# 2 Embryological Background of Congenital Vascular Malformations

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## Introduction

The study of the embryological development of the circulatory system began in earnest during the nineteenth century. Early pioneer researchers in this field used intravascular injection of various dye solutions of India ink, silver nitrate, and Prussian blue for demonstration of minute vessels [1, 2]. The injected tissues were fixed and histological investigation was conducted. The researchers' extensive and careful observations enabled them to map the development of the vascular and lymphatic systems in both humans and other mammals.

During the development of the arterial system, construction of aortic arch goes through the most complicated process and is thus recognized as the key to most congenital vascular malformations. The aortic arch originates from symmetrical brachial arches. After tremendous alteration, involving systemic and segmental fusion and separation, the brachial arches transform into the aortic arch. Rathke's diagram is useful and provides a general idea of which components persist and which degenerate to enable transformation into the matured structure [3].

In the development of the venous system, formation of paired anterior and posterior cardinal veins is a significant event. The paired veins take on the important roles of blood drainage in this early developmental stage, but most of their parts degenerate after completion of their roles. Formation of the inferior vena cava is a complex process. Chronological diagrams by McClure and Butler demonstrate precisely how the primitive venous system transforms into the inferior vena cava [4]. Following a sequential, elaborate process, any misplaced degenerations trigger rerouting of blood drainage to the heart and cause persistence of the primary veins.

Sabin used swine embryos and Lewis used rabbit embryos to investigate the development of the lymphatic system [5, 6]. They proposed that the lymphatic system originates from several sites on the primary vein and sprouts centrifugally. In contrast, Huntington and McClure proposed that lymphatic vessels arise in the mesenchymal tissue, independently from the primary veins, growing centripetally, and then subsequently connecting to the venous system [7]. A recent study using molecular markers suggests that in fact both centripetal and centrifugal growths appear to contribute to the development of the lymphatic system [8].

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Y.-W. Kim et al. (eds.), *Congenital Vascular Malformations*, DOI 10.1007/978-3-662-46709-1_2

Maldevelopment of the lymphatic system causes dysfunction of interstitial fluid drainage, namely, heredity or primary lymphedema.

## Development of the Blood Vascular System

The blood vascular system develops in two distinct, consecutive phases: (1) vasculogenesis, the de novo differentiation of blood vessels from mesoderm-derived precursor cells, and (2) angiogenesis, the remodeling of these vessels to form arteries and veins [9].

Vasculogenesis first occurs in the yolk sac. Structures called blood islands form as hemangioblasts differentiate into endothelial and red blood cells. The endothelial cells migrate from the blood islands and form a random vascular network called the capillary plexus. Meanwhile, the dorsal aorta forms inside the embryo; eventually, it connects the heart to the capillary plexus of the yolk sac thus completing the circulation loop.

In human embryos, angiogenesis begins at day 21 of embryogenesis, when the heart begins to beat and blood starts circulating in the capillary plexus. Biomechanical and hemodynamic input induces active vascular remodeling. The capillary plexus is remodeled into a functional structure that includes large-caliber vessels for low-resistance rapid flow and small-caliber capillaries for diffusional flow. This remodeling occurs by the regression, sprouting, splitting, or fusion of preexisting vessels. Endothelial cells in the capillary plexus start differentiating into cells with arterial and venous identities.

Biomechanical factors and fluid dynamics have long been recognized as important regulators of angiogenesis. Thoma, a pioneer angiogenesis research, observed that within embryos, increases in local blood flow cause vessel diameters to enlarge, whereas decreases in local blood flow cause vessel diameters to shrink [10]. Chapman studied the angiogenesis of chicken embryos in which he removed the hearts and observed that the initial vessel patterns laid down during vasculogenesis remained undisturbed. He hypothesized that subsequent angiogenesis occurred by mechanical forces [11]. Murray proposed that vessel caliber is proportional to the amount of shear stress at the vessel wall [12].

## Development of the Arterial System

After the heart starts circulating blood through the primitive vascular network, two aortas form at the dorsal region. Fusion starts in the middle section and then extends cranially and caudally; thus the single dorsal aorta develops (Fig. 2.1) [13, 14]. The dorsal aorta connects to the vitelline arteries in the mid portion and to the umbilical arteries in the caudal portion. In the cranial portion of the embryo, five pairs of aortic arches form sequentially at both sides. They originate from the aortic sac and connect to the ipsilateral dorsal aorta.

