCAs)];

**e.** Persistence of fetal circulation and high pulmonary resistances;

**f.** Hypoxemia (Bochdalek hernia, right-to-left shunt, ventilatory issues);

**g.** Horseshoe lung is an aggravating poor prognosis condition;

**h.** Reflex mechanism;

**i.** Hypoxemia.

It is theoretically possible that some patients may develop a segmental PAH, as has been suggested as a pulmonary hemodynamic pattern of postsurgical PA stenosis in tetralogy of Fallot with major aortopulmonary collateral arteries. The pulmonary arterioles supplied by the aortopulmonary shunt are exposed to systemic blood pressure and hence develop pulmonary vascular obstructive lesions in contrast to lobes supplied by hypoplastic pulmonary arteries [19–20].

Similarly, in patients with SS, local differences in blood pressure may affect pulmonary circulation and cause segmental pulmonary arteriolar changes.

In order to explain the sometime disproportionate pulmonary vascular lesions observed in infants with relatively mild pulmonary hypertension, Haworth et al. [21–22] postulate that the pulmonary circulation fails to adapt normally after birth in the presence of even a mild left-to-right shunt. In the normal lung, intraacinar arteries show the most rapid reduction in wall thickness after birth. In all four infants studied by Haworth et al. and in experimental animals in which the pulmonary blood flow doubled after birth [21], these arteries remain thick-walled. It is unclear, however, why the lung should fail to adapt normally only in some cases of the SS. A possible explanation is that symptomatic children may have a larger systemic-to-pulmonary arterial flow which is forced to pass through a diminished pulmonary capillary bed. The increased pulmonary flow and high pressure within the pulmonary arterial vasculature increases shear stress and endothelial dysfunction resulting in loss of endothelial barrier function and imbalance of vasoactive mediators, favoring vasoconstriction, inflammation, thrombosis, cell proliferation, apoptosis, and fibrosis. As a consequence, the abnormal pulmonary vascular remodeling causes irreversible PAH and right heart failure [23].

## 5.3 CLINICAL TYPES OF SCIMITAR SYNDROME

The clinical spectrum of SS is wide. Patients with SS can be divided into two groups, depending on the time of clinical presentation and severity of symptoms.

The infantile form carries a high morbidity and mortality and generally presents symptoms within the first 6 months of life, associated with pulmonary hypertension and/or other coexisting congenital heart defects [3,4]. Main symptoms at diagnosis include failure to thrive, tachypnea, and heart failure. Mortality rate of this group of patients is quoted at 45% [6,13].

On the other hand, patients in the "adult" presentation group, usually are asymptomatic during infancy, with a more benign prognosis. The majority of them are diagnosed incidentally during a routine clinical examination (murmur, right-sided heart sound), or after a chest X-ray. Frequent bronchitis or mild dyspnea can occur. Some present with recurrent pulmonary infections mainly involving the right lung. Right lung hypoplasia is usually less severe when compared with the infantile form. Pulmonary functional studies reveal also a milder reduction in vital capacity and FEV-1 (approximately 80% predicted) in adult forms [10]. Atrial fibrillation associated with chronic right-sided overload has been reported.

Natural history of SS can lead to precapillary irreversible PAH, RV failure, arrhythmias. The severity of the symptoms depends on the size of the lung sequestration and the degree of functional lung impairment. Small lesions may remain asymptomatic. Extreme hypoplasia of the right lung reduces, on one hand, the right-to-left shunt (small arterial flow to the lung, small venous flow from the lung) and on the other hand can result in pulmonary hypertension.

The factors that differentiate the two clinical types are not clearly elucidated and probably are multiple, including one or more of the following anomalies:

- importance of the left-to-right shunt;
- lung and RPA hypoplasia;
- associated lesions;
- presence and number of ASA;
- stenosis of the scimitar vein;
- PAH.

In a two-center study (data non-published) from Padua (Italy) and Lyon (France), we analyzed data from 52 patients (35 from Lyon center, France, and 17 from Padova, Italy). Patients presented (median age 4.9 months) with respiratory symptoms in 48% or heart failure in 6% or were asymptomatic in 46%. Mean Z-scores for RV diameter, LV diameter, right PA, and left PA branch were respectively +0.79, −0.6, −1.9, and +2.2. Mean pulmonary systolic pressure was 59 mmHg: 52.5% of cases had no or mild PAH and 47.5% moderate or severe PAH. Fifteen patients were operated on, 26 received medical treatment, and 9 percutaneous embolization of systemic artery were performed at a median age of 0.6 years. Nine deaths occurred (17%) at a median age of 0.4 years: mortality was 35.7% in neonates, 16.6% in infants, and 5.5% in children. Median follow up (FU) was 13.4 years. Survival rates were 87% at 6 months, 85% at 1 and 5 years, and 78% at 12 years of FU.

Stenosis of the scimitar vein, neonatal onset, symptoms at onset, systemic artery, and moderate/severe PAH were associated with worse survival ($P < .0001$). RV systolic pressure, PA systolic, diastolic, and mean pressure were higher (respectively: 70 vs. 39.6, 61.9 vs. 33.3, 22.7 vs. 13.5, and

38.1 vs. 20.5 mmHg), and LV was lower (20.5 vs. 29.9 mm) in deceased cases than in survivors ($P < .0001$).

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# CHAPTER 6

# Diagnosis and Imaging

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## 6.1 DIAGNOSIS

### 6.1.1 Clinical Examination

Neonatal presentation, typically characterized by recurrent pneumonia, hemoptysis, respiratory distress, cyanosis, and pulmonary hypertension, is associated with severe form of the disease. The coexistence of respiratory distress, right lung hypoplasia, and dextroposition of the heart should raise suspicion of scimitar syndrome (SS) [1].

On the other hand, adult patients, because of a mild form of the syndrome, are often asymptomatic or may present with shortness of breath or atrial arrhythmias.

The coexistence of horseshoe abnormality, an isthmus of pulmonary parenchymal tissue arising from the right lung base, bridging the right and left lungs posterior to the pericardial sac, should be suspected in neonates with SS. Indeed, all cases with a coexistent horseshoe lung have been diagnosed with pulmonary problems in young children [2].

Classical findings on clinical examination include a shift to the right of the cardiac impulse and heart sounds and a systolic murmur. In cases of increased pulmonary blood flow, the right parasternal lift reflects right ventricular dilation, while the impulse in the second right intercostal space reflects pulmonary artery dilation.

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A soft systolic ejection murmur is heard over the pulmonary area, reflecting turbulence in the pulmonary trunk due to increased right ventricular ejection volume. The second heart sound is commonly widely split but may have normal respiratory variation and is not always fixed [3,4]. When pulmonary arterial hypertension is present, the second sound is accentuated.

A mid-diastolic murmur due to increased trans-tricuspid right ventricular filling may be heard over the tricuspid valve area at the lower left sternal border. Right-sided heart failure signs in adults include hepatomegaly, jugular venous distension, ascites, and peripheral edema.

Auscultation of the left chest is usually normal, while breath sounds may be diminished on the right [5].

### 6.1.2 Electrocardiogram

The electrocardiogram (EKG) is often normal. However it can show nonspecific features such as (Fig. 6.1):

- Changes due to dextroposition (R waves are prominent in V1 through V3 and decrease in amplitude from V4 through V6) (73).
- An "s" or "S" wave may be observed in V1 in absence of atrial septal defect (ASD).
- First-degree atrioventricular (AV) block and incomplete RBBB, in case of right ventricular (RV) volume overload, tall and pointed "p" wave, tall "R" wave, and positive "t" wave in V4r and V1 in case of pulmonary hypertension and RV systolic overload.

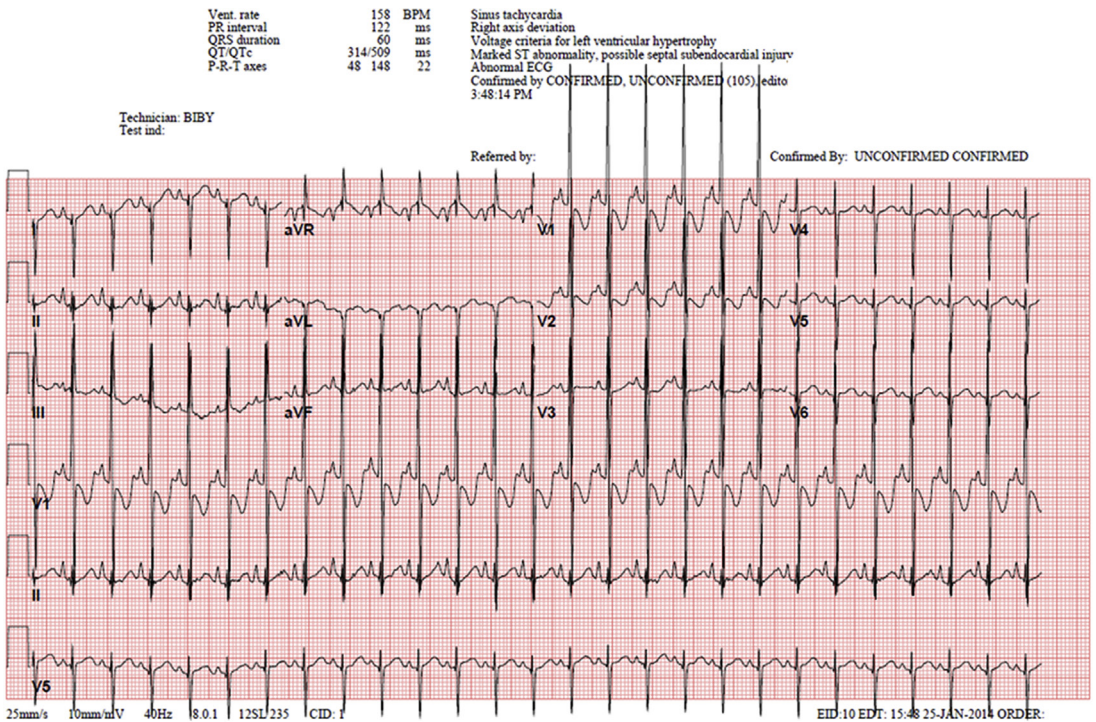


**Figure 6.1** Electrocardiogram of a 4-month-old boy with scimitar syndrome and pulmonary hypertension. Note the right axis deviation, the very tall R waves from V1 to V3 and short R waves in V4 and V5. "Pulmonary" P waves.

## 6.2 IMAGING

### 6.2.1 Chest X-Ray

The patients with SS almost always show abnormal chest radiographic findings. These findings can be:

- small right lung and right hemithorax;
- mediastinal shift to the right with dextroposition of the heart;
- indistinct right heart border;
- blunted costophrenic angle;
- vertically oriented curvilinear opacity (scimitar vein collector) on the right border of the heart coursing toward right cardiophrenic angle;
- diminished right pulmonary vascularity.

The findings vary significantly according to the degree of right lung hypoplasia (Cases 1–3). When the right lung hypoplasia is minimal, the scimitar vein (SV) can be identified in the right lower lung (Fig. 6.2A). With a greater degree of the right lung hypoplasia, the heart and mediastinal structures are displaced to the right, overlying the SV (Fig. 6.2B and C). The SV is often not identifiable and in infants is hardly seen [3,6–10]. The cases with a moderate degree of right lung hypoplasia usually show the right heart border indistinct or blurred on the frontal view (Fig. 6.2B) and a retrosternal bank-like haziness on the lateral view. These findings are due to rightward displacement and rotation of the heart and the interposition of a piece of mediastinal soft tissue between the anterior chest wall and the

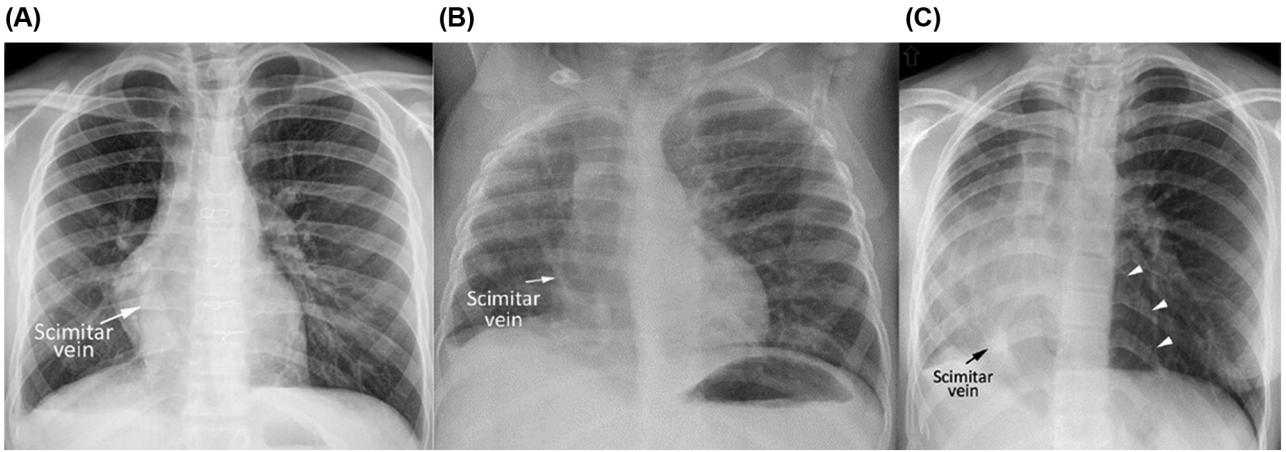


**Figure 6.2** Chest X-ray demonstrating: (A) The scimitar vein (SV) (*white arrow*) is seen as an enlarged curvilinear tubular structure at the right paracardiac region in case of mild right lung hypoplasia. (B) Moderate right lung hypoplasia with the right heart border indistinct or blurred on the frontal view. (C) Associated horseshoe or cross-over lung is seen as a tongue of aerated right lower lung extending into the left thorax (*white arrowheads*).

right lung. Because of the blurring of the right heart border, the diagnosis of pneumonia can be mistakenly entertained, resulting in unnecessary antibiotic treatment. Interestingly these findings are not seen in other causes of right lung hypoplasia such as ligamental ductal origin of the right pulmonary artery and right pulmonary vein atresia/severe stenosis. Associated horseshoe or cross-over lung is seen as a tongue of aerated right lower lung extending into the left thorax (Fig. 6.2C) [11]. The aberrant systemic arterial branch supplying the right lower lung is rarely identifiable. It is noteworthy that the radiographic findings in so-called meandering right pulmonary vein are similar to those of SS. As the majority of the reported cases of meandering right pulmonary vein show other features of SS including right lung hypoplasia and aberrant systemic arterial supply, they can be considered a variant of SS [12].

### 6.2.2 Two-Dimensional Echocardiography

The diagnosis is usually confirmed by transthoracic or transesophageal echocardiography, as well as angiography, computed tomography (CT), and magnetic resonance angiography.

Echocardiography may delineate both the SV, as well as, any systemic arterial supply to the right lung. Additional cardiovascular anomalies have been noted in 60%–70% of infants with severe symptoms, mainly including an ASD ostium secundum type [13,14] or other congenital heart diseases (CHD) such as tetralogy of Fallot [15,16], ventricular septal defect [14,17], coarctation of the aorta [18–20]. As many other CHDs can be associated to the SS [18,20–25],

echocardiographers have to perform a complete and detailed examination on each referred patient.

Prenatal 2D echo diagnosis of SS in the fetus has been reported [26–32]. The key finding to prenatal diagnosis is the abnormal position of the heart in the chest; the visualization of a confluence behind the right atrium (RA) and a vertical vein are the most consistent echo clues. Unfortunately, abnormal pulmonary veins are not easily visualized on fetal echocardiography due to insufficient acoustic windows [26,27].

Whenever this diagnosis is considered, early postnatal work-up is important to complement the details of vascular anatomy [33].

A high index of clinical suspicion is necessary to ensure an accurate echocardiographic diagnosis of SS. Echocardiographic findings can be either nonspecific or specific [13].

Nonspecific features include:

- presence of dextrocardia or mesocardia;
- increased RV dimension.

Specific features include:

- detection of the scimitar vein collector (Fig. 6.3);
- disproportion between the smaller right and the larger left pulmonary artery (Fig. 6.4);
- right pulmonary vein(s) not joining the left atrium (Fig. 6.5); and
- the presence of aortopulmonary collateral arteries.

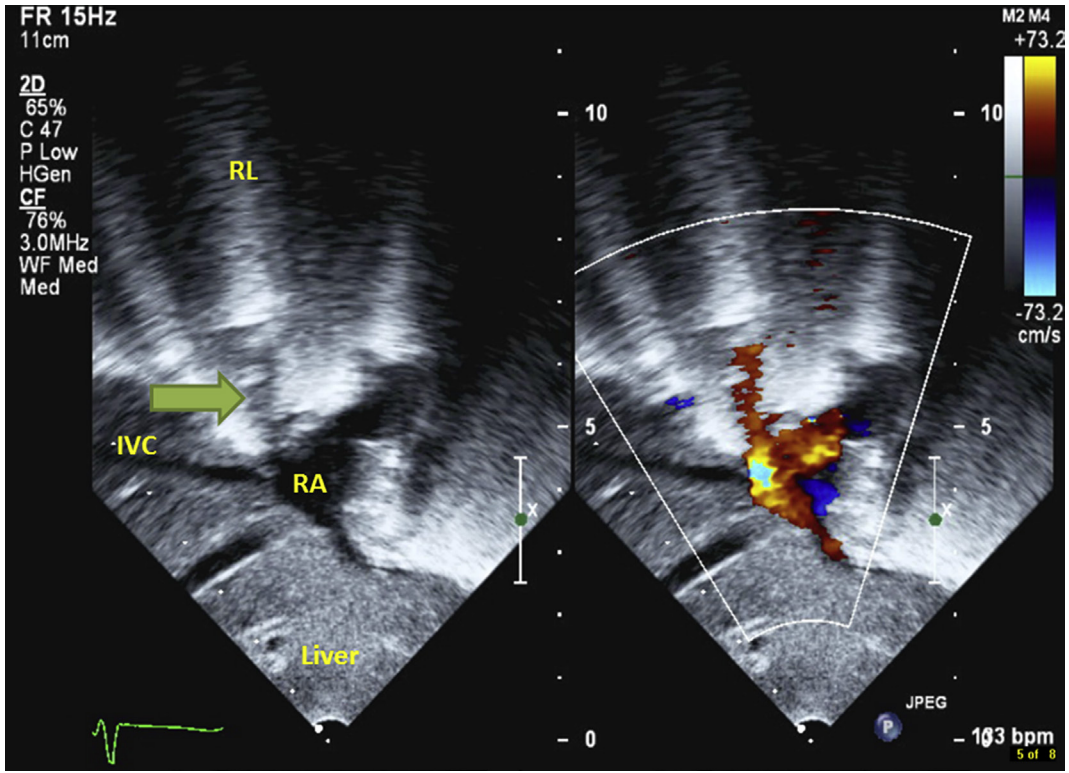


**Figure 6.3** Subcostal view (anatomic orientation) showing the scimitar vein (SV) (*green arrow*) coming from the right lung (RL) entering the junction between the inferior vena cava (IVC) and the right atrium (RA).

