

De Start van het Hart



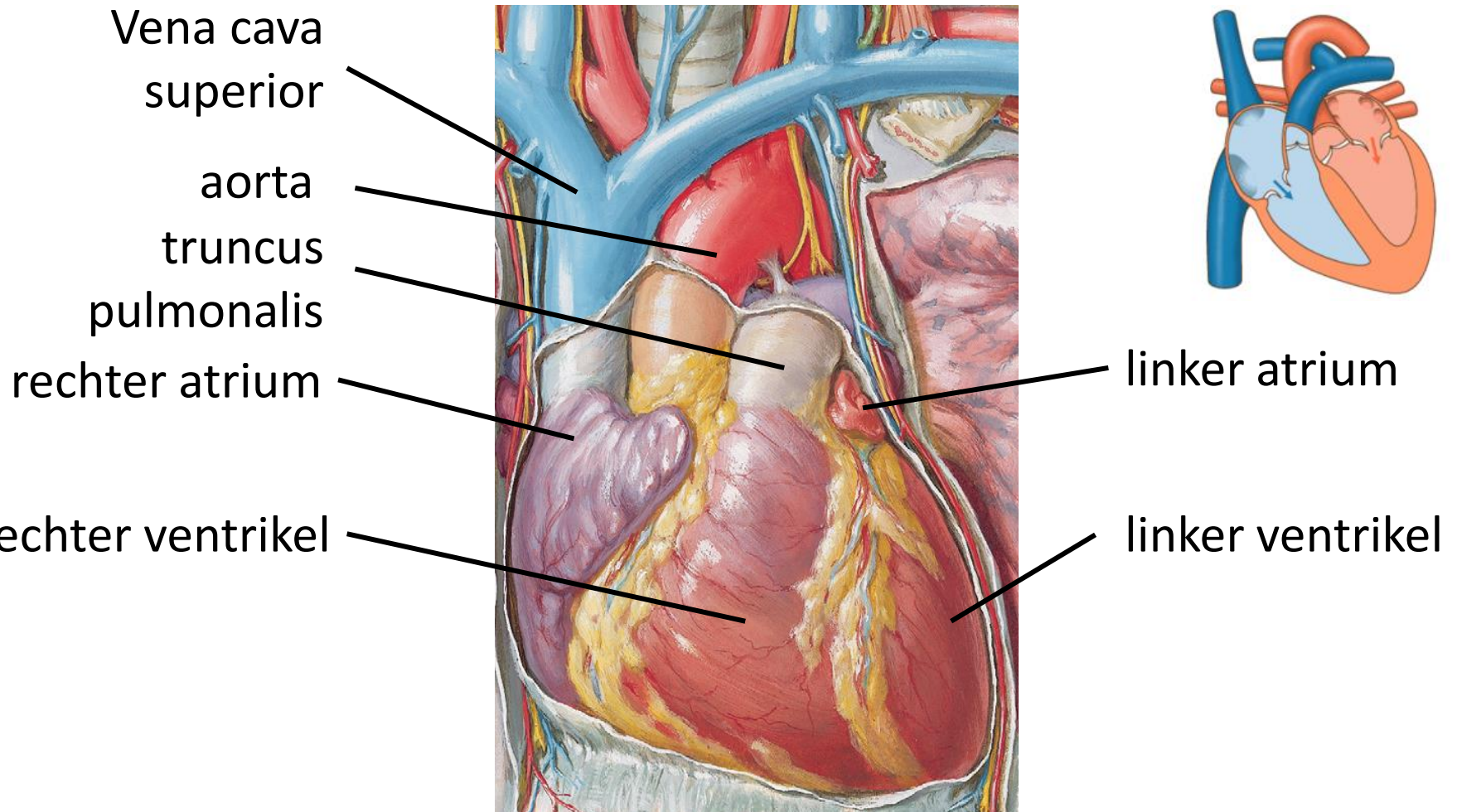
Marco de Ruiter

afd. Anatomie & Embryologie

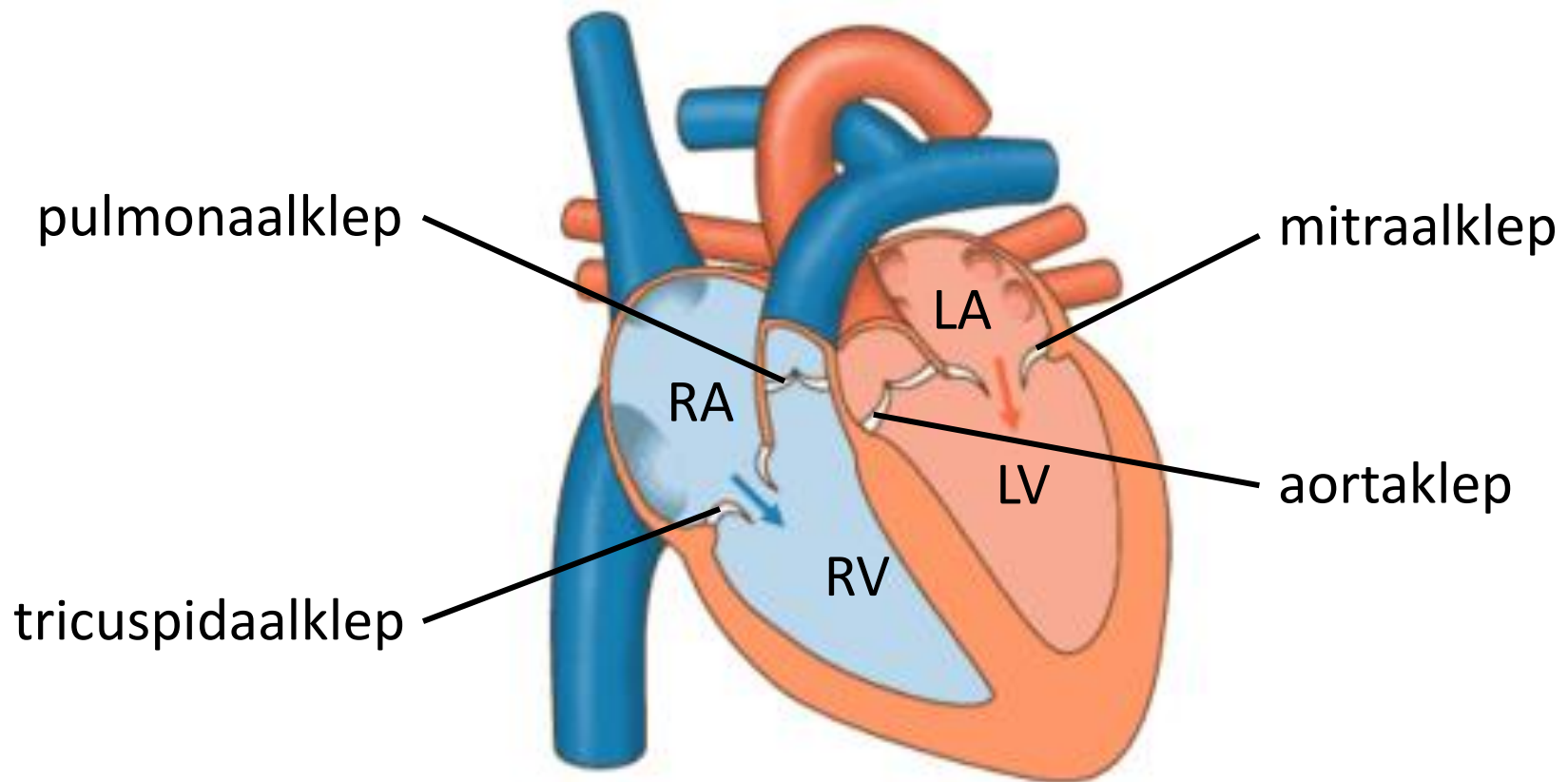
WAT KUNT U IN HET KOMENDE UURTJE VERWACHTEN ??

1. **Wat zijn de belangrijkste morfologische kenmerken van het hart?**
2. **Kunnen we deze morfologie embryologisch verklaren?**
