Development of Cardiovascular System

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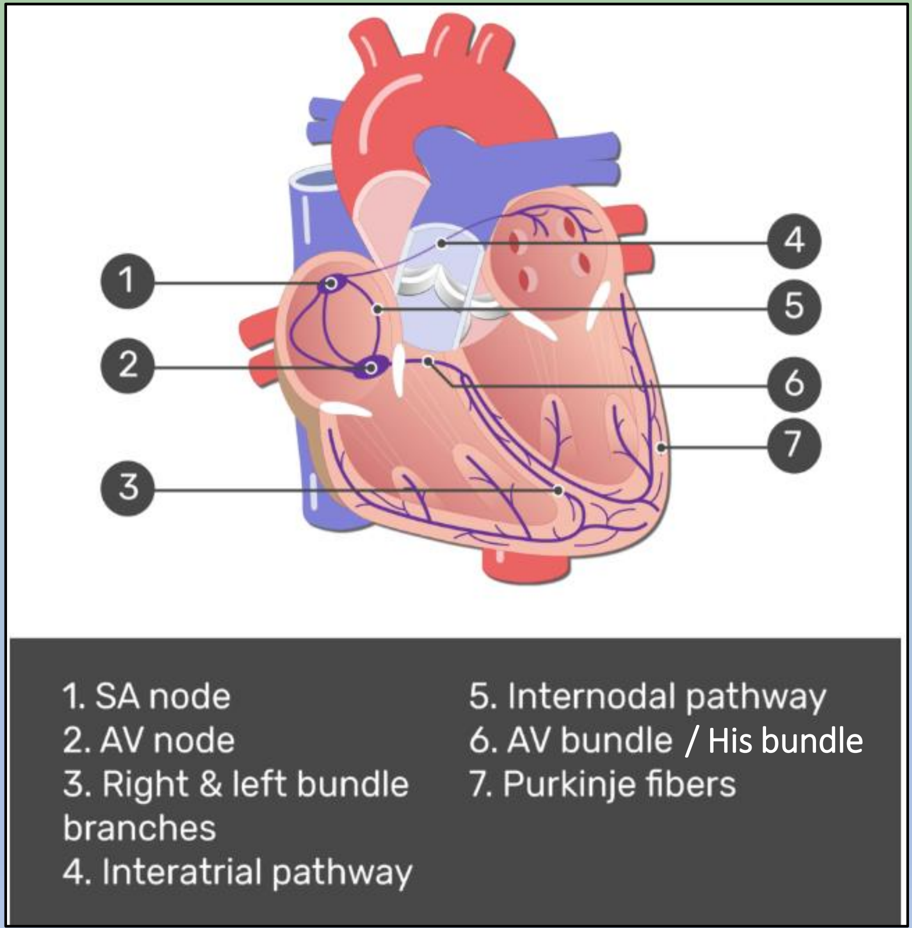
Conducting system of the heart

- **<u>Specialised myocardial cells</u>** responsible for the initiation and conduction of the electrical impulses which regulate the rate of cardiac contractions, develop in the embryonic heart. These myocardial cells form structures referred to as pacemakers. The first pacemaker is located in the caudal part of the left cardiac tube. Subsequently, a site in the right horn of the sinus venosus assumes this role.
- When the right horn of the sinus becomes incorporated into the definitive right atrium, this specialised pacemaker tissue is referred to as the sino-atrial node. At an early stage in cardiac development, prior to the formation of separate cardiac chambers, the entire myocardium functions as a unit. As the chambers of the heart develop, a band of connective tissue, derived from epicardium, separates the musculature of the atria from the musculature of the ventricles.
- Specialised myocardial cells form the atrio-ventricular node, the atrio-ventricular bundle (His bundle) and Purkinje fibres, which conduct impulses from the musculature of the atria to the musculature of the ventricles.



Development of the arterial system

- The intra-embryonic blood vessels develop in a manner similar to that described for the extra-embryonic vessels. The dorsal aortae, which are the first major vessels to develop, fuse with the endocardial tubes. As a result of the cranio-caudal body folding, the cranial portions of the dorsal aortae form arches which are lateral to the foregut and are surrounded by the mesenchyme which forms the first pharyngeal arches.
- These segments of the dorsal aortae are referred to as the first aortic arch arteries. The junction of the aortic arch arteries with the truncus arteriosus, which becomes dilated, is called the aortic sac. As subsequent pharyngeal arches develop, pairs of arch arteries, which arise from the aortic sac, pass through the arches before joining the dorsal aortae. A total of six pairs of aortic arch arteries are formed, and from them other major vascular structures arise (Figure 1).
- Although it is usual to represent the paired arch arteries diagrammatically as if they were all present simultaneously, in reality they develop sequentially. At the stage of development when the first and second arch arteries are formed, the fourth and sixth arteries have not yet developed. By the time the sixth pair of arteries have formed, the first two pairs have largely atrophied.

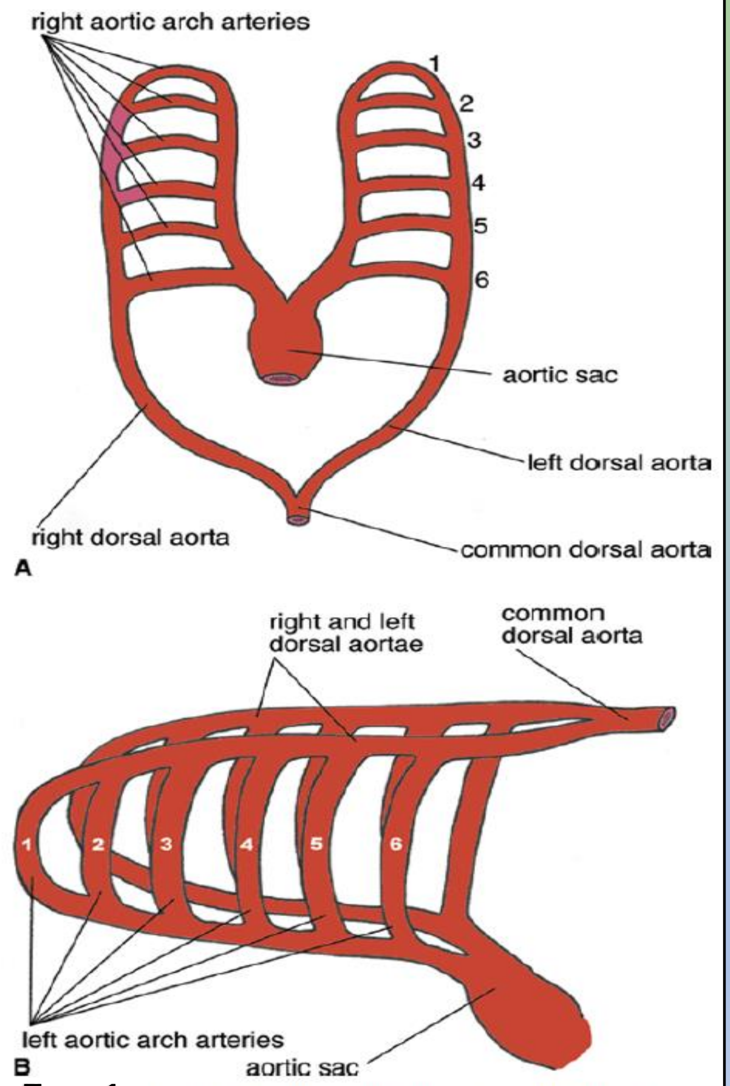


Figure 1 lustration showing a ventral view, A, and a left lateral view, B, of the six pairs of aortic arch arteries. Although they develop sequentially, the illustration represents them as if they were present contemporaneously.

Derivatives of the aortic arch arteries

- Major developmental changes occur in the aortic arch arteries of dogs between the third and fourth weeks of gestation, and in humans and horses between the third and seventh weeks of gestation.
- These changes take place contemporaneously with the establishment of separate venous and arterial circulations. The dorsal aortae caudal to the heart fuse, forming the single caudal aorta; cranial to the heart they remain paired.
- Apart from the portions which persist as the small left and right maxillary arteries, the first pair of aortic arch arteries atrophy (Figure 2).
- Small remnants of the second pair of aortic arch arteries persist as branches to the left and right middle ears, the stapedial arteries.
- The left and right third aortic arch arteries form the common carotid arteries and contribute to the formation of the internal carotid arteries. The cranial portions of the dorsal aortae form the remainder of the internal carotid arteries. The portions of the dorsal aortae between the third and fourth arch arteries atrophy (Figure 2).
- The external carotid arteries form as outgrowths of the third aortic arch arteries.