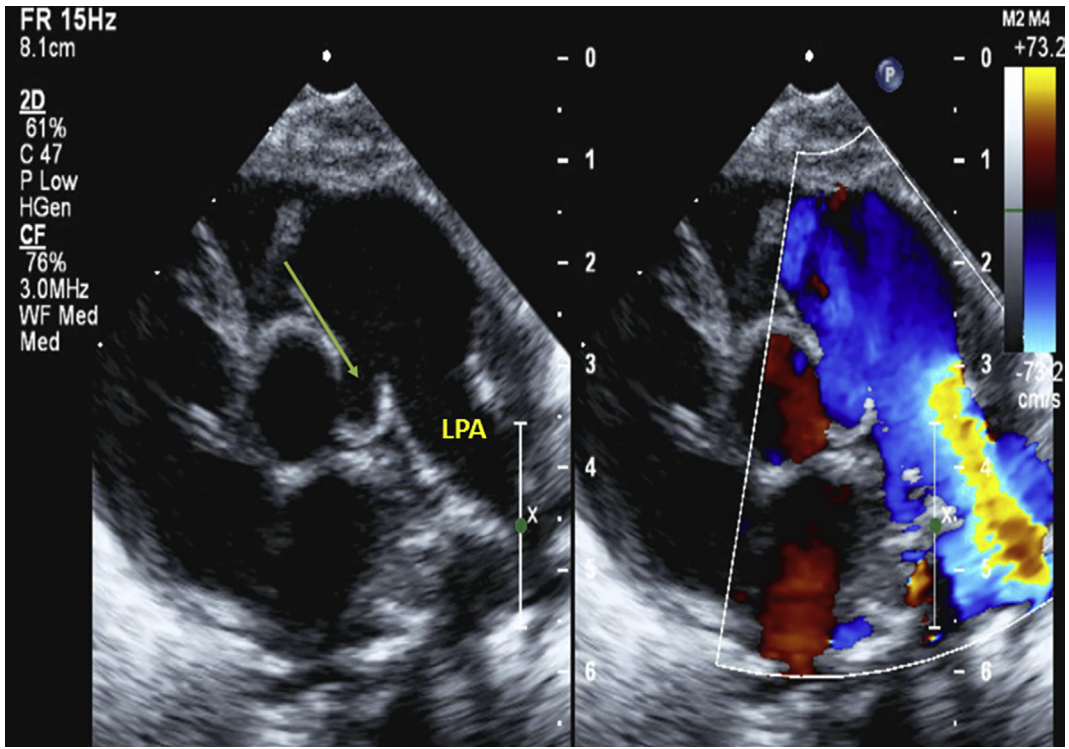


**Figure 6.4** Parasternal short axis view showing the disproportion from the left pulmonary artery (LPA) and the hypoplastic right pulmonary artery (*green arrow*).

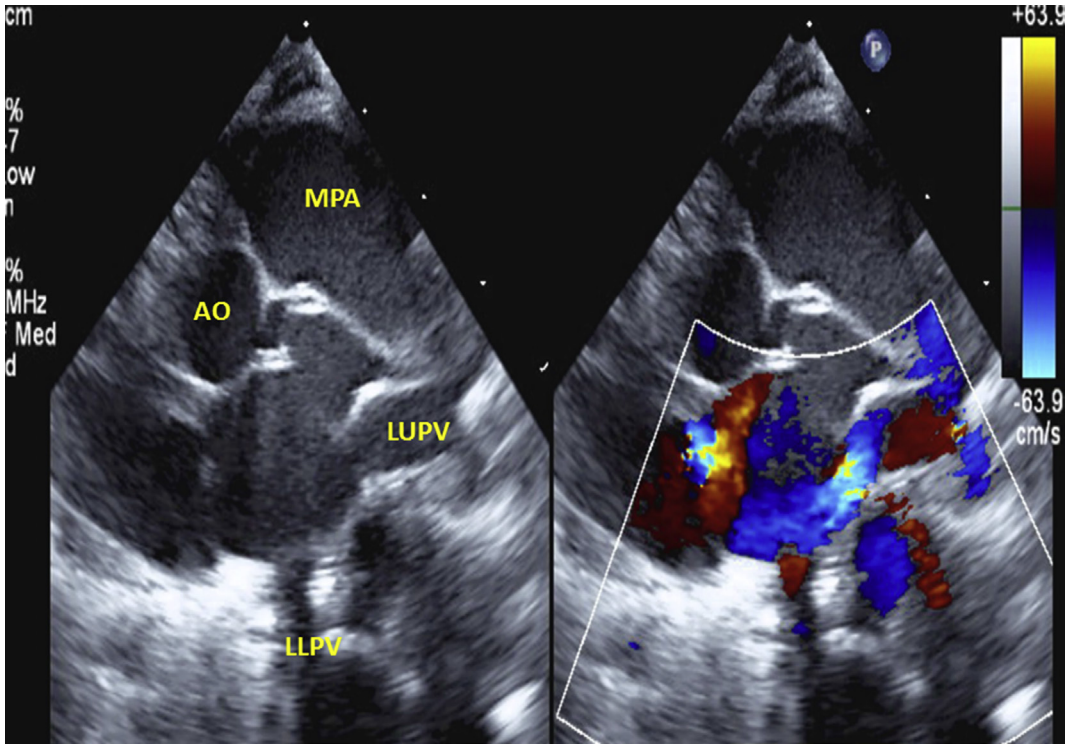


**Figure 6.5** Suprasternal short axis view (crab view). In this patient with scimitar syndrome only the left pulmonary veins could be demonstrated. *AO*, Aorta; *LLPV*, Left lower pulmonary vein; *LUPV*, Left upper pulmonary vein; *MPA*, Main pulmonary artery.

The subcostal views can give many of the earlier-mentioned features. Firstly, cardiac dextroposition can be demonstrated (the heart is shifted toward right because of the right lung hypoplasia), while levocardia (cardiac apex pointing the left) may be preserved. A large pulmonary vein from the right lung entering the inferior vena cava (IVC) just below the RA–IVC junction can also be visualized, as well as aortopulmonary collaterals arising from the aorta. Both abnormal arterial collaterals and stenosis of the anomalous pulmonary vein can be assessed by means of color flow mapping and pulsed Doppler techniques, paying close attention on the color-box while moving it from the lower RA toward the descending aorta.

Echocardiographic analysis of blood flow can be extremely useful during anomalous pulmonary vein drainage definition. It is noteworthy that the flow velocity pattern in the SV is different from the normal pulmonary venous flow. The normal flow is triphasic, with a systolic and a diastolic peak (peak velocity of about 0.5 m/s), and a reverse flow during atrial contraction (peak velocity of about 0.2 m/s). The flow pattern in SV is monophasic extending throughout the cardiac cycle with no reverse flow at atrial contraction [4].

The parasternal short axis view can show the hypoplasia of the right pulmonary artery in comparison to the left one.

The suprasternal short axis view, the so-called "crab view," demonstrates the absence of the right pulmonary vein(s).

A restricted acoustic window can limit the use of transthoracic echocardiography. A transesophageal echocardiography (TEE) provides a good visualization of the entire

interatrial septum and of the vein entering the atrium. The diagnostic accuracy of pulmonary veins by TEE varies from 60% to 93% [26]. The strongest clue that confirms suspicion of pulmonary anomalous venous return is the non-visualization of normal pulmonary venous commitment to the left atrium [34]. However, physiological anatomic variation of the normal veno-atrial connection can make the diagnosis challenging [35].

Furthermore, even if the four pulmonary veins are visualized, the absence of additional anomalous pulmonary veins (APVs) cannot be taken for granted and TEE does not easily provide recognition of multiple branching APVs or atypical drainage patterns. Information regarding the extent or abnormally drained region of the lung can also be limited [36].

A detailed definition of pulmonary vein anatomy is of great importance in patients undergoing surgery and this can be provided by angiography, CT scan, or magnetic resonance angiography.

### 6.2.3 Lung Scintigraphy

Right lung perfusion can be assessed by lung scintigraphy with human albumin macro-aggregates labeled with 99 m technetium (Fig. 6.6). Preoperative and postoperative lung scintigraphy can add important additional information about the right lung functional status and therefore on patients' clinical conditions. Moreover it may helps in understanding the real magnitude of the flow to the "scimitar" lung, which is helpful in the evaluation of the surgical risk and in postoperative management [18].

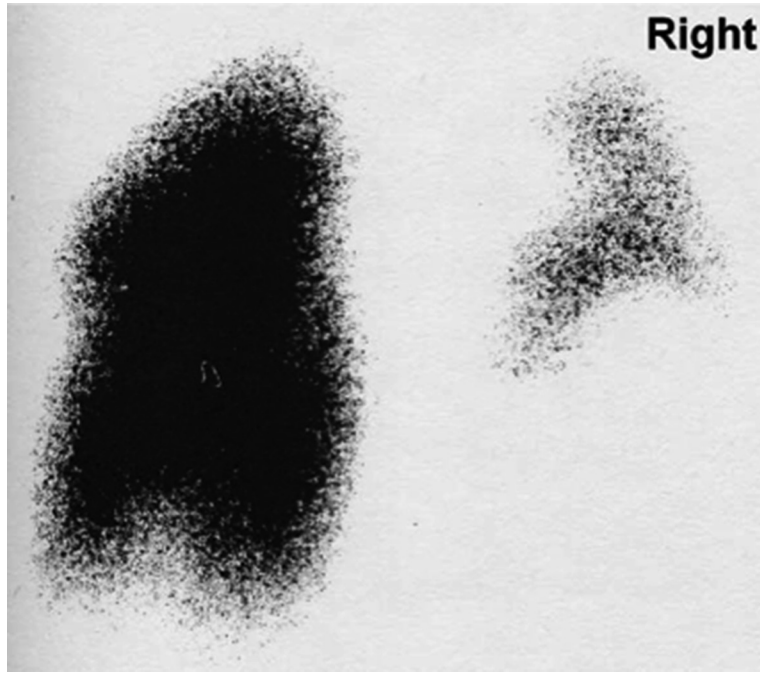


**Figure 6.6** Lung scintigraphy showing right lung hypoperfusion compared to the left lung.

### 6.2.4 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) offers several advantages for cardiovascular imaging: Firstly, it does not use ionizing radiation and provides fast data acquisition with high resolution. Secondly, it allows optimal anatomical visualization of anomalous draining vessels into IVC, hepatic circulation, RA, right ventricle (RV), pulmonary arteries, or coronary sinus with the possibility to build three-dimensional (3D) reconstructions (Figs. 6.7–6.9). Furthermore, phase-contrast velocity mapping at MRI allows quantification of blood flow volumes and velocities and, therefore, calculation of the amount of left-to-right shunt and the

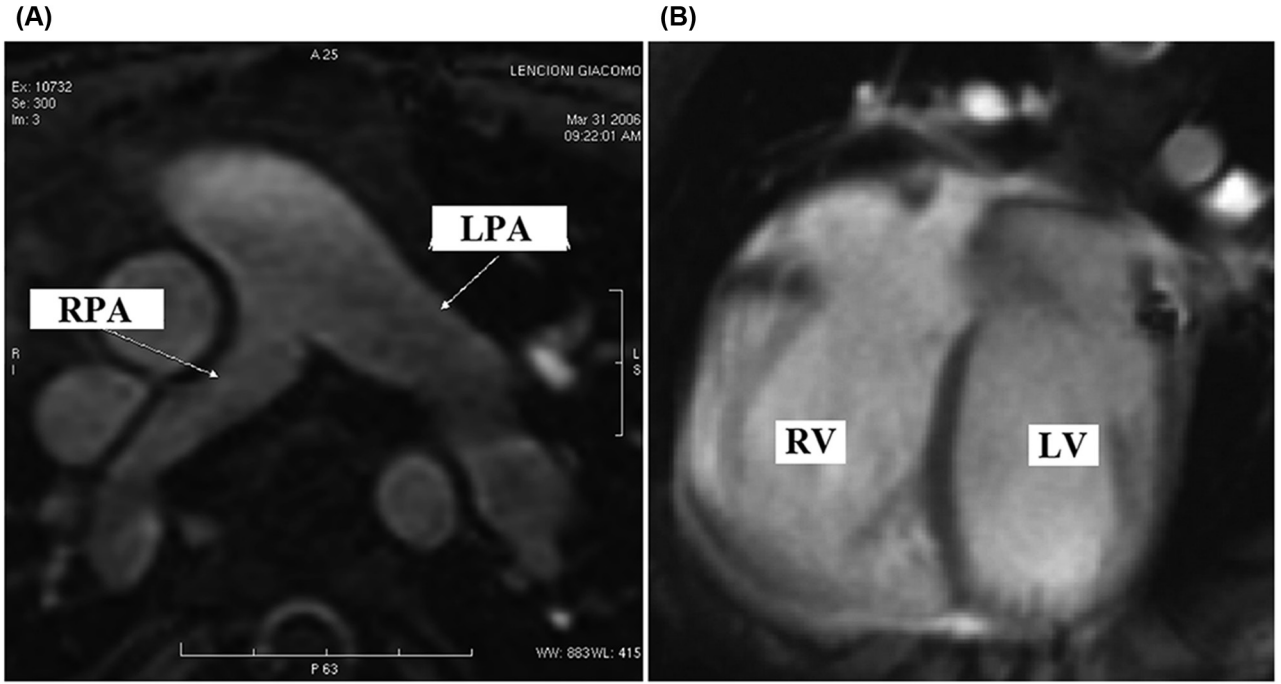


**Figure 6.7** MRI with (A) visualization of size discrepancy between left pulmonary artery (LPA) and right pulmonary artery (RPA) (B) visualization of right ventricle (RV) overload and the left ventricle.

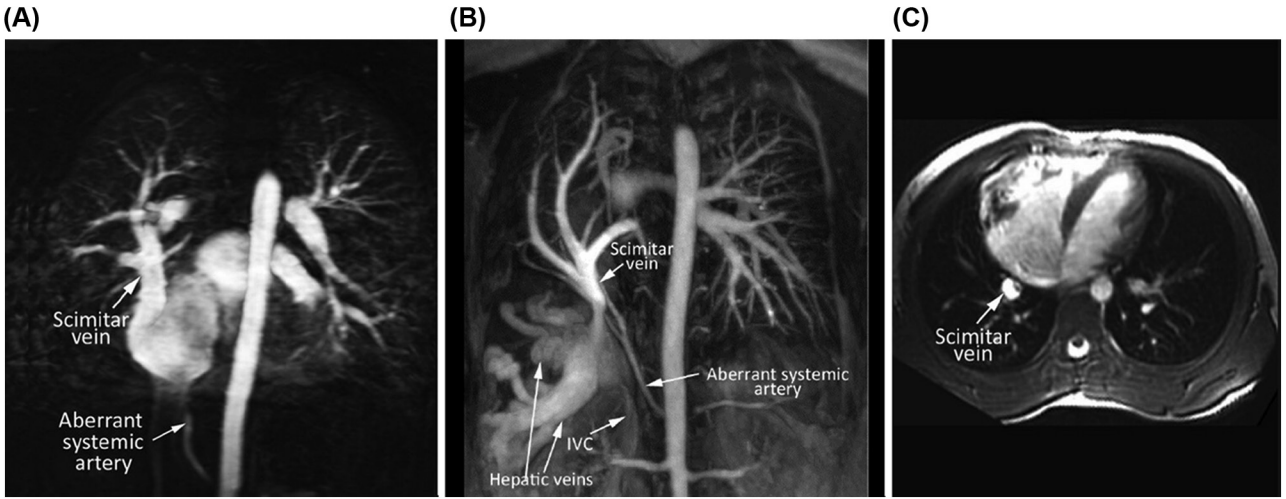


**Figure 6.8** MRI panel with characteristic details from patients with the scimitar syndrome (A) MRI coronal view where the scimitar vein (SV) and its connection to the right atrium is visible. One aortopulmonary vessel directing toward the right lower lobe is also detected coming from below the diaphragm level. (B) MRI coronal view where the upper segment of the SV can be appreciated. Hepatic veins near the inferior vena cava (IVC) are well recognizable, together with an aortopulmonary vessel directing to the right lung. (C) MRI axial view through the chest highlighting the SV near the posterior aspect of the right atrium (RA).

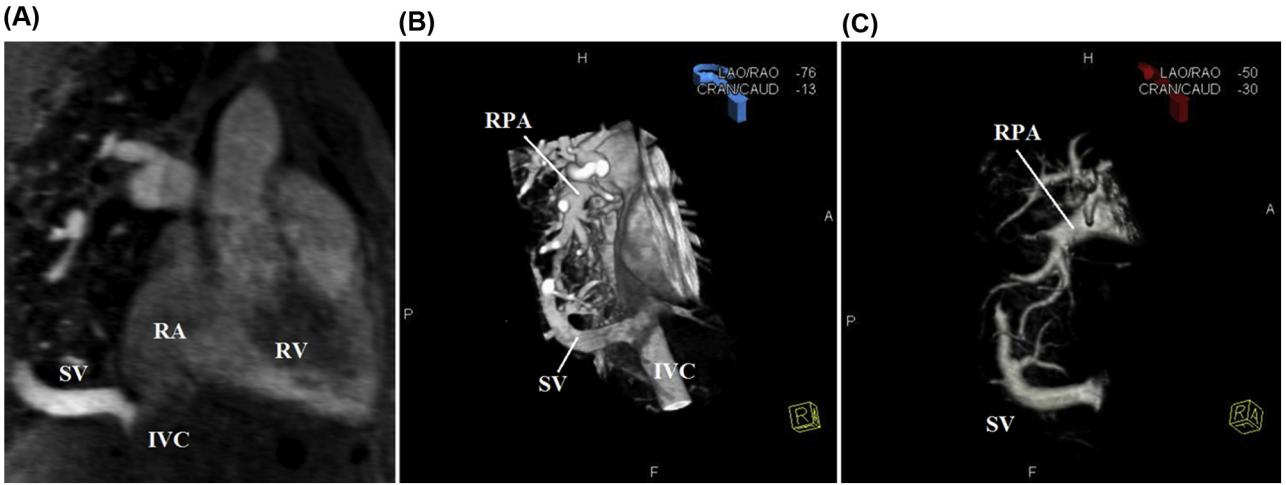


**Figure 6.9** Magnetic resonance angiography images with: (A) The scimitar vein (SV) draining in the inferior vena cava (IVC). Right atrium (RA) and right ventricle (RV) are visible too. (B) and (C) 3D reconstruction of the scimitar vein (SV) with its surrounding cardiac structures (RPA—right pulmonary artery, IVC) are then selectively highlighted. *Courtesy of Dr. R.Crepaz and Dr. J. Steufer.*

ratio between the pulmonary and systemic blood flow volumes (Qp:Qs). Lastly, ventricular volumes and ejection fractions can be measured using cine-imaging technique, avoiding the need for more traditional invasive techniques.

Technical improvements have also permitted high-resolution 3D images acquisition of the entire mediastinum in a single 10 s to 30 s breath-hold. Fast cine-MRI with 3D contrast-enhanced MRI can offer rapid and comprehensive anatomic definition both of APVs and cardiac defects such as ASDs [36,37].

This technique can be particularly helpful in detecting an associated horseshoe lung, in which there is a posterior fusion of portions of the right and left lungs behind the heart and in front of the esophagus and spine. Approximately 80% of infants with a horseshoe lung also have SS.

### 6.2.5 Computed Tomography Scan

CT of the chest is the imaging technique of choice for patients presenting with predominantly respiratory infection or dyspnea. CT can demonstrate the lung anatomy down to the sub-segmental level [38–40] and its association with ventilation scintigraphy, bronchoscopy, and bronchography is used to evaluate the bronchial anatomy and estimate functional lung volume.

CT has the advantages of easy availability and very short scanning times. Multi-planar reconstruction, currently readily available, reduces the inherent disadvantage of the CT image acquisition exclusively in the trans-axial plane.

Multi-slice CT angiography is broadly used for noninvasive assessment of vascular pathologies of the chest too

(Figs. 6.10 and 6.11). It can provide a complete evaluation of complex vascular anatomical structures, including the abnormal collaterals originating from the aorta as seen in SS [41].

CT disadvantages are patient exposure to ionizing radiation and the risks of iodinated contrast agents.