3. **Hoe bestuderen we de ontwikkeling van hart?**
4. **Waarom zijn de meeste hartafwijkingen na de geboorte schadelijk?**
5. **Wat leren de harten van andere tetrapoden ons?**

De morfologische kenmerken van het hart

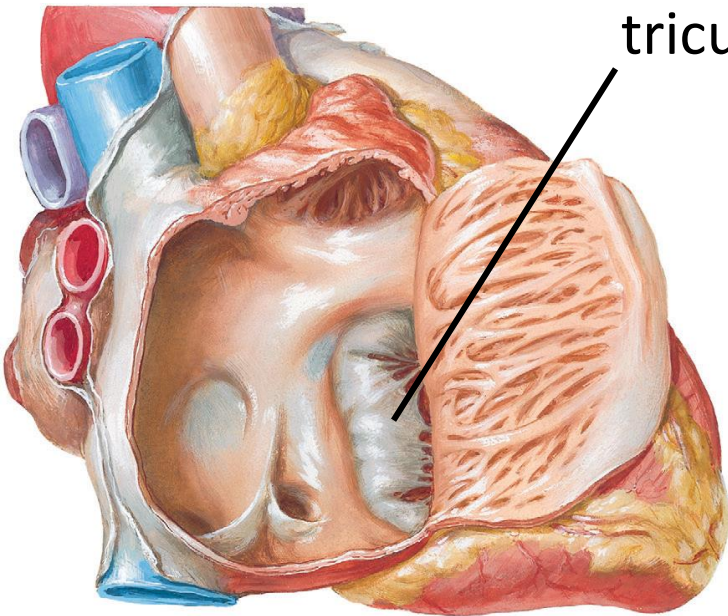
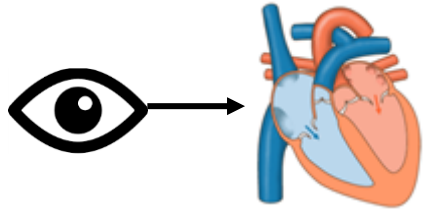


