Embryology

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Morphogenesis of the Cardiovascular System

The heart is the first organ that is formed and becomes functional in the human embryo [1, 2]. It bears the circulatory system from the early embryonic period and alters its morphology to each stage of an embryonic growth according to its demand. The early morphogenesis of the heart and great vessels is conserved across species of living things. In the mammals, the complicated process of morphogenesis results in the separable systemic and pulmonary circulation after birth by which oxygen is efficiently supplied to different internal organs in order to maintain their function.

The morphogenesis of the cardiovascular system is started around 3 weeks of gestation and mostly completed by 8 weeks of gestation in human. First, immediately after gastrulation, the cardiac-fated cells of anterior lateral plate mesoderm origin form a crescent-shaped cardiac precursor in front of a notochord (Fig. 2.1a). The cardiac crescent constructs bilateral endocardial tubes that fuse to form the primitive heart tube in the midline of embryo (Fig. 2.1b). The primitive heart tube is a beating tubular structure that maintains blood flow from caudal to rostral direction of the embryo. Along with rightward looping of the primitive heart tube, the right and left ventricles and atria become morphologically apparent (Fig. 2.1c). Endocardial cushions are formed in extracellular matrix (also known as cardiac jelly) of the atrioventricular canal region from the mesenchymal cells which were separated from the endocardium and transformed. An atrioventricular canal is divided by the coalescence of the superior and inferior endocardial cushions. Endocardial cushions also participate in the formation of interatrial septum (closing of ostium primum), atrioventricular valves (mitral and tricuspid valve), and the membranous portion of the interventricular septum. Formation of interatrial septum, interventricular septum, and atrioventricular valves results in the 2-atrium and 2-ventricle heart (Fig. 2.1d).

In the cardiac outflow tract, the conotruncal swellings or cushions form the conotruncal septum that divides a tubular structure into two great vessels, namely, the aorta and the pulmonary trunk, in a spiral fashion (Fig. 2.1e). At the bases of great vessels, semilunar valves are formed. A proper connection of the left ventricle to the aorta and the right ventricle to the pulmonary trunk is indispensable for establishment and separation of the systemic and pulmonary circulation after birth.

The great vessel system arises from six pairs of pharyngeal arch arteries which run through pharyngeal arches symmetrically (Fig. 2.1f).

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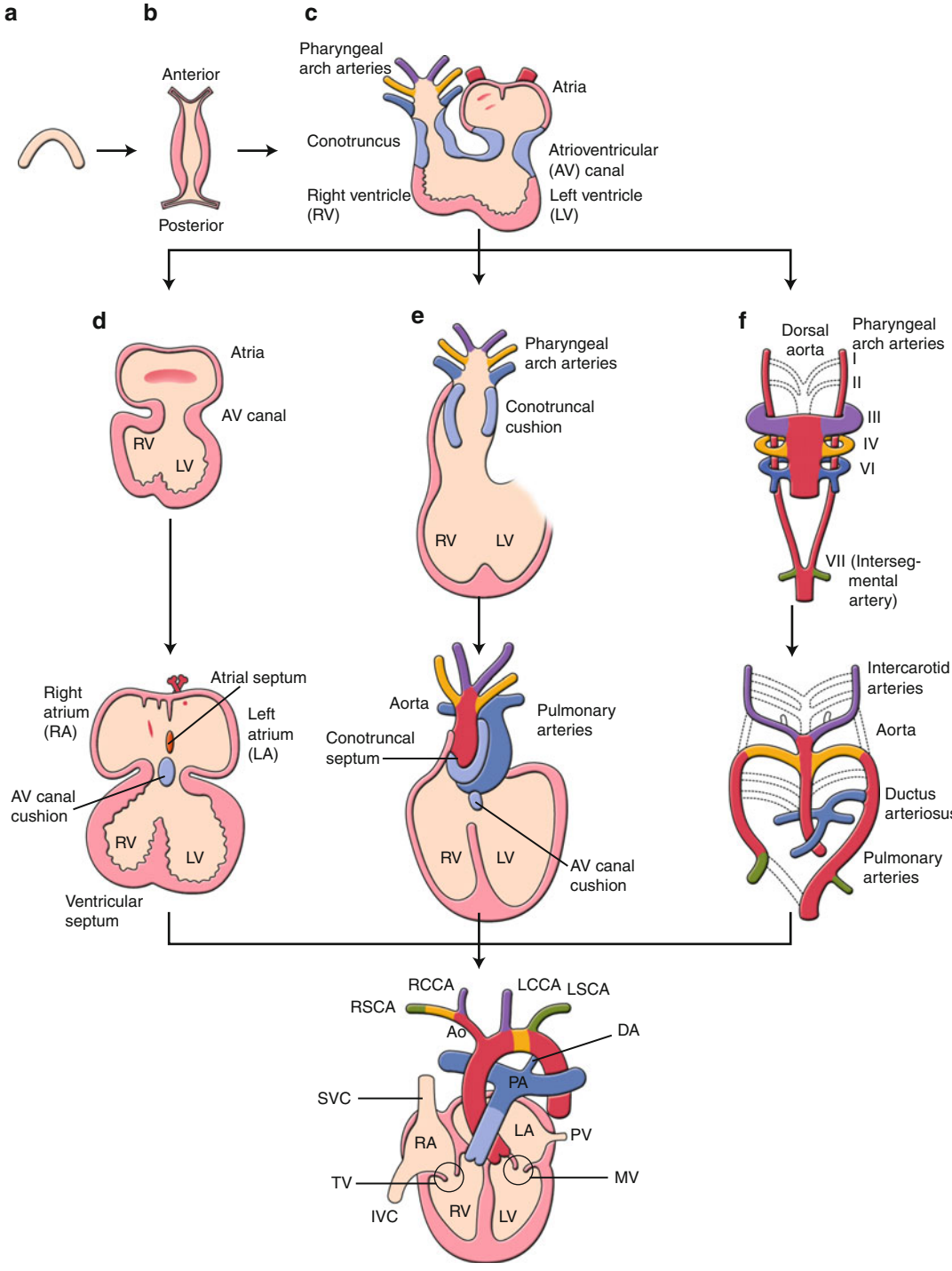

Fig. 2.1 Morphogenesis of the cardiovascular system. (**a**) Cardiac crescent. (**b**) Primitive heart tube. (**c**) Looping. (**d**) Atrioventricle. (**e**) Outflow tract. (**f**) Great vessels. See detail in text. *Ao* aorta, *DA* ductus arteriosus, *IVC* inferior vena cava, *LCCA* left common carotid artery, *LSCA* left subclavian artery, *MV* mitral valve, *PA* pulmonary arteries, *PV* pulmonary veins, *RCCA* right common carotid artery, *RSCA* right subclavian artery, *SVC* superior vena cava, *TV* tricuspid valve

The third, fourth, and sixth pharyngeal arch arteries will remodel and transform to a portion of the aortic arch, arch branches, ductus arteriosus, and a part of branch pulmonary arteries.