### 6.2.6 Magnetic Resonance Imaging Versus Computed Tomography

When echocardiographic information is insufficient, contrast-enhanced CT or MRI angiography is an excellent adjunct for clear demonstration of the abnormal and normal vessels including SV and aberrant systemic artery (Cases 1–6). Both CT and MRI are useful in the evaluation of the associated abnormalities of the airways, lungs, and diaphragm such as abnormal branching of the airway (Cases 4 and 5), horseshoe lung (Case 3), chronic lung infection (Case 4), accessory diaphragm, or diaphragmatic defect.

They allow for the differentiation of the pulmonary arteries from the pulmonary veins and for the assessment of the number of pulmonary lobes draining into SV, which is crucial for surgical strategies decision. Moreover the entire course of anomalous pulmonary vein can be followed from the connection to the RA or to the IVC backward to the lung lobe from where it originates.

Generally, MRI is preferred to CT because of its non-ionizing basis and the combination of structural and functional data. Usually the patients over the age of 7 years tolerate MRI well. In young infants aged less than 3–6 months, MRI can also be performed without sedation

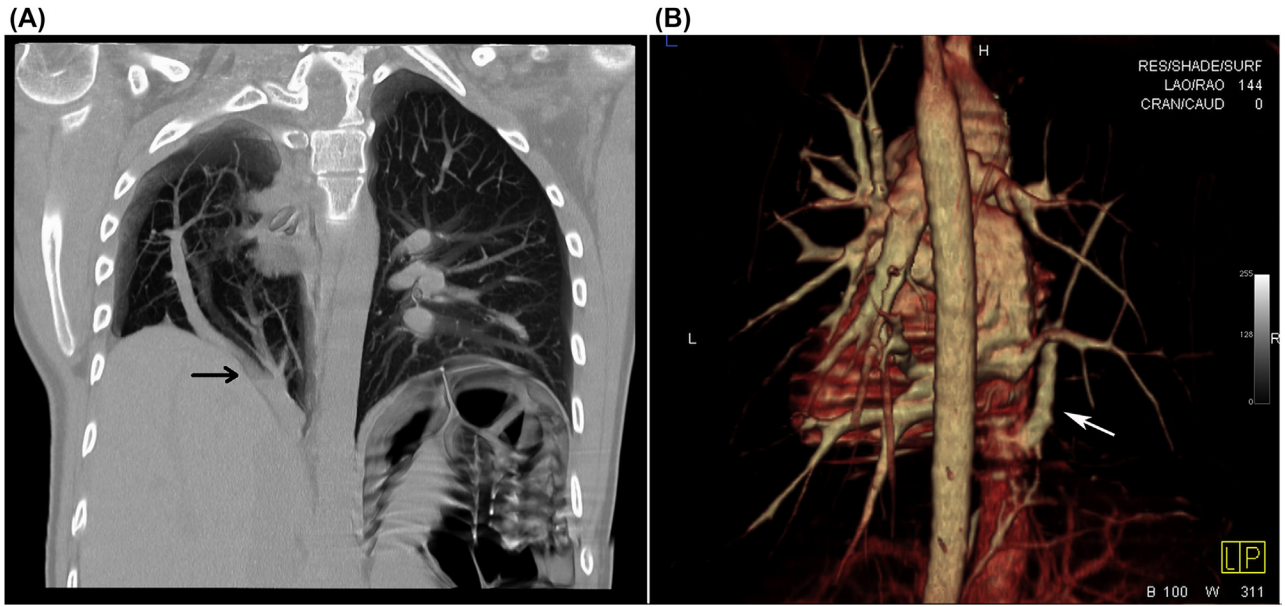


**Figure 6.10** CT panel. (A) CT angiograms reconstructed on frontal view with maximum intensity projection (MIP) showing the scimitar vein (SV) draining into the inferior vena cava (IVC); (B) CT angiograms reconstructed on posterior view with volume rendered reconstruction showing the SV (*white arrow*) draining below the diaphragm.

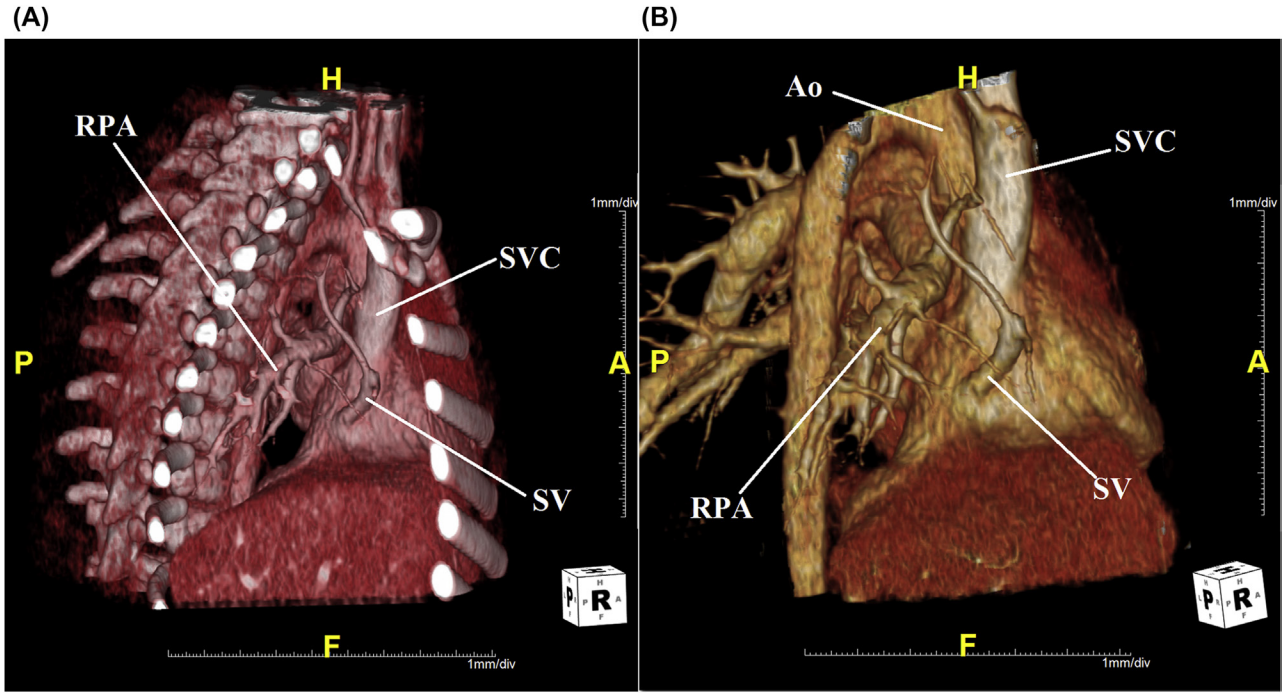


**Figure 6.11** 3D volume rendered CT reconstruction on a right lateral view. (A) Chest reconstruction with the superior vena cava (SVC), right pulmonary artery (RPA), and the scimitar vein (SV) clearly visible as it connects to the right atrium (RA). (B) 3D chest reconstruction after bone removal.

or general anesthesia using so-called feed-and-sleep technique (Shariat). In this technique, the infant is fed with a generous amount of milk after 4 h of fasting and is swaddled within a vacuum immobilizer.

The choice between CT versus MRI is anyway based on institutional equipment, scheduling and availability, as well as the patient's ability to cooperate. It may also be guided by the need to answer to specific questions [40].

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# CHAPTER 7

# Natural History and Medical Treatment

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The scimitar syndrome (SS) is often associated with several congenital heart defects in infancy. The most frequent comorbidities involve right lung (RL) and right pulmonary artery (RPA) hypoplasia, systemic arterial blood supply to the right lower lung from the infra-diaphragmatic aorta, secundum type of atrial septal defect (ASD), and diaphragmatic hernia. As a consequence, clinical presentation, prognosis, and management are strictly intertwined with the related diseases presented in the past chapters.

An Italian multi-centric study [1] showed that about one-third of the patients present SS as an isolated feature, while the remaining two-thirds exhibit cardiac or respiratory comorbidities. The median age at diagnosis is 6 months; however, prenatal diagnosis is increasing, while a late diagnosis is not rare (up to 20% in adulthood). The diagnosis may be incidental or due to cardiac or respiratory symptoms. Cardiac symptoms are often an early finding (30%–50% in the first year of life), while respiratory complications are more common in late diagnosis (33%).

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## 7.1 NATURAL HISTORY IN ISOLATED FORMS OF SCIMITAR SYNDROME

The natural history of SS is strongly influenced by comorbidities. The isolated forms may be asymptomatic for a very long time; the probability to develop symptoms after the diagnosis is about 1% per year [1].

The most important parameter that impacts on the follow-up is the Qp:Qs. Patients with a single aberrant vein have more often a low Qp:Qs and have more probability to remain free from symptoms and from surgery [2]. On the other hand, in this subgroup of patients, symptoms and right ventricle dilatation are very common (50% for both the findings). The total venous drainage of the RL in the right atrium (RA) usually determinate a Qp:Qs around 2:1; however, in these patients a number of variables may affect this data. An important point is the relative size of the RPA and of the RL compared with the left one. In SS the RPA may be hypoplastic and the dextrocardia can make the RL become smaller than the left lung. As a consequence, the Qp:Qs may be lower than 2:1. On the other hand, the more the RPA is hypoplastic, the higher is the probability to have associated aortopulmonary supplies for the RL [3,4].

Systemic arterial collaterals are aberrant vessels connecting the aorta with the pulmonary arteries [4,5]. Collaterals are defined "direct" if they arise directly from the thoracic aorta, while are called "indirect" if the origin is from the great vessels or from their ramifications (most frequently mammalian artery and vertebral artery). Sometimes the origin of these vessels is from abdominal arteries as the celiac trunk, and they may drain into the lobar arteries or, more distally, in segmental arteries.

Large systemic arterial supply may affect the Qp:Qs and increase the pulmonary artery pressure. Sometime the first clinical presentation of systemic to pulmonary arterial collaterals is the hemoptysis. In all these cases percutaneous embolization is indicated (see Chapter 8) [6,7].

Surgical correction of the anomalous venous drainage is usually necessary when the SS determines a significant left-to-right shunt or when it shows symptoms. The surgical techniques and the outcome will be discussed in Chapter 9. Surgery of isolated forms is affected by a low early mortality and morbidity and a not negligible incidence of stenosis/occlusion of the scimitar drainage, which needs to be taken into account at the time of surgical planning, especially in small infants [1]. The normalization of right chambers volume, as well as the disappearance of heart symptoms, is quite common [1].

## 7.2 NATURAL HISTORY IN COMPLICATED FORMS OF SCIMITAR SYNDROME

SS can be associated with different comorbidities that may complicate the clinical scenario. About 90% of patients have few symptoms in childhood and become adults; however, some patients may be highly symptomatic in infancy and may die in the first years of age, despite optimal care [8–10]. Among all the comorbidities, lung dysplasia and pulmonary hypertension are the most feared. In addition, lung dysplasia and pulmonary hypertension often coexist, making the clinical scenario very complicated.

RL hypoplasia is often associated with the RPA hypoplasia [11]. Sometimes the RL may appear as a horseshoe

lung [12,13]. This is a radiological finding, which denotes a sort of herniation of the RL parenchyma, through the posterior mediastinum, in the left side of the thorax.

The RL vascularization may be reduced compared with the left lung. This may be a primitive characteristic or may be secondary to pulmonary hypertension sequestration or to a scimitar vein obstruction. Generally, the more hypoplastic the pulmonary artery or the lung is, the higher is the probability of the presence of aortopulmonary collaterals.

Pulmonary hypertension (PH) can be found in about one-third of patients with SS [1]. It is often part of the clinical features of the complicated SS, where it can be the cause of death in a high number of infants. PH may have different etiologies in these patients: hypercapnia, hypoxemia, congenital left-to-right shunt, pulmonary veins obstruction, or idiopathy. The prognosis of PH depends on the underlying mechanism and on the appropriate timing of intervention.

Aortopulmonary collaterals can be frequently found in SS. Sometimes the diagnosis may be incidental, but more often their presence is directly related to hemoptysis. In some patients these vessels are very large and numerous, causing PH. In other patients these vessels may supply aberrant lung parenchyma (lung sequestration).

Bronchopulmonary sequestrations are masses of nonfunctioning lung tissue that are supplied by an anomalous systemic artery and do not have a bronchial connection to the native tracheobronchial tree [14]. These masses may be intrapleural (intralobar sequestrations) or extra-pleural (extra-lobar sequestrations). Arterial feeding comes usually

from the thoracic aorta; venous drainage is usually into systemic veins in the extra-lobar sequestration and into pulmonary veins in intralobar sequestrations. Symptoms involve respiratory distress, recurrent infection, feeding difficulties, hemoptysis and hemothorax, congestive cardiac failure, rarely pneumothorax, and fetal hydrops. Clinical presentation is earlier in extra-lobar sequestration (within the first year of life).

ASD is the most common associated cardiac defect (60%–65% of all the patients). The clinical impact of ASD on the follow-up depends on the size of the defect and the right atrial pressure. When ASD is the only associated defect, it may increase the right-to-left shunt. As a consequence, the right chamber dilatation is more common, as well as an indication to surgery. If PH coexists, the left-to-right shunt through the ASD is less relevant and a paradoxical shunt may appear during pulmonary hypertensive crisis.

Ventricular septal defect (VSD) and patent ductus arteriosus (PDA) are present (alone or in association) in about a quarter of patients with SS. The natural history of these lesions is related to the size of the defect: small defects run asymptomatic for a very long time while large defects show symptoms in infancy.

SS is rarely associated (<10%) to other congenital heart diseases like tetralogy of Fallot, aortic coarctation, valvular disease, etc.

The most frequent causes of death in SS are: congestive heart failure (30%), respiratory insufficiency (15%), PH (15%), bleeding (5%), pulmonary vein stenosis (5%). As a

general rule, patients requiring treatment under 1 year of age are usually very ill, bearing a relatively high operative mortality and complication rate, whereas those who are older have a better outcome both immediately and in the long term.

SS can be rarely associated to pulmonary artero-venous fistulae [15]. This fistula is a direct connection between a segmental pulmonary artery and a segmental pulmonary vein, creating a bypass of the capillary tree. The peculiar clinical feature of this lesion is desaturation and polyglobulia. In SS the clinical scenario is quite different, because these fistulae, if present, generally involve the RL. As a consequence, the desaturated blood returns in the RA and the systemic saturation is normal. On the other hand, the fistulae decrease the arteriolar resistances and the final result is an additional increase of Qp:Qs. The diagnosis can be done by echo with a bubble test and the exact localization and the quantification of the artero-venous fistulae can be done with computed tomography or by heart catheterization. When indicated, the percutaneous embolization with coil or vascular plug is the treatment of choice. In more complex lesions, surgical RL lobectomy or pneumonectomy can be considered.

Another rare evidence in SS is the persistence of the primitive hepatic vein plexus [16–18]. It is seen as a network of racemose venous channels in the hepatic parenchyma and it may represent the precursor of hepatic veins, which contributes to the formation of the inferior vena cava too. This plexus may also represent a manifestation of the abnormalities of venous development that leads to the development of anomalous pulmonary venous return in

SS. In these patients, the inferior vena cava can be hypoplastic, stenotic, or interrupted. Despite the aberrant drainage, this lesion is benign and does not require correction.

## 7.3 MEDICAL TREATMENT

Medical therapy is usually indicated in the infantile presentation to treat heart failure and to allow growth before undertaking surgical repair. Pharmacological treatment is also suitable for poor surgical candidates. It aims to control congestive heart failure and in treating pulmonary arterial hypertension and recurrent respiratory infections. In symptomatic patients with usual anatomy, surgical correction represents the treatment of choice.

The main goals of medical treatment are:

- improve the respiratory function;
- reduce the lung congestion;
- reduce the pulmonary resistances.

### 7.3.1 Treatment of Respiratory Insufficiency

Bronchodysplasia is frequent in the complicated form of SS. Usually the first-line treatment is based on oxygen supplementation, having as target a $SpO_2$>90%. The increase in $O_2$ saturation improves oxygen delivery, reduces the cardiac output, and reduces pulmonary arteriolar resistances. If oxygen support alone is unsuccessful to maintain an adequate gas exchange, noninvasive ventilation or mechanical ventilation is indicated.

In infant patients with acute or chronic lung dysplasia, thiazide diuretics, alone or in association with spironolactone, may be helpful. In literature, thiazide and spironolactone decreased the risk of death and tended to increase the rate of extubation after 8 weeks in intubated infants who did not have access to corticosteroids, bronchodilators, or aminophylline. Usually the recommended daily dose is 1 mg/kg of thiazide and 1–2 mg/kg of spironolactone. Some guidelines for respiratory distress syndrome in infants now favor calcium-sparing thiazides if diuretics are considered for therapy, because loop diuretics, especially at high doses (>10 mg/kg/die), increase the risk of nephrocalcinosis [19–21].

### 7.3.2 Heart Failure

The treatment of heart failure should be customized on the underlying mechanism. Usually heart failure is given by the left-to-right shunt through the ASD and to the anomalous venous return, to PH or to aberrant vein stenosis. In these patients diuretics represent the first line of treatment. Diuretics reduce the circulating blood volume and improve symptoms, reduce the breathing rate, and the lung congestion. In infants and in small children, if bronchodysplasia coexists, thiazide and spironolactone are the preferred drugs. In older children the loop diuretics are the most preferred therapeutic solution (i.e., furosemide 1 mg/kg in one to three administrations, intravenous or oral). In both the cases the blood electrolytes should be periodically monitored.

Angiotensin converting enzyme inhibitors are indicated in heart failure secondary to VSD or PDA. The mechanism of action consists in the reduction of the left-to-right shunt

by reducing the systemic arteriolar resistances. In small infants, captopril (0.5–2 mg/kg/dose, oral administration, every 6–12 h) is preferred; in older infants ramipril or lisinopril (0.1–0.2 mg/kg/die, oral administration) is preferred for a single administration.

Based on the last evidence and guidelines, digoxin and beta-blockers are not indicated in the treatment of heart failure secondary to left-to-right shunt.

In symptomatic patients, elective surgical treatment of the congenital defect is indicated. Surgical options will be described in Chapter 9.

### 7.3.3 Pulmonary Hypertension

The treatment of PH depends on the underlying etiology [22–24]. PH related to bronchial dysplasia in infants may be treated with sildenafil (0.5 mg/kg/dose up to 20 mg, three times daily). In uncomplicated cases, right heart catheterization is not mandatory. Invasive assessment of pulmonary pressures and resistances is indicated in patients with suspected supra-systemic right ventricular systolic pressure by echo, if a pulmonary vein stenosis is suspected in patients non-responsive to sildenafil and in all the patients older than 1 year. In these patients, the first-line therapy is based on endothelin receptor antagonists. Between all, bosentan (2–4 mg/kg twice daily, up to 125 mg/dose) is the most commonly used drug in pediatric age. Ambrisentan and macitentan may be interesting alternatives; however, there are no data about the use of these drugs in pediatric age. If the single drug therapy is insufficient, combination therapy protocols (i.e., association of sildenafil and bosentan) may be considered.

Nitric oxide (NO) is often used in acute setting in patients who are mechanically ventilated. The dose is between 10 and 40 ppm and it can be associated or imbricated with sildenafil and/or bosentan. In the most severe forms of PH, prostanoids represent the third line of therapy.