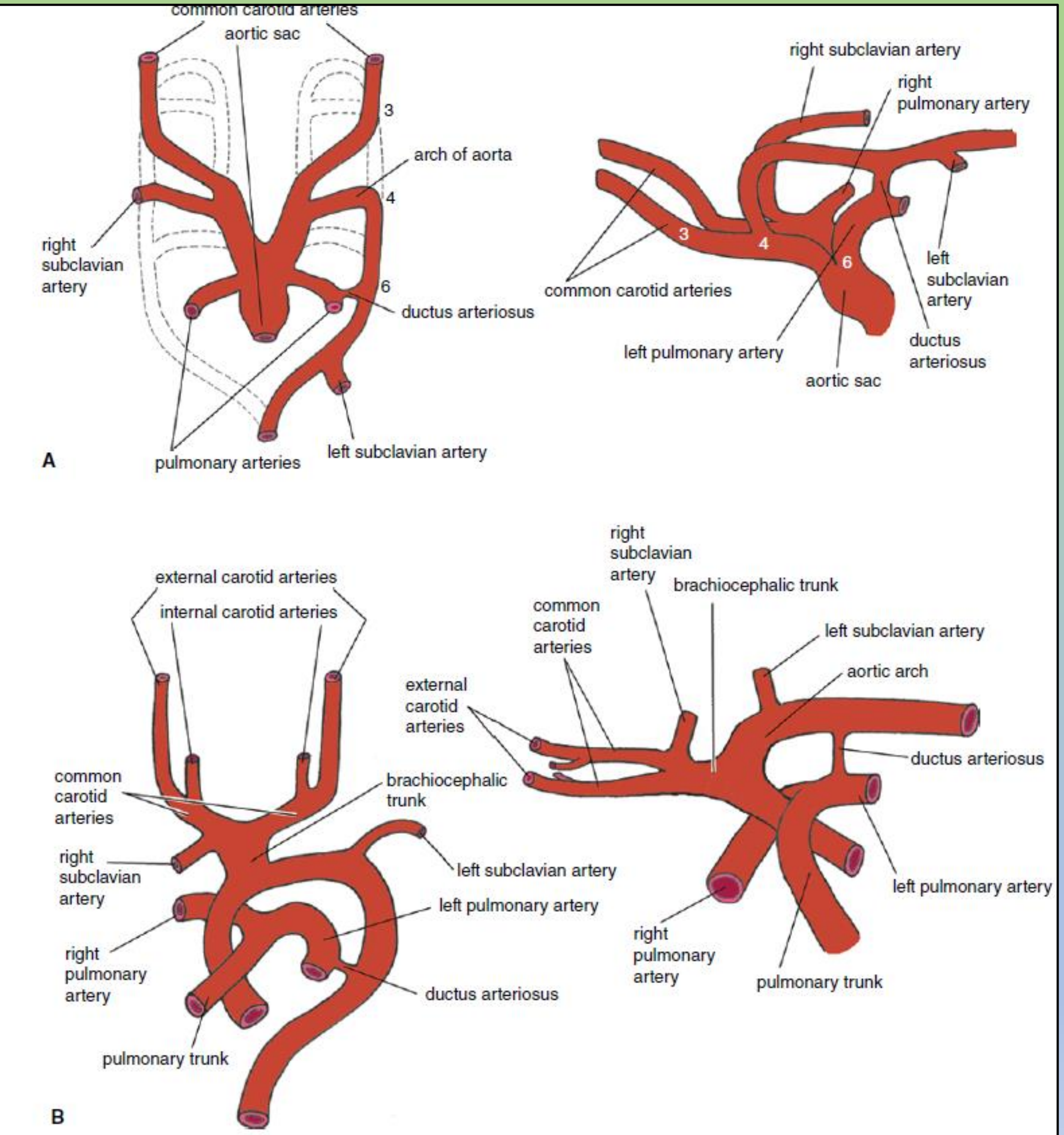


Figure 2 Ventral and left lateral views of the aortic arch arteries at an early stage of development, A, and at a later stage of development, B. Dotted lines indicate degenerating vessels.

Derivatives of the aortic arch arteries

- The fate of the fourth pair of aortic arch arteries differs. The left fourth aortic arch artery forms part of the arch of the aorta. The remainder of the arch of the aorta is derived in part from the aortic sac and the left dorsal aorta. The right fourth aortic arch artery forms the proximal segment of the right subclavian artery. The remainder of the subclavian artery is derived from the right dorsal aorta and the right seventh dorsal intersegmental artery. The segment of the right dorsal aorta between the origin of the right subclavian artery and the common caudal aorta atrophies.
- The fifth pair of aortic arch arteries are usually rudimentary and subsequently atrophy.
- The sixth pair of aortic arch arteries supply branches to the developing lungs. On the left side, the proximal segment of the sixth aortic arch artery, between the pulmonary branch and the aortic sac, persists as the proximal part of the left pulmonary artery.
- In the foetus, the distal segment persists as a shunt, the ductus arteriosus, which links the pulmonary artery with the dorsal aorta. The proximal part of the right sixth aortic arch artery becomes the proximal part of the right pulmonary artery, while the distal segment atrophies.

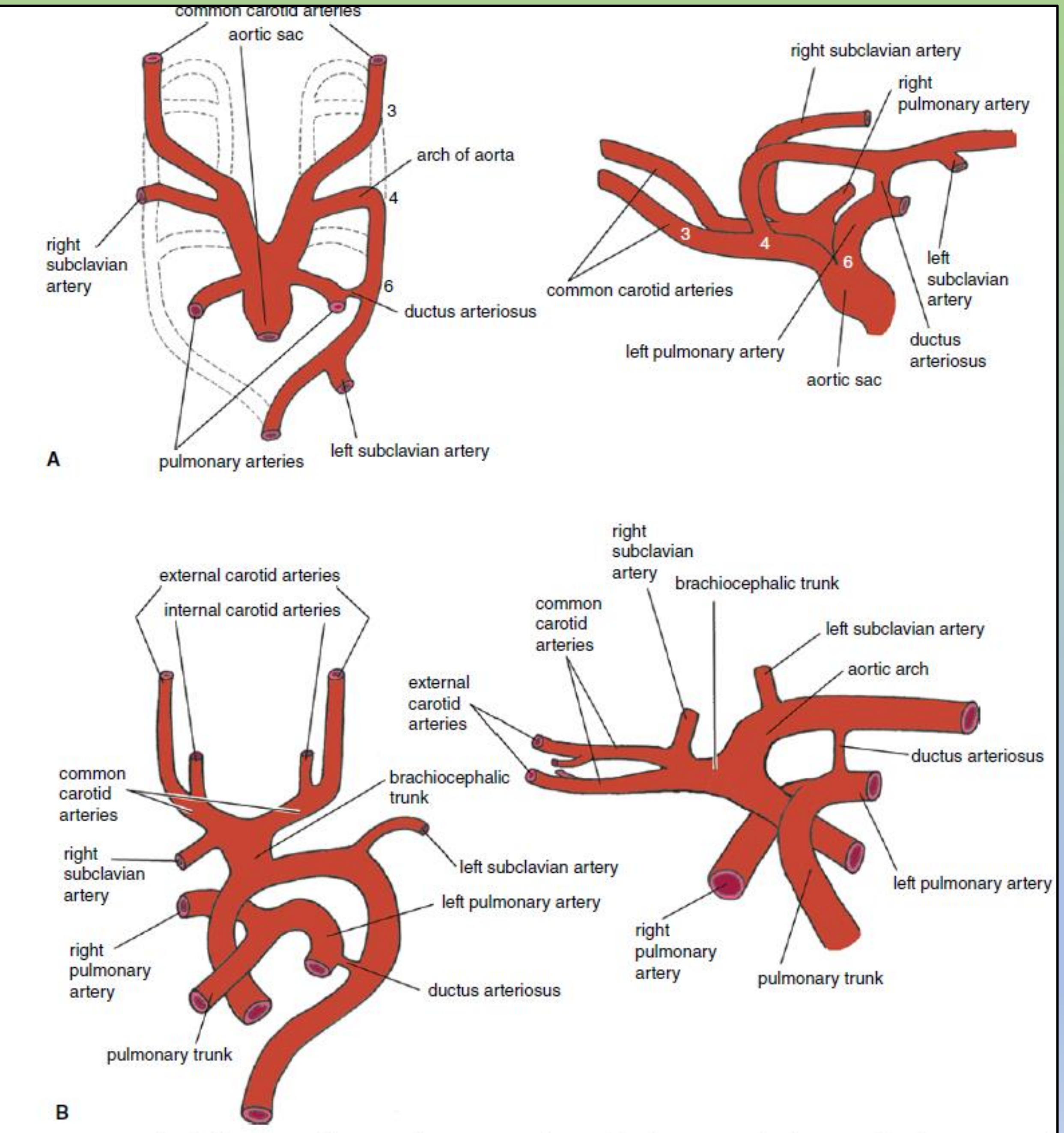


Figure 2 Ventral and left lateral views of the aortic arch arteries at an early stage of development, A, and at a later stage of development, B. Dotted lines indicate degenerating vessels.

