CARDIOVASCULAR SYSTEM DEVELOPMENT

After the first 3 weeks of embryonic development the systems begin to develop. The first system that develops inside the embryo is the cardiovascular system.

The cardiovascular system is active from the beginning of the 4th week, when the placenta is no longer able to give the requirements to the growing embryo.

It is the first system capable of functioning in the embryo. The development of the heart and the circulatory system are described together as the cardiovascular system.

The heart is the first functional organ that forms in the embryo. Development begins very early in mesoderm both within (embryonic) and outside (extra- embryonic, yolk sac and placental) the embryo.

The heart grows rapidly creating an externally evident heart bulge on the early embryo. The heart forms initially in the embryonic disc as a simple paired tube inside the forming the pericardial cavity, which, when the disc folds, brings the tube into the correct anatomical position in the chest cavity.

Throughout the mesoderm, some small regions differentiate into blood islands which contribute to the formation of both blood vessels (the walls) and red blood cells. These islands connect together to form the first vessel that connects with the heart tube.

FORMATION OF THE PERICARDIAL CAVITY

Coelom:

is a greek term (koilma =cavity) used to describe a cavity or space filled with liquid. Placental vertebrate development have both extra-embryonic (outside the embryo) and intra-embryonic (inside the embryo) coeloms.

The extra-embryonic coelom includes:
- amniotic cavity;
- chorionic cavity;
- yolk sac;
- allantoid.

While the intra-embryonic coelom forms as a single cavity developing into the lateral plate of the mesoderm during the 3rd week.

The coelom divides the lateral plate into somatic and splanchnic mesoderm and will later be portioned into the three main body cavities:
- pleural cavity;
- pericardial cavity;
- peritoneal cavity.

All coelomic cavities are closed and independent cavities containing lubricating liquid that allows the surfaces to move against each other without friction. The organs (lung, heart, etc.) develop adjacent to the cavities and are pushed against the wall of the coelomic cavity.

During the folding of the germinative disc, the coelomic cavity surrounding the heart will constitute the future pericardial cavity.

The heart pushes against the dorsal wall of the pericardial cavity and is surrounded by it, thus forming the dorsal mesoderm. Through this membrane the heart is suspended, for a short time, in the pericardial cavity. Subsequently the dorsal mesoderm degenerates to allow the heart tube to grow. Once the organ is inside this cavity, it is surrounded by a visceral serous, which derives from the wall of the cavity against which the organ has pushed. Externally, the cavity is delimited by a parietal serous which corresponds to the wall of the primitive cavity against which the organ has not pushed.

Visceral serous is the visceral pericardial leaflet. Parietal serous is parietal pericardial leaflet, and the space between the two sheets is the pericardial cavity.

PRIMITIVE HEART TUBE

The development of the heart begins with the formation of the primitive heart tube following the folding of the embryo at the end of the 3rd week.

The lateral ventral fold creates the heart tube, in fact the two endocardial tubes merge into a single heart tube, around the 21st day.

The heart starts beating on the 22nd day.

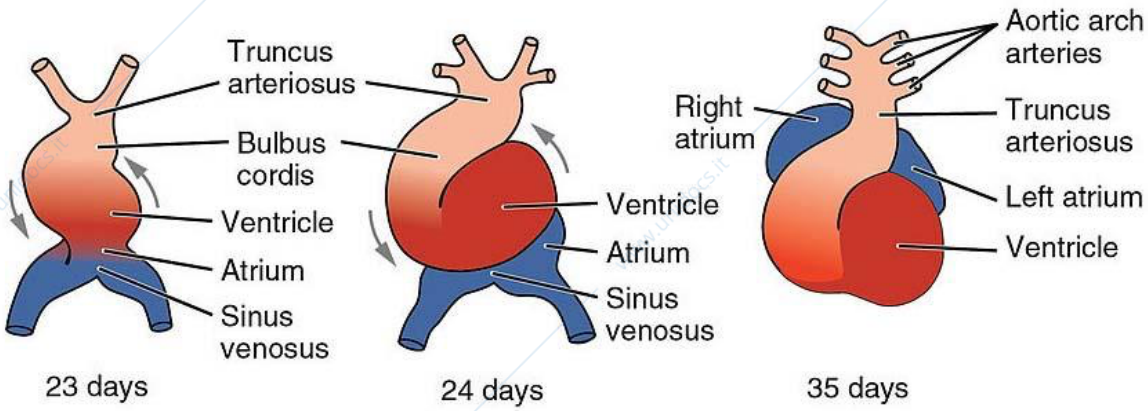
Then we have the caudal cephalus fold which places the primitive heart tube inside the future thorax.