In neonates a severe PH with supra-systemic pressure in the right ventricle and right ventricular dysfunction can be relieved by maintaining open the PDA by prostaglandin-E infusion. In this way the pulmonary artery can be decompressed in the aorta, leaving a lower half of the body with a lower saturation. This maneuver is useful to decompress the right ventricle and to maintain an adequate cardiac output. In older patients showing a supra-systemic PH, despite a maximal pharmacological therapy, a PDA stenting (working like a trans-catheter Potts shunt) may sometimes be considered [25].

In some patients the parenchymal and vascular dysplasia may be so severe that pneumonectomy can represent the last therapeutic option.

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# CHAPTER 8

# Cardiac Angiography and Interventional Therapy

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## 8.1 DIAGNOSTIC CARDIAC CATHETERIZATION AND ANGIOGRAPHY

Cardiac catheterization and angiography are probably the most useful tools to confirm the diagnosis and clarify the exact anatomy and degree of pulmonary hypertension. Patients with scimitar syndrome (SS) should undergo aortography and catheterization of the right and left side of the heart.

The first step is the collection of relevant hemodynamic data including:

- measurement of pulmonary artery pressure and resistances, which are pivotal parameters in the management of these patients;
- quantification of left-to-right shunting (by hemoglobin saturation data and Fick method).

The following step consists in performing angiographies in the right heart and aorta.

The main elements of SS can be easily evaluated and include [1,2]: the "scimitar vein" (Fig. 8.1A), the hypoplasia of right pulmonary artery (Fig. 8.1B), and the aortopulmonary connection to the lower right lobe (Fig. 8.1C).

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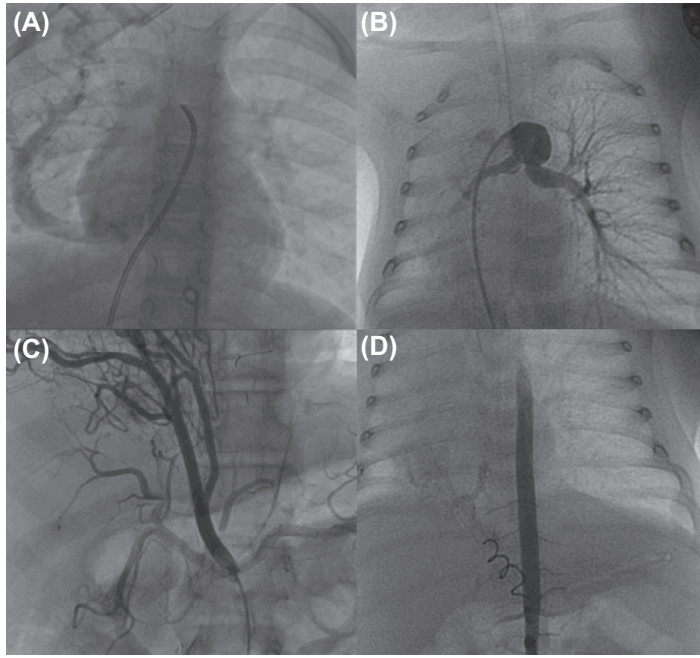


**Figure 8.1** (A) Scimitar vein visualization after selective pulmonary dye injection. The vein drains into the inferior vena cava; (B) selective pulmonary artery angiography with right pulmonary artery hypoplasia; (C) aortopulmonary connection to the lower right lobe; (D) coil embolization.

However there are several other variants that should be looked after and include: (1) pulmonary vein stenosis [3]; (2) right and left pulmonary artery stenosis [4]; (3) a bilateral scimitar associated to total anomalous venous return to the right atrium [5]; (4) left-sided SS associated with pulmonary venous return to the azygos vein [6]; (5) meandering right pulmonary vein associated to pulmonary artery sling [7]; (6) normal pulmonary venous drainage; (7) association to the persistent primitive hepatic venous plexus [8,9]; (8) associated intracardiac defects [1].

Other associated anomalies including horseshoe lung and bronchomalacia should be investigated by using other diagnostic tools [10,11].

## 8.2 INTERVENTIONAL CARDIAC CATHETERIZATION

SS may have various presentations and may require individualized treatment [2]. In a multi-center study by Dupuis et al., it has been shown that in the case of asymptomatic small left-to-right shunt and normal pulmonary artery pressures, a conservative follow-up is a valid option [12].

In patients with congestive heart failure or Qp:Qs > 1.5 and pulmonary hypertension, significant clinical benefit can be expected following rerouting of the anomalous right pulmonary veins and repair of the associated cardiac defects, such as an atrial septal defects (ASDs) [2]. An intermediate option is to embolize the aortopulmonary collateral in order to reduce the pulmonary overflow and all signs and symptoms that are related.

In fact, systemic aortopulmonary collaterals may be associated to risks of pulmonary overflow, hemoptysis, pulmonary infection, pulmonary bleeding, and pulmonary hypertension. This is why it is usually advisable to disconnect these vessels from the systemic circulation. Before ligating or occluding these collaterals, it is important to verify that the affected lobe has a pulmonary artery supply to avoid creating an infarction.

Surgery could allow a complete correction in a single step. However, a two-step approach with a trans-catheter

procedure may be an appealing option considering that usually a cardiac catheterization is performed to define diagnostic details.

Trans-catheter collateral embolization is performed by using:

- vascular occlusion coils [13–16],
- detachable silicon balloon [17],
- Amplatzer duct occluders [15,16,18],
- plugs of the Amplatzer family [18,19].

In particular the Amplatzer vascular plugs II and IV (Figs. 8.1D and 8.2) are very useful to perform vascular occlusion. Amplatzer vascular plugs II are deployed through small guide catheters (4–7 F), and are easily extracted and redeployed when required. This device is available in diameters starting at 3 mm upto 22 mm in 2-mm increments. The length varies from 6 to 18 mm with respect to the device diameter. The Amplatzer vascular plug IV is more limited in diameter availability (4–10 mm), but can be delivered through smaller diagnostic catheters (4–5 F) [19,20]. Therefore, collateral embolization can be easily performed even in newborns if needed.

In the literature there are contradictory reports about the impact of interruption of systemic arterial collaterals in the management of patients diagnosed with SS. Some authors consider the impact of coil embolization insignificant because usually the systemic arterial collaterals supply too small segments of the lung to influence shunt volume and pulmonary artery pressure [21]. Coil

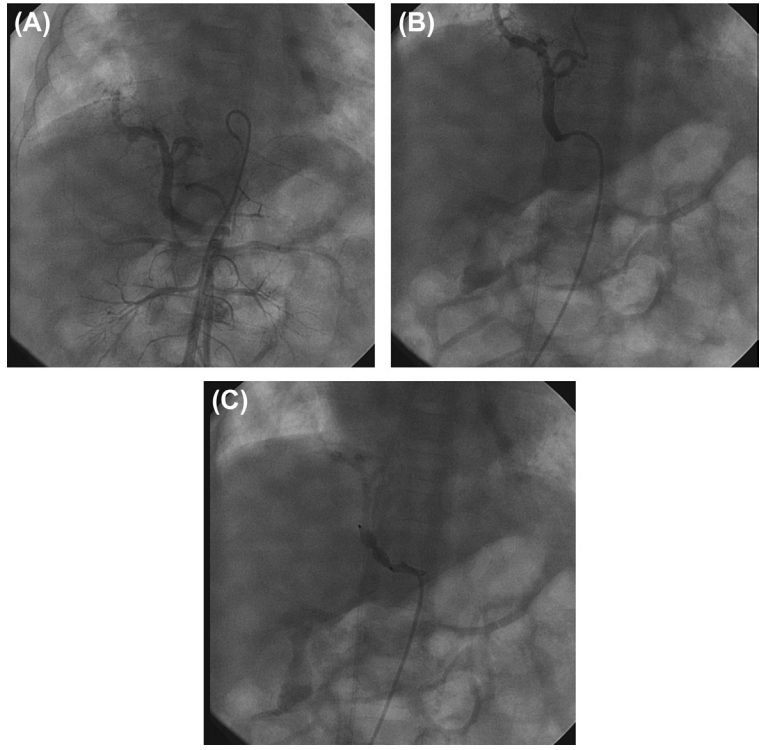


**Figure 8.2** Aortopulmonary connection to the lower right lobe (A and B); embolization by using Amplatzer plug IV (C).

embolization is more likely to be successful in reducing symptoms in a large aberrant artery to be embolized. Other investigators [13–16] suggest coil embolization as initial palliation, particularly if symptoms are well controlled by medical treatment, in order to let the child grow and become an optimal candidate for complex surgery. Postponing surgery could be a theoretical advantage in promoting clearance of pulmonary parenchyma and growth of the right lung. Moreover preoperative coil embolization does avoid the need for searching and

ligating aberrant arteries during surgery. Both factors could potentially improve surgical results and decrease postoperative complications.

Coil embolization of a large arterial collateral is also useful to prevent pulmonary hypertension, to treat respiratory symptoms from a sequestered lung lobe, or even to reverse the deteriorating course of the disease [14–16].

Weems at al., also proposed the use of an Amplatzer vascular device to occlude a large aberrant artery to potentially prevent the need for surgical intervention in carefully selected patients [16]. Since embolization may be helpful and is unlikely to harm the patient, it has also been suggested that the artery should be coil embolized at the time of diagnostic angiography [22].

In few patients with a dual communication between the pulmonary vein and both the inferior vena cava and the left atrium, the inferior draining vein can be successfully occluded with a coil or a device. Subsequently, rerouting of the abnormal pulmonary venous return of the right lung can be performed by conventional surgery [2] or rarely by trans-catheter approach when a scimitar vein is connected not only to the inferior vena cava but also through collaterals to the left atrium [23–25].

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# CHAPTER 9

# Surgical Treatment and Outcomes

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## 9.1 HISTORY OF SURGICAL CORRECTION

In 1956, John Kirklin and coauthors [1] from the Majo Clinic reported the first correction, without the aid of cardiopulmonary bypass (CPB), of an infradiaphragmatic type of scimitar syndrome (SS) associated with an atrial septal defect (ASD). Since the vein was not long enough to be implanted directly into the left atrium, it was anastomosed to the right atrium. Then, by adding a Bailey [2] atrioseptopexy-type procedure, the right pulmonary veins flow was directed to the left atrium through the ASD. Gerbode and Hultgren [3] established the experimental basis for this method and demonstrated in dogs that such an anastomosis remained patent.

After Kirklin's first report, quite a few cases of total correction using open and closed heart techniques have been reported [4–17]. Several methods of repair included the use of the CPB, using a direct anastomosis of the scimitar collector to the left atrium (LA) by Honey [11], or a division with reimplantation of the anomalous pulmonary vein into the right atrium (RA) with baffle insertion to redirect the flow into the left atrium by Shumacker and coworkers [17]. Alternatively, an

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intraatrial patch was used to create a tunnel, redirecting flow from the anomalous pulmonary vein to the LA through an ASD, as described by Zubiate and Kay in 1962 [18]. Puig-Massana and Revuelta [19] described the use of the free wall of the RA to create a tunnel from the scimitar vein (SV) to the LA across an ASD. It is worthy to note that these last two operations required the use of deep hypothermic circulatory arrest for accurate suturing of the intraatrial baffle around the orifice of the anomalous vein within the inferior vena cava (IVC).

Technical aspects have been evolving through the years and a constant research to improve procedural safety and long-term efficacy goes on in the modern era of surgery. Examples of these continuous efforts are given by Brown and coworkers [20] who described the reimplantation of the SV collector directly into the LA through a right thoracotomy without the use of CPB in 2003, or by Lugones and colleagues [21] who proposed an in situ pericardial tunnel as a new repair option in 2013.

## 9.2 SURGICAL STRATEGIES

Two surgical approaches are currently recommended to treat patients with SS:

- A resective approach: consisting of the resection of a part or the whole right lung;
- A corrective approach: re-routing the "scimitar vein" (SV) flow into the LA.

Any anomalous aortopulmonary collateral, when present, needs to be ligated (if not yet coil embolized) and any associated intracardiac defect must be simultaneously corrected at the time of repair.

Common indications for surgical treatment include:

1. The presence of symptoms such as:
   a. congestive heart failure;
   b. recurrent severe respiratory symptoms;
   c. recurrent hemoptysis and upper respiratory tract infections.
2. The association of other simple and complex congenital heart malformations;
3. Significant left-to-right shunts (Qp:Qs > 1.5:1) and right heart chamber dilatation;
4. Lung sequestration;
5. Secondary reactive pulmonary arterial hypertension.

A **resective approach** is usually reserved for patients with persistent severe respiratory symptoms and with severe right lung hypoplasia [22]. Pulmonary lobectomy can be safely performed when an anomalous vein drains only one lobe. In case of anomalous communication of more than one lobe, a simple lobectomy can lead to infarction of the remaining lung. A hypoplastic right lung often presents an abnormal lobation, which makes any lobe resection technically difficult. Pneumonectomy is often required in children especially when severe right lung hypoplasia is present. Before resection, a preoperative evaluation of the adequacy

of the remaining lung function is necessary in order to face the loss of viable lung tissue.

A post-pneumonectomy syndrome can occur when the heart further deviates into the right thorax. Further more, post-pneumonectomy potential complications in infants include late scoliosis and respiratory insufficiency [20,23–27].

A "resective technique" can also be adopted in case of post-corrective approaches where the scimitar collector becomes stenotic and patients continue to complain of severe respiratory symptoms.

A **corrective approach** of SS consists of redirecting the pulmonary venous drainage into the LA [4,20,22,28]. Surgical repair abolishes the left-to-right shunt, prevents the progressive dilatation of the right heart chambers and the progression of pulmonary arterial hypertension. Nonetheless, corrective approaches do not improve blood flow and function of the hypoplastic right lung, which is usually supplied by a hypoplastic pulmonary artery.

## 9.3 TYPES OF CORRECTIVE APPROACHES

Different corrective techniques have been proposed over the years for SV correction and their evolution is based on the necessity to create a wide low-flow pathway for blood toward LA.

Some general aspects of patient preparation are common. A double lumen endotracheal tube is preferred, when possible, to selectively deflect the right lung. A full

continuous monitoring is secured with 12-leads ECG, arterial line, central venous pressure, peripheral saturation, bispectral index, and infrared spectroscopy. Intraprocedural transesophageal echocardiography is used according to body weight. Two accesses are possible: (1) full sternotomy or (2) right anterolateral thoracotomy through the 5th–6th intercostal space. Regardless of the selected incision, right pleural space is opened widely and the pulmonary venous drainage is identified through a careful dissection to confirm preoperative diagnosis. The clue to the procedure is to establish the length and route of the SV collector accurately in order to choose the most appropriate technique for vein re-routing. The pericardium is then usually opened and an aortic-bicaval cannulation is performed to establish CPB. Attention must be paid during pericardial manipulation and incision in order not to damage the phrenic nerve. Moderate hypothermia is recommended during CPB; aorta is cross-clamped and cardioplegic solution is given in the aortic root. Afterward, the specific procedural strategy and technical details depend on the presence of associated intracardiac defects and to the chosen corrective technique for the SV. Circulatory arrest has been used to reduce venous return during CPB, especially during intracardiac baffle suturing in the IVC zone (see below). Nevertheless, the use of CPB has decreased and a constant research on techniques that do not employ CPB is largely pursued.

### 9.3.1 Intracardiac Baffle Repair Technique

The method consists in the creation of a long intracardiac tunnel by baffling the orifice of the SV into the LA through a

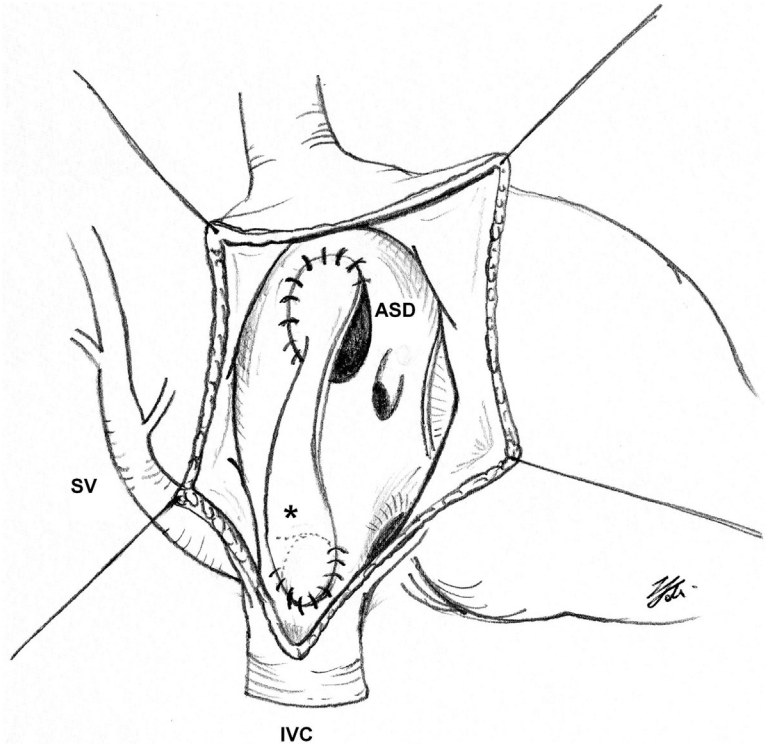


**Figure 9.1** Intracardiac baffle technique. The right atrium is wide opened. A patch (*) is sutured between the scimitar vein (SV) orifice in the inferior vena cava (IVC) and an atrial septal defect (ASD). Attention must be paid during suturing to the coronary sinus and the tricuspid valve.

newly created or an enlarged atrial septal communication. A large vertical right atriotomy is necessary to place the baffle. The SV anomalous collector is left "in situ" (Fig. 9.1) [18,22,28].

Limitations of this method are:

- inability to fix any stenosis of the SV, if present;
- the frequent need for deep hypothermic circulatory arrest to reduce venous return;
- the risk of tunnel distortions and thrombosis, especially in infants;

- risk of SV stenosis at the junction between pulmonary vein and IVC: when a baffle is created vertically, the right-angle connection of the pulmonary vein to the IVC almost invariably creates a junctional stenosis at that site. To solve this problem, a modified baffle technique has been proposed: both the posterolateral wall of the right atrium and the medial wall of the SV are incised and then joined together in a side-to-side fashion, in order to create a wide patent anastomosis (Fig. 9.2).

### 9.3.2 Reimplantation Technique

This technique includes the disconnection of the SV collector from the IVC. The SV orifice is excised with a cuff of IVC tissue and then reimplanted directly onto the lateral side of the LA with an end-to-end anastomosis [20,22] (Fig. 9.3). If no other intracardiac defects are present, no right atriotomy is necessary. In this procedure, it is anyway mandatory that the vein lies correctly; distortion of this vessel can obstruct blood flow with consequent thrombosis.

Limitations of this technique are:

- risk of kinking during reimplantation leading to stenosis of the anastomosis (especially in small infants).
- poor mobilization of SV collector if distance between SV and lobar branches is short. In literature, direct implantation of SV to LA has also been described with the interposition of a polytetrafluoroethylene graft to extend the length of the SV collector and reduce tension, angulation, or kinking [13] (Fig. 9.4).
- necessity to open the diaphragm and IVC manipulation.