- The brachiocephalic trunk develops from remodelling of the aortic sac and its fusion with portions of the left and right third and fourth aortic arch arteries. In its definitive form, this trunk arises from the aortic arch. In dogs, the brachiocephalic trunk gives off the right subclavian artery, and at its point of bifurcation forms the right and left common carotid arteries (Figure 3A).
- In horses, pigs and ruminants, the left and right common carotid arteries arise from bifurcation of a single branch from the brachiocephalic trunk (Figure 3B). The seventh dorsal intersegmental artery, which arises from the left dorsal aorta at the level of the seventh somite, contributes to the formation of the left subclavian artery.
- During remodelling of the aortic arch arteries, the seventh intersegmental artery migrates cranially from a position caudal to the ductus arteriosus to a location close to the aortic arch. In pigs and dogs, the left subclavian artery arises directly from the aortic arch, distal to the origin of the brachiocephalic trunk, while, in horses and cattle, the left subclavian artery which migrates to a more cranial position, arises directly from the brachiocephalic trunk (Figure 3B).

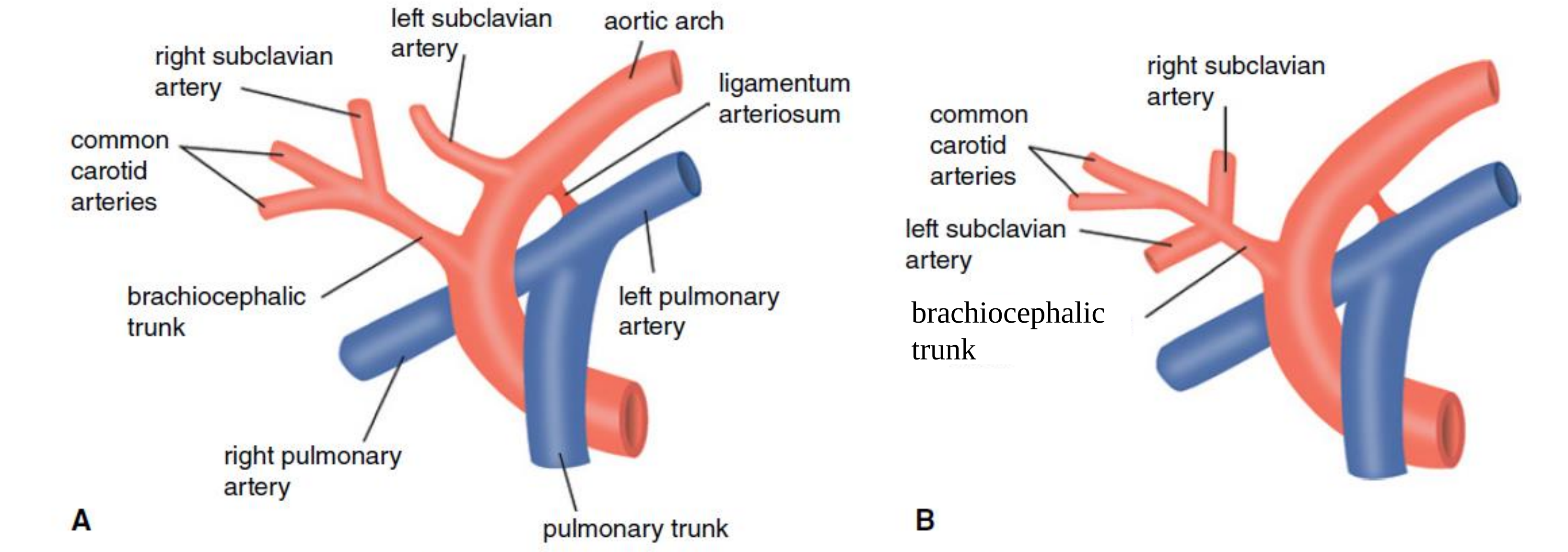


Figure 3 Arrangement of the major blood vessels which arise from the arch of the aorta and the pulmonary trunk of domestic carnivores, A, and of horses and ruminants, B.

- The recurrent laryngeal branch of the vagus nerve on either side, which passes caudal to the developing sixth aortic arch artery, innervates the musculature of the sixth pharyngeal arch. When the heart and associated vessels are displaced to the thoracic cavity, the recurrent laryngeal nerves are drawn caudally. Because the distal part of the right sixth aortic arch artery and the entire fifth aortic arch artery atrophy, the right recurrent laryngeal nerve becomes hooked around the right subclavian artery which accounts for its more cranial position in comparison with the left recurrent laryngeal nerve. On the left side, the recurrent laryngeal nerve loops around the sixth aortic arch artery, the blood vessel which subsequently gives rise to the ductus arteriosus (Figure 4). After birth, as the ductus arteriosus persists as the ligamentum arteriosum, the left recurrent laryngeal nerve remains hooked around the ligamentum arteriosum and the aortic arch.
- The close relationship of the left recurrent laryngeal nerve to the aortic arch has been proposed as a factor in the aetiology of laryngeal hemiplegia in horses. It has been suggested that the functioning of the nerve becomes impaired by the pulsations of the arch of the aorta. Because the right subclavian artery is less rigidly fixed than the aortic arch, the right recurrent laryngeal nerve, which is hooked around the right subclavian artery, is less likely to become damaged by stretching.

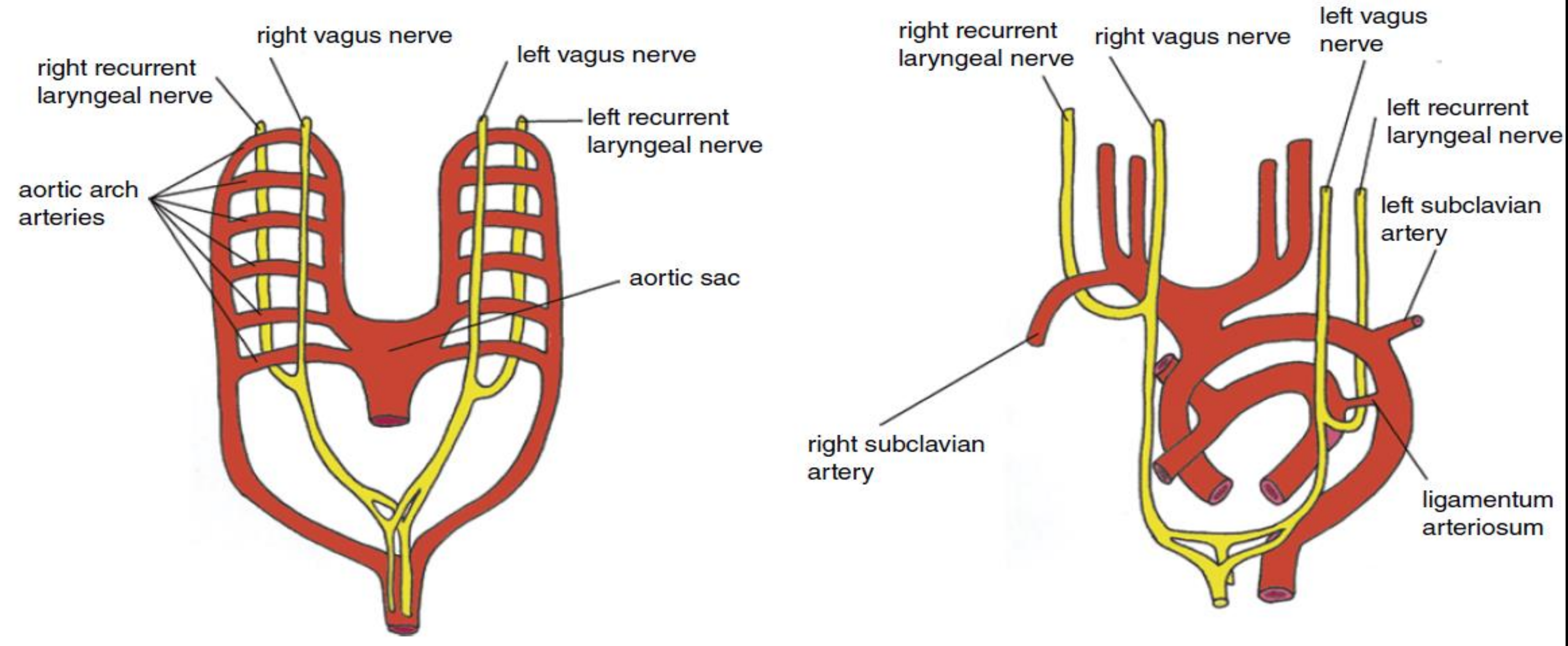


Figure 4 The initial relationships of the recurrent laryngeal nerves to the aortic arch arteries and their subsequent relationships to the blood vessels which arise from the aortic arch arteries.