The upper to lower heart tube consists of six regions:
- aortic roots;
- truncus arteriosus;
- bulbus cordis;
- ventricle;
- atrium;
- sinus venosus.

The primitive heart tube that is free in the pericardial cavity stretches into a narrow space undergoing specific folding around the 23rd day of development.
The bulbus cordis moves ventrally, caudally and to the right (forward, down and to the right) and the caudal portion, the primitive ventricle, moves dorsally, cranially and towards the left (backwards, up and left).

Region of the primitive heart bulb will evolve:

the lower end will give rise to a large part of the right ventricle, the upper end forms the outflow tract.
The caudal part of the heart tube is initially made up of 2 atria which then merge to form the primitive atrium. The right and left venous sinuses are located in the pericardial cavity, dorsally to the primitive atrium. The venous sinuses then undergo a partial fusion forming a venous sinus that opens into the primitive atrium. The unfused portions of the venous sinuses constitute the right and left horns of the definitive venous sinus.



ATRIA

At the fourth week, the venous sinus is responsible for the blood supply to the primitive heart, and empties into the primitive atrium. This receives venous blood from the left and right sinus horn.
As the heart develops, the venous return passes to the right side of the heart, causing the left horn to recede and form the coronary sinus, which is responsible for draining venous blood from the heart. The enlarged right sinus horn is absorbed by the growing right atrium and finally forms part of the inferior vena cava in the adult.

In the left atrium, a similar process occurs with the pulmonary veins. The four pulmonary veins are incorporated in the left atrium, forming the smooth inflow portion of the left atrium and the oblique sinus pericardium.

FORMATION OF THE HEART CHAMBERS

At the end of the fourth week, septation begins, a complex process that converts the simple heart tube into the four-chamber heart. Septation of the heart in the right and left chambers occurs first, when the endocardial cushions that are developing in the atrioventricular region expand to divide the heart.

Atrial septation
The septation of the primitive atrium involves the formation of two septa and three holes. Initially from the roof of the heart atrium a sickle-shaped sagittal fold is formed, the septum primum which extends down towards the endocardial cushions and divides the primitive atrium into a right half and a left half .The primary hole (ostium primum) is a hole present before the primitive septum completes fusion with the endocardial cushions. The ostium primum is interatrial communication, in fact it allows the passage of oxygenated blood from the right to the left atrium.

Before the primary hole is closed, a second hole, the secondary hole (ostium secundum), appears inside the primary septum. The ostium secundum ensures blood flow from the right to the left atrium.
Later septum secundum, the secondary septum forms from the ventro-lateral wall of the atrium, to the right of the septum primum as a sickle-shaped membrane. The septum secundum develops with a hole known as the foramen ovale. The simultaneous presence of the secondary foramen and foramen ovale allows for right-to-left communication in the developing heart.

The timing of this process is carefully controlled. At all times there is always a hole in the septum to allow communication between the left and right atria. This allows the blood to be pushed to the left side of the heart, bypassing the still non- functional lungs.

Ventricular septation
The interventricular septum of the ventricles has two components: one muscular and one membranous.
The muscular portion forms most of the septum and develops from the floor of the ventricles towards the fused endocardial cushions, but a small empty space, the primary interventricular foramen, remains.

The interventricular foramen allows communication between the right and left ventricles. The hole is filled with the membranous portion of the interventricular septum, which is made up of connective tissue from the endocardial cushions.

Septation of the cone and arterial trunk
The outflow component of the primary cardiac tube extending distal to the primitive right ventricle is known as the conotruncal region and is formed by the conus cordis and arterial trunk. This region and the primitive right ventricle form the bulb of the heart. The outflow tract extends to the edge of the pericardial cavity where it continues with the aortic sac. In the proximal part of the bulb, a right bulbar crest and a left bulbar crest are formed. These crests progressively grow and merge, thus forming in the cone of the heart and the arterial trunk, the pulmonary aortic spiral septum during the eighth week of development. The appearance of this septum leads to the formation of the great vessels of the aorta and the pulmonary trunk.