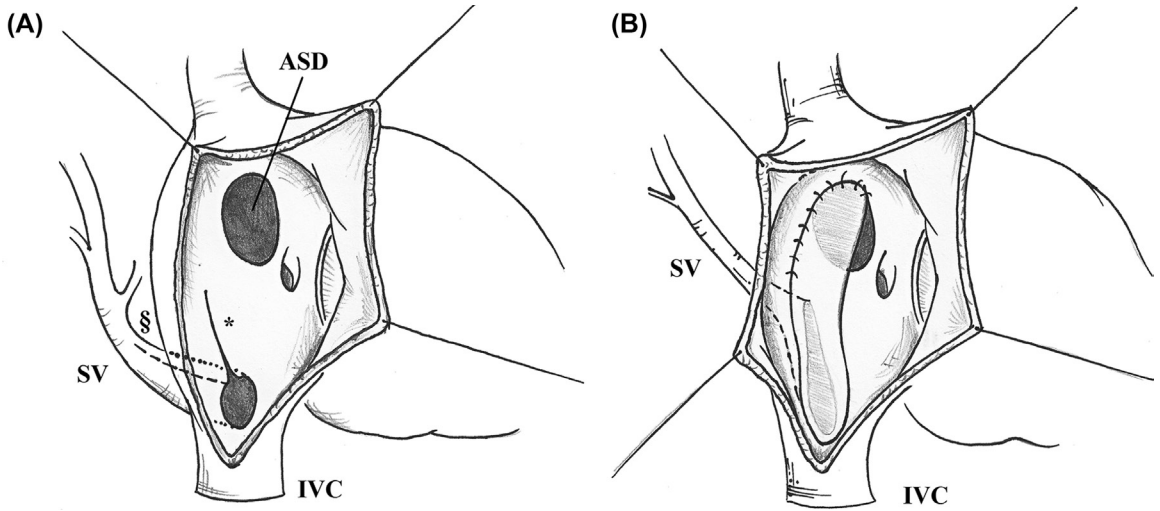


**Figure 9.2** Modified intracardiac baffle technique. (A) Both the posterolateral wall of the right atrium (just above the SV orifice *) and the medial wall of the SV (§) are incised and then connected in a side-to-side fashion to create a wider longitudinal orifice into the right atrium. (B) A patch is the secured upon this newly created orifice to redirect blood flow toward an atrial septal defect (ASD) and the left atrium (B).

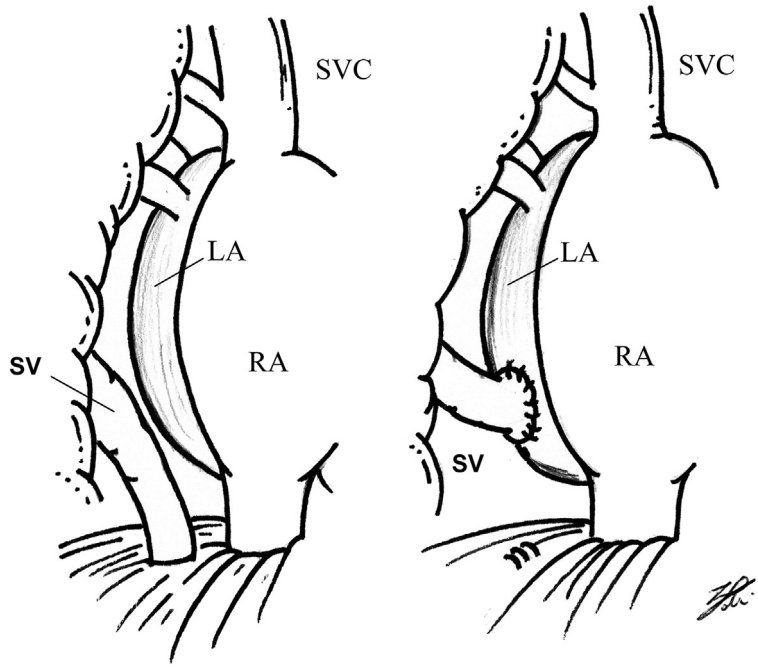


**Figure 9.3** Reimplantation technique. The scimitar vein (SV) is detached from the inferior vena cava (IVC) and directly connected to the posterior aspect of the left atrium (LA). *RA*, right atrium; *SVC*, superior vena cava.

### 9.3.3 Modified Reimplantation Technique

This technique includes the disconnection of the SV collector from the IVC. The SV orifice is excised with a cuff of IVC tissue and then reimplanted higher up onto the RA (end-to-end anastomosis), adjacent to a preexisting ASD or by creating a new one. Thus the flow is baffled to the LA with a shorter tunnel with respect to the intracardiac baffle repair technique [29] (Fig. 9.5).

The major advantage of this procedure over the reimplantation technique is the avoidance of kinkings and distortions of the reimplanted SV collector.

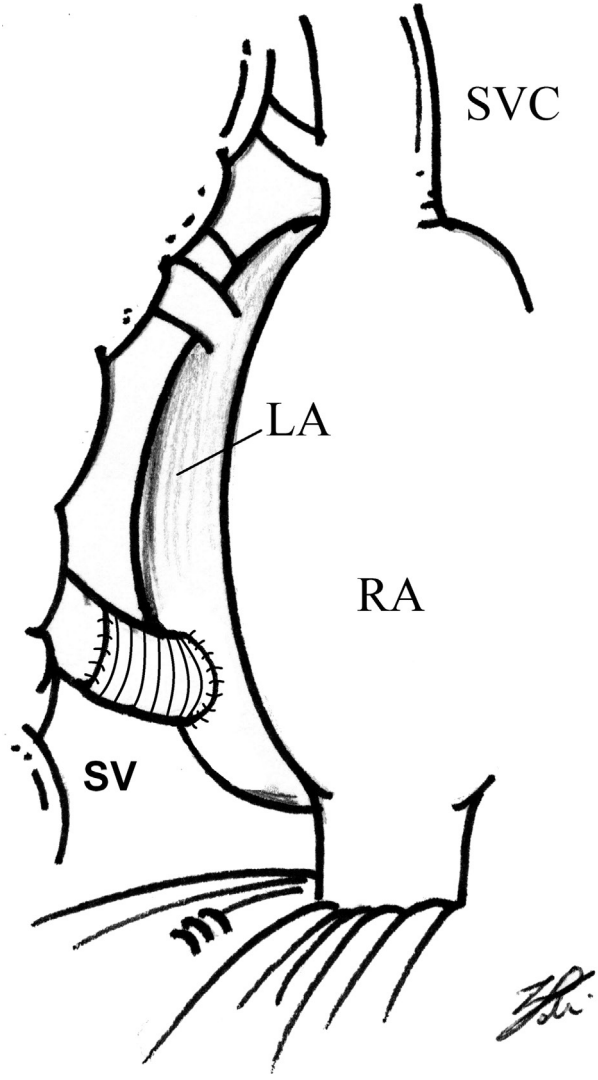


**Figure 9.4** Reimplantation technique with the interposition of a PTFE graft to extend the length of the scimitar vein (SV) collector to the left atrium (LA). *RA*, right atrium; *SVC*, superior vena cava.

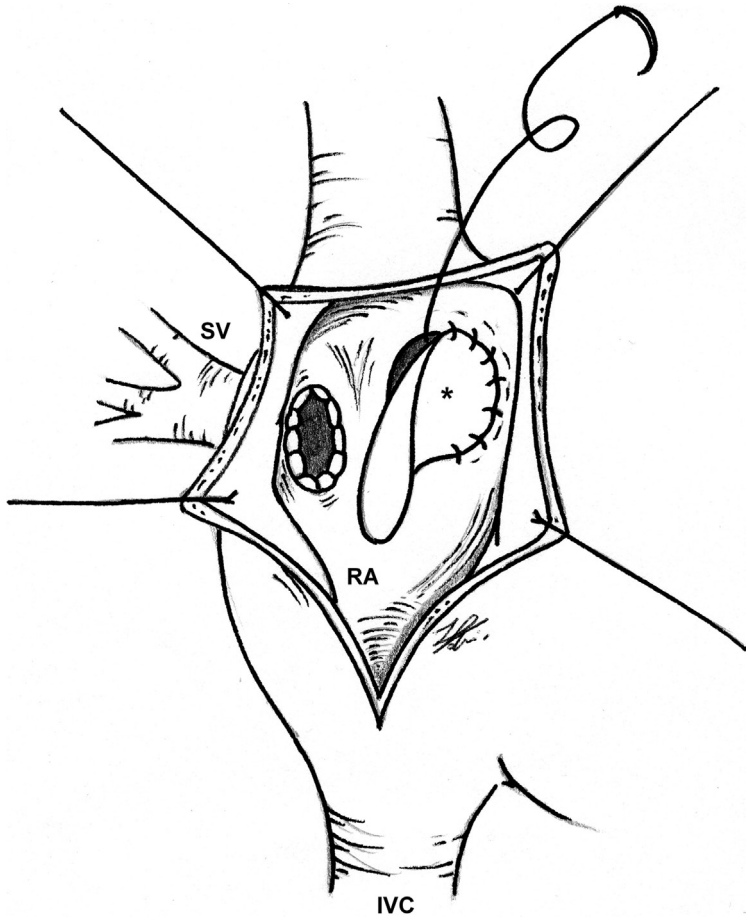


**Figure 9.5** Modified reimplantation technique. The scimitar vein (SV) collector is detached from the inferior vena cava (IVC), re-implanted higher up onto the right atrium (RA), adjacent to an atrial septal defect (ASD). Thus a patch will connect the newly created SV orifice and the ASD, guiding blood toward the left atrium. *RA*, right atrium.

The choice of the right or left atrium for the SV-end anastomosis depends on the SV length and mobility and on its relationship to the lung hilum. If the VS runs anterior to the hilum, then implanting it into the posterolateral wall of the right atrium is recommended. If the SV courses deep

within the hilum, then implanting it into the posterior wall of the LA may be the best option.

Limitations of the modified reimplantation technique are:

- Diaphragm opening and IVC manipulation;
- The risk of intracardiac tunnel distortions and thrombosis, especially in infants.

### 9.3.4 Off-Pump Reimplantation Technique

This option has been described by Brown and coworker and consists of direct reimplantation of the SV collector into the LA without the aid of CPB. This technique has been utilized for patients without associated intracardiac defects [20]. Through a right thoracotomy and entering the chest through the 5th intercostal space, the SV is disconnected from its junction with the IVC. Keeping the patient under full anticoagulation, the right pulmonary artery and SV drainage can be temporarily occluded. The lung is cooled with ice slush and topical pad. The distal SV's end is carefully dissected to minimize the risk of stenosis, and it is connected to the right-sided aspect of the LA, which is free from any connection of right pulmonary veins, using a partial occluding clamp (Fig. 9.6).

Advantages of this technique are:

- avoidance of CPB (and circulatory arrest); and
- suitable option for clinically unstable patients.

Limitations of this technique are:

- risk of kinking or distorting of the SV collector leading to stenosis (especially in small infants);

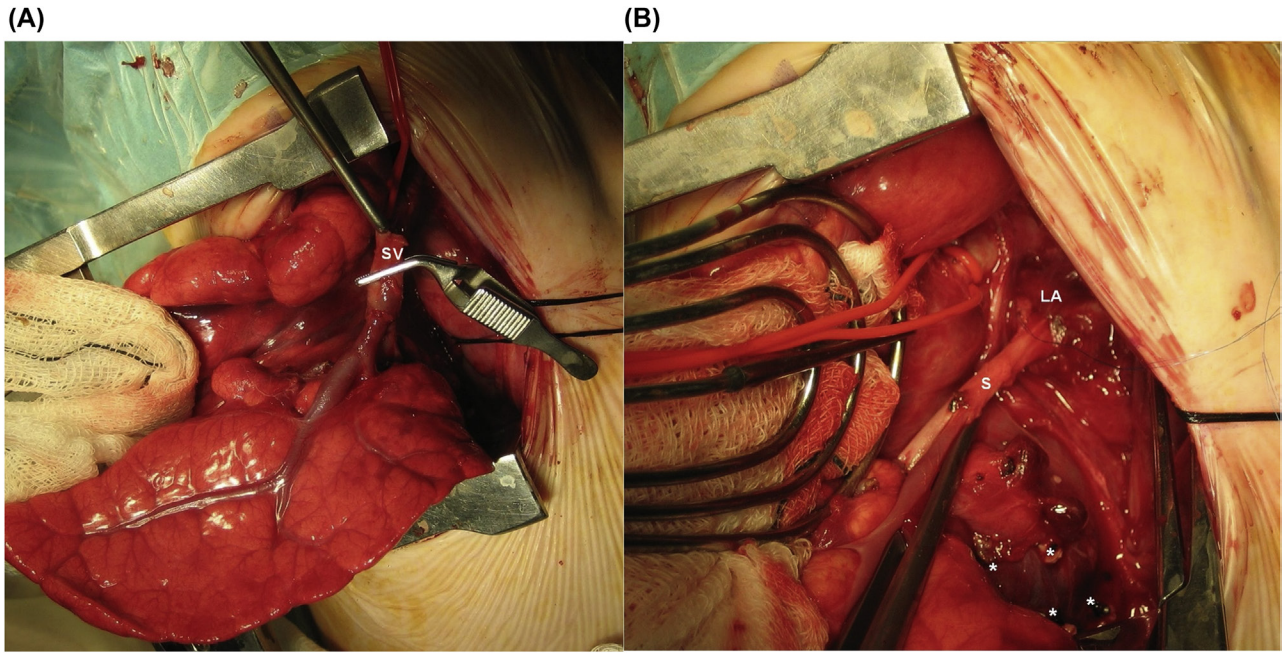


**Figure 9.6** Intraoperative pictures during off-pump reimplantation of the SV into the left atrium: (A) Venous collector disconnected from the inferior vena cava and thoroughly dissected. Red vessel loop tightened around the right pulmonary artery. (B) View from the assistant. Anastomosis of the pulmonary venous channel to the left atrium. Notice the red vessel loop already loosened in the right pulmonary artery. *With permission from Right thoracotomy, off-pump, scimitar syndrome repair in infants. Asian Cardiovasc Thorac Ann 2014;22(3):353–55.*

- risk of ischemic injuries to the lung;
- air embolism to left chambers;
- diaphragm opening and IVC manipulation;
- hemodynamic instability during pulmonary artery/vein clamp.

### 9.3.5 Pericardial Tunnel Technique

Lugones and coworkers have presented this procedural variant where an in situ pericardial tunnel connects the pulmonary venous return to the LA [21]. After a median sternotomy and confirmation of the presence of the SV, the pericardium is opened and mobilized to reach the pulmonary vein drainage without tension. The SV collector is interrupted before entering the diaphragm, and after being opened longitudinally on its left lateral aspect, it is connected to a large incision on the lateral wall of the pericardium (side-to-side anastomosis). A wide vertical left atriotomy is performed and its left margin is sutured to the posterior pericardium. Eventually, from both vertices of the incision, the suture is continued attaching the pericardium to the external right atrial wall, creating a new cardiac chamber which leads blood from the SV to the LA (Fig. 9.7).

Advantages are:

- low risk of stenosis, kinking, or traction of the SV collector;
- no need to open interatrial septum or diaphragm; and
- no need of circulatory arrest.

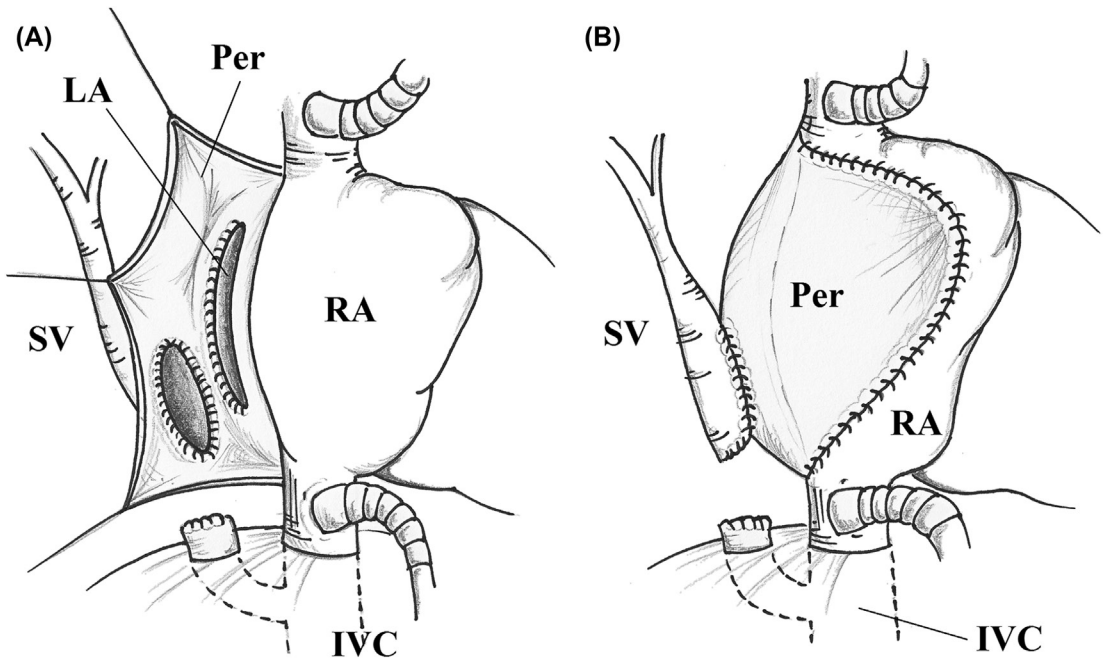


**Figure 9.7** Pericardial tunnel technique. (A) The scimitar vein (SV) collector is dissected before entering the diaphragm, and after being opened longitudinally on its left lateral aspect, it is connected to the lateral wall of the pericardium (Per). A vertical left atriotomy is created close to the right atrium (RA) and its left margin is sutured to the posterior Per. (B) The free margin of the Per is sewn on to the RA wall.

Limitations are:

- risk of phrenic nerve damage during SV-to-pericardium connection; and
- difficult bleeding control in the posterior aspect of the pericardial suture.

## 9.4 OPERATIVE RESULTS

SS is treated either by surgery or by clinical monitoring depending on a series of defined patient's characteristics [14,22,23]. Treatment decisions are often challenging and a dilemma is how to treat borderline cases, namely patients with isolated SS (i.e., without associated congenital heart defects), who often are asymptomatic and might be diagnosed serendipitously.

Both the intracardiac repair and the reimplantation techniques have been reported for many years as the most frequently used reparative technique, and their use much depends on the surgeon's preference and on the anatomic and pathologic features of each patient with SS [4,22,25,28]. At present, however, there is no consensus for which is the best surgical treatment option. For sure, a detailed preoperative knowledge of the course and connections of the anomalous pulmonary venous return and of systemic collateral arteries is mandatory to plan the most appropriate surgical strategy.

As a general rule, the result of surgical treatment is linked to the age of patients [14,23]. Patients requiring treatment who are under 1 year of age are usually very ill, and have a

relatively high operative mortality and complication rate, whereas older patients have a better outcome both immediately and in the long term.

Data from a previously published multicenter study of the European Congenital Heart Surgery Association (ECHSA) on 68 patients [22] who underwent surgical treatment for SS demonstrated that SS is a rare and complex congenital heart malformation which presents in a majority of cases in association with other CHDs. In this study, 59 patients underwent a "corrective" approach and 9 a "resective" approach consisting of a right pneumectomy in 8 and in a right lower lobe lobectomy in 1 patient. Overall hospital mortality was 6% and was significantly higher for patients in the "resective group" (3 out of 9 patients, 33%) than for patients in the "corrective group" (1 out of 59 patients, 1.6%) ($P = .008$). Almost one-third of patients had pulmonary arterial hypertension and this was associated with significantly higher hospital mortality ($P = .03$). The presence of pulmonary arterial hypertension needs to be accurately investigated by preoperative cardiac catheterization to evaluate if it is a primitive phenomenon or it is secondary to increased pulmonary blood flow consequent to the anomalous venous drainage and other associated congenital heart malformations (the flowchart of our suggested treatment decision strategy is shown in Fig. 9.8).