Branches of the aorta

- Dorsal, lateral and ventral branches arise from the paired dorsal aortae. Following fusion of the aortae, paired dorsal intersegmental arteries which pass between the somites arise along the length of the fused vessel.
- These intersegmental arteries give off dorsal branches to the developing spinal cord and the epaxial musculature and ventral branches to the hypaxial musculature.
- The seventh intersegmental arteries supply the developing forelimb buds. A series of longitudinal anastomoses develop between the intersegmental arteries.
- In the cervical region, the first six intersegmental arteries between the longitudinal anastomoses and the dorsal aortae atrophy. The artery formed from these anastomoses, the vertebral artery, arises from the seventh intersegmental artery.
- In the thoracic region, the anastomoses form the internal thoracic artery, and the intersegmental arteries persist as the intercostal arteries (Figure 5).

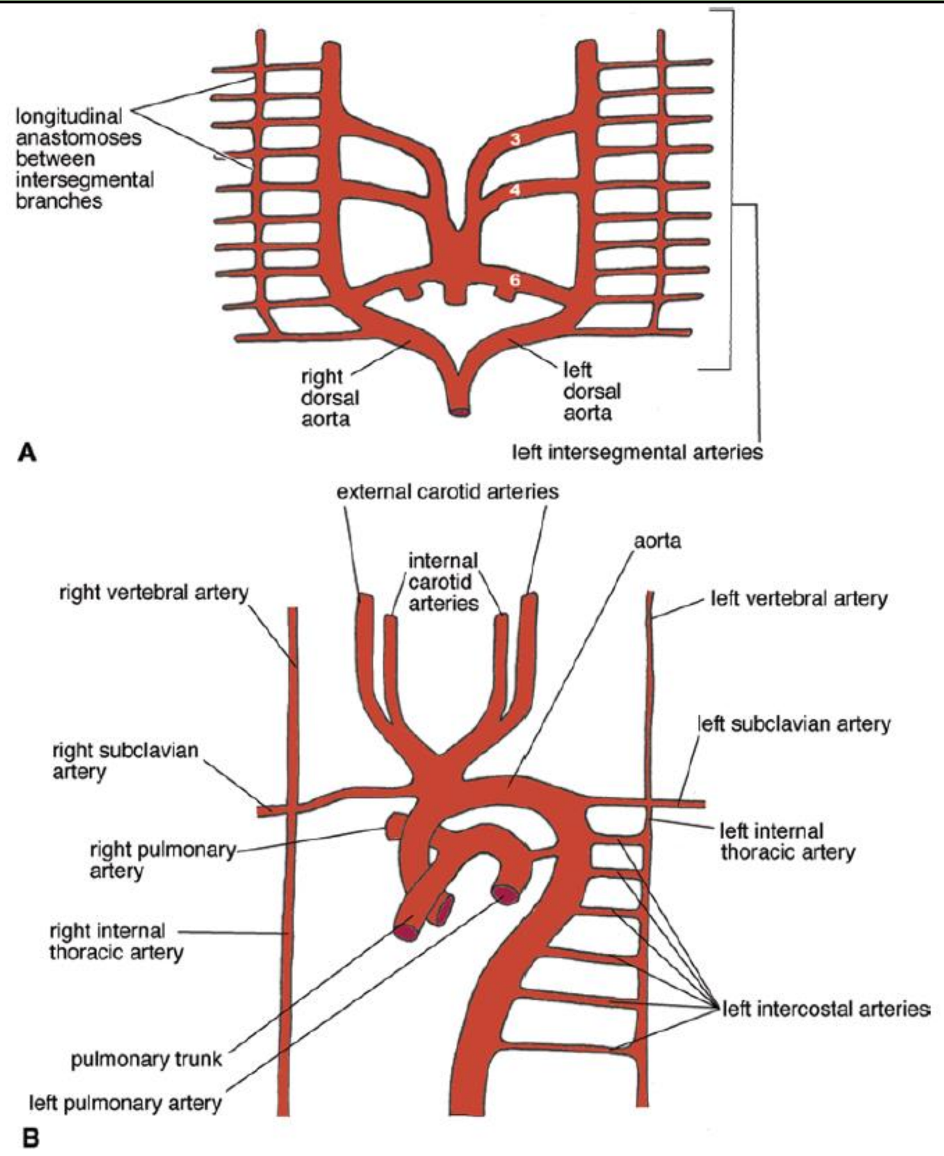


Figure 5 Early (A) and late (B) stages in the formation of the vertebral, internal thoracic, subclavian and intercostal arteries. Vessels in A labelled 3, 4 and 6 are the aortic arch arteries which persist and from which definitive arteries arise.

Branches of the aorta

- The intersegmental arteries in the lumbar region form the lumbar arteries. The most caudal lumbar intersegmental arteries supply the pelvic limb buds and form the external iliac arteries. The umbilical arteries, which arise directly from the paired dorsal aortae, supply the allantois.
- With the formation of the common aorta and the intersegmental arteries, the umbilical arteries appear as branches of the internal iliac arteries.
- The paired lateral branches of the aorta give rise to renal, phrenico-abdominal, gonadal and deep circumflex arteries on either side.
- The unpaired ventral aortic branches, which supply the splanchnopleure of the thoracic and abdominal cavities, give rise to the broncho-oesophageal, coeliac, cranial and caudal mesenteric arteries.
- Endothelial sprouts, which arise near the commencement of the aorta and anastomose with a plexus of vessels in the subepicardial layer of the developing heart, form the coronary vessels, the principal blood supply to the heart.

Development of the venous system

- The venous system develops under the influence of specific growth factors in a manner similar to the development of the arterial system. Early in embryological development, three pairs of major veins are formed, vitelline veins, umbilical veins and cardinal veins.
- Arterial and venous differentiation
- While endothelial cells possess the inherent capability of ultimately developing along the venous pathway, VEGF and Notch signalling promote arterial formation.
- The membranes of the endothelial cells of the developing arterial system possess the transmembrane protein Ephrin-B2, while the endothelial cells of the venous system contain a receptor for Ephrin-B2 called Eph-B4 on their surface membranes (Figure 6).
- During angiogenesis, interaction between ephrin-B2 and Eph-B4 at the points of anastomosis of the arterial and venous systems ensures that end-to-end fusion can occur only between arterial and venous capillaries, while lateral fusion between arterial and venous capillaries is prevented.

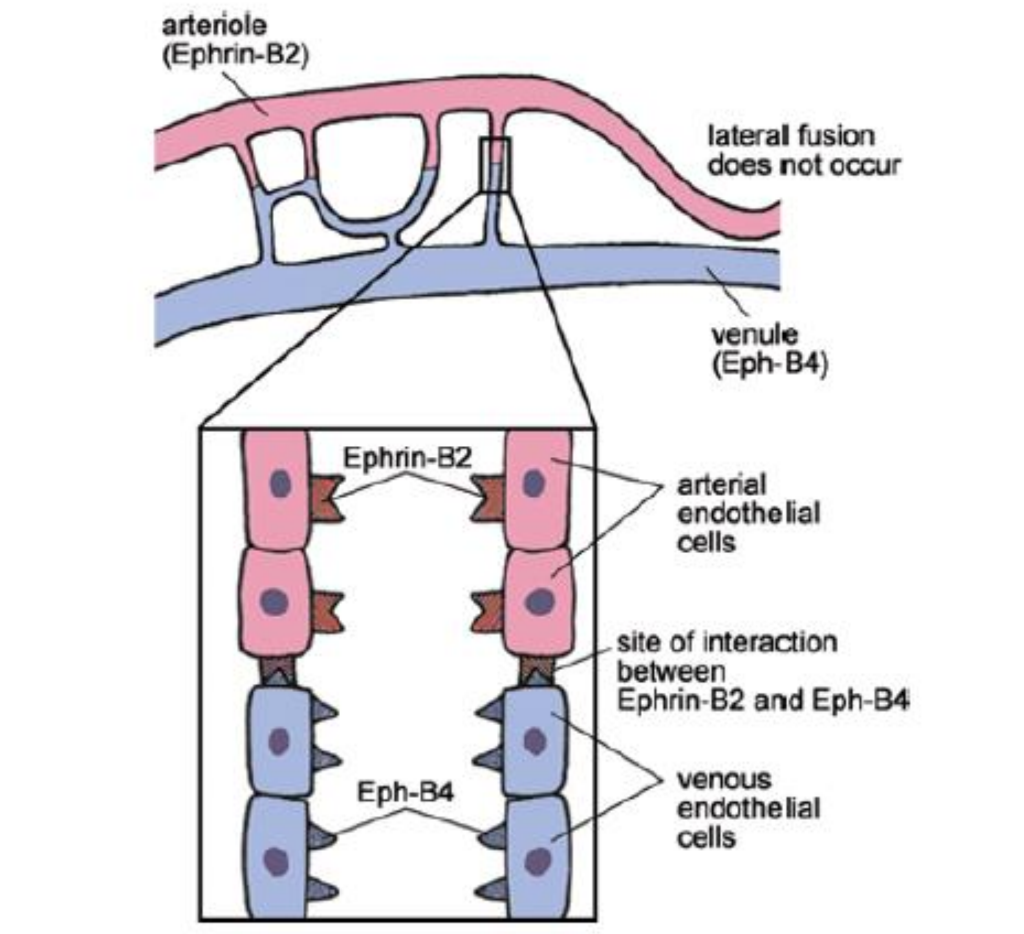


Figure 6 The role of receptor–ligand interactions in fusion of arterial and venous endothelial cells.

