

6. Development of circulatory system II. Cardiac looping. Septation of atria and ventricles. Common heart malformations.

Formation of heart tube

- paired endothelial-lined heart tube is formed from blood islands within cardiogenic splanchnopleuric mesoderm
- within mesoderm, cardiac myoblasts are formed
- the cardiogenic heart tube forms in late presomitic embryo anteriorly to the oropharyngeal membrane (day 18) and descends to the cervical and thoracic regions during weeks 3-4
- the pericardial cavity is separated from the primitive coelomic cavity
- the heart tube bulges into the pericardial cavity
- the heart tube is temporarily attached to the dorsal wall of the pericardial cavity with a mesodermal fold named dorsal mesocardium;
- three layers of the heart tube differentiate:
  - endocardium = the internal endothelial lining
  - myocardium = the muscular wall
  - epicardium = visceral layer of pericardium; later on, coronary vessels will originate by vasculogenesis within in this layer

Formation of the heart loop

- the heart tube grows, elongates and bends between the day 23-28, thus forming a loop
- the loops consists of:
  - atrial portion: initially a paired structure; contains venous portion of heart, the right and the left horn of sinus venosus, each of which receives a set of three veins:
    - common cardinal vein (← blood from the body)
    - umbilical vein (← blood from the placenta)
    - vitelline vein (← blood from the yolk sac)
  - atrioventricular canal = connecting the primitive atria with the primitive ventricles
  - primitive ventricle, which later on develops mainly into the primitive left ventricle
  - bulbus cordis, the primitive right ventricle, which later on develops into:
    - conus arteriosus, becoming the outflow parts of heart ventricles
    - truncus arteriosus, from which proximal aortic roots and pulmonary trunk are sprouting
- trabecular myocardium develops especially in the ventricular part of the cardiac loop

Development of sinus venosus and atria

- first, it receives blood symmetrically from the right and left sinus horns; each horn receives blood from three veins on the left and three veins on the right
- during the cardiac looping, the atria move dorsally; the atrioventricular canal is shifted to the left
- the three veins become incorporated into the growing sinus venosus
- the right umbilical vein obliterates (week 5); also the left vitelline vein and the left common cardinal vein obliterate (week 10) → the left horn of the sinus venosus is reduced and receives only the oblique vein of the left atrium and the coronary sinus

- the right sinus venosus receives more venous blood, it becomes large and it is incorporated into the growing wall of the right atrium
- the entrance to the right atrium = the sinoatrial orifice has a valvular fold on each side, the right and the left venous valves; the right one persists as valve of the inferior vena cava and the valve of the coronary sinus
- these valves dorsocranially fuse, forming a ridge named septum spurium
- the left atrium develops into the left heart auricle with the pectinate muscles; the smooth-walled part of the left atrium originates from the pulmonary veins;
- the right atrium forms the right heart auricle with pectinate muscles; the smooth-walled sinus venarum cavarum develops from the right sinus horn

Atrial septation

- the sinoatrial opening is attached to the wall of the right ventricle with a ridge named septum spurium
- the ventral and the dorsal walls are interconnected by an endocardial cushion named septum intermedium; the atria communicate with the ventricles via the right and the left atrioventricular canals on both sides if the septum intermedium
- at the end of the week 4, the roof of the common atrium proliferates towards the septum intermedium and forms a thin septum primum
- the temporary opening between the septum primum and the endocardial septum intermedium is named the ostium primum
- the ostium primum closes, but simultaneously, cell death produces perforations in the upper portion of the septum primum; the perforations form a bigger opening within the septum primum; it is named the ostium secundum
- right to the septum primum, a new crescent-shaped fold is formed = septum secundum; the opening in the septum secundum is called the foramen ovale
- before birth, the blood flows from the right atrium through the foramen ovale into the left atrium
- after birth, respiration starts → expansion of lungs → the vascular resistance of pulmonary arteries drops → blood enters the pulmonary circulation instead of the ductus arteriosus → increased venous return into the left atrium → septum primum is compressed against the septum secundum → foramen ovale closes (it fuses during the 1st year in 80% individuals; it persists in 20% of individuals as a potential communication between the left and the right atrium (probe patent foramen ovale)

Septum formation in the atrioventricular canal

- four atrioventricular endocardial cushions appear dorsally, ventrally, and on the right and left side; as they grow and fuse, they surround the right and the left atrioventricular canal
- local proliferation of mesenchyme derived from the endocardial cushions forms atrioventricular valves, attached to the ventricular wall by muscular cords; the cords are replaced by dense connective tissue = chordae tendinae; these are connected the papillary muscles of the ventricular trabecular myocardium

Septum formation in the ventricles, bulbus and conus cordis

- the primitive ventricle grows and during week 4, muscular trabecules are formed

- the ventral and the dorsal walls are interconnected by an endocardial cushion named septum intermedium
- the muscular part of the interventricular septum partially separates the left and the right ventricles, but there is still a temporary communication between the both ventricles, named the interventricular foramen
- during the week 5, pairs of opposing ridges appear in the truncus and conus arteriosus; these bulbar ridges are named truncus swellings (cushions)
- the bulbar ridges rotate spirally; they grow and they fuse in the week 7; the results of this fusion are as follows
  - the outflow parts of the right and the left ventricles become fully separated and the interventricular foramen is closed; the membranous part of the interventricular septum is finished and fuses with the conotruncal septum
  - in the region of conus arteriosus, the outflow parts of the ventricles are separated as well
  - in the region of truncus arteriosus, the aorta is separated from the pulmonary trunk