The layout of the primitive aortic arches is transformed to the adult aortic arch from week 6–8 of development. The first asnd second aortic arches exist only for a short period of time and then regress (Fig. 2.2a). The vertebral arteries form on the lateral side of the dorsal arteries and the intersegmental arteries connect between them horizontally. After the first and second aortic arches disappear, the segment of the dorsal aorta between the third

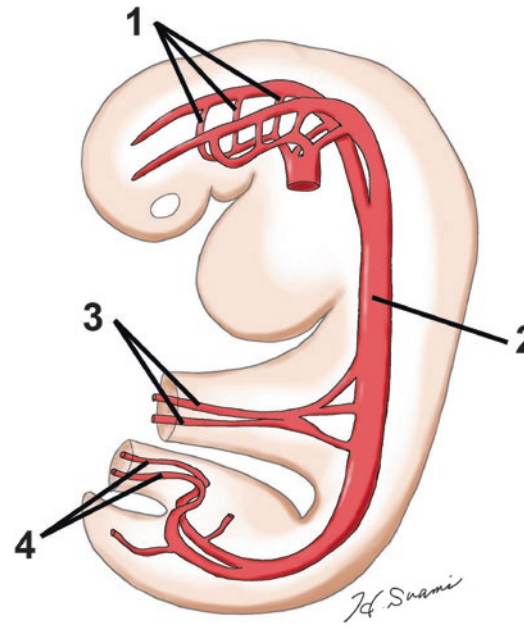


**Fig. 2.1** Embryonic arteries at the fourth week of gestation (*1* aortic arches, *2* dorsal aorta, *3* vitelline arteries, and *4* umbilical arteries)

and fourth aortic arches regresses on both sides (Fig. 2.2b). The sixth pair of aortic arches forms from the aortic sac, and they give branches to the lung (Fig. 2.2c). A segment of only the right dorsal artery involutes between the bifurcation and the right seventh intersegmental artery. The pair of seventh intersegmental arteries elongates laterally; however other pairs of intersegmental arteries regress because of maturation of the vertebral arteries. The intermammary arteries derive from the seventh intersegmental arteries and extend caudally. The next involution occurs at the segment of the right sixth aortic arch between the right dorsal artery and pulmonary branch (Fig. 2.2d). The same segment of the left sixth aortic arch persists as the ductus arteriosus until the time of birth. The pulmonary trunk is separated from the aortic sac and with the sixth aortic arches. The seventh intersegmental arteries move cranially and elongate to limb buds to start supplying blood to the upper limbs.

In summary, the first and second aortic arches regress completely. The third aortic arches form a