Vitelline veins

- The paired vitelline veins, which convey blood from the yolk sac to the heart, pass through the umbilicus into the embryo and run cranially, one on either side of the foregut, through the septum transversum and enter the sinus venosus (Figure 7).
- Cells of the developing liver cords extend into the septum transversum, leading to the formation of a venous plexus which arises from the middle segments of the vitelline vessels. This vascular network becomes incorporated into the developing liver, forming the hepatic sinusoids. The fate of the cranial segments of the left and right parts of the vitelline veins, located between the developing liver and the sinus venosus, differs. The left cranial segment of the vitelline vein, which enters the left horn of the sinus venosus, atrophies.
- The right cranial segment of the vitelline vein persists and becomes that segment of the caudal vena cava which conveys blood from the liver into the right horn of the sinus venosus. Two anastomoses, one cranial and one caudal, form between the caudal segments of the left and right vitelline veins. The cranial anastomosis is located dorsal to the midgut, while the caudal anastomosis is located ventral to the midgut.
- Following rotation of the stomach and a gradual alteration in the patency of segments of the left and right vitelline veins, redirection of blood flow occurs. The portal vein is formed from the patent segments of the left and right vitelline veins and their anastomoses. The non-patent segments of the left and right vitelline veins atrophy.

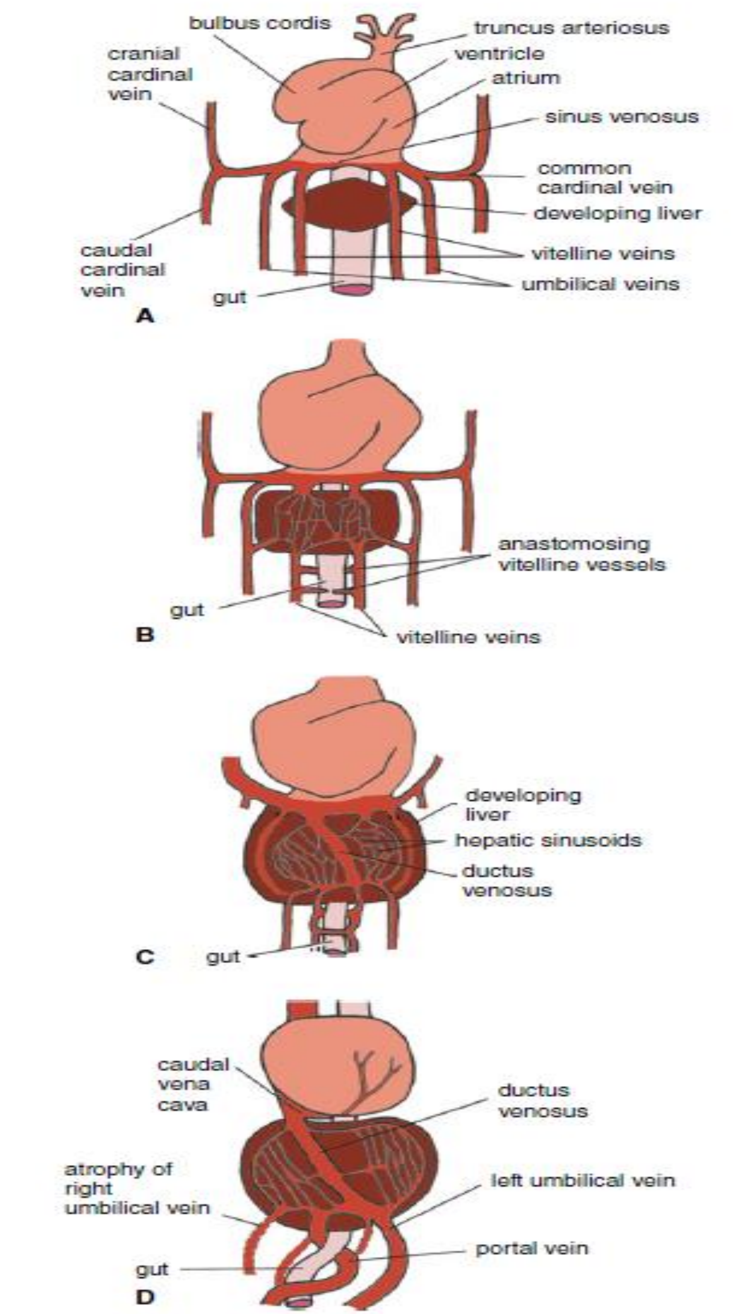


Figure 7 Sequential stages in the differentiation of the vitelline and umbilical veins. During this differentiation, the hepatic sinusoids and the portal vein are formed (A to D).

Umbilical veins

- Paired umbilical veins, which convey blood from the allantois through the umbilical cord, pass through the septum transversum and enter the sinus venosus (Figure 7). As a consequence of the enlargement of the developing liver, the umbilical veins become subdivided into cranial, middle and caudal segments, each with a different developmental fate. As the liver expands laterally, the middle portions of the umbilical veins become incorporated into the hepatic tissue and contribute to the formation of the liver sinusoids.
- The cranial segments of the left and right umbilical veins atrophy. At the umbilicus, fusion of the left and right umbilical veins occurs. Subsequently, the caudal segment of the right umbilical vein atrophies and, as a consequence, the caudal segment of the left umbilical vein enlarges and conveys oxygenated blood from the placenta to the embryonic liver. Initially, blood flows through the hepatic sinusoids to reach the right horn of the sinus venosus.
- Most of the blood follows a more direct course with the development of a venous shunt between the left umbilical vein and the cranial segment of the right vitelline vein. This venous shunt is referred to as the ductus venosus. The ductus venosus persists up to birth in carnivores and ruminants but atrophies during gestation in horses and pigs.
- As a consequence, in both equine and porcine foetuses, blood from the umbilical vein passes through the sinusoids of the liver. The patent remnant of the left umbilical vein, which persists in the adult as the round ligament of the liver, is contained within the falciform ligament.

Cardinal veins

- The paired cranial cardinal veins drain blood from the head and neck region while the paired caudal cardinal veins drain the body wall. These cranial and caudal cardinal veins on the left and right sides fuse, forming the left and right common cardinal veins which open into the sinus venosus (Figure 8).
- As the venous system continues to develop, the cranial cardinal veins give rise to the internal and external jugular veins, brachiocephalic veins and the cranial vena cava.
- Two sets of paired veins arise from the caudal cardinal veins.
- The subcardinal veins drain the developing mesonephros and the supracardinal veins drain the dorsal region of the body wall.
- The caudal vena cava arises from a combination of atrophy and anastomosis of the right vitelline vein, the caudal cardinal veins and the supracardinal veins. The azygos veins arise from atrophy and anastomosis of the supracardinal veins.

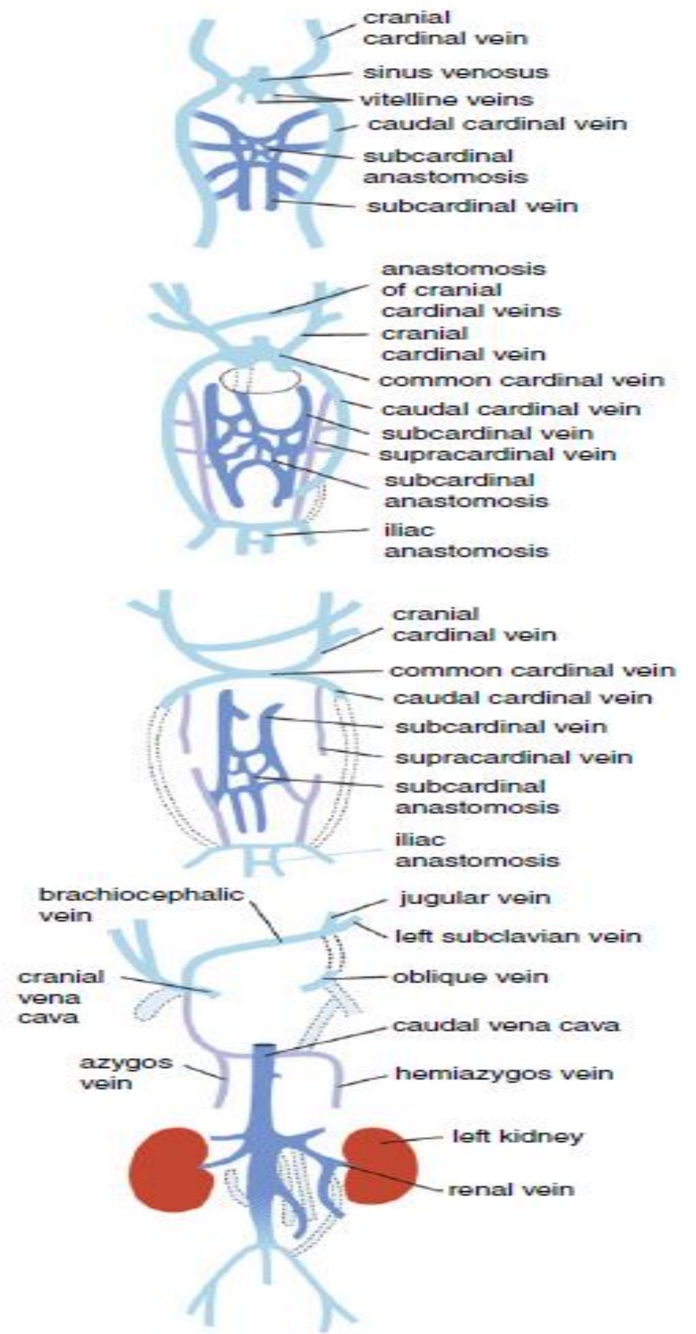


Figure 8 hanges in the arrangement of the cardinal veins and their branches leading to the formation of the cranial vena cava and the caudal vena cava and their associated veins. Dotted lines denote structures which atrophy.