Subsequently, the cone-truncal region through a twisting movement will give rise to the anatomical curvature of the aorta and pulmonary artery.

CIRCULATORY SHUNTS

In fetal circulation, vascular shunts are required to bypass the non-functional liver and lungs.

The lungs are bypassed by two separate shunts, first the foramen ovale between the two atria, which is responsible for bypassing the increased circulation. The blood that does not pass through the oval shape enters the pulmonary trunk, which is linked to the distal arch of aorta by the ductus arteriosus. These two separate shunts (shunt means circulation, direct communication) allow the circulation to bypass the lungs.

The oxygenated blood entering the fetus also needs to bypass the primitive liver, which ensures that enough oxygen reaches the developing brain.

All this is achieved by passing through the ductus venosus, it is estimated that this duct diverts (let us pass) approximately 30% of the umbilical blood directly to the inferior vena cava.

At birth these shunts must close to allow normal adult circulation to establish: Foramen ovale: inspiratory acts cause pulmonary resistance to disappear. The pressure on the intent of the left atrium is now greater than that on the right. Since blood cannot pass through the foramen ovale from left to right, this effectively shuts off the circulation (the shunt). It closes in most individuals at the age of about one year.

Ductus arteriosus: the muscle wall contracts to close it after birth (a process mediated by bradykinin) Immediately after birth the arterial duct narrows, allowing blood to escape from the right ventricle go to the lungs through the pulmonary arteries.

The foramen ovale closes, leaving a small depression called the fossa ovale. This isolates the deoxygenated blood from the oxygenated blood inside the heart.

The adult remnant of the foramen ovale is the fossa ovalis.

The adult remnant of the ductus arteriosus is the ligamentum arterium, while the adult remnant of ductus venosus is the ligamentum venosum.

The adult remnant of the fetal shunt, such as umbilical vein is the ligamentum teres (hepatis).

FETAL CIRCULATION

Until birth, the metabolic and respiratory exchanges of the embryo and fetus take place at the placental level.

Venous blood from the placenta, where it has oxygenated, returns to the heart via the umbilical vein. The left umbilical vein, near the liver, opens into the venous duct, after anastomosis with the intrahepatic portal circulation. Blood from the umbilical vein through the venous duct (when the sphincter is relaxed) and through the hepatic veins (when the sphincter is contracted), reaches the inferior vena cava, which opens into the right atrium. The blood flow from the inferior vena cava

is directed from the septum secundum towards the foramen ovale and, through the ostium secundum, flows into the left atrium. Non-oxygenated blood from the superior vena cava forms a hemodynamically separate current in the right atrium from blood from the inferior vena cava and passes mainly into the right ventricle. The left atrium then receives a small amount of blood from the lungs through the pulmonary veins and, through the foramen ovale, oxygenated blood from the lower vein. The oxygenated blood from the left atrium passes into the left ventricle, from where it enters the initial tract of the aorta.

The non-oxygenated blood, from the right ventricle enters the pulmonary trunk, from where, through the left pulmonary artery and the Botallo arterial duct, it flows into the aorta. Only downstream of the Botallo duct do the two blood flows mix. This ensures that the head and cranial portion of the trunk are supplied with oxygenated blood. Arterial blood, from the descending aorta, through the iliac arteries, enters the umbilical arteries, thanks to which it returns to the placenta to oxygenate.

TETRALOGY OF FALLOT

Tetralogy of Fallot is a congenital heart defect in which there are 4 abnormalities: - Overriding aorta: an aorta that is connected to both the left and right ventricles - Pulmonary stenosis: a narrowing of the outflow tract of the right ventricle

- Ventricular septal defect: failure of interventricular septum to fully close.

- Right ventricular hypertrophy: the right ventricle is more muscular than normal.

It is the most common cyanotic congenital heart defect and is often diagnosed before birth by echocardiography. Treatments are in the form of surgery in the first year of life, in which the pulmonary valve can be widened and the ventricular septal defect repaired. If the condition is not treated, Tetralogy of Fallot results in progressive worsening of right ventricular hypertrophy, also leading to heart failure.