Developmental Origins of the Heart

Decades of descriptive embryology, including cell lineage tracings have improved our understandings of developmental origins [1–5]. Cells derived from the anterior lateral plate mesoderm form a crescent shape at approximately 2 weeks of gestation, and by 3 weeks of gestation, these cells coalesce along the ventral midline to form a primitive heart tube, consisting of an interior layer of endocardial cells and an exterior layer of myocardial cells, separated by extracellular matrix, or cardiac jelly, for reciprocal signaling between the two layers. The crescent-shaped pool of cardiogenic progenitor cells is now termed "first heart field" (Fig. 2.2a). The first heart field that forms the heart tube eventually contributes to specific chambers of the future heart, exclusively to the left ventricle and all other parts of the heart, except the cardiac outflow tract.

In addition to the first heart field, it was reported 10 years ago that there was a second source of myocardial cells. In mammalian embryos, this source is lying medially to the cardiac crescent (Fig. 2.2a) and then behind the forming heart tube (Fig. 2.2b), extending into the mesodermal layer of the pharyngeal arches (Fig. 2.2c). This second source is termed "second heart field." The heart tube derived from the first heart field may predominantly provide a scaffold upon which cells from the second heart field migrate into both arterial and venous poles of the heart tube, where they subsequently construct the requisite cardiac components. The contribution of the second heart field to both myocardium and smooth muscle of the arterial pole has been well studied. When the heart tube forms, the second heart field cells migrate into the midline and position themselves dorsal to the heart tube in the pharyngeal mesoderm (Fig. 2.2b). Upon rightward looping of the heart tube, the second heart field cells cross the pharyngeal mesoderm into the anterior and posterior portions, populating a large portion of the outflow tract including future right ventricle and atria (Fig. 2.2c). The addition of the second heart field-derived myocardium to the outflow tract results in its elongation. This elongation is necessary to allow the outflow tract to rotate and shorten sufficiently for correct alignment of the pulmonary and aortic trunks with their respective ventricles.

The third lineage represents cardiac neural crest cells originating from the dorsal neural tube between the mid-otic placode and the caudal boundary of the third somite. After they delaminate from the dorsal neural tube, cardiac neural crest cells migrate into the caudal pharyngeal arches, and the outflow tract where they contribute to the conotruncal cushions that give rise to the outflow tract septum (Fig. 2.2c, d). Migration of the cardiac neural crest cells is also targeted to

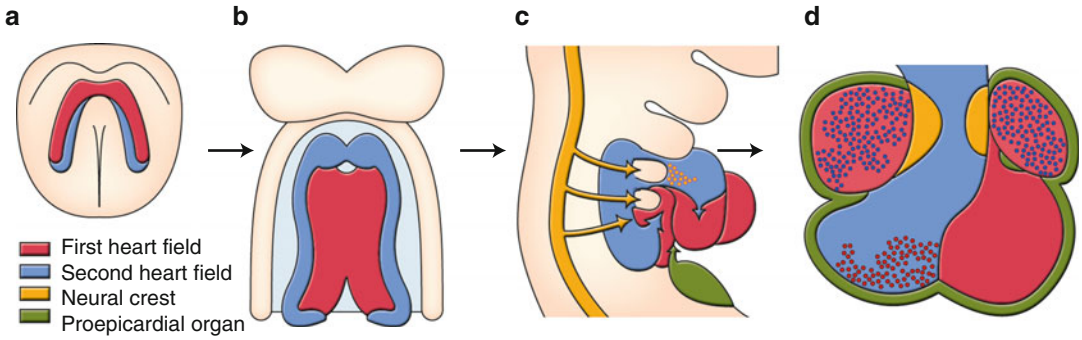

Fig. 2.2 Developmental origins of the heart. (**a**) Cardiac crescent. (**b**) Primitive heart tube. (**c**) Looping heart tube. (**d**) Four chambered heart. See detail in text

pharyngeal arches 3, 4, and 6 which give rise to the future great vessels (Fig. 2.2c). Many signaling pathways are involved in the migration and condensation of cardiac neural crest cells, including reciprocal signaling between the cardiac neural crest cells and the second heart field, which are essential for the development of the outflow tract and the aortic arch system.

The fourth lineage of cardiac precursor cells is the proepicardium. The proepicardium develops from the coelomic mesothelium which overlays the liver bud, and the expression of proepicardium-specific genes is induced in naïve mesothelial cells in response to a localized liver-derived signal. Almost all cells of the epicardium and the coronary vessels arise from the proepicardium, which develops as multiple epithelial villi protruding from the pericardial mesothelium immediately posterior to sinoatrium of the looping stage embryonic heart. The proepicardium extends toward the primitive heart and attaches and spreads over the myocardial surface to form the epicardium (Fig. 2.2c, d). During proepicardium growth and epicardial formation, some proepicardial/epicardial cells undergo an epithelial–mesenchymal transformation (EMT) and give rise to the precursors of the coronary vessels and connective tissue cells.

Embryology of the Heart and Congenital Heart Diseases

Congenital heart diseases are considered to occur as a result of the abnormalities of each step in the morphogenesis of the heart and the great vessels. Current embryological concepts for the genesis of congenital heart diseases are discussed below although not all are proved.

Normal and Abnormal Looping of the Heart [6, 7]

The normal left–right development results in situs solitus with all the asymmetric internal organs placed on the body where they should be, and the looping of the primitive heart tube happens to a rightward convex direction (Fig. 2.3b: dextro-loop; d-loop). When left–right specification does not process normally, the direction of looping will be altered and a range of visceroatrial heterotaxia occurs that is usually associated with complex congenital heart diseases. In case of complete mirror-image reversal of all organs, the looping becomes a leftward convex direction (Fig. 2.3a: levo-loop; l-loop), resulting in a benign dextrocardia without significant cardiac malformations and untoward clinical consequences.

Corrected Transposition of Great Arteries (l-TGA)[8]

This phenotype occurs when the primitive heart tube becomes l-loop; at the same time, an arterial trunk is linearly divided into an anteriorly located left-sided aorta and a posteriorly located right-sided pulmonary arterial trunk (Fig. 2.3c). As a result, there is atrioventricular discordance and ventriculoarterial discordance where the right atrium is connected to the left ventricle contiguous to the pulmonary artery and the left atrium is connected to the right ventricle contiguous to the aorta.