Patients who underwent surgical treatment were also exposed to a high incidence of postoperative morbidities; in fact, 35 patients (51%) presented postoperative complications, which were more frequently in the "resective group" (7 out of 9 patients, 78%) than compared to the

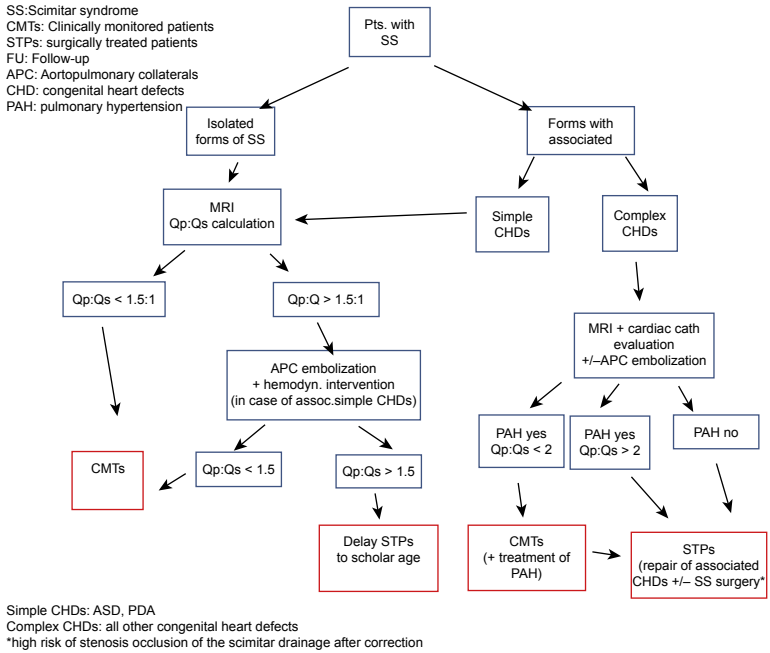


**Figure 9.8** The flowchart of our treatment decision strategy for patients with scimitar syndrome.

"corrective group" (28 out of 59 patients, 47%) ($P = .02$). The incidence of postoperative complications was also significantly associated with younger age at the time of surgery ($P = .003$).

The authors in this study concluded that after a median follow-up time of 4.5 years from surgery, a majority of the patients were asymptomatic (52 out of 61, 85%); while the remaining nine patients (15%) still complained with symptoms, including persistent dyspnea and recurrent respiratory infection. Two patients died late, both for severe pulmonary arterial hypertension. It is worthy to note that the relatively high incidence of postoperative stenosis/

occlusion of the scimitar drainage (9 patients, 15.5%), which in the majority of cases (7 out of 9 patients, 78%) required either a reoperation (n = 4 patients) or a hemodynamic intervention [balloon dilatation/stenting of the SV drainage (n = 3 patients)]. The incidence of postoperative SV stenosis/occlusion was similar to the two reported corrective surgical techniques (intracardiac baffle repair and reimplantation techniques). However, postoperative SV stenosis was more frequently reported in patients younger than 3 months of age in case of SV reimplantation, possibly due to a kinking of the SV during its reimplantation.

Regarding patients with isolated forms, they usually are asymptomatic and maintain a good clinical status and often suffer from respiratory symptoms only, which partially regress with age in a vast majority of them without any treatment [30]. However, a majority of these patients present a significantly increased pulmonary blood flow (Qp:Qs > 1.5:1) with consequent dilatation of the right heart chamber. Due to the fact that SS is almost always associated with right lung hypoplasia, and scimitar vein often carries a small amount of blood flow, surgical correction of the anomalous pulmonary venous return should be considered only when the scimitar drainage has been proven itself to be responsible for a considerable amount of pulmonary overload.

The Qp:Qs in isolated SS is usually 2:1 or less for unilateral total anomalous drainage (all right pulmonary veins to SV) and much less for unilateral partial anomalous drainage (right lower or right lower and middle pulmonary veins only). Any case showing Qp:Qs higher than 2:1 should have associated intracardiac shunts (other associated congenital

heart malformations) or extracardiac shunts (aberrant collaterals from the descending aorta to part of the right lung).

Forms associated to simple CHDs (i.e., atrial septal communications or patent ductus arteriosus), which are transformed to "isolated" by correcting only the associated CHDs seem to have a benign outcome just as the primarily isolated forms, when correctly selected [30]. Based on these results, we may speculate that, in selected patients, the correction of associated simple CHDs (as interatrial communications) together with the therapeutic occlusion of any anomalous arterial supply to the lung may be beneficial in improving a patient's clinical status. The latter may be accomplished either by preoperative coil embolization or at the time of surgical repair, reducing the amount of blood flow to the lungs and intracardiac shunts and it is associated with a decrease in cardiac symptoms.

In conclusion, current surgical results demonstrate that corrective surgery can be done safely with a low mortality and morbidity rate, irrespective of the type of corrective surgical technique used. Right lung lobectomy or pneumectomy (either as primary therapy or if postoperative stenosis is present after failed repair) may be required in patients with severe clinical features and usually carry higher mortality and morbidity rates.

Surgical repair of less severe forms of SS, especially in asymptomatic patients is safe and lowers the risk of developing late symptoms; however, it needs to be tailored to the patient and based on a comprehensive hemodynamic evaluation (i.e., the magnitude of Qp:Qs, presence of right chamber dilatation etc.).

A continuous clinical and noninvasive follow-up is indicated in patients with SS to identify any clinical or physiological variation, in order to administer timely appropriate treatment, and to check postoperative outcomes. MRI is particularly useful as it allows accurate quantification of Qp:Qs using phase-contrast velocity mapping technique. The blood flow through the sizable aberrant systemic artery to the right lung can also be quantified. Cardiac catheterization can be avoided for cases not having intra- or extracardiac shunts; however, it is still necessary when pulmonary hypertension is suspected.

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CHAPTER 10

# Other Pulmonary Vascular Anomalies: Anatomy, Epidemiology, Diagnosis, and Treatment

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Pulmonary vascular malformations consist of a spectrum of anomalies, ranging from abnormal vascular connection to normal lung tissue to vascular malformations that connect to abnormal lung tissue [1]. These are rare lesions, the most common being bronchopulmonary sequestration (BPS), hybrid lesions containing both congenital cystic pulmonary airway malformation (CPAM) and BPS features, lesions of aberrant venous or arterial systemic anastomoses and pulmonary arteriovenous malformations (PAVM) [1].

Various classifications have been proposed using different terminologies, such as "congenital bronchopulmonary vascular malformation" to describe an abnormal anastomosis in the bronchovascular system and "congenital bronchopulmonary foregut malformation," which encompasses a wide variety of anomalies, occurring because of abnormal differentiation of the respiratory and alimentary tract, abnormal separation of the two systems, or abnormal development of arterial blood supply [2–6].

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A proper classification is not defined yet, as many of these lesions share common elements, such as a systemic arterial blood supply; moreover, the term "sequestration" has been used to describe the lung tissue in BPS, but also in the hybrid lesions and in the scimitar syndrome (SS). However, the lung tissue does not connect to the tracheobronchial tree in BPS; it contains CPAM features in the hybrid lesions, and it is hypoplastic in the SS.

Bush et al., in 2001, proposed to use a simple language to classify these lesions, not considering their possible embryologic origin, but only their simplest components, and searching for potential multiple or associated anomalies [7]. In 2003, Langston proposed a classification of bronchopulmonary malformations based on histology of the lung parenchyma [8]. This classification included: bronchial atresia (intralobar sequestration), CPAM with large cysts, CPAM with small cysts, and extra-lobar sequestration. Thus, cases with normal lung tissue associated with aberrant systemic vessels, could not be included, being better considered as vascular malformations [1,7].

Ultimately, the proposed suggestions for simplification and unification of nomenclature have not been widely adopted, because none of the proposed theories is able to explain the origin of the various malformations [9]. However, a simplified classification and a multidisciplinary approach may allow a better understanding of their etiology, natural history, and associated anomalies, leading to the more appropriate treatment.

## 10.1 BRONCHOPULMONARY SEQUESTRATION

BPS was first described in 1861 by Rokitansky [10]. The term "sequestration" was coined by Price [11] in 1946 to describe a "disconnected, non-functioning" bronchopulmonary mass, characterized by abnormal lung tissue non-connected to the tracheobronchial tree, with an aberrant systemic arterial supply, usually from the thoracic or abdominal aorta [1,12,13]. According to Price, such abnormal pulmonary tissue had previously been said to be ectopic or dislocated [11].

BPS may be intralobar or extra-lobar, based on their pleural investment [14]: the intralobar form shares the pleura with the normal lung and usually drains into the pulmonary venous system, whereas the extra-lobar form has its own pleural investment and systemic venous drainage [13].

The intralobar BPS account for 75% of all BPS. They are located in the lung base, adjacent to normal parenchyma (Fig. 10.1A). In 10% of the cases, they are associated with diaphragmatic hernia, tracheoesophageal fistula, congenital heart disease, foregut duplication, and aneuploidy [15]. The blood supply is provided by a systemic artery (Fig. 10.1B) and the venous drainage is usually via the pulmonary veins.

The extra-lobar BPS account for 25% of all BPS. The majority is located at the base of the left chest (Figs. 10.2, 10.3, 10.4). In 10% of the cases, they are located in or below the diaphragm. When located below the diaphragm, they may mimic a neuroblastoma or adrenal hemorrhage [16].

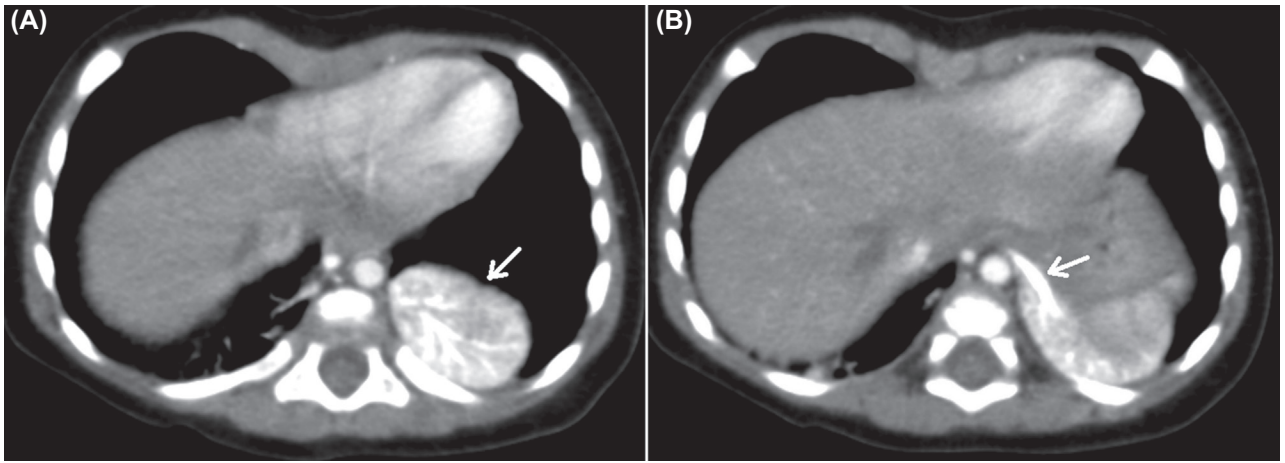


**Figure 10.1** (A) Intralobar sequestration on CT (*arrow*) at the base of the left lung with (B) its blood supply from the abdominal aorta above the celiac tripod (*arrow*).

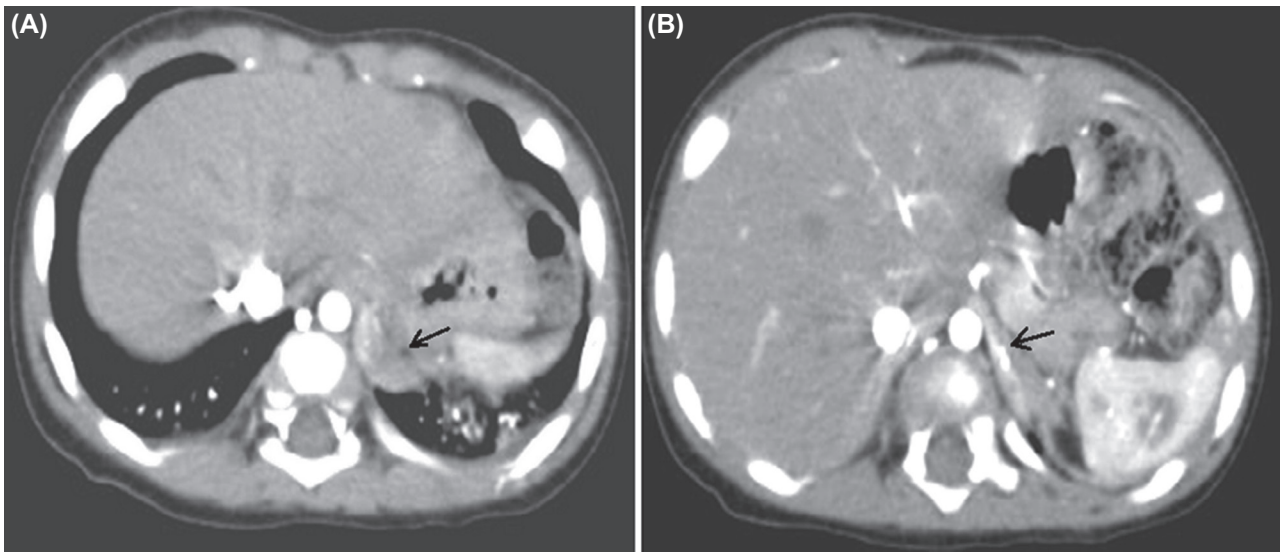


**Figure 10.2** (A) Extra-lobar sequestration on CT (*arrow*) at the base of the left lung with (B) its blood supply coming from below the diaphragm.

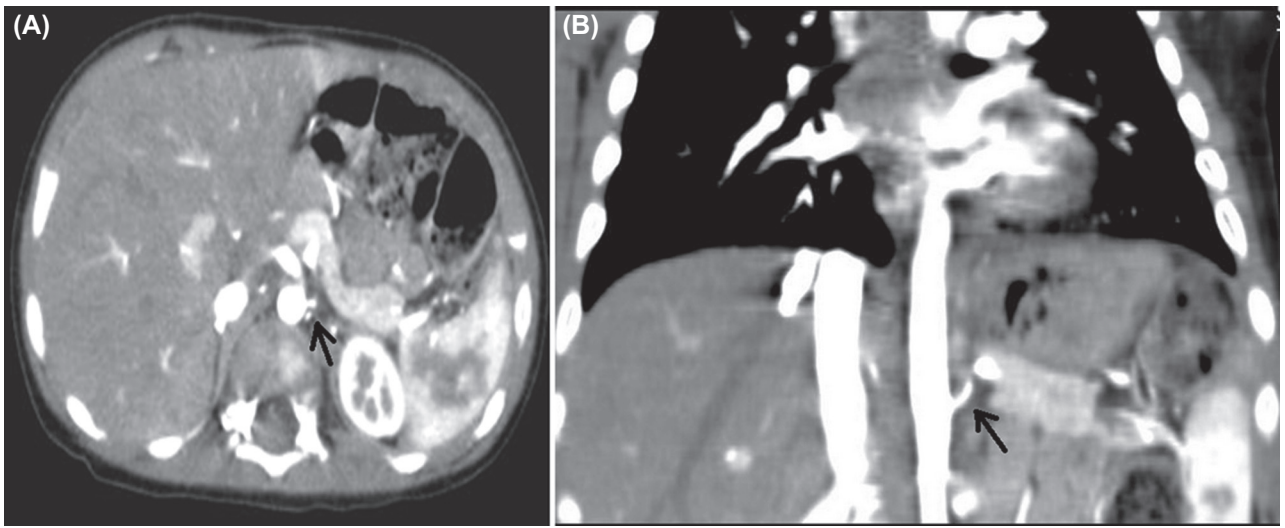


**Figure 10.3** Extra-lobar sequestration blood supply coming from the aorta between the celiac tripod and superior mesenteric artery (*arrow*) on axial (A) and coronal (B) CT images.

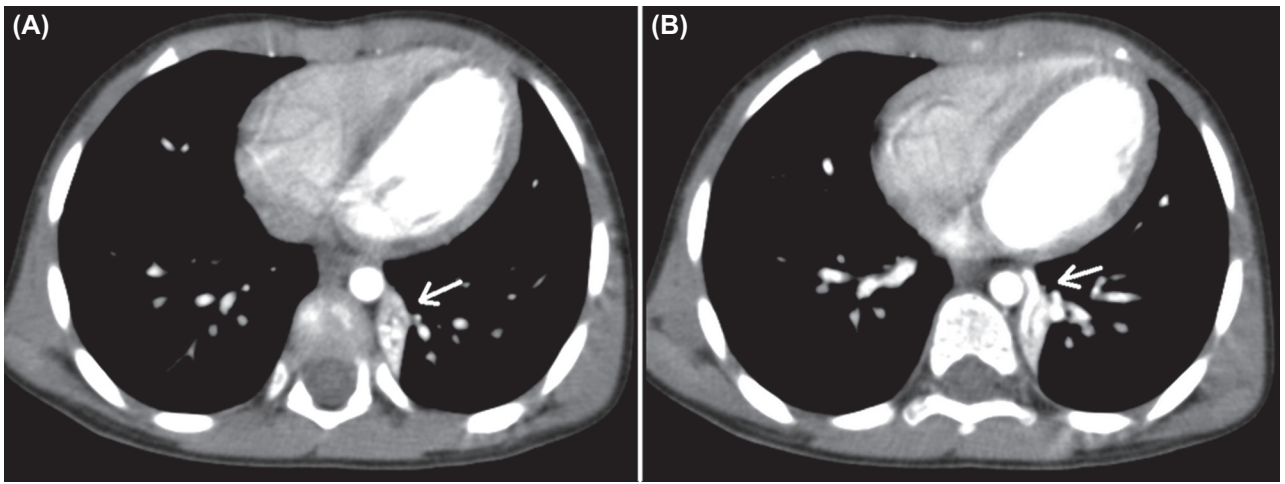


**Figure 10.4** (A) Extra-lobar sequestration at the level of the middle right lobe (*arrow*) with (B) its blood supply from two branches originating from the aorta under the left inferior pulmonary vein (*arrow*).

Extra-lobar BPS has a male predominance of 3:1, compared with 1.5:1 in intralobar BPS. In addition, they have a higher incidence of associated anomalies [15].

BPS have an estimated incidence of 1 in 1000 births but the incidence is probably underestimated since some patients, especially those with intralobar sequestration, are asymptomatic [9]. The availability of prenatal screening, however, has contributed to identify more cases, with a better definition of their incidence.

The most widely accepted theory of the etiology of BPS is based on the timing of the formation of the pleural investment and the formation of a supernumerary lung bud [1]: an extra lung bud arises caudally to the normal lung bud and migrates with the esophagus. If this supernumerary lung bud develops before the development of the pleura, the bud becomes invested with the adjacent lung pleura and results in an intralobar BPS. If it develops after pleural investment, it becomes invested in its own pleura and results in an extra-lobar BPS. The concern of this theory is represented by the fact that the lung buds become invested with parietal pleura in the sixth week of gestation, while the tracheoesophageal septum dividing the esophagus from the laryngotracheal tube develops in the fourth week [1]. Communication with the alimentary tract has been reported in both intra- and extralobar BPS, and from an embryological point of view, for an extra-lobar BPS to communicate with the alimentary tract, the supernumerary lung bud must form before formation of the tracheoesophageal septum. There is also considerable controversy over the cause of intralobar BPS. Since these lesions were previously diagnosed in

older children, and show evidence of chronic inflammation, it has been suggested that they are acquired lesions due to repeated lung inflammation [13]. The increased prenatal diagnosis, however, confirms they are truly congenital malformations.