Conducting system of the heart

- initially, all embryonic cardiomyocytes are abel to create and propagate action potential → initially, the whole heart tube contracts
- later on, the myocardium differentiates into contractile cardiac myocytes and the conducting system
- the sinus venosus has the pacemaker function, it incorporates into the right atrium and forms the sinoatrial node
- the atrioventricular node develops from the cardiac myocytes of the atrioventricular canal
- the atrioventricular bundle of His, its right and left bundle branch and the Purkinje fibres develop from the ventricular myocardium

Heart defects

- present in up to 1% of live born infants
- the largest category (40%) of all birth defects; a major cause of death of newborns and infants
  - the morphogenesis of heart is quite a long and complicated process; remodeling of embryonic heart is vulnerable to any damage; also postnatally, circulatory changes occur
- multifactorial causes
  - genetics – trisomia (21, 13, 18), point mutations
  - epigenetic factors and teratogens – maternal infection (rubella virus), alcohol, drugs (Lithium), diabetes mellitus, etc.
- prenatal sonography used for screening;
- atrial septal defects
  - normally, the atria are divided by the septum primum (in which the foramen secundum is formed) and the septum secundum (in which the foramen ovale develops)
  - four types (secundum, primum, superior and inferior venous sinus)
  - the most common type: the patent foramen ovale; the f. ovale or the f. secundum are too large to be closed

- up to 25% of population have asymptomatic potential communication through the fossa ovalis
- serious atrial septal defects result postnatally into a left-to-right cardiac shunt → hypertrophy of RV and pulmonary arteries → pulmonary hypertension develops due to remodeling and thickening of pulmonary arteries

– persistent (patent) ductus arteriosus
  - normally, it is closed within three days after birth in 60% of newborns; otherwise it is obliterated no later than three months after birth
  - it is more common in prematurely bone babies
  - before birth, the E1 prostaglandin keeps the duct open (NSAID are inhibitors of the synthesis of prostaglandings, they facilitate the closure of the ductus arteriosus; substances similar to prostaglandins prevent the spasm of DA and keep it open)
  - postnatálně levopravý zkrat → hypertrofie plicnice, hrozí plicní hypertenze → hypertrofie PK (→ změna LP zkratu na PL = Eisenmengerův syndrom s cyanózou, dušností, insuficiencí PK (event. i trojcípé chlopně)
– coarctation of the aorta
  - narrowed aortic lumen below the origin of the left subclavian artery, closely to the ductus arteriosus
  - abnormal closure reflex (spasm) skips from the ductus arteriosus to the aorta
  - frequently associated with bicuspidal aortic valve
  - preductal type and postductal type
  - pressure gradient across the constricted area; post-stenotic dilatation
  - collateral circulation develops
    - internal thoracic artery → superior and inferior epigastric artery → external iliac artery
    - intercostal arteries → retrograde blood flow to the thoracic aorta
– ventricular septal defects
  - the most common developmental heart defect (up to 25%)
  - occurs as isolated condition or may be associated with multiple heart defects
  - perimembranous defects are located in the superior membranous septum
  - muscular defects are located in the inferior muscular part of the interventricular septum; these are more common and often heal spontaneously
  - abnormal partitioning of the bulbus cordis; abnormal development of the conotruncal region; incomplete fusion of the conus septum with the endocardial cushions
  - after birth, these defects cause left-to-right shunt, overload of the RV, and pulmonary hypertension
– tetralogy of Fallot
  - abnormality of the conotruncal region, unequa division of the conus, displacement of the conotruncal septum; it consists of following alterations:
    1. a large ventricular septal defect
    2. the overriding aorta arises above the septal defect
    3. stenosis of the pulmonary trunk
    4. hypertrophy of the right ventricular wall due to its overload
    5. *if atrial septal defects is also present, the condition is called the pentalogy of Fallot*

- other heart defects
  - aortic and pulmonary valvular stenosis or atresia (complete fusion)
  - transposition of the great vessels: the spiral conotruncal septum fails to separate the aorta from the pulmonary trunk properly → aorta originates from the RV and the pulmonary trunk receives blood from the LV → systemic and pulmonary circulations are parallel and separated; the only possible connection is the persisting ductus arteriosus
  - hypoplasia of left heart
  - ectopia cordis – failure of the closure of thee ventral body wall → the heart lies on the surface of the chest
  - dextrocardia (due to abnormal sense of the cardiac looping, the heart forms on the right side); it can be either isolated or may occur as a part of situs inversus (major visceral organs are reversed or mirrored)
- the heart defects may be classified according to the absence/presence of central cyanosis
  - acyanotic ("pink babies"); e.g., atrial septal defect or ventricular septal defect (Left-to-right shunts)
  - cyanotic ("blue babies"): Right-to-left shunts; the systemic circulation receives blood unsaturated with oxygen (reduced and unsaturated hemoglobin > 50 g/l); e.g., tetralogy of Fallot