Abnormality of Rightward Shift of the Atrioventricular Canal (Inflow Tract): Tricuspid Atresia (TA) [6, 9, 10]

Around 4 weeks of gestation, the heart looping results in a series circulation from the right atrium, to the left atrium, the left ventricle, and the right ventricle that resembles a hemodynamics of tricuspid atresia (Fig. 2.4). Soon later, the atrioventricular canal shifts rightward and the final relation of the right atrium to the right ventricle and the left atrium to the left ventricle is established, resulting in a parallel circulation (Fig. 2.4 lower). The tricuspid atresia is considered to result from an obstacle of the rightward shift of the atrioventricular canal that leads to complete absence of the tricuspid valve with no direct communication between the right atrium

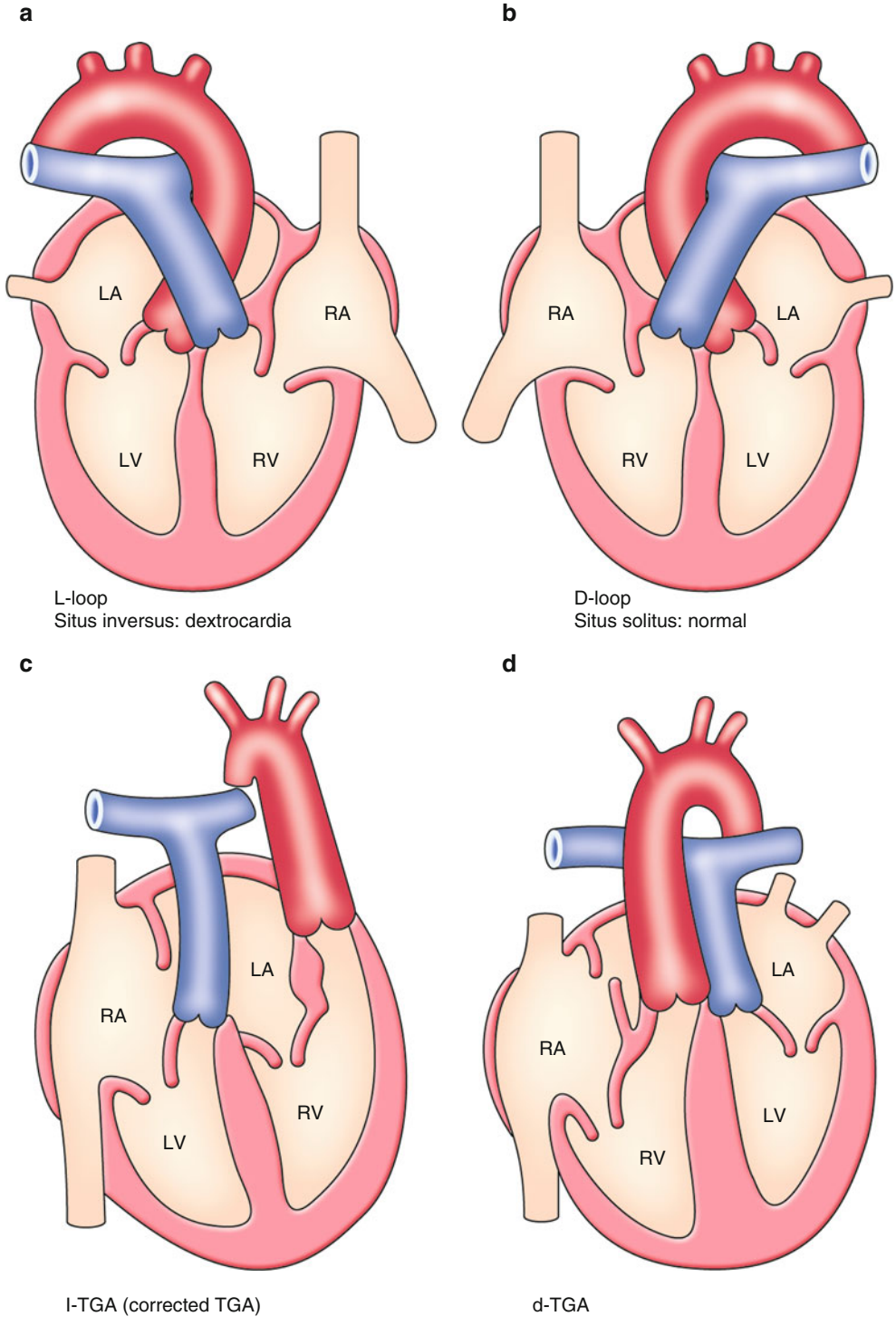

Fig. 2.3 Normal and abnormal looping of the heart. (**a**) Leftward looping. (**b**) Rightward looping. (**c**) L-loop + transposition. (**d**) D-loop + transposition. See detail in text

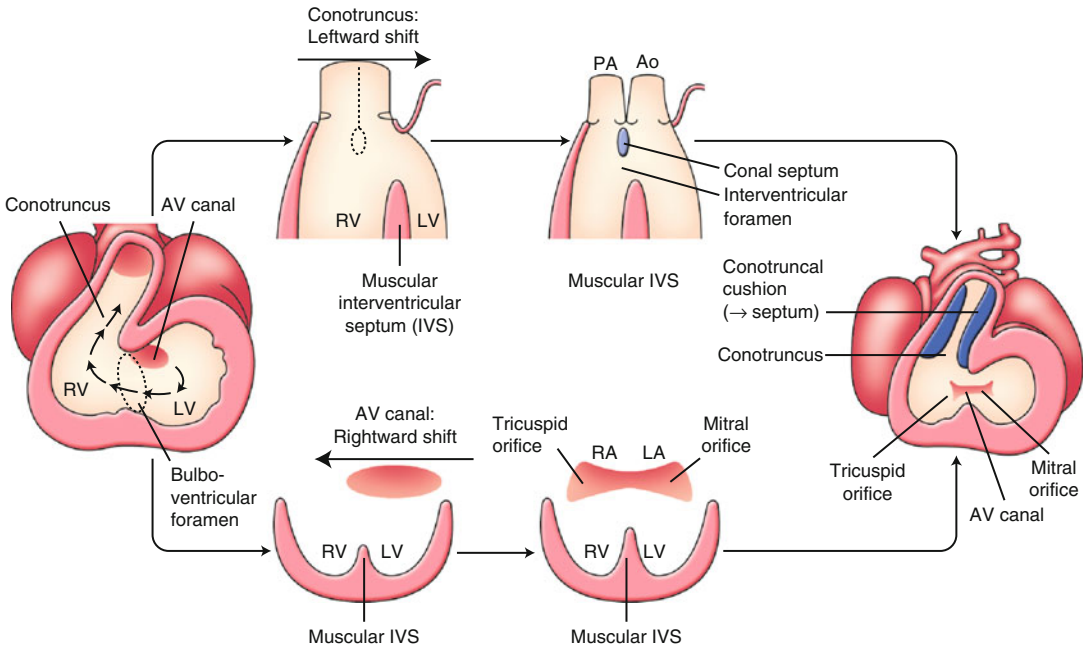

Fig. 2.4 Early development of the inflow tract and the outflow tract. See detail in text. *AV* atrioventricular, *Ao* aorta, *IVS* interventricular septum, *LA* left atrium, *LV* left ventricle, *PA* pulmonary artery, *RA* right atrium, *RV* right ventricle

and the right ventricle. The atretic tricuspid valve is represented by a dimple in the floor of the right atrium. The resulting membrane is usually muscular, but may be fibrous.