Vierkamerbeeld: Hartkleppen

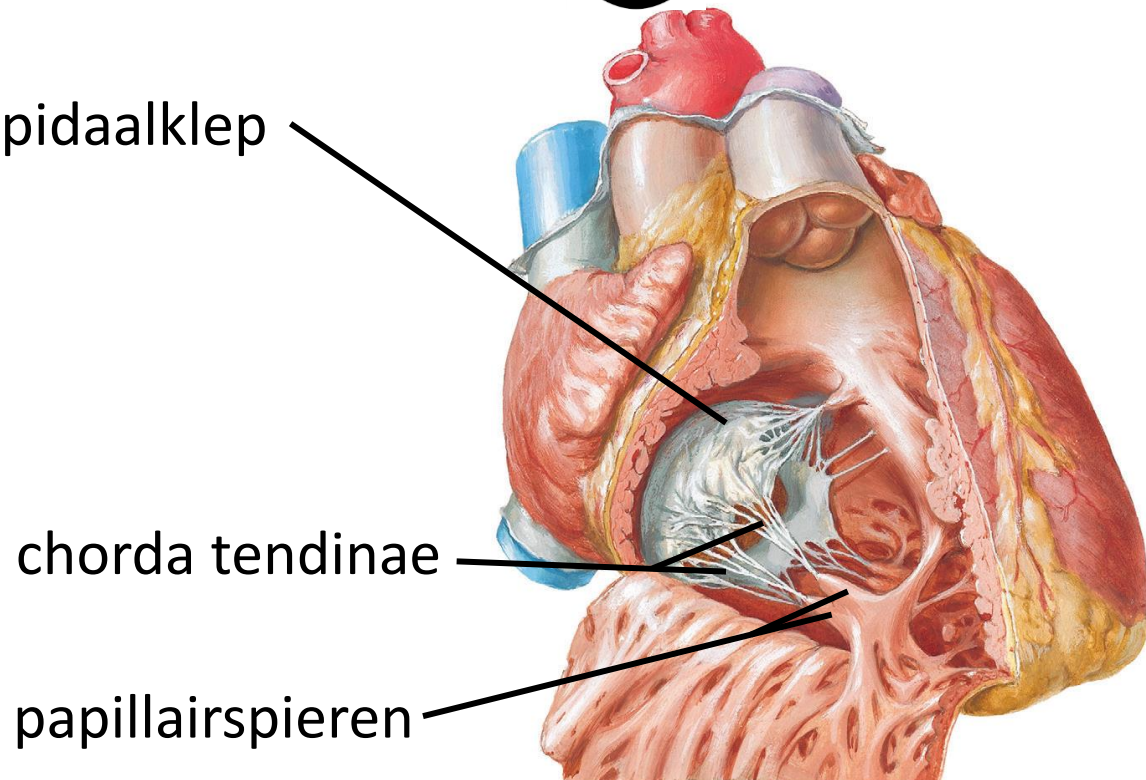
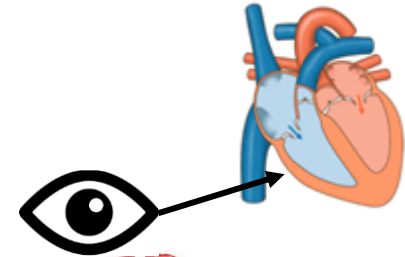