The embryological origins of the cells, tissues and structures of the mammalian cardiovascular system

Figure 9 Derivatives of germ layers from which cells, tissues, structures and organs of the cardiovascular system are formed. Structures in bold print are arranged alphabetically (based on Figure 9.3).

Lymphatic vessels and lymph nodes

- In common with arteries and veins, lymphatic vessels arise from mesoderm by vasculogenesis and angiogenesis. Shortly after the establishment of the cardiovascular system, lymphatic vessels develop in a manner similar to that described for blood vessels.
- Initially, six primary lymph sacs develop in the late internal jugular veins, followed by a single retroperitoneal sac close to the root of the mesentery. An additional sac, the cisterna chyli, develops dorsal to the retroperitoneal sac. A pair of iliac sacs also develop at the junction of the iliac veins.
- Lymphatic vessels draining the head, neck and forelimbs arise from the jugular sacs. Drainage of lymph from the pelvic region and hind limbs occurs through the iliac sacs, while the retroperitoneal sac and cisterna chyli drain the viscera.
- Each jugular sac is connected to the cisterna chyli by a large lymphatic vessel. Anastomoses between these two vessels gives rise to a plexus of lymphatic vessels. From the combination of fusion, atrophy and remodelling of these vessels, the thoracic duct is formed.
- At a later stage of lymphatic development, the lymphatic sacs become interconnected by a series of lymphatic vessels and a lymphatic drainage system becomes established (Figure 10).
- The plexus between the jugular sacs and the cisterna chyli gives rise to the thoracic duct which opens into the jugular vein. Other connections between the lymphatic system and the venous system atrophy.

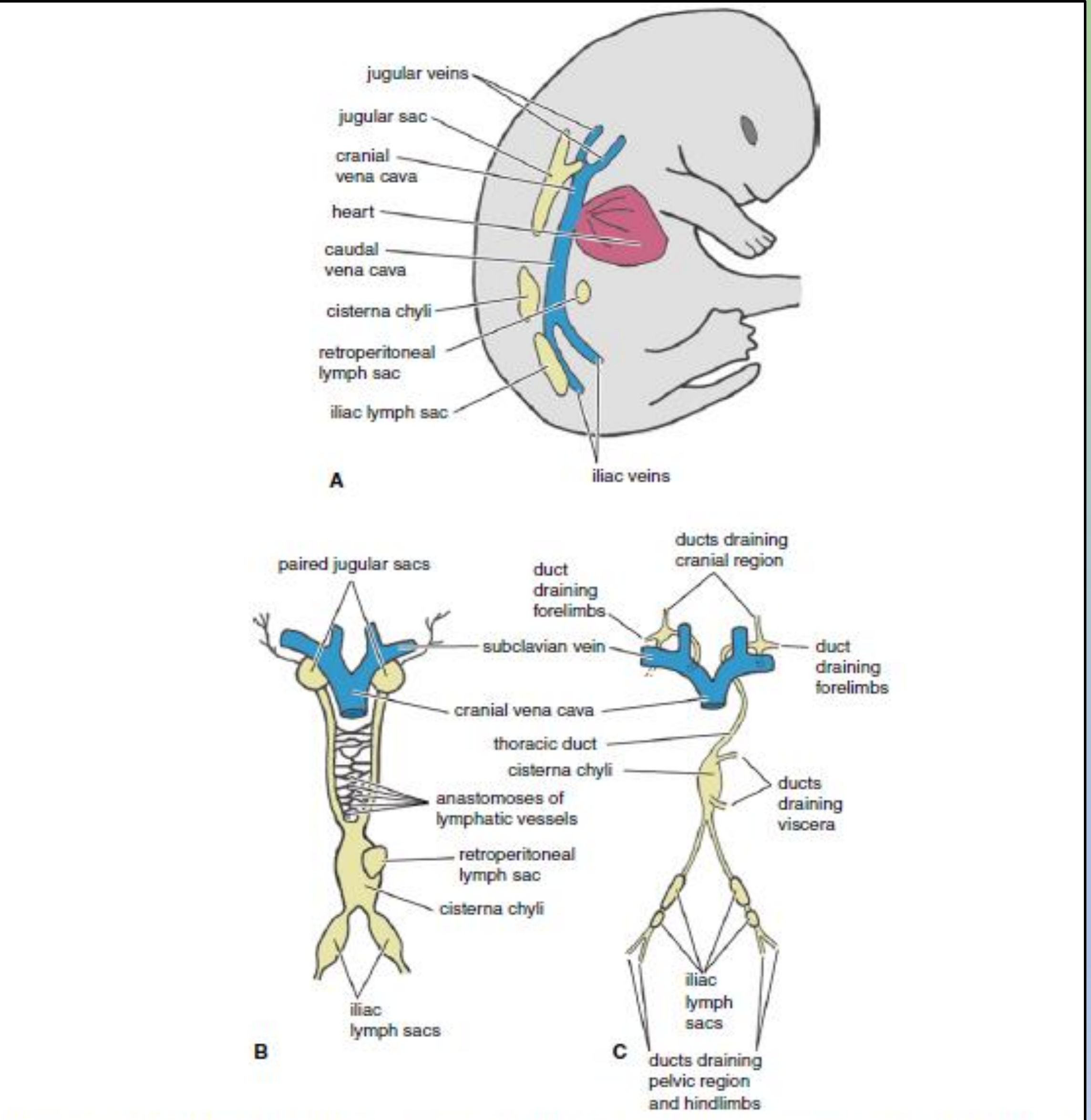


Figure 10 Outline of the developing lymphatic system, A and B, and the ducts draining lymph from regions of the embryo into the venous system, C.

Development of lymph nodes

- Apart from the cisterna chyli, the lymph sacs become converted into lymph nodes by aggregation of lymphoid tissue around the sacs. Mesenchymal cells which surround the sacs infiltrate these structures and convert them into a network of lymph channels. Later in development, additional lymph nodes develop along the course of the lymphatic vessels throughout the body. Lymph nodes are encapsulated structures composed of a meshwork of reticular cells containing numerous lymphocytes. The capsule and connective tissue framework of lymph nodes is also mesenchymal in origin. Developing lymph nodes become seeded by differentiated lymphocytes from the thymus and bone marrow which give rise to the nodular lymphoid masses. A typical mammalian lymph node consists of a cortical region and a medullary region (Figure 11A). The cortical parenchyma at the periphery contains lymph nodules while the central medullary region contains anastomosing cords of lymphoid tissue.
- In most species the direction of lymphatic drainage is from the cortical region through the medulla to the hilus. The structure of the porcine lymph node differs from other domestic animals in that the lymph nodules are centrally located with the cords at the periphery (Figure 11B). The flow of lymph in the porcine lymph node is in the opposite direction to that in other domestic animals, with lymph entering at the hilus and leaving from the cortex.