Abnormality of Leftward Shift of the Conotruncus (Outflow Tract): Double Outlet Right Ventricle (DORV) [11–13]

Around 4 weeks of gestation, in a process of the looping, the conotruncus shifts leftward, and the relation of the left ventricle to the aorta and the right ventricle to the pulmonary trunk will be established (Fig. 2.4 upper). DORV, in which both great vessels arise from the right ventricle, is presumed to result from an obstacle to leftward shift of the conotruncus. DORV is also implicated in abnormalities of conotruncal rotation, conus formation, and septal formation. It seems reasonable to accept these abnormalities as a spectrum representing a relatively primitive embryologic condition with the origin of both great arteries from the morphologic right ventricle (Fig. 2.5b). The subaortic conus is normally absorbed during the leftward shift of the conotruncus, and fibrous continuation between mitral and aortic valves can be observed. In DORV, bilateral subarterial conus and discontinuity of both semilunar valves with their respective atrioventricular valve are common.

Normal and Abnormal Septation and Alignment of the Outflow Tract [1, 2, 11–14]

The embryonic outflow tract (conotruncus) consists of a distal part, the truncus, and a proximal part or the conus. At 4–5 weeks of gestation, two big swellings in the truncal region (right superior and left inferior truncal cushions) and two small swellings in the conal region (right dorsal and left ventral conal cushions) develop in the outflow tract (Fig. 2.5a). The coalescence of these four cushions is carried out in a spiral fashion that accounts for the adult gross anatomical relationship between the aorta (to the left ventricle) and the pulmonary arterial trunk (to the right ventricle) (Fig. 2.5a).

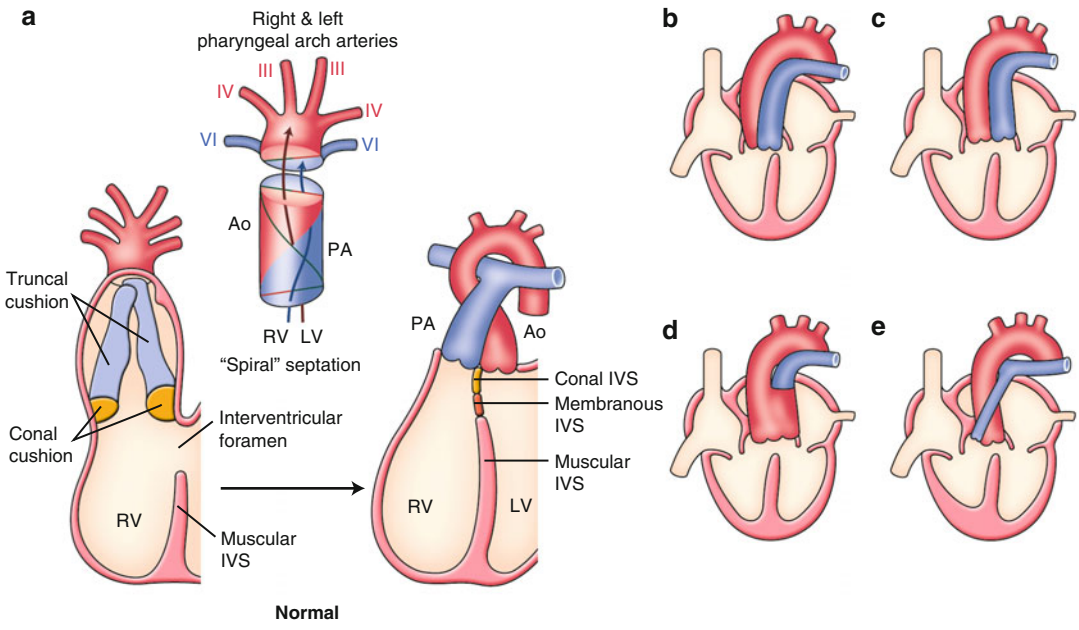

Fig. 2.5 (**a**) Normal and (**b–e**) abnormal septation and alignment of the outflow tract. (**b**) Double outlet right ventricle (DORV). (**c**) Transposition of the great arteries (TGA). (**d**) Persistent truncus arteriosus (PTA). (**e**) Tetralogy of Fallot (TOF). See detail in text. *Ao* aorta, *IVS* interventricular septum, *LV* left ventricle, *PA* pulmonary artery, *RV* right ventricle

There are a variety of clinically important congenital heart diseases associated with abnormalities of the outflow tract. Although they are commonly explained by the developmental abnormalities of cardiac neural crest cells, recently, the involvement of the second heart field for outflow tract defects has been extensively investigated. 22q11.2 deletion syndrome is well known to be highly associated with outflow tract defects.

Transposition of the Great Arteries (TGA) [15]

TGA results from a failure of the outflow tract septation to develop in a spiral fashion, instead it develops in a parallel fashion (Figs. 2.3d and 2.5c). The detailed developmental aspects of the outflow tract septation in a parallel fashion remain largely uncertain. Abnormal development, growth, and absorption of subarterial conus are presumed to be a major factor. Although the normal conus is subpulmonary, left-sided, and anterior, there usually is a subaortic, right-sided, and anterior conus in patients with TGA.

Persistent Truncus Arteriosus (PTA) [1, 2, 12, 14, 16]

PTA results from incomplete formation of the conotruncal septum (Fig. 2.5d). The pathogenesis of PTA is suggested by a key experimental model in which ablation of the cardiac neural cells in chick lead to failure of partitioning of the embryonic truncus arteriosus and disrupted the conotruncal development by interfering with the addition of the myocardium derived from the second heart field. If vestiges of distal truncal septation develop, a short pulmonary arterial trunk can be formed from which the pulmonary arteries arise (Fig. 2.5d). A partial developmental failure of distal truncal septum may result in aorticopulmonary window (AP window). In contrast to PTA, in AP window, semilunar valves are completely divided by the conal septum.

Tetralogy of Fallot (TOF) [1, 2, 12, 14, 17]

TOF refers to the tetrad of overriding aorta, pulmonary stenosis, ventricular septal defect, and right ventricular hypertrophy (Fig. 2.5e). It results

from aortic overriding and subpulmonary stenosis created by the deviation of the conal septum, leading to a malalignment between the aorta and the left ventricle with a malalignment-type ventricular septal defect. The anatomic spectrum of TOF is diverse, including cases with pulmonary atresia and those with absent pulmonary valve.

Normal and Abnormal Growth of Ventricles and Alignment of Atrial and Ventricular Septum: Univentricular Heart [18, 19]

At 4 weeks of gestation, right and left ventricles grow and the muscular interventricular septum carries out normal alignment at interatrial septum by looping, and the normal four-chambered heart can be formed (Fig. 2.6c, d). Abnormal growth of the primitive right or left ventricle may result in hypoplasia of the right or left ventricle. Malalignment between the interventricular septum and the interatrial septum could result in unilateral atresia of the atrioventricular valve (tricuspid or mitral atresia) or double inlet ventricle (double inlet right, left or indetermined ventricle) (Fig. 2.6c). These abnormalities consist of a wide spectrum of functional univentricular heart.