Rechterzijde hart

Hartkleppen - tricuspidaalklep



rechter atrium geopend

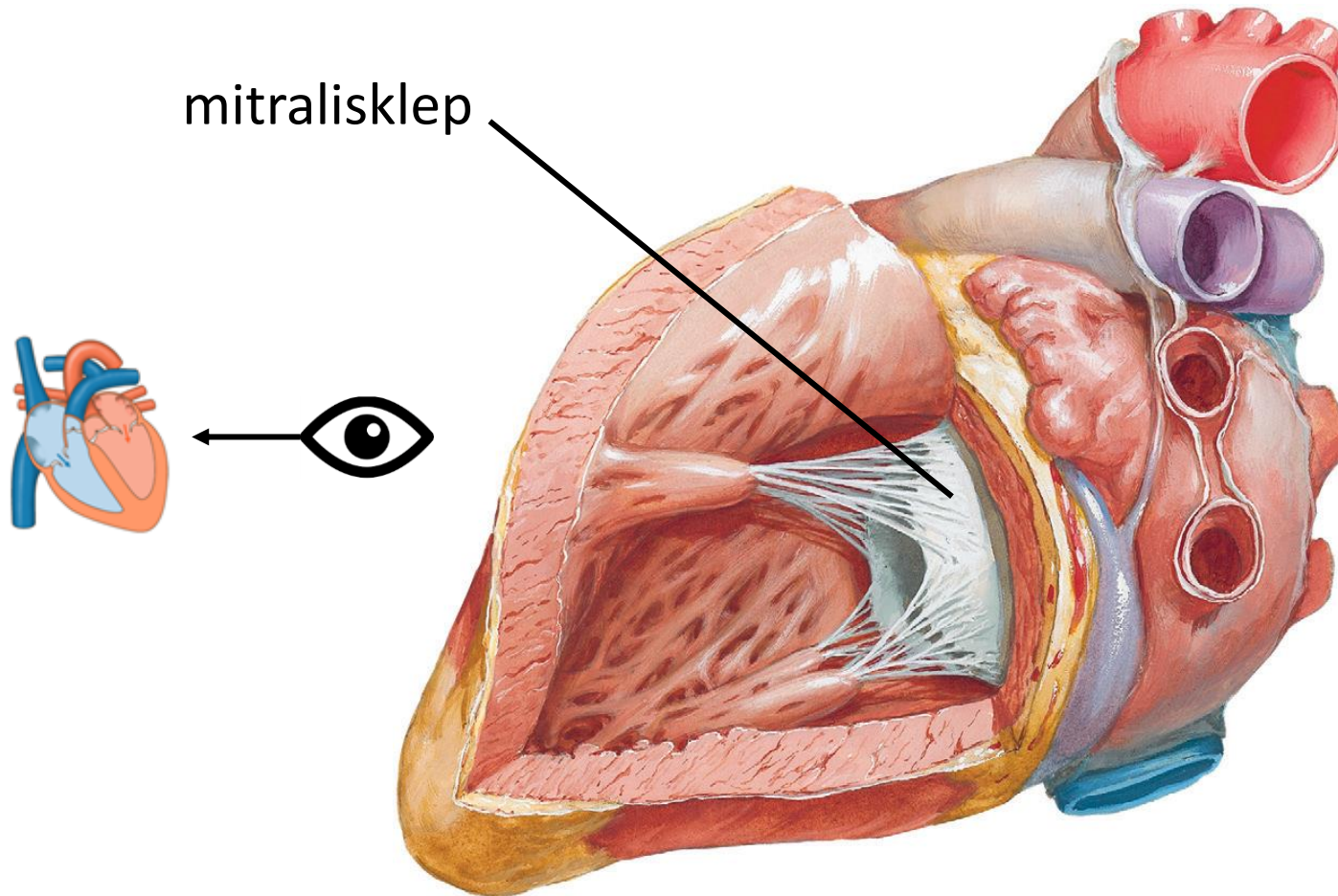


rechter ventrikel geopend

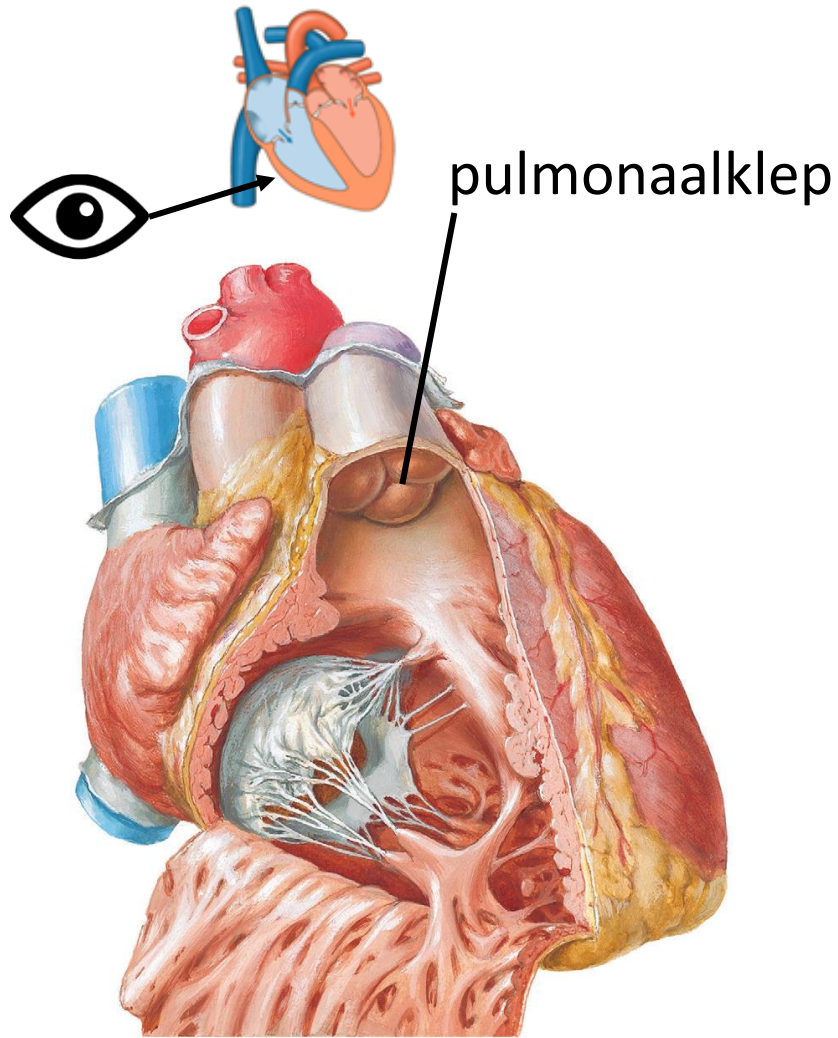
Netter's Atlas of Anatomy, 6th ed., 2014