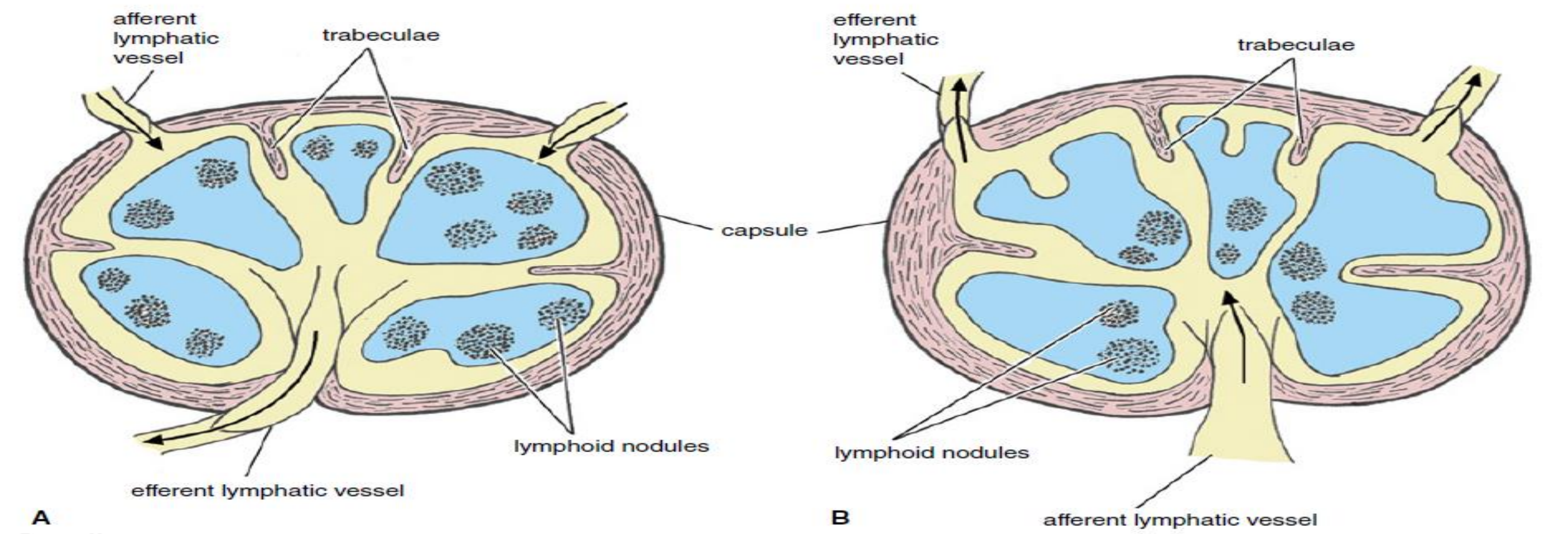


Figure 11 Comparative structural features of a typical mammalian lymph node, A, and a porcine lymph node, B, illustrating the distribution of lymph nodules and the direction of lymph flow (arrows).

Derivatives of foetal blood vessels and associated structures in mature animals

- 1 The remnant of the intra-abdominal portion of the **left umbilical vein** persists in the adult animal as the round ligament of the liver (**ligamentum teres hepatis**).
- 2 The **ductus venosus** becomes the **ligamentum venosum**.
- 3 After anatomical closure, the **foramen ovale** is represented by a depression known as the **fossa ovalis**.
- 4 The **intra-abdominal portions of the umbilical arteries** form the round **ligaments of the bladder** which are located in the lateral ligaments of the bladder. The **remains of the urachus** persist in **the median ligament of the bladder**.
- 5 The **ductus arteriosus** becomes the **ligamentum arteriosum**.

Developmental anomalies of the cardiovascular system

- In view of the complexity of the processes involved in the development of the heart and the major blood vessels, and the dramatic circulatory changes which occur at birth, it is not surprising that congenital anomalies occur occasionally in mammals.
- The prevalence of congenital cardiovascular anomalies in dogs is approximately 1%, with a higher incidence in pedigree animals than in mixed breeds. Although patent ductus arteriosus, pulmonary stenosis, aortic stenosis, vascular ring anomalies, tetralogy of Fallot, ventricular defects and atrial defects are reported periodically in many dog breeds, the frequency of their occurrence is not constant worldwide.
- Approximate frequencies of cardiovascular anomalies in horses is 0.2%, in cattle 0.17% and, in pigs, up to 4%.
- In horses, cattle and pigs, ventricular septal defects and aortic stenosis are the most common cardiovascular anomalies reported.
- The lower recorded frequency of cardiovascular anomalies in food-producing animals may be attributed to the fact that many are slaughtered before clinical signs become evident.

Patent ductus arteriosus

- If the ductus arteriosus remains patent after birth, rising pressure in the aorta and left ventricle forces blood from the aorta into the pulmonary artery and occasionally into the right ventricle (Figure 12B).
- In order to maintain adequate systemic circulation for normal function, the cardiac output must be increased.
- The condition may be suspected by the presence of a machine-like or continuous murmur on auscultation over the region of the aortic and pulmonary valves.
- Patent ductus arteriosus may be hereditary in some breeds of dogs such as poodles, collies and German shepherds and occurs more commonly in bitches than in male dogs.

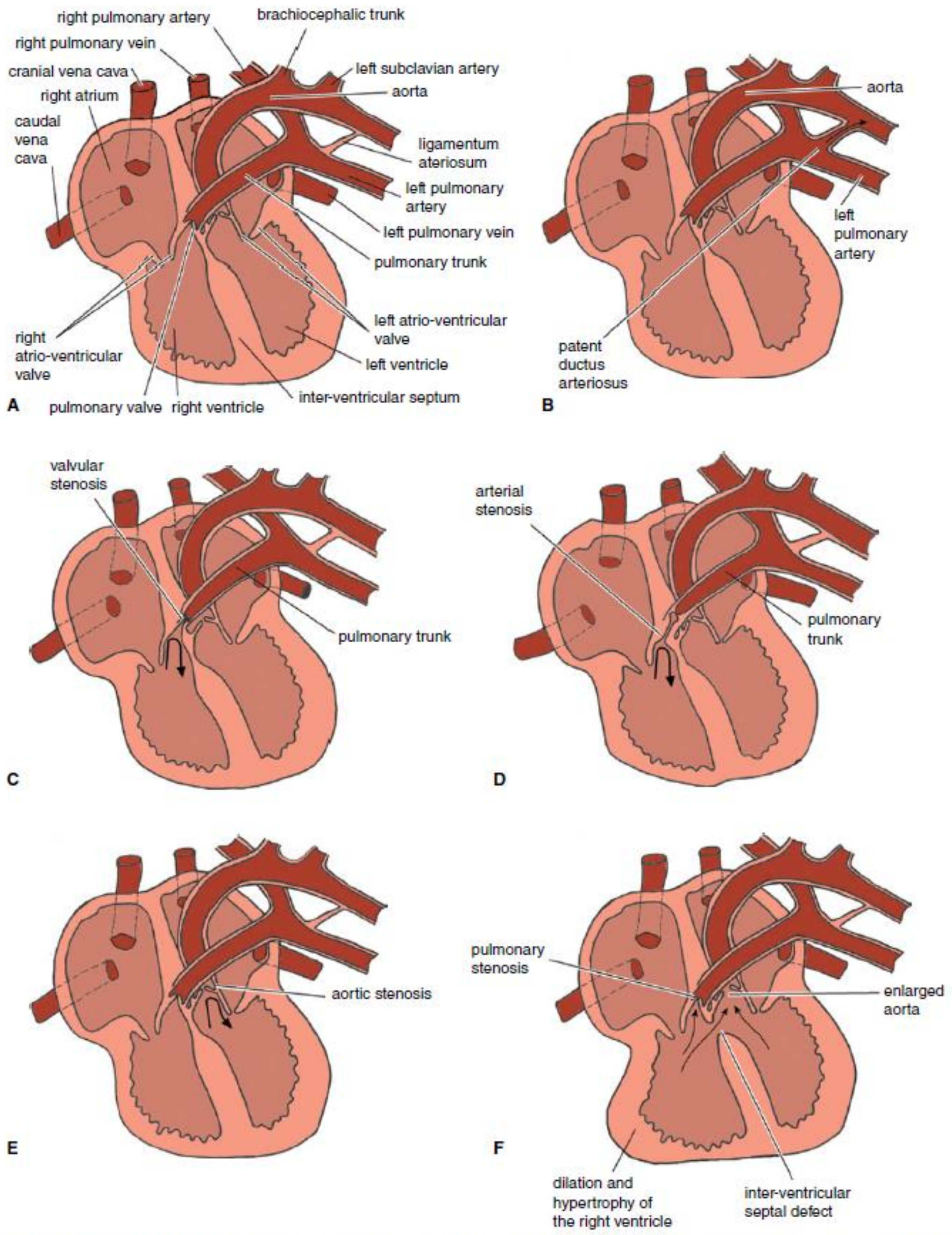
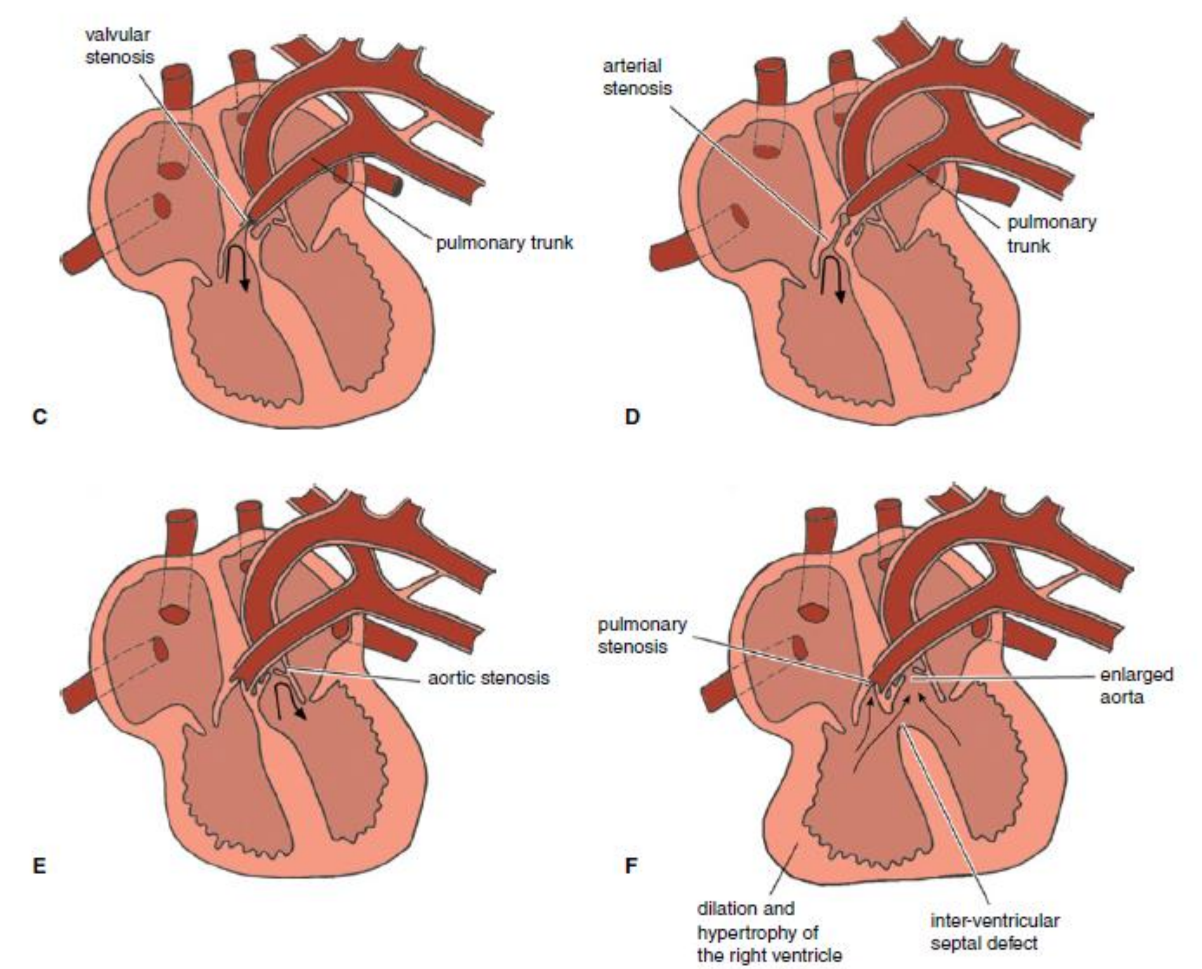