Normal and Abnormal Development of Atrial Septum: Atrial Septal Defects (ASD) [20]

At 4–5 weeks of gestation, the crescent-shaped septum primum forms in the roof of the primitive atrium and grows toward to and fuses with the atrioventricular cushions in the atrioventricular canal where the foramen primum between the free edge of the septum primum and the atrioventricular cushions is closed (Fig. 2.6a, d). Meanwhile, the foramen secundum is created in the center of septum primum which is later covered by the septum secundum arising from the atrial roof on the right of the septum primum. The foramen ovale remains patent to maintain blood flow from the right to the left atrium during fetal life.

ASDs are classified according to their location relative to the foramen ovale (Fig. 2.6b). The secundum type is the most common and is considered to result from excessive resorption of the septum primum or secundum. The primum type is probably caused by abnormal development of the atrioventricular cushions and/or dorsal mesenchymal protrusion that arises from the posterior part of second heart field, contributes to the venous pole of the heart tube, and gives rise to the myocardial base of the primary atrial septum. The sinus venosus type is usually associated with anomalous return of the right pulmonary veins. The coronary sinus type is often associated with an unroofed coronary sinus and left atrial connection of a persistent left superior vena cava.

Normal and Abnormal Development of Ventricular Septum: Ventricular Septal Defects (VSD) [21]

At 4 weeks of gestation, the muscular interventricular septum develops in midline on the floor of the primitive ventricles and grows toward the atrioventricular canal (Fig. 2.6d). By 7 weeks of gestation, muscular interventricular septum connects with the bottom edge of conal septum through the atrioventricular cushions, and the interventricular foramen is ultimately closed by the membranous interventricular septum that is formed by the proliferation and fusion of tissues from three sources, partly from the right and left conal cushions and mostly from the atrioventricular cushions (Fig. 2.6e).

The conal type of ventricular septal defect occurs as a result of failure to fuse of the conal cushions (Fig. 2.6f). The muscular type occurs by simple single or multiple perforations in the muscular septum (Fig. 2.6f). The inlet type results from abnormal development of atrioventricular cushions (Fig. 2.6f). The membranous-type ventricular septal defect is the most common congenital heart defect. It can be caused simply by failure of the membranous interventricular septum to develop, but also by malalignment between the conal septum and the muscular septum (Fig. 2.6f–h). The malalignment type is usually associated with complex heart malformations.

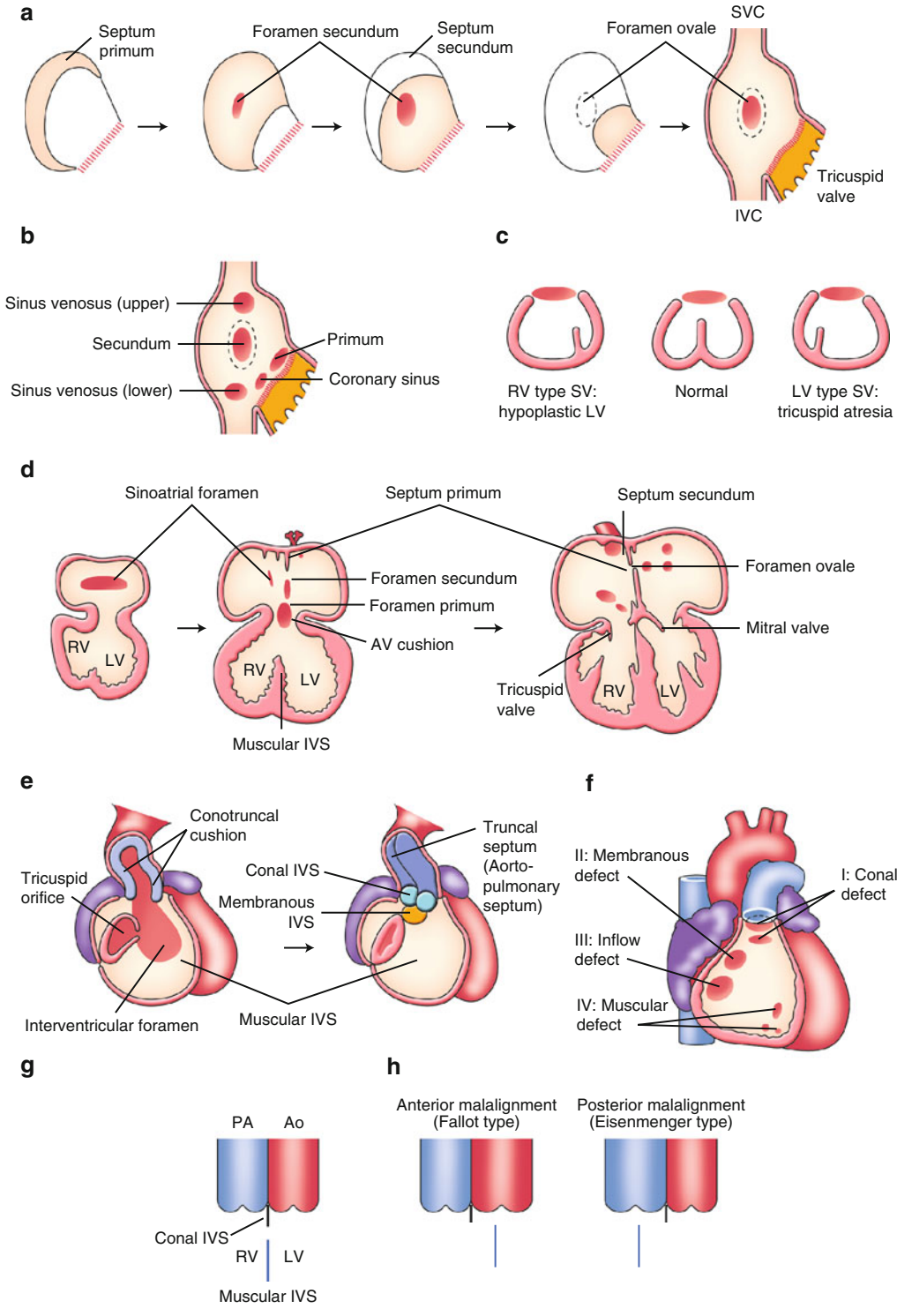

Fig. 2.6 Normal and abnormal development of atrial septum, ventricular septum, and ventricles. (**a**) Atrial septum from right atrium view. (**b**) Atrial septal defect. (**c**) Alignment of AV valves & IVS. (**d**) Atrial and ventricular septum from four chamber view. (**e**) Ventricular and outflow tract septation from right ventricle view. (**f**) Ventricular septal defects. (**g**) Simple perforation. (**h**) Malalignment (of conal septum). See detail in text. *Ao* aorta, *AV* atrioventricular, *IVC* inferior vena cava, *IVS* interventricular septum, *LV* left ventricle, *PA* pulmonary artery, *RV* right ventricle, *SVC* superior vena cava

Usually, anterior malalignment of the conal septum is associated with TOF, while posterior malalignment of the conal septum is associated with coarctation or interruption of the aorta.