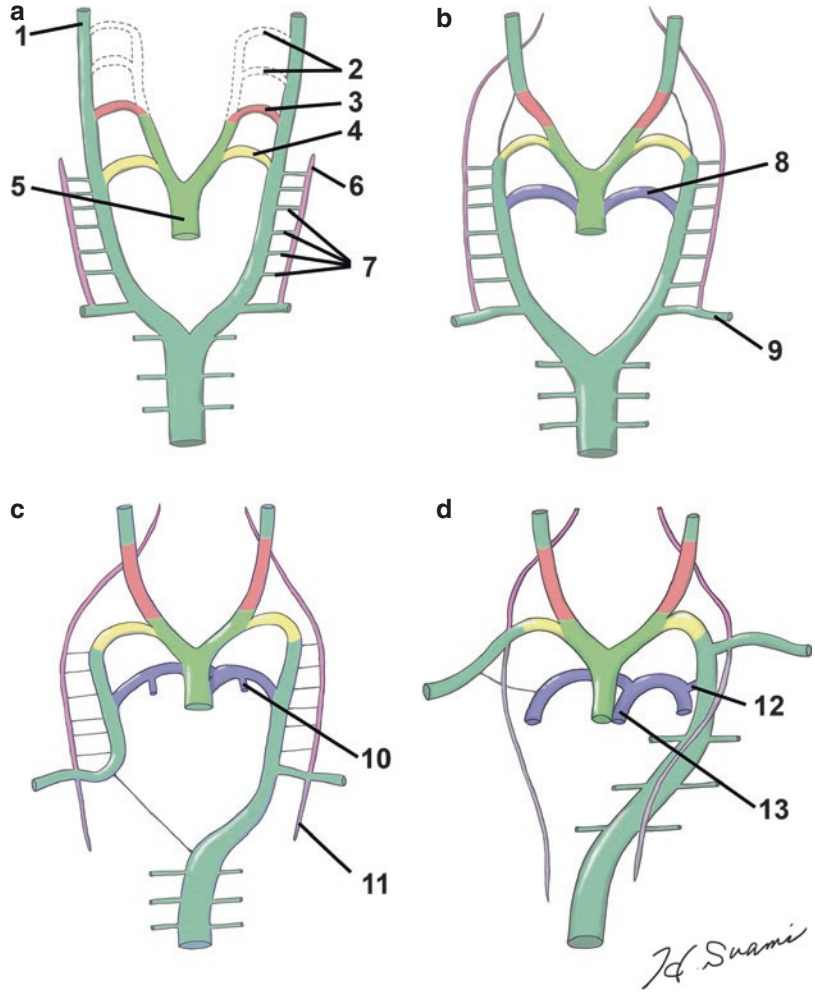


**Fig. 2.2** Embryological development of the arterial system from the sixth to eighth week of gestation. (**a**) The first and second aortic arches exist only for a short period of time (*1* dorsal aorta, *2* the first and second aortic arches, *3* the third aortic arch, *4* the fourth aortic arch, *5* aortic sac, *6* vertebral artery, and *7* intersegmental arteries). (**b**) The sixth aortic arch forms from the aortic sac (*8* the sixth aortic arch and *9* the seventh intersegmental artery). (**c**) A segment of the right dorsal artery involutes between the bifurcation and the right seventh intersegmental artery (*10* pulmonary artery and *11* internal mammary artery). (**d**) A segment of the right sixth aortic arch involutes between the right dorsal artery and pulmonary brunch (*12* ductus arteriosus and *13* pulmonary trunk)

part of the carotid arteries. The fourth aortic arches form a part of the aortic arch and a part of the right subclavicular artery. The sixth aortic arches form the pulmonary arteries and the ductus arteriosus. The seventh intersegmental arteries form the subclavicular arteries.

## Anomalous Development of the Aortic Arch

Due to the complex nature of the evolution and involution that occurs during the development of the major arteries, and the fact that multiple processes must occur correctly, anomalous conditions of the aortic arch can occur. For example, a patent ductus arteriosus is one of the most common abnormalities, occurring in around 8 out of 10,000 births [14]. Coarctation of the aorta is another one of the more commonly occurring at around 3.2 out of 10,000 births [14]. This abnormality is classified into two types: pre-ductal and post-ductal corresponding to the anatomic position of the lesion with the ductal arteriosus.

Abnormal involution and persistence of primitive arteries cause several other malformations. "Abnormal origin of the right subclavicular artery" occurs when the right fourth aortic arch and a part of the right dorsal artery cranial to the seventh intersegmental artery involute and the right dorsal artery caudal to the seventh intersegmental artery persists. "Double aortic arch" occurs when all parts of the right dorsal artery persist. "Interrupted aortic arch" occurs when both fourth aortic arches involute and the right dorsal artery caudal to the seventh intersegmental artery persists. Thus, knowledge of abnormal involution and persistence during the early stages of embryological development helps our understanding of the pathogenesis of congenital arterial malformations.

## Development of the Venous System

The primitive vascular structure in capillary and reticular plexuses in the early embryonic stage soon develops distinguishable arteries and veins. The part of the body distal to the developing heart drains through paired anterior cardinal veins, whereas the caudal portion of the body drains through paired posterior cardinal veins (Fig. 2.3) [15].