Linkerzijde hart

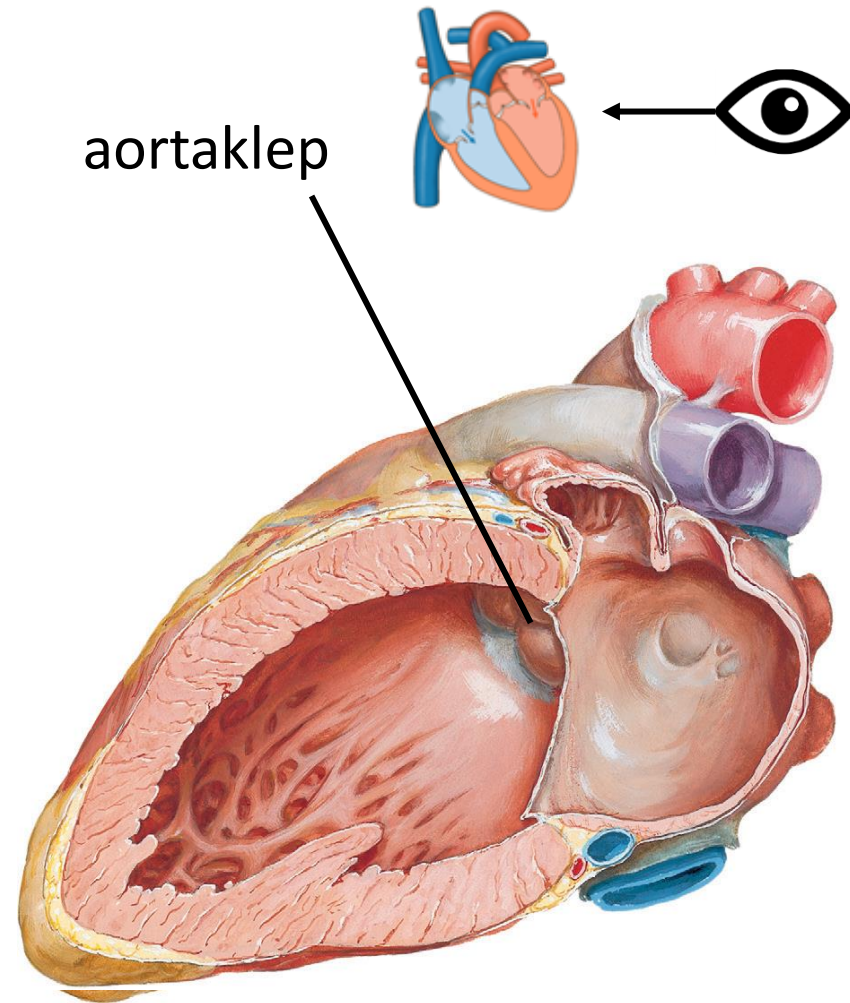
Hartkleppen - mitralisklep



Pulmonaal- en