Normal and Abnormal Development of Atrioventricular Cushions: Atrioventricular Septal Defects (AVSD) [22]

At 4 weeks of the gestation, an endocardial cushion is formed in the atrioventricular canal by a process called "epithelial–mesenchymal transformation" where the mesenchymal cells are separated from the endocardium and transformed in the extracellular matrix. At 5 weeks of the gestation, the atrioventricular canal is divided by the coalescence of the superior and inferior endocardial cushions into the right-sided tricuspid and the left-sided mitral orifices (Fig. 2.7a). Endocardial cushions also participate in formation of the interatrial septum (closing of the ostium primum), atrioventricular valves (mitral and tricuspid valve), and membranous interventricular septum.

A complete failure of development of atrioventricular endocardial cushions results in complete atrioventricular septal defect which comprises common atrioventricular valve with variable degree of insufficiency (Fig. 2.7a), primum type of ASD (cf. Fig. 2.6b) and membranous/inlet type of VSD (cf. Fig. 2.6f). Partial type of AVSD manifests by a primum ASD with insufficiency of the tricuspid and/or mitral valves.

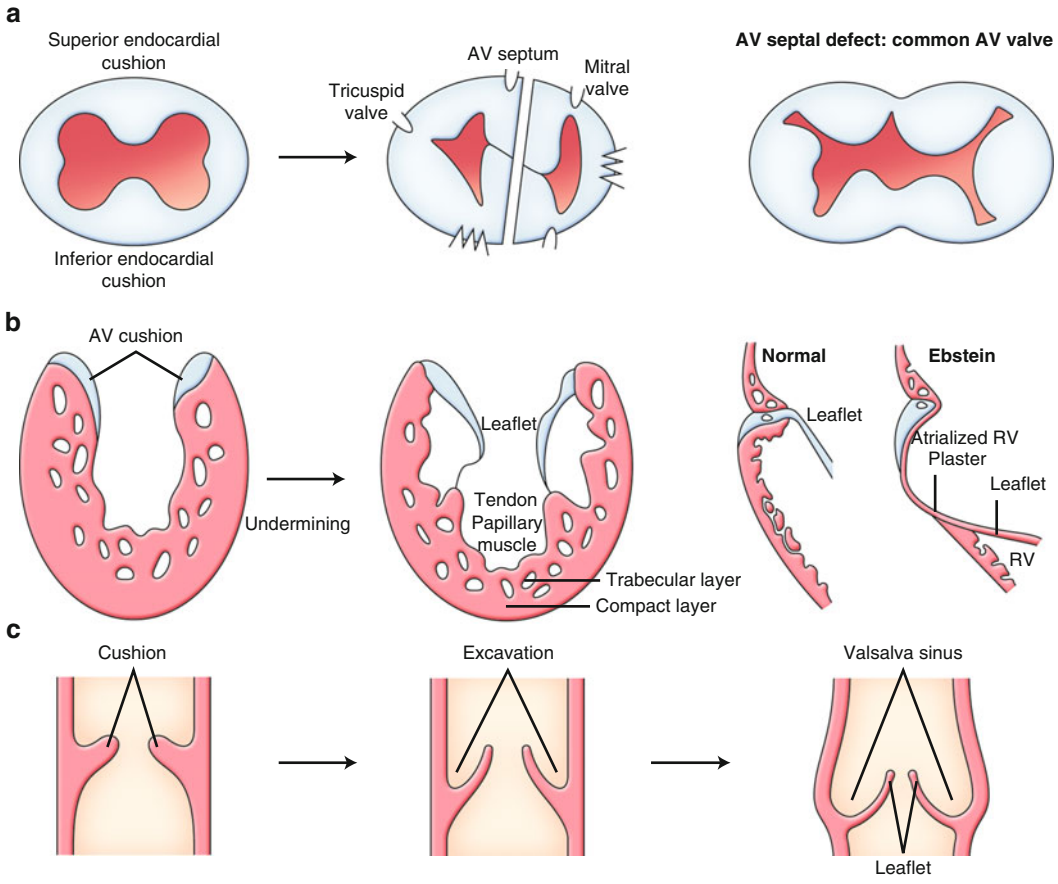

Fig. 2.7 Normal and abnormal development of atrioventricular (*AV*) septum and cardiac valves. (**a**) Development of AV septum. (**b**) Development of AV valve. (**c**) Development of semilunar valve. See detail in text. *RV* right ventricle

Normal and Abnormal Development of Cardiac Valves [9, 23]

Ebstein's Anomaly

The leaflets of atrioventricular valves are derived from the atrioventricular cushions. The leaflets and tendon apparatus which consist of the chordae tendineae and their myotendinous junctions with the papillary muscles are formed mostly by a process called "undermining" (Fig. 2.7b). This process is probably involved by myocardial cell death which delaminates the inner layers of the ventricular inlet and frees the fibrous leaflets.

Ebstein's anomaly of the tricuspid valve includes displacement of the septal and posterior leaflets of the valve into the right ventricle to varying degrees. The portion of the right ventricle between the true valve annulus and the downwardly displaced valve leaflets forms an "atriarized" portion of the right ventricle that is continuous with the true right atrium. It is supposed to result from a defect in undermining that leads to plastering of the valve leaflets to the myocardial layer (Fig. 2.7b).

Abnormalities of Semilunar Valves [9, 24–26]

After division of the outflow tract, the mesenchyme that forms the truncal cushions is remodeled into the aortic and pulmonary valves (Fig. 2.7c). Each valve has three cusps and leaflets. The cushion mesenchyme is derived from epithelial–mesenchymal transformation and from cardiac neural crest cells. The early cusps consist of a core of cushion tissue covered by the endocardium. Excavation of the arterial face of the cusps results in thinning to the final shape that consist of the valve leaflets and Valsalva sinuses (Fig. 2.7c).

A defective process of excavation in the pulmonary valve region results in thick, fused, and/or dysplastic pulmonary valve with stenosis (PS). Pulmonary atresia with intact ventricular septum (PA-IVS) probably occurs after cardiac septation is completed, whereas a diminutive right ventricle and ventriculo-coronary artery connections represent an earlier insult than a well-formed right ventricle and tricuspid valve with fused imperforated pulmonary valve. Aortic valve stenosis (AS) is associated with thickening and increased rigidity of the valve tissue like pulmonary valve stenosis. The aortic valve is often bicuspid with a single, fused commissure and an eccentrically placed orifice which may lead to aortic stenosis and/or insufficiency.

Normal and Abnormal Development of the Arterial System [1, 2, 12, 27]

The great arterial system arises from six pairs of pharyngeal arch arteries that run through pharyngeal arches symmetrically. During 4–5weeks of gestation, the bilaterally symmetric pharyngeal arch arteries and the right and left dorsal aortae undergo remodeling (Fig. 2.8). The first and second pharyngeal arch arteries almost completely regress except to form the maxillary and stapedial arteries, respectively. The third, fourth, and sixth pharyngeal arch arteries result in a portion of the aortic arch and its branches, the ductus arteriosus, and part of branch pulmonary arteries through their remodeling, while the fifth pharyngeal arch arteries completely regress before fully develop.