DEVELOPMENT OF THE CIRCULATORY SYSTEM

The vessels are formed by vasculogenesis and angiogenesis. The development of blood vessels begins in the yolk sac wall and is associated with that of the hematopoietic progenitors. In the mesenchyme of the extraembryonic splanchnopleura, by induction of the endoderm, groups of cells, the hemangioblasts, are condensed, which constitute the blood islands. While the peripheral cells of the islands become the angioblasts, precursors of the endothelial cells, the central ones become the hematopoietic progenitors. Not all endothelial cells arise from hemangioblasts. In the embryo, the endothelial progenitors arise from all the mesoderm, except the notochord.

Blood vessel development begins in the yolk sac wall around the 17th day. The development of intraembryonic blood vessels begins a day later, when the first angioblasts appear in the mesenchyme of the splanchnopleura. Angioblasts form angioblastic cords from which, after the formation of the lumen, a primitive endothelial network originates. The process of formation of de novo vessels, through the confluence of angioblasts that unite and delimit a lumen, is called vasculogenesis. The primitive vascular network extends, adapting itself to the growth of the embryo, through the elongation of new vessels, which are formed by budding from pre-existing ones, through a process called angiogenesis. The endothelial channels, distinguished in the arterial and venous compartment, undergo successive phenomena of maturation and remodeling and the cells that form the vessel wall (smooth muscle cells, fibroblasts) are recruited. After the twenty-first day, the embryonic and extra-embryonic vascular networks are united and circulation begins.

The embryonic heart is connected to the circulatory system consisting of a symmetrical vascular system. The outflow routes, with the cephalic folding, are formed by the ventral components of the aortas, which subsequently merge near the primitive heart to form the aortic sac, connected to the bulb. The aortic arches branch off from the aortic sac, joined to the dorsal aortas around the twenty-fifth day. The aortic arches are visible in the pharyngeal arches.

The inflow pathways consist of the common cardinal, vitelline and umbilical veins, right and left, which are collected in the right and left horns. The horns open into the venous sinus which is joined to the primitive atrium via the sinoatrial orifice.

THE DORSAL AORTA

The two dorsal aortas are born by vasculogenesis around the 19th day in the dorsal region of the splanchnopleura. Their cephalic end connects to the endocardial tubes and assumes a dorso-ventral curvature which constitutes the first aortic arch, when the cardiac sketch moves ventral and caudal (22nd-24th day). With the development of the pharyngeal arches, the aortic arches are formed that join the aortic sac with the dorsal aortas. These remain separate in the pharyngeal region, while caudally between the fourth thoracic segment and the fourth lumbar segment merge into the dorsal, uneven and median aorta.

AORTIC ARCHES

The development of the aortic arches follows a craniocaudal course. The first aortic arches of our greatest interest are the 1st, 2nd and 3rd pair as they constitute the vascularity of the head and neck. The 1st pair is placed in the mesenchyme of the 1st pharigeal arch (mandibular arch). As the 2nd pair of aortic arches develops (26th day), the 1st regresses. Subsequently, around the 29th day, the 2nd arc also regresses. The regression of the first two arcs is incomplete. In fact, the remains of the 1st arch form the maxillary arteries, while the hyoid and stapedial arteries derive from the 2nd.

3rd aortic arch

The carotid system develops from the first three aortic arches and their roots. After the regression of the 1st and 2nd arch, the ventral roots remodel and form the external carotids. The dorsal roots of the first two arches joined to the cephalic extensions of the dorsal aortas form the internal carotids. When the dorsal aortic tract between the 3rd and 4th arch disappears (35th-38th day), the 3rd arch arteries form the proximal tract of the internal carotids, while their ventral roots become the common carotids.

4th arch	Right arch forms the right subclavian artery Left arch forms part of the arch of the aorta
5th arch	Either never forms, or forms incompletely and regresses
6th arch	Right arch forms the right pulmonary artery Left arch forms the left pulmonary artery and the ductus arteriosus.

Each of the arches has a corresponding nerve during development. The most important of these is the recurrent laryngeal nerve (a branch from cranial nerve X) which is associated with the 6th arch:

- *Right recurrent laryngeal nerve:* initially hooks around the right 6th aortic arch. However, when the distal part of the right 6th arch disappears, it moves up to hook around the right subclavian artery (4th arch).

- *Left recurrent laryngeal nerve:* hooks around the left 6th aortic arch. The distal part of the left 6th aortic arch persists as the ductus arteriosus, and so the nerve remains in this position.

The long course of the left recurrent laryngeal nerve is clinically relevant, as it is susceptible to pathology in the chest (e.g. compression by an aortic aneurysm).