aortaklep RV en LV myocard

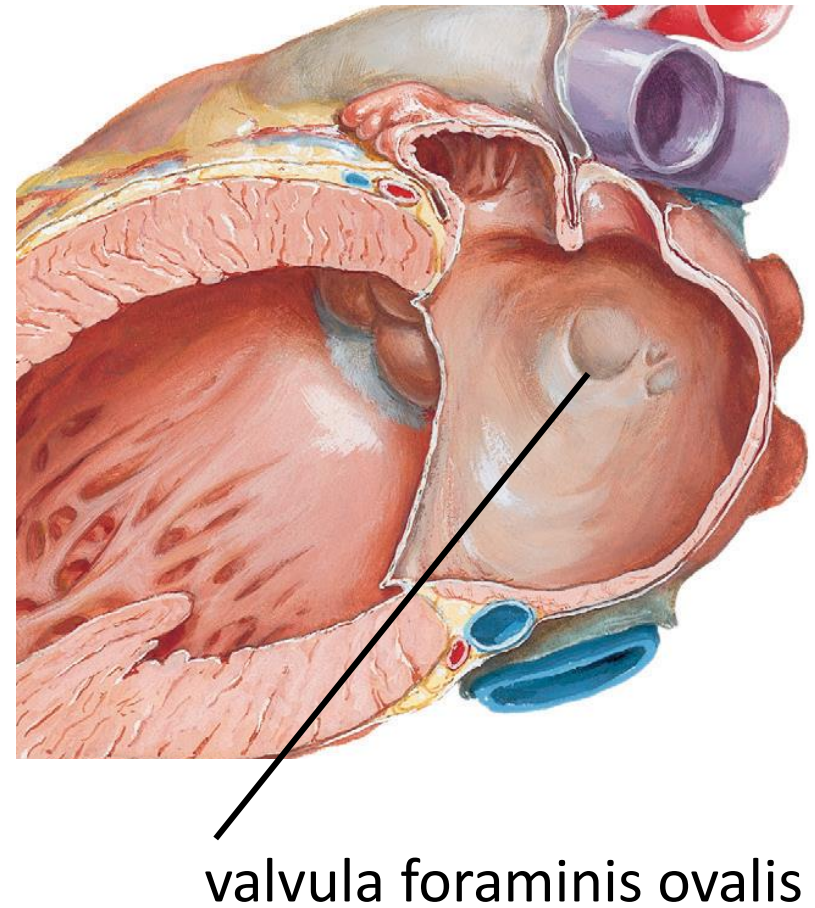
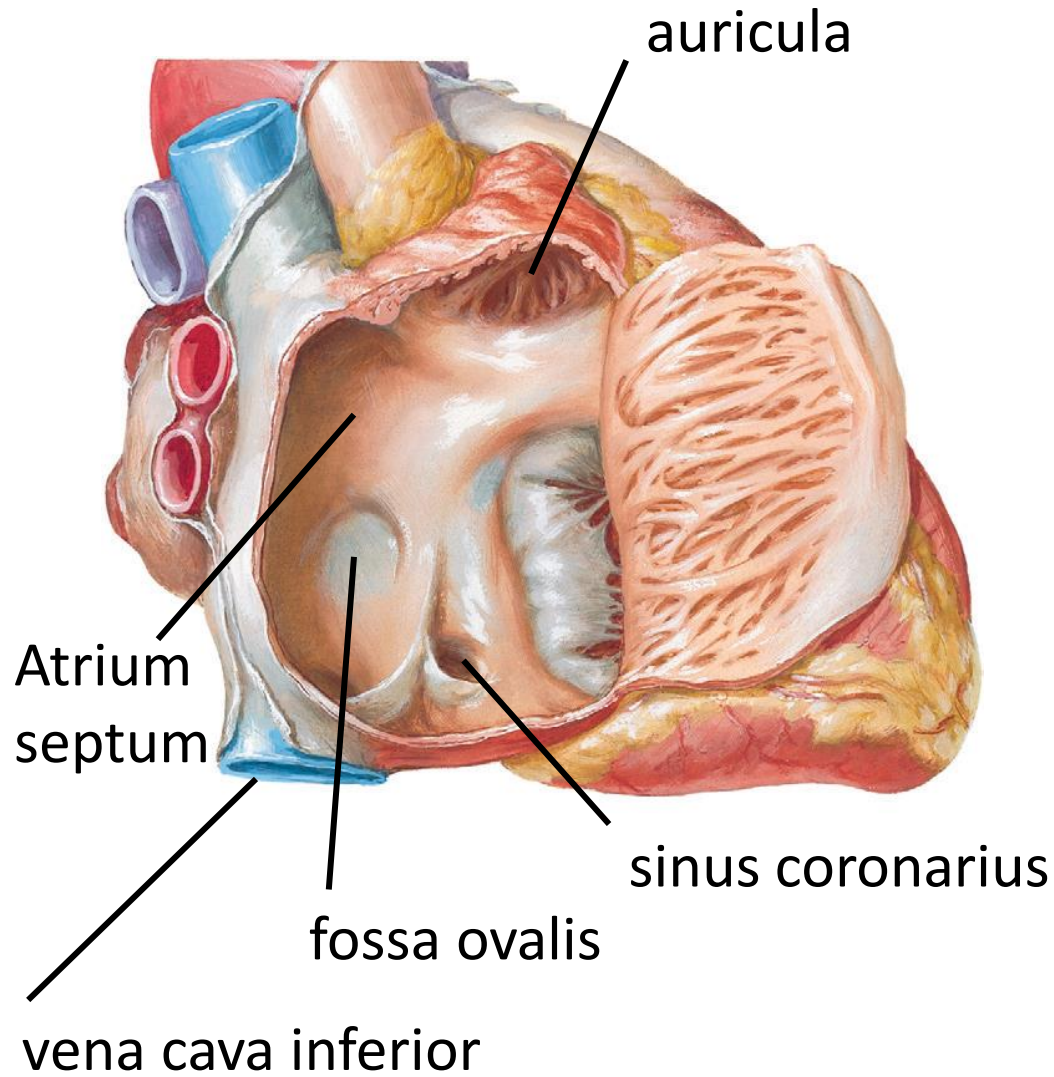