Interrupted Aortic Arch Type B (IAA-B) [2, 12, 27]

Most anomalies of the aortic arch system result from persistence of parts of the pharyngeal arch arteries and dorsal aortae that normally regress and regression of parts that normally persist. Interrupted aortic arch type B results from abnormal regression of the left fourth pharyngeal arch artery (Fig. 2.8a).

Aberrant Right Subclavian Artery [2, 12, 27]

Aberrant right subclavian artery occurs when the right fourth pharyngeal arch artery abnormally regresses and the right dorsal aorta cranial to the seventh intersegmental artery abnormally persists and forms the retroesophageal portion of the right subclavian artery (Fig. 2.8b).

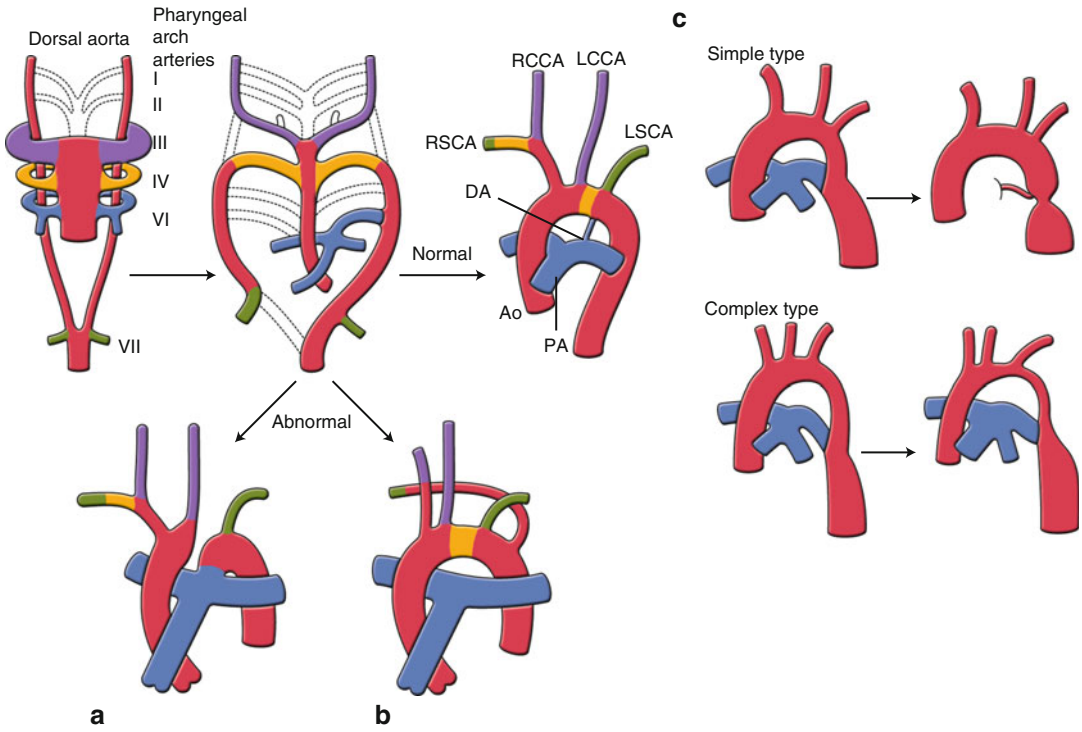

Fig. 2.8 Normal and abnormal development of the arterial system. (**a**) Interrupted aortic arch type B. (**b**) Aberrant right subclavian artery. (**c**) Coarctation of the aorta. See detail in text. *Ao* aorta, *DA* ductus arteriosus, *LCCA* left common carotid artery, *LSCA* left subclavian artery, *PA* pulmonary arteries, *RCCA* right common carotid artery, *RSCA* right subclavian artery

Coarctation of Aorta (CoA) [27]

The simple, or post-ductal, type of coarctation of the aorta may result from abnormal constriction of the aorta together with the ductus arteriosus (Fig. 2.8c). The complex, or preductal, type of coarctation of the aorta may result from a decreased blood flow through preductal aortic arch due to a posterior malalignment of the conal septum, bicuspid aortic valve with aortic stenosis, or other causes (Fig. 2.8c).

Patent Ductus Arteriosus (PDA) [28]

The ductus arteriosus normally develops from the distal portion of the left sixth pharyngeal arch artery and connects the pulmonary trunk to the descending aorta (Fig. 2.8). With a right aortic arch, the ductus arteriosus is commonly on the left, joining the left pulmonary artery and the proximal portion of the left subclavian artery. The exact mechanisms underlying postnatal closure of the ductus arteriosus are not fully understood. An increase in partial pressure of oxygen and release of vasoactive substances, such as acetylcholine, bradykinin, or catecholamines, may contribute to closure of the ductus arteriosus under physiologic conditions. On the other hand, prostaglandins play an active role in maintaining the ductus arteriosus in an open state during normal fetal life. Patency or closure of the ductus arteriosus may represent a balance between the constrictive and relaxing effects by multiple factors.

Normal and Abnormal Development of Pulmonary Veins [29]

At 4 weeks of gestation, the primordial lung buds are enmeshed by the vascular plexus, called the splanchnic and pulmonary venous plexus, that connects to the systemic veins, but not to the heart (Fig. 2.9). By the end of 4 weeks of gestation, the common pulmonary vein derived from pulmonary venous plexus connects to the sinoatrial