The extra-lobar sequestration is histologically characterized by uniformly dilated bronchioles, alveolar ducts, and alveoli. A well-formed bronchus can be found in 50% of extra-lobar BPS. The alveolar septae are thickened with foci of extramedullary hematopoiesis. Prominent blood vessels are present in close proximity of the anomalous systemic artery. The lymphatic vessels are ectatic and show features of congenital lymphangiectasia of the lung in subpleural spaces and septae in 55% of the cases. Lymphoplasmacytic inflammatory infiltrate or endoalveolar hemorrhages are frequent [8,17]. In cases of hybrid lesions (extra-lobar sequestration and CPAM), histology is similar to that of CPAM type 2, and is characterized by bronchiolar like cysts, arranged back to back with islands of intermingled normal parenchyma. In about 48% of cases, skeletal muscle fibers are seen around blood vessels and bronchioles (rhabdomyomatous dysgenesis) [18].

The intralobar sequestration is characterized by the architectural distortion of the lung parenchyma related to the extensive inflammatory changes with fibrosis and lymphoplasmacellular infiltrate. Cystic spaces lined by cuboid or columnar epithelium and filled by amorphous eosinophilic material and macrophages are scattered in the context of the fibrosis. Interstitial elastic and muscular arteries show features of arteritis, hypertrophy of media and thrombosis. These inflammatory changes are important in the histologic differential diagnosis of intralobar sequestration and CPAM [17].

Extra-lobar BPS is more commonly diagnosed in the prenatal–neonatal period, whereas intralobar BPS is usually diagnosed later in childhood.

On prenatal ultrasound, BPS usually appears as a solid, homogenous, hyperechogenic mass with at least one feeding vessel from the thoracic or abdominal aorta (Fig. 10.5). Rarely, the celiac axis, internal mammary, subclavian, or renal artery may be involved.Venous drainage is usually via the systemic veins.

Until the systemic blood supply is demonstrated by Doppler ultrasound, the diagnosis cannot be confirmed [1]. Hydrops or polyhydramnios represent poor prognostic factors and indicate the need for fetal intervention [19,20]. Prenatal magnetic resonance imaging (MRI) is mandatory to evaluate the malformation and possible associated lesions, such as congenital diaphragmatic hernia, foregut duplication and tracheoesophageal fistula. On MRI, BPS is a well-defined, uniformly hyperintense mass on T2-weighted images [21] (Fig. 10.6).

Most BPS undergo a spontaneous regression [22]. The mechanism, not clear, may be related to decreased fetal fluid within the lesion or they involute as they outgrow their vascular supply.

Children with BPS may be asymptomatic but they may also have important respiratory distress and severe congestive heart failure secondary to the volume loading from a large systemic artery for the sequestered segment [9]. In young infants, a sub-diaphragmatic extra-lobar sequestration may mimic a malignant tumor, such as neuroblastoma; older children may present with recurrent chest infection,

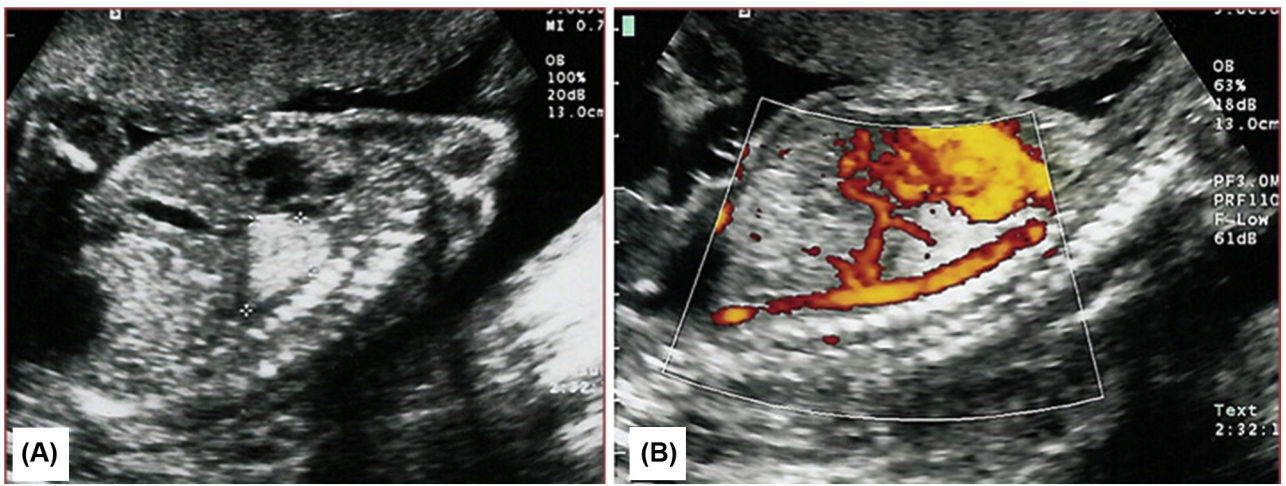


**Figure 10.5** (A) lung sequestration on ultrasound usually appears as a solid, homogenous, hyperechogenic mass with (B) at least one feeding vessel from the thoracic or abdominal aorta (Doppler technique).

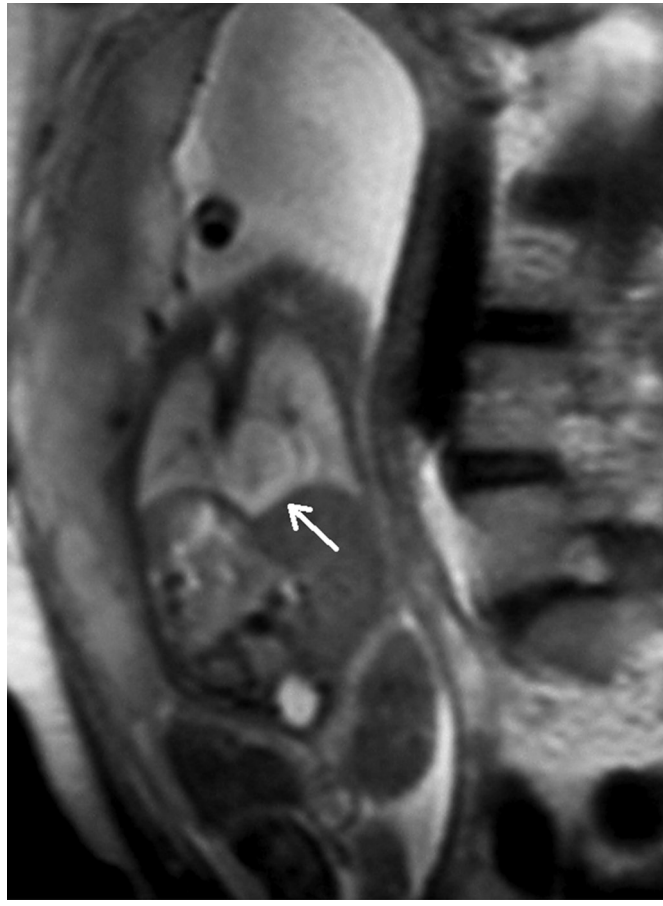

**Figure 10.6** Fetal MRI with sequestration visible as a well-defined, uniformly hyperintense mass on T2-weighted images.

respiratory distress, and again cardiac failure in the absence of congenital cardiac malformations [23]. In adults, BPS may cause recurrent bronchitis, pneumonia, or hemoptysis, which develops silently over the years [24,25].

Fetuses with prenatal diagnosis of BPS should be delivered in a setting where immediate resuscitation and

pediatric surgery are available [1]. A complete postnatal evaluation is mandatory, especially if children present symptoms. Usually, however, children are asymptomatic and in this case the evaluation may be performed later during infancy, at the age of 5–6 months. Computed tomography (CT) and MRI are the most valuable tools for imaging [1,9,26]. Angiography better describes the vascular characteristics, but it is rarely required, especially in those cases considered for arterial embolization [27–30].

Intralobar BPS should be resected because of the presence of alveolar airspace communication and the risk of infection. Lobectomy is the treatment of choice. Large BPS clearly need a surgical resection, as well those characterized by macrocysts (hybrid lesions), which indicate the coexistence of CPAM elements, prone to malignant transformation.

In case of extra-lobar sequestration, the mass should be removed after a careful ligation of the systemic vessel, avoiding the retraction of the vessel below the diaphragm, which may cause intensive bleeding, difficult to control. Some surgeons do not consider the resection if the extra-lobar sequestration is stable over time, proven by documentation of systemic and not pulmonary venous drainage [1]. This approach is especially acceptable when lesions are sub-diaphragmatic, considering an appropriate follow-up.

The actual surgical approach for these conditions is thoracoscopy. Since the first publication by Albanese and coworkers in 2003 [31], several reports have described the feasibility and safety of thoracoscopic lung resection, even in small children [32–34].

In children, lobectomy, segmentectomy, or sequestrectomy is easily performed by thoracoscopy [35]. This procedure offers few postoperative complications, limited chest deformation during growth, and limited impact on pulmonary growth [34]. Moreover it is associated with a lower rate of scarring, a reduced length of hospitalization time, and the rate of conversion is low [36]. Arterial embolization is based on the occlusion of the feeding vessel with consequent reduction in size and involution of the sequestration. The current modalities include microcoils, alcohol, histoacryl, and gelatin sponge particles. The complications however include migration of the embolizing substance and infection, as well as a partial or no regression of the lesion [37].

## 10.2 BRONCHOPULMONARY SEQUESTRATION AND SCIMITAR SYNDROME—PRENATAL ISSUES

It has been long acknowledged that some features of BPS overlap with those of SS [12], and it is clear that the differential diagnosis at the time of prenatal ultrasound is of utmost importance for the more appropriate management of these malformations after birth.

In literature there have been many examples of confounding prenatal overlapping features, but nowadays the similarities and differences between the two conditions seem better identifiable. In a series of BPS cases reported by Collin in 1987, 60% of the right-sided intralobar sequestration had an abnormal venous return compatible with SS [14], and in a series of SS cases reported by Najm in 1996, 53% had an accompanying BPS, defined as having a systemic arterial

supply [38]. Bhide and coworkers, in their series of 11 cases, described a clear distinction between the prenatal ultrasound features of SS and BPS [12]. In particular, they observed that the mediastinal shift was ipsilateral in SS and contralateral in BPS, and lung echogenicity was normal in SS and focally increased in BPS; difficulties, however, were encountered in the identification of blood supply. It is normally easy to track the venous drainage from the affected lung and the sequestration, but in SS a targeted search is necessary in the region of the inferior vena cava and right atrium, and, despite this, it was not demonstrated in two cases. These two cases, however, were diagnosed postnatally as a variant of SS, since the venous drainage could not be seen even after birth. As for the venous drainage, the abnormal arterial supply from the descending aorta was a diagnostic feature in all sequestration cases, but it was not identified in any of the SS cases.

In prenatal ultrasound, SS and BPS are distinct entities on the basis of echogenicity and mediastinal shift. The vascular pattern is however still not perfectly detectable, especially in SS. A postnatal thorough work up is needed to exactly differentiate these conditions.

## 10.3 ABERRANT SYSTEMIC ARTERY TO NORMAL LUNG

The aberrant systemic artery to normal lung, without bronchial sequestration, is a rare congenital malformation [11]. Sade et al. [3] and Thilenius et al. [39] included this lesion as a variant of pulmonary sequestration; however, the bronchial supply to the corresponding segment of lung is normal, therefore this kind of classification is

questioned [9]. Two types of aberrant arteries are recognized: isolated systemic arterial supply to normal lung and systemic arterial supply associated with normal pulmonary artery (dual supply) [40]. The embryogenesis is believed to be due to failure of regression of the primitive aortic branches to the developing lung bud [9,41].

The basal segments of the left lower lobe are the most commonly affected sites, and the systemic artery most commonly arises from the thoracic aorta, but also from the abdominal aorta and the celiac axis. Rarely, it may arise from the left subclavian or internal mammary artery.

The lung is normal and the risk of infection or malignant transformation does not exist. But the increased systemic arterial blood flow to the lung may cause high-output heart failure, congestive heart failure, and hemoptysis [1,42]. Other manifestations are dyspnea and murmur in the lower chest [43]. Pulmonary vascular changes in that section of the lung supplied by the anomalous systemic artery depend on the age at which the anomaly is detected, and the caliber of the anomalous artery. Occasionally, the anomalous supply may result in congestive heart failure in neonates and infants [9].

CT and MRI demonstrate the origin and course of the aberrant vessel.

Patients should be monitored and in case of signs of high systemic blood flow, the vessels should be ligated through a thoracoscopy procedure [1]. Ligation without lobectomy would likely result in infarction, due to inadequacy of collateral vessels between lobes or segments of lung with normal pulmonary arterial supply and the systemic arterialized lobe.

Aberrant systemic artery to normal lung is included in the differential diagnosis of SS, but in this last condition the lung is normal but hypoplastic.

## 10.4 PULMONARY ARTERIOVENOUS MALFORMATIONS

PAVM are structurally abnormal pulmonary vascular lesions characterized by an abnormal direct capillary-free communication between pulmonary arteries and pulmonary veins, and resulting in an intrapulmonary right-to-left shunt [44]. Gas exchange, filtration, and other processing of systemic venous blood are impaired [45]. Physiologic consequences depend on the degree of right-to-left shunt and include hypoxemia, dyspnea, and cyanosis [44]. PAVM are substantially more prevalent than expected. Population-wide cancer screening programs using thoracic CT suggest that PAVM sufficiently large to be detected by CT affect 1 in 2630 [46].

The most common cause of PAVM is the hereditary hemorrhagic telangiectasia (HHT). HHT, which affects about 1 in 5 to 8000 people, is transmitted as an autosomal dominant trait, and is most commonly caused by different mutations in ENG (endoglin), ACVLI/ALK1, Smad4. Arteriovenous malformations and smaller telangiectatic vessels develop at multiple sites. The prevalence of PAVM differs according to HHT genotype [47–49]. PAVM may also be sporadic. PAVM may be single or multiple, unilateral or bilateral, and simple or complex. Most are located in the lower lobes, especially the left [44]. Very few cases are diagnosed in neonates [1].

PAVM may be clearly visible on chest radiograph; however, in many cases chest radiographs are normal, even in case of significant clinical signs. CT is considered the gold standard investigation to demonstrate size, number, and suitability for embolization [50,51] (Fig. 10.7). Diagnostic angiograms are very rarely required and may be performed at the time of embolization, limited to the lung where PAVM are localized [45] (Figs. 10.8, 10.9, 10.10).

The embolization of PAVM is recommended as first-line treatment, if feasible, and is generally performed by the interventional radiologist through a femoral vein approach [52]. The advantages include being less invasive and easy to repeat, even if the possibility of revascularization over time exists. The anatomic resolution of PAVM reduces right-to-left shunt, improves oxygenation, and prevents lung hemorrhage and neurologic complications, due to paradoxical embolism (stroke). Lung transplantation has been performed but it is rarely indicated because of the life expectancy of severely hypoxemic patients. In Shlovin series, three patients referred for lung transplantation and elected not to proceed remain stable more than 20 years later [45].

## 10.5 PERSISTENT PRIMITIVE HEPATIC VENOUS PLEXUS

Persistent hepatic venous plexus is a rare anomaly of the systemic venous return due to the postnatal persistence of the fetal intrahepatic venous drainage. The etiology is unknown. Embryologically, the intrahepatic portion of the inferior vena cava derives from the proximal portion of the right vitelline

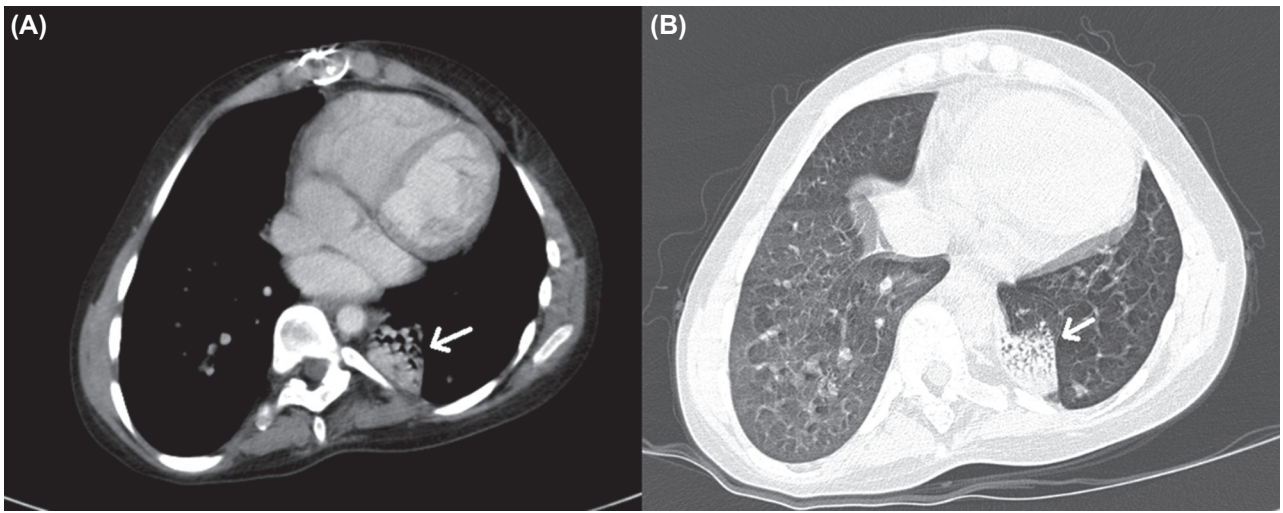


**Figure 10.7** Pulmonary arteriovenous malformation at the base of the left lung on (*arrow*) axial CT images. (A) Bone window and (B) lung window.

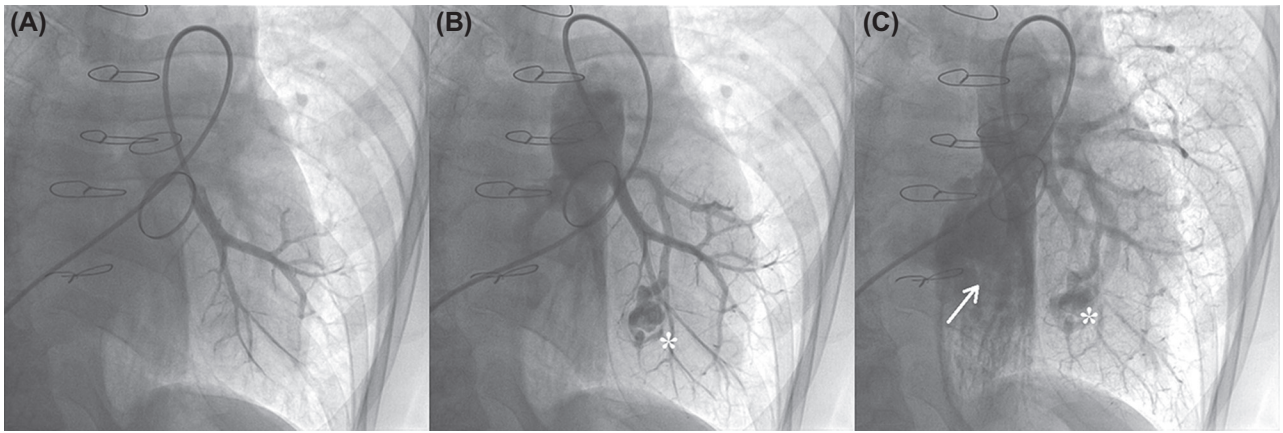


**Figure 10.8** (A) Selective angiography of the left pulmonary artery with (B) and (C) visualization of two pulmonary arteriovenous malformation (*asterisk* and *arrow*).