In the fifth week, paired anterior cardinal veins and posterior cardinal veins form, and they are the first embryonic veins to drain the cerebral and caudal portion of the body, respectively. Soon, subcardinal veins sprout from the posterior cardinal veins (Fig. 2.4a) [4]. The following alterations occur over the fifth to seventh week. Paired supracardinal veins form from the posterior cardinal veins. The sub- and supracardinal veins anastomose on both sides to form the "subsupracardinal anastomoses" (Fig. 2.4b). The posterior cardinal veins regress because now subcardinal and supracardinal veins supersede them (Fig. 2.4c). Longitudinal segments of left subcardinal vein cranial to the subcardinal anastomosis also regress. Paired anterior cardinal veins form a new anastomosis to let the blood drain from the left anterior cardinal vein into the right anterior cardi-

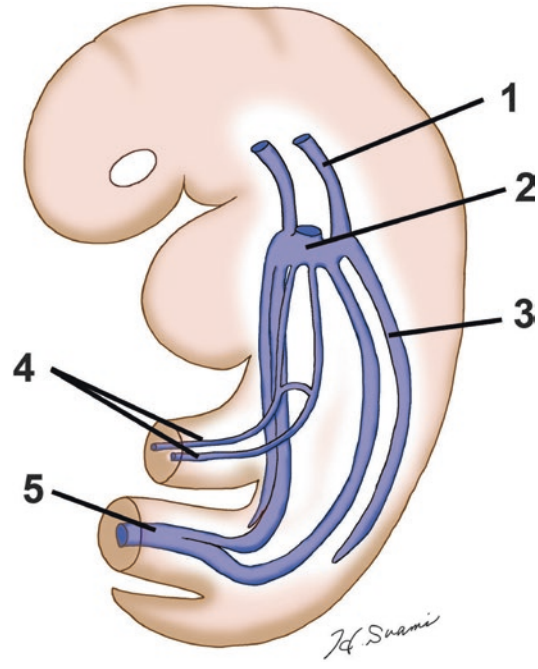


**Fig. 2.3** Embryonic veins at the fourth week of gestation (*1* anterior cardinal vein, *2* sinus venosus, *3* posterior cardinal vein, *4* vitelline veins, and *5* umbilical vein)