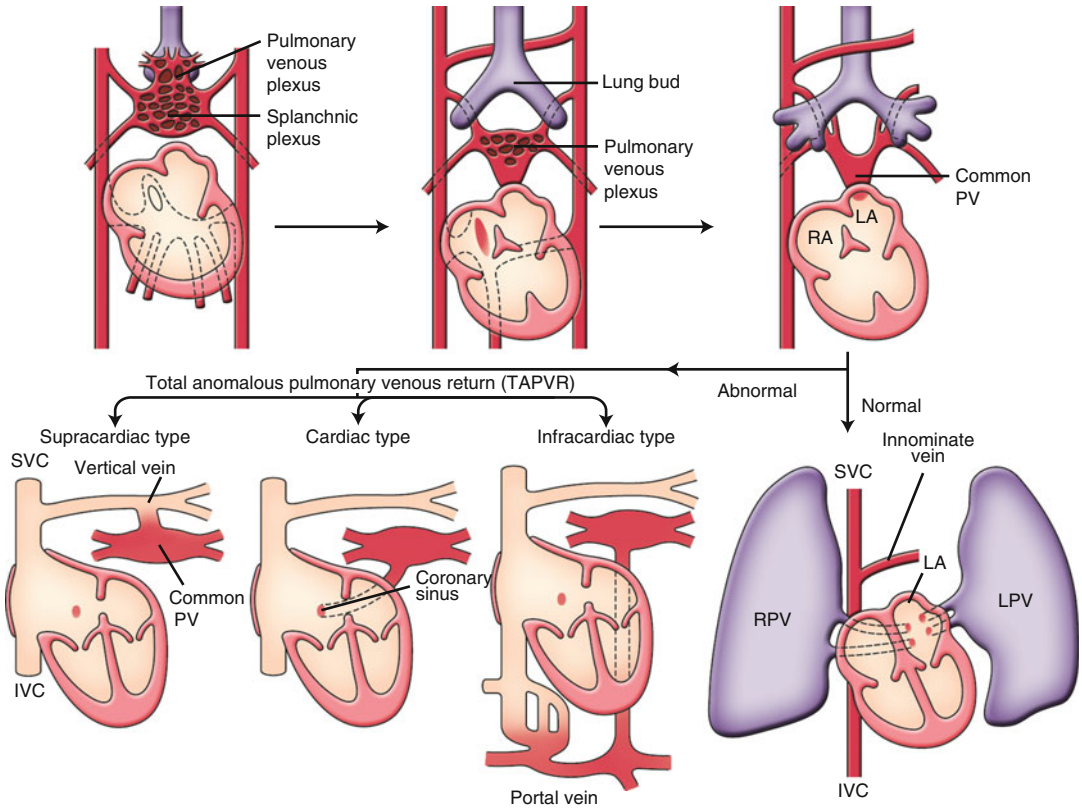

Fig. 2.9 Normal and abnormal development of pulmonary veins. See detail in text. *IVC* inferior vena cava, *LA* left atrium, *LPV* left pulmonary veins, *PV* pulmonary vein, *RA* right atrium, *RPV* right pulmonary veins, *SVC* superior vena cava

portion of the heart. Later, the connections between the pulmonary venous plexus and the systemic veins involute, and finally, the common pulmonary vein is absorbed into the left atrium so that the two right and the two left pulmonary veins connect separately and directly to the left atrium (Fig. 2.9).

Total Anomalous of Pulmonary Venous Return (TAPVR) [29]

TAPVR occurs as a result of developmental failure or early atresia of common pulmonary vein when collateral channels for pulmonary venous return are available in the form of primitive connections between the pulmonary venous plexus and the systemic veins. The type of TAPVR is classified according to the persistent collateral channels from pulmonary to systemic veins as follows: Supracardiac type includes connections to the left innominate vein, the superior vena cava, or the azygos vein; cardiac type includes connections to the coronary sinus or directly to the right atrium; and infracardiac type includes connections below the diaphragm to the inferior vena cava, the portal vein, the hepatic veins, or the ductus venosus (Fig. 2.9).

Normal and Abnormal Development of Coronary Arteries [30–32]

During the early development of the heart, the epicardial precursor cells derived from proepicardial organ contribute to form epicardium spread over the heart (Fig. 2.2c, d). Epithelial–mesenchymal transition provides cells that delaminate and migrate into the myocardium to transform into the vasculogenic mesenchymal cells (Fig. 2.10a). These vasculogenic cells

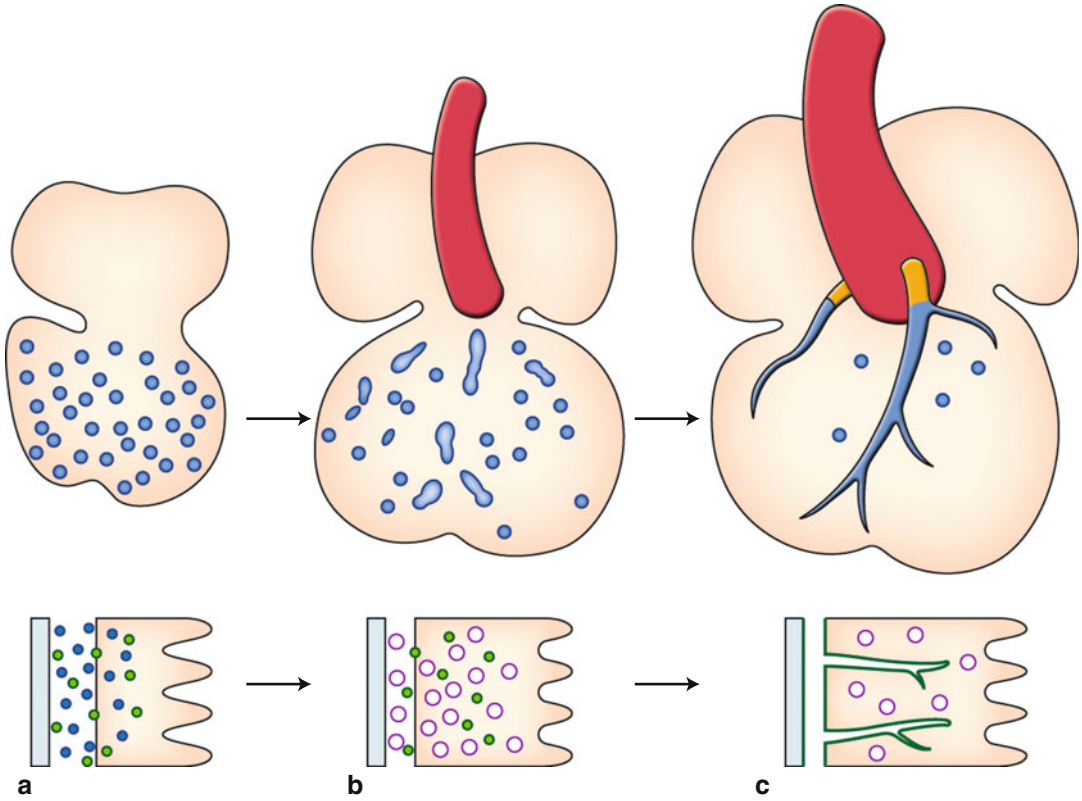

Fig. 2.10 Development of coronary arteries. (**a**) Mesenchymal cells. (**b**) Vascular plexus. (**c**) Coronaries connecting to the aorta. See detail in text. *Small blue circles* represent vasculogenic mesenchymal cells that are derived from epicardium by epithelial–mesenchymal transformation and migrate into the myocardium. A *red* vessel represents the aorta. *Orange* area represents the connection of coronary artery to the aorta

differentiate and link locally to form vascular plexus that induce other mesenchymal cells to become smooth muscle (Fig. 2.10b). Later, these vascular plexi are remodeled into sprouting definitive arteries. Finally, the vascular plexus in the most proximal region links up and gives rise to the major coronaries that eventually connect to the aorta (Fig. 2.10c).

Congenital anomalies of the coronary artery may occur alone or in association with structural heart defects, such as TGA and TOF. There are numerous types of anomalous origin of coronary arteries, including anomalous origin of left coronary arterial branches from the right coronary sinus, anomalous origin of right coronary arterial branches from the left coronary sinus, and anomalous origin of left main coronary artery from the pulmonary artery (Bland–White–Garland syndrome).

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