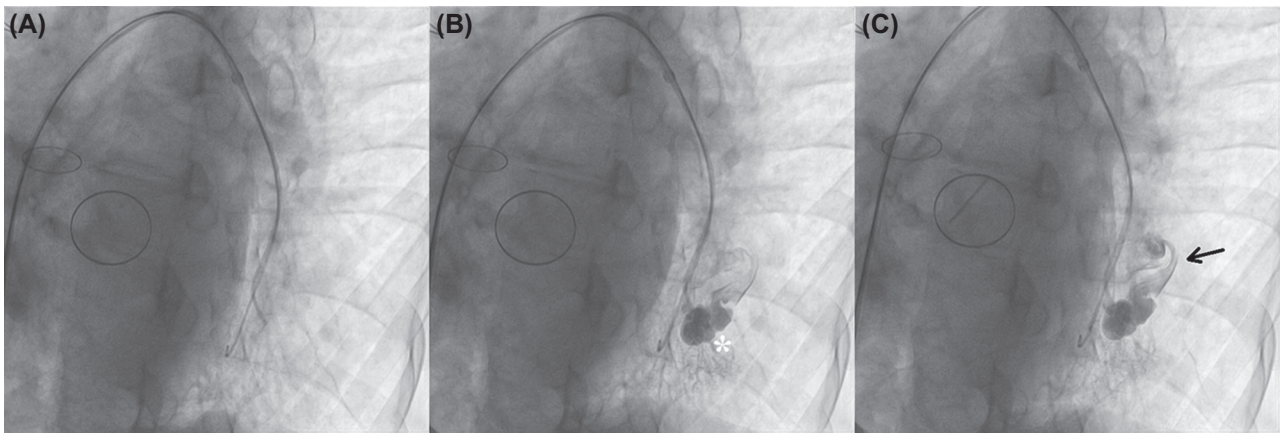


**Figure 10.9** (A and B) selective angiography of one of the previous pulmonary arteriovenous malformation of the left lung (*asterisk*) with (C) its whirling venous return (*arrow*).

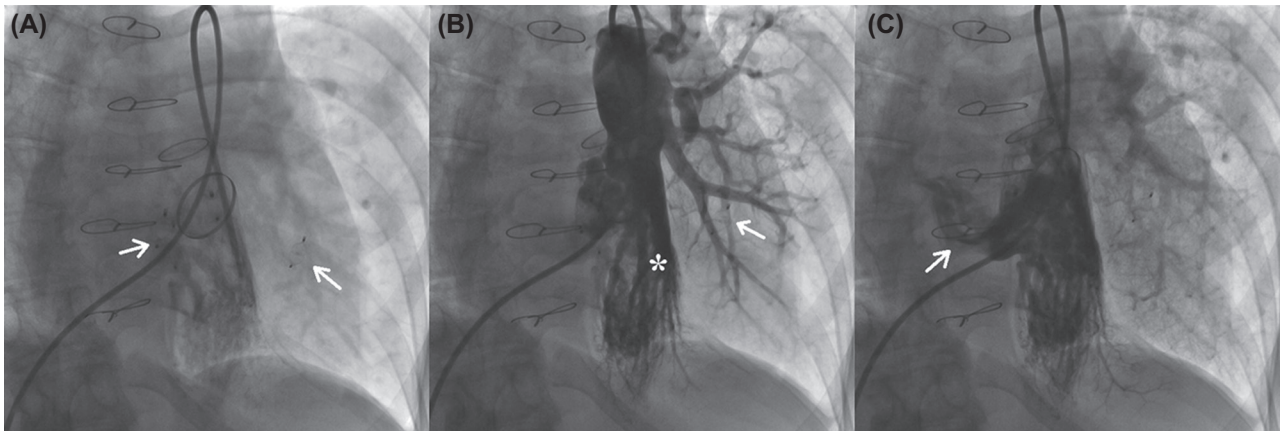


**Figure 10.10** Selective angiography of branches of the left pulmonary artery to visualize multiple pulmonary arteriovenous malformations (PAVM) after percutaneous treatment: (A) vascular plugs (*arrow*). (B) Large PAVM (asterisk) that was not completely controlled. The minor PAVM previously seen in Fig. 10.9 is closed by the vascular plug (*arrow*); (C) whirling venous return of the PAVM (*arrow*).

vein and the hepatic sinusoids. The hepatic venous plexus could represent the precursor of the hepatic veins, and its persistence may lead to an abnormality in the development of the hepatic veins, as well as of the inferior vena cava [53]. Agnoletti et al., as well as Madan et al., believe that the venous plexus represents a primary developmental anomaly [54,55].

This condition was first reported in 1991 by Jolly et al., in a patient with patency of the arterial duct who also had azygos continuation of the inferior caval vein [56]. Subsequently other doctors reported this anomaly associated with the SS [54,57]. In 2000, Freedom et al. divided the eight patients they observed into two groups: patients with pulmonary venous problems, which they termed "the scimitar group," and those with complex congenital cardiac disease, characterized by mixing of systemic and pulmonary venous blood, all candidates for cavopulmonary connection (Kawashima type) [9].

Besides the SS and congenital cardiac disease [9,58], it has been described in literature associated with renal lymphangiomatosis [59] and Sturge-Weber syndrome [60].

Persistent primitive hepatic venous plexus is usually unsuspected as in most cases it is hemodynamically insignificant. Normally it is an incidental finding during a femoral access for cardiac catheterization or during imaging for other abnormalities [53,55,61] (Fig. 10.11). All cases of persistent primitive venous plexus and SS were diagnosed by angiography. In the case reported by Restrepo et al., the diagnosis was obtained by cardiac MRI with three-dimensional reconstruction [57].

There is no specific management of this entity. Usually, associated lesions take precedence, and rerouting of venous

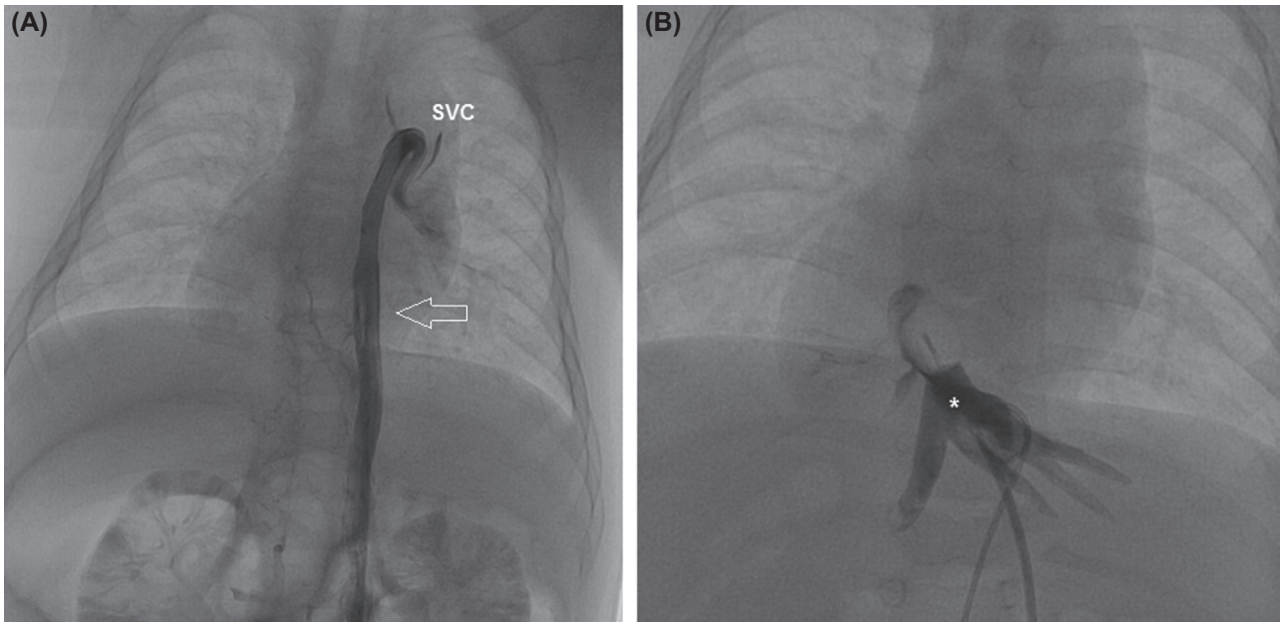


**Figure 10.11** Angiographic image showing a persistent primitive hepatic venous plexus in a patient with heterotaxy syndrome with polysplenia, double outlet right ventricle, common atrium, complete atrio-ventricular canal defect, pulmonary stenosis, destrocardia, interruption of left positioned inferior vena cava with azygos continuation (*white arrow*) on the left superior vena cava (A) and separate drainage of the hepatic veins (*asterisk*) in the common atrium (B). *SVC*, superior vena cava.

return is performed when necessary. Embolization of the venous fistula before or early after Kawashima operation has been described in patients with left atrial isomerism and complex congenital heart disease [9,58].

## 10.6 HORSESHOE LUNG

Spencer published the first complete description and designation of horseshoe lung (HL) in 1968 [62], although Morestin and Porregaux described a similar anomaly in 1894 [63]. The embryological mechanism is not clear. HL could result from the non-separation of the splanchnic mesodermal mass [64].

The HL is a rare congenital anomaly in which the right and left lungs are fused due to the formation of a narrow isthmus of lung parenchyma tissue between the heart and aorta, without an intervening pleural fissure [9,62,64,65]. The right and left pleural cavities communicate through a mediastinal tunnel between the heart anteriorly and the aorta and esophagus posteriorly, thus creating a passage for the parenchymatous pulmonary connection. The pulmonary tissue extending from one side to the other through the pleural tunnel in some cases may be in direct contact with the other lung, but with an intervening pleural fissure because the herniated pulmonary tissue maintains its visceral pleural envelope.

A similar anomaly was described by Clements and Warner [65] and is called cross-over lung segment: in this form, the right lower pleural cavity extends behind the heart into the left hemithorax. Either in HL and

cross-over lung segment, the isthmus receives its arterial supply from the right pulmonary artery and its bronchial investment from the right bronchial tree. Vessels and bronchus supplying the isthmus cross the midline and are well described in angiography and CT. The multidetector-row CT and 128-slice dual-source CT scanner are nowadays the best tools able to describe exact anatomy and hopefully aid the elucidation of pathophysiology of HL (Figs. 10.12, 10.13, 10.14).

HL almost always involves unilateral lung hypoplasia and more frequently affects the right side. Bando and coworkers in their review refer about only 10 cases involving the left lung in the literature from 1974 to 2015 [64].

It was reported that 80% of cases of HL involving typical right lung hypoplasia also involved SS [61]. A majority of patients with HL and cross-over lungs are associated with SS, in its complete or incomplete expression. Kelly and coworkers published a most comprehensive review and found an association with SS in 33 of 48 cases of HL [66].

Congenital heart defects are present in 25% of the cases, the most common being the atrial septal defects. Other lesions include ventricular septal defects, tetralogy of Fallot, coarctation of the aorta, and univentricular heart [67].

It is also of interest that HL has been observed in patients with VATER or VACTERL syndromes and in patients with other bronchopulmonary foregut malformations [68,69].

The clinical symptoms may begin early with lung problems in young children, infants, and neonates. Respiratory

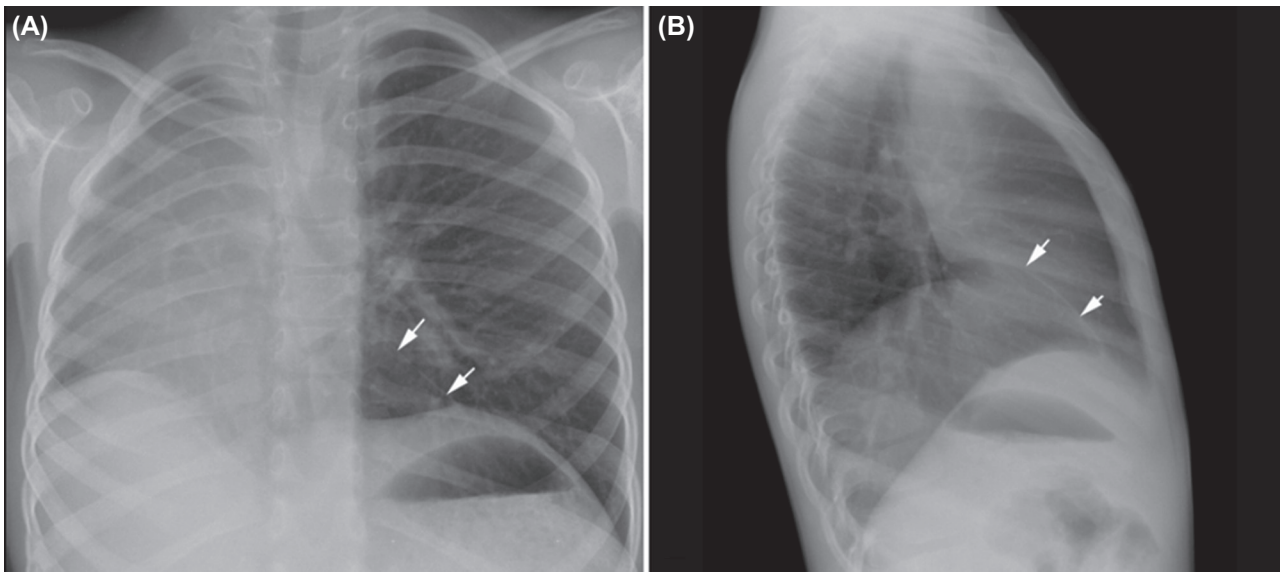


**Figure 10.12** Typical features of horseshoe lung at posterior-anterior (PA) and latero-lateral chest X-ray. (A) A triangular lucent area in the medial region of the basal left lung is seen on the PA imaging (*arrow*). (B) The previous triangular area is demarcated laterally either by a curvilinear or linear density (*arrow*).

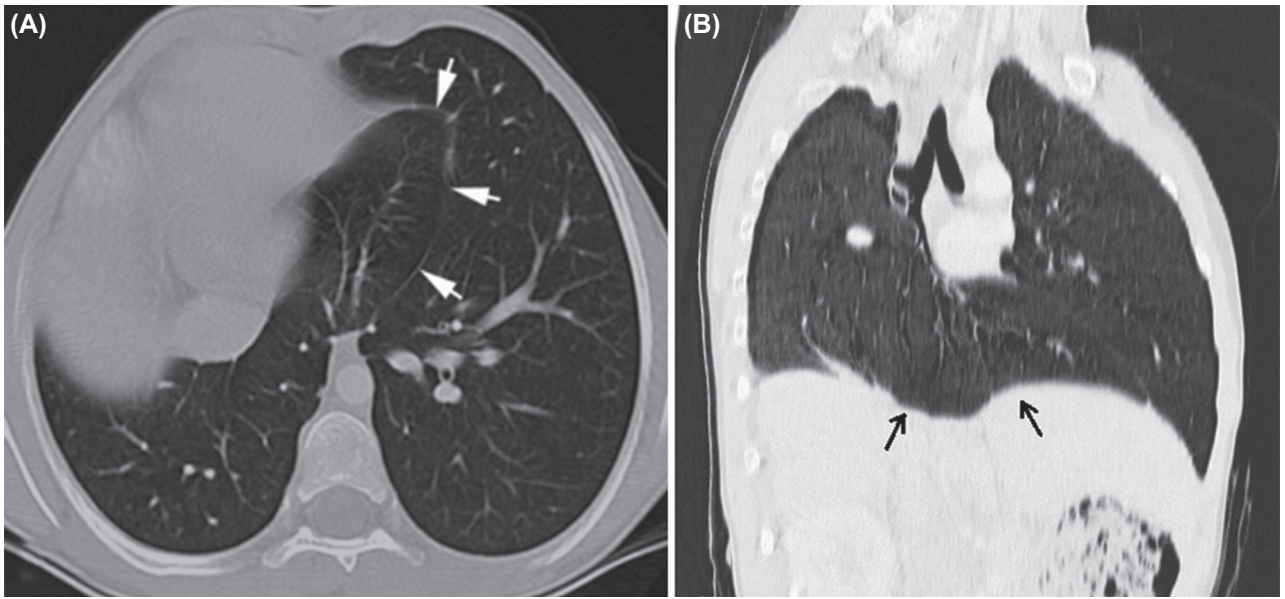


**Figure 10.13** Horseshoe lung on (A) axial and (B) coronal CT pictures where the connection between the right and left lung is clearly visible.

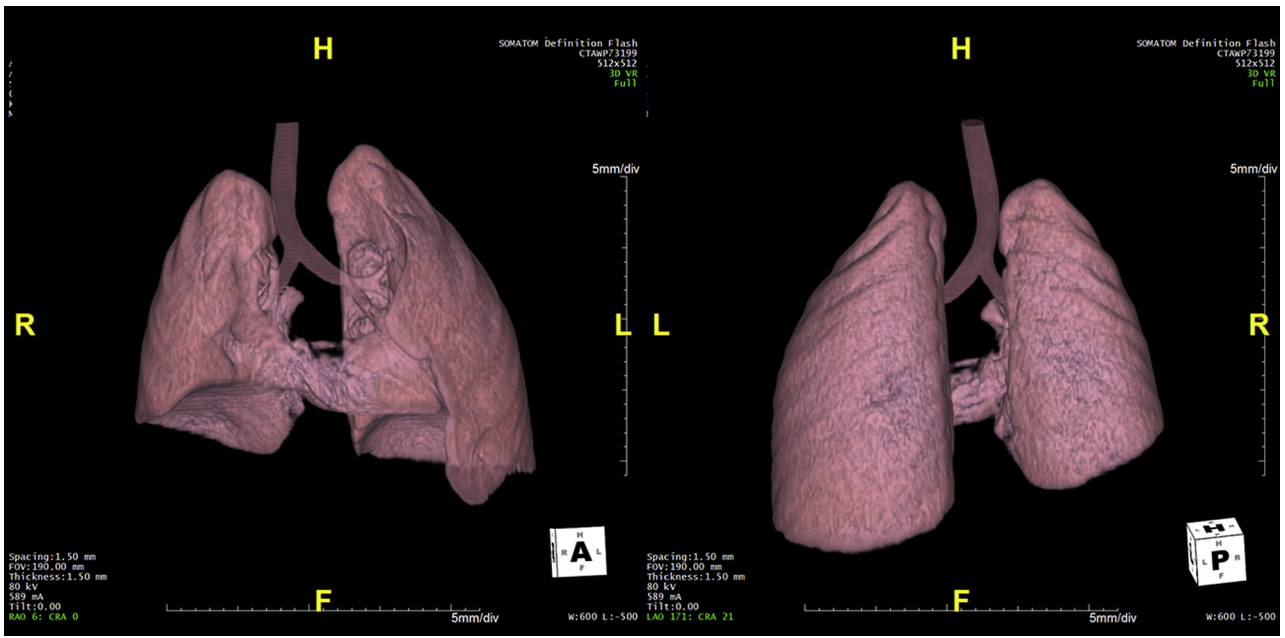


**Figure 10.14** Horseshoe lung on 3D CT reconstruction images.

distress, recurrent pneumonia, and episodes of cyanosis are the most common. Pulmonary hypertension is usually present when the left lung is involved and is related with poor outcome.

Symptoms, however, are unlikely related to the anomaly, but rather to the associated cardiac malformations. Their presence has a significant impact on the prognosis of HL and makes any decision difficult regarding the more appropriate treatment. The indications for surgery include recurrent infections, severe left-to-right shunt in the presence of progressive pulmonary hypertension, and cardiovascular malformations. The lung fusion may make some forms of therapy more difficult (i.e., lobectomy).

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