rechter ventrikel geopend



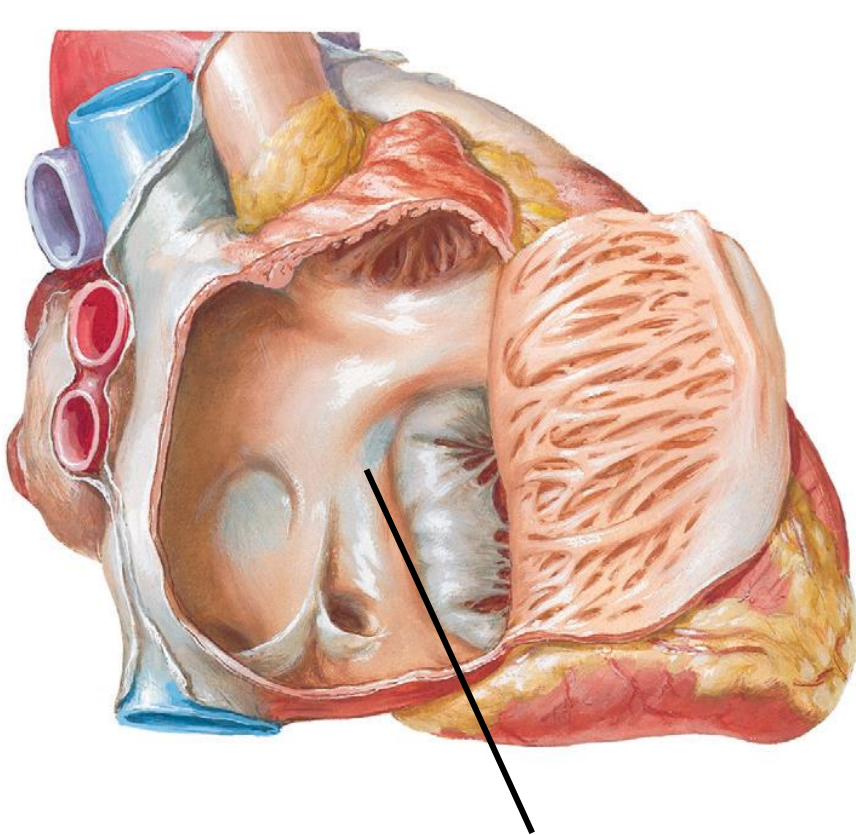
linker ventrikel geopend

Rechter en linker atrium

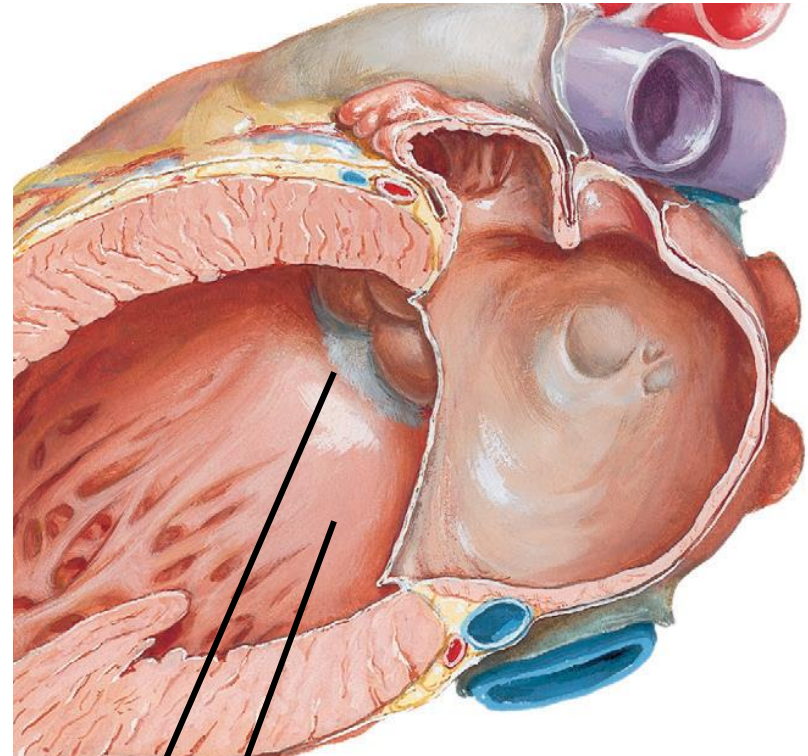


Musculeuze interventriculaire septum