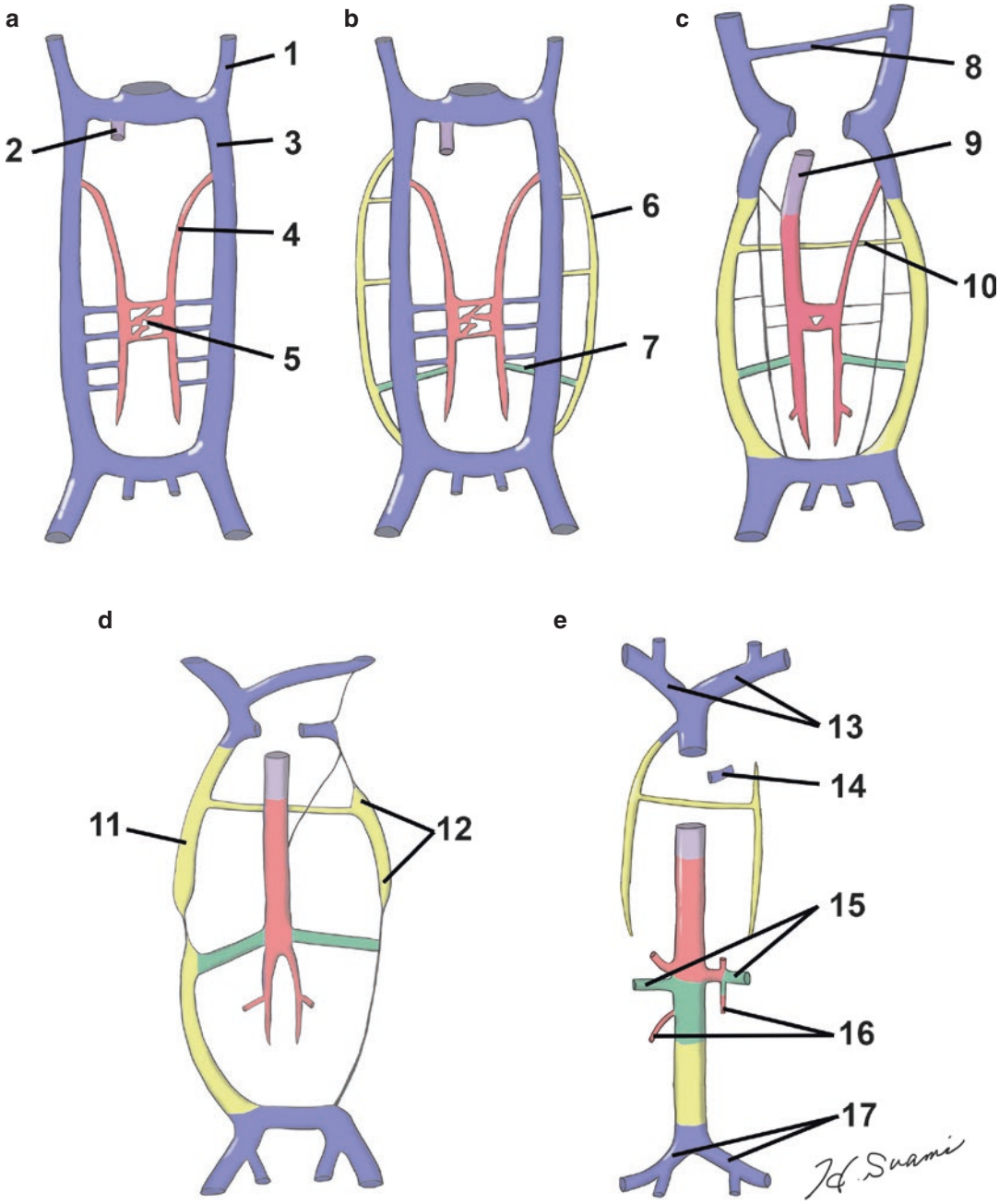


**Fig. 2.4** Embryological development of the venous system from the fifth to seventh week of gestation. (**a**) The subcardinal veins form from the posterior cardinal veins (*1* anterior cardinal vein, *2* right vitelline vein, *3* posterior cardinal vein, *4* subcardinal vein, and *5* subcardinal anastomosis). (**b**) Paired supracardinal veins form from the posterior cardinal veins (*6* supracardinal vein and *7* subsupracardinal anastomosis). (**c**) The posterior cardinal veins regress. New anastomoses form between the anterior cardinal veins and between the posterior cardinal veins (*8* anastomosis between the anterior cardinal veins, *9* hepatic vein, and *10* anastomosis between the posterior cardinal veins). (**d**) Cranial part of the supracardinal veins remains as azygos, hemiazygos, and accessory hemiazygos veins (*11* azygos vein and *12* hemiazygos and accessory hemiazygos veins). (**e**) A right-sided inferior vena cava forms (*13* brachiocephalic veins, *14* coronary sinus, *15* renal veins, *16* spermatic or ovarian veins, and *17* common iliac veins)

nal vein via the newly formed "brachiocephalic vein." A new anastomosis forms between supracardinal veins. The right supracardinal vein remains as the "azygos vein" together with the cranial part of the right posterior cardinal veins forms the "arch of azygos vein," while the left supracardinal vein becomes the "hemiazygos vein" and also the "accessory azygos vein" (Fig. 2.4d). Most of the veins on the left side regress, resulting in a right-sided "inferior vena cava" (IVC), to meet the new conditions to be faced upon birth (Fig. 2.4e). The portion of the left anterior cardinal vein caudal to the brachicephalic anastomosis regresses, and it transforms into the "oblique vein" of the left atrium (vein of Marshall) on the back of the left atrium and the "coronary sinus." The right anterior cardinal vein forms the superior vena cava (SVC) [16].

## Anomalous Development of the Superior and Inferior Vena Cava

Due to the complex evolutional process to form the SVC, from various segments of three different embryonic/cardinal veins, there is a high risk of defective development of the SVC. In addition, there are various conditions of the stenosis or dilatation and/or aneurysm formation, either with or without internal defect. "Double superior vena cava" is the outcome of the persistence of the left caudal anterior cardinal vein [17]. It is due to the failed degeneration and/or involution of the left anterior cardinal vein proximal to brachiocephalic anastomosis. Left SVC is the outcome that results from persistence of the entire left cardinal vein. In the absence of the right proximal superior vena cava, the blood from the right upper body drains to the "left SVC" via right brachiocephalic vein.

There is a high risk of developmental anomalies arising as a result of errors of the IVC developmental process. "Absence of the suprarenal inferior vena cava" (IVC) may arise as a result of the complexity of fusion process of multiple blocks of three different cardinal veins, which needs to occur to meet the new conditions following birth [18]. It occurs when the right subcardinal vein fails to make a connection with the liver. The IVC drains into the arch of the azygos and the hepatic veins drain independently to the right atrium. "Double inferior vena cava" occurs when iliac anastomosis of the postcardinal vein regresses or shrinks and the left subcardinal vein, caudal to anastomosis of the subcardinal veins, persists to maintain drainage from the left iliac veins [19].