Figure 12 Sections through the heart showing normal anatomical arrangement, A. B. Patent ductus arteriosus. C and D. Pulmonary stenosis. E. Aortic stenosis. F. Tetralogy of Fallot. Arrows indicate direction of blood flow.

Pulmonary stenosis

- Narrowing of the pulmonary artery or pulmonary valves impedes the normal flow of blood from the right ventricle to the lungs, a condition referred to as pulmonary stenosis (Figure 12 C and D).
- The valvular form of the condition occurs more frequently than the arterial form.
- The condition is reported more frequently in bulldogs, fox terriers, beagles and keeshounds than in other breeds of dogs.
- Clinical signs may not be detected in pups, but evidence of right heart failure can become obvious between six months and three years of age, characterised by weakness, shortness of breath, syncope and venous congestion.
- In this condition, a systolic murmur can be heard on auscultation over the region of the pulmonary valve.



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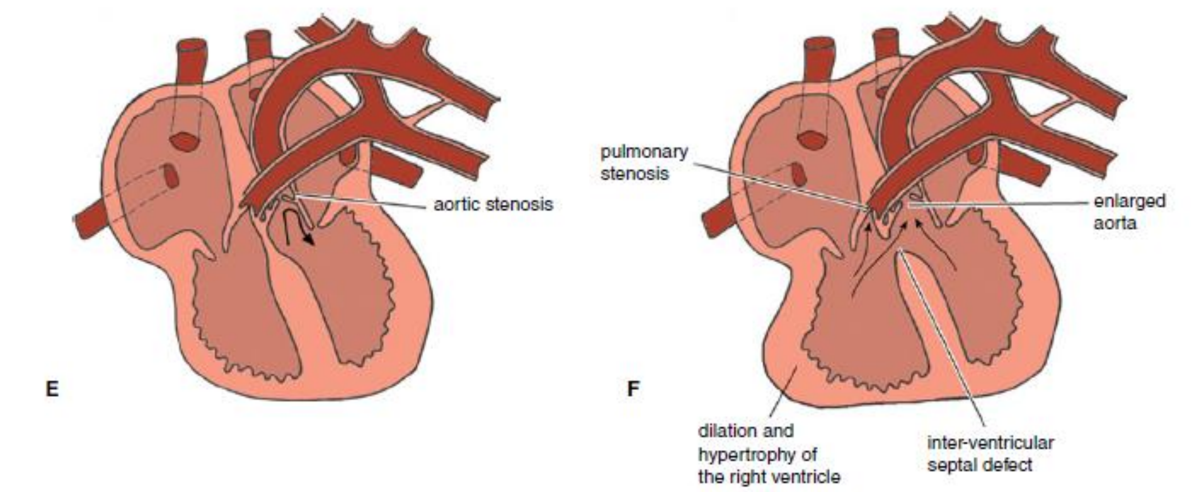
Aortic stenosis

- Narrowing of the aorta or aortic valves impedes normal aortic outflow from the left ventricle, a condition referred to as aortic stenosis.
- It occurs most commonly in Newfoundland dogs, Rottweilers, boxers and German shepherds.
- The condition is usually caused by a subvalvular proliferation of fibromuscular tissue or by defective valve formation which leads to left ventricular dilatation and hypertrophy.
- In dogs with this condition, a systolic murmur is often heard on auscultation in the region of the fourth left intercostal space (Figure 12E).



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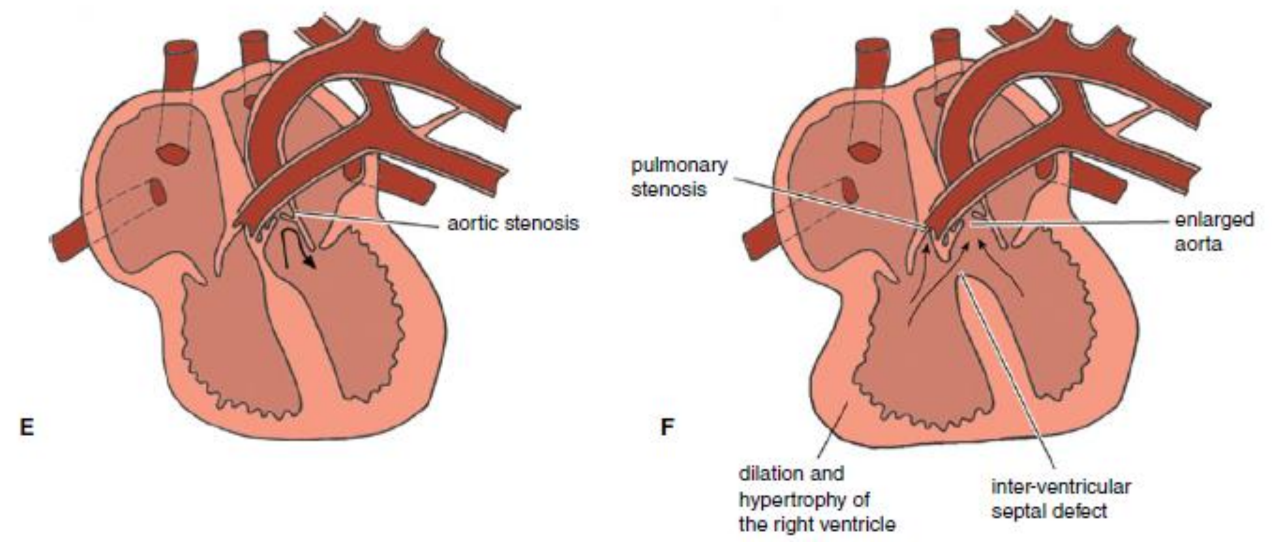
Tetralogy of Fallot

- Tetralogy of Fallot is characterised by an inter-ventricular septal defect, pulmonary stenosis and an enlarged aorta which is partially positioned over the right ventricle, thereby allowing deoxygenated blood from the right ventricle to enter the aorta (Figure 12F).
- This anomalous development, which results in right ventricular hypertrophy, a compensatory response to pulmonary stenosis, occurs occasionally in domestic animals.
- Signs of this defect become evident early in life and include stunted growth and exercise-induced cyanosis.



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Thank you for your attention.