Membraneuze atrioventriculaire septum



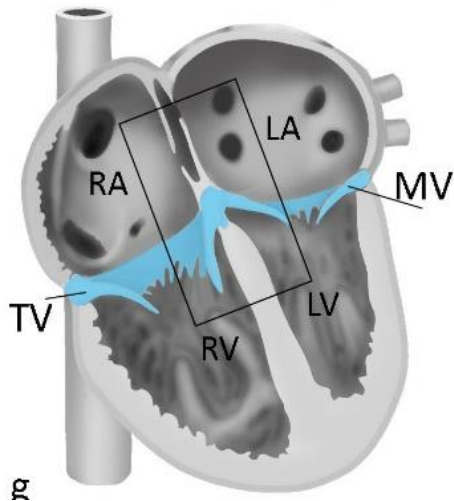
atrioventriculaire septum



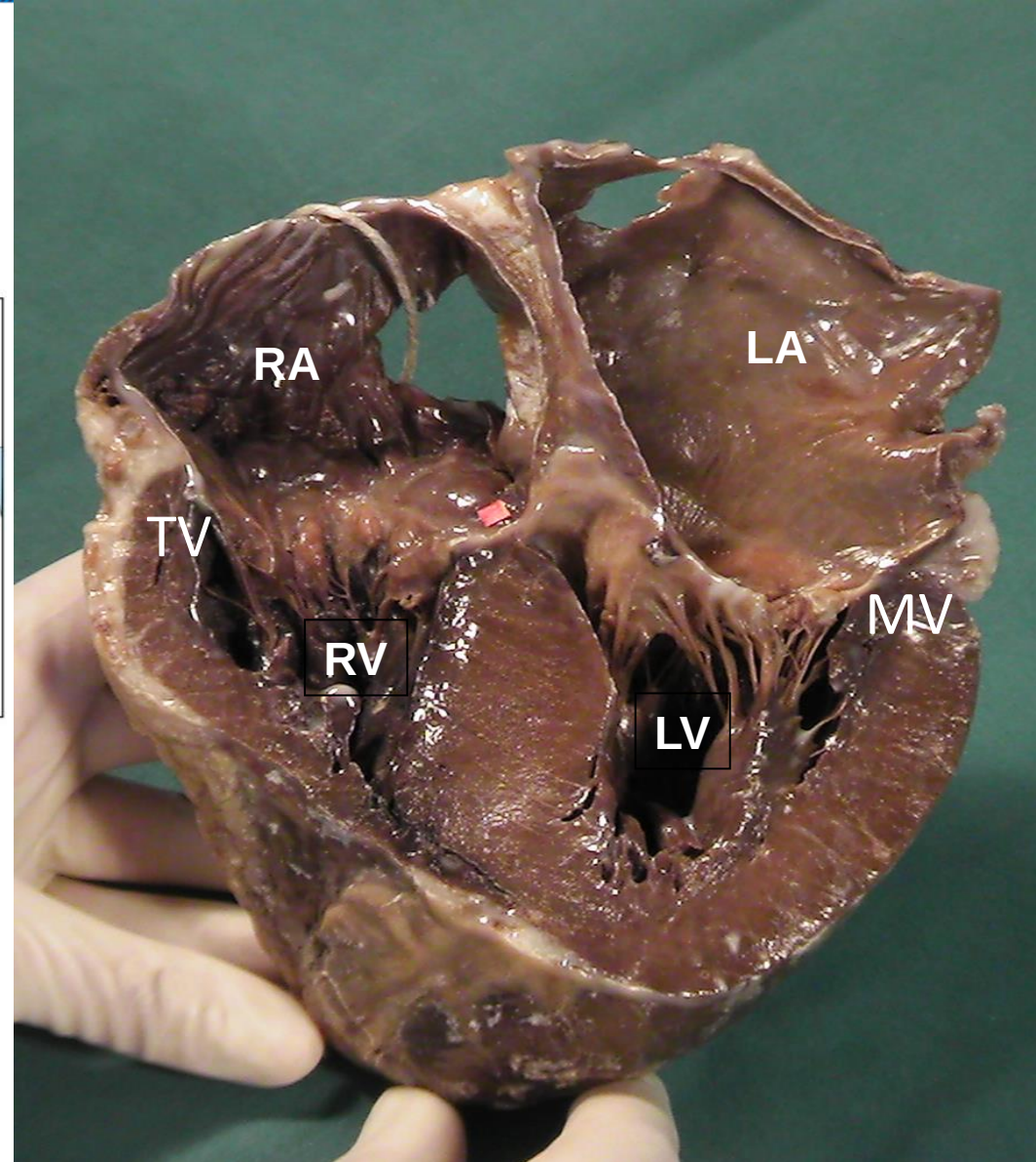
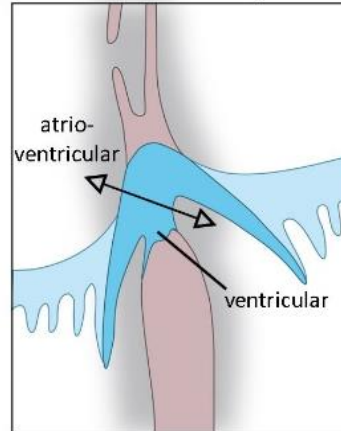
ventriculaire septum