## Development of the Lymphatic System

Development of the human lymphatic system begins in the sixth or seventh week of embryogenesis following development of the primitive vascular system. First, paired jugular lymph sacs, which originate from the anterior cardinal veins, develop near the junction of the subclavicular and internal jugular veins [5, 6]; lymphatic capillaries and vessels sprout centrifugally toward the head and neck, upper extremities, and upper torso. Each jugular sac maintains connection to the subclavicular vein. Secondary to this, the retroperitoneal lymph sac derives from the mesonephric veins and lies in the root of the mesentery. The sac forms visceral lymphatic vessels including the thoracic duct. The retroperitoneal sac joins the cisterna chili and they drain into the thoracic duct. Initially, two thoracic ducts form connecting the jugular sacs and the cisterna chili. Anastomoses form between them. The single thoracic duct develops from the cranial left thoracic duct, the anastomosis, and the right distal thoracic duct. Lastly, paired posterior lymph sacs develop near the junctions of the primitive iliac veins and posterior cardinal veins. The lymphatic vessels from these sacs spread toward the lower torso and lower extremities (Fig. 2.5).

## Anomalous Development of the Lymphatic System

Lymphatic malformations often manifest clinically as congenital or heredity lymphedema resulting from insufficient development of the

lymphatic system during the late stages of embryological development. Lymphatic congenital defects present in various forms, including hypoplastic, hyperplastic, or aplastic lesions of the lymphatic vessels and/or lymph nodes. Such lesions are associated with malfunctions of the lymphatic system.

Truncular lymphatic malformations do not always result in an evident morphological defect of the lymphatic system, however. For example, patients with "Milroy-Meige syndrome," or inherited primary lymphedema, which occurs right after birth, do not have any apparent structural defects of the lymphatic system but rather have functional impairment at the capillary lymphatic or initial lymphatic level [20]. In addition, patients with "lymphedema-distichiasis syndrome" have impairment of the endoluminal valves, which causes lymphatic reflux. The syndrome is associated with other clinical symptoms including cardiac malformations, cleft palate, ptosis, double eyelashes, and yellow nails.

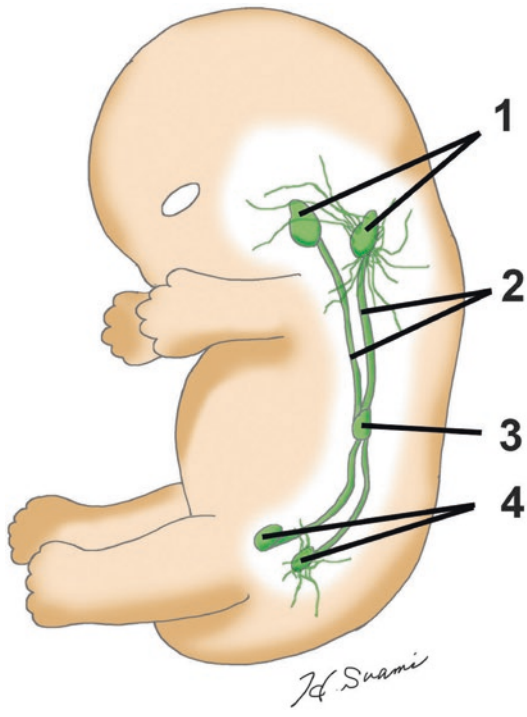


**Fig. 2.5** Embryonic lymphatics at the seventh week of gestation (*1* jugular lymph sacs, *2* thoracic ducts, *3* retroperitoneal lymph sac, and *4* posterior lymph sacs)

## Summary

Embryological development of the vascular system is an intricate sequential process involving evolution, involution, generation, and degeneration. Anomalous involution often triggers formation of abnormal circulation that then requires and promotes persistence of the primitive vascular structure. Congenital vascular malformations demonstrate a wide variety of clinical manifestations in terms of not only their pathological presentation but also their response to therapy. Understanding the embryological background of these lesions, which also relates to their clinical prognoses, is fundamental to comprehending dynamic circulatory alterations following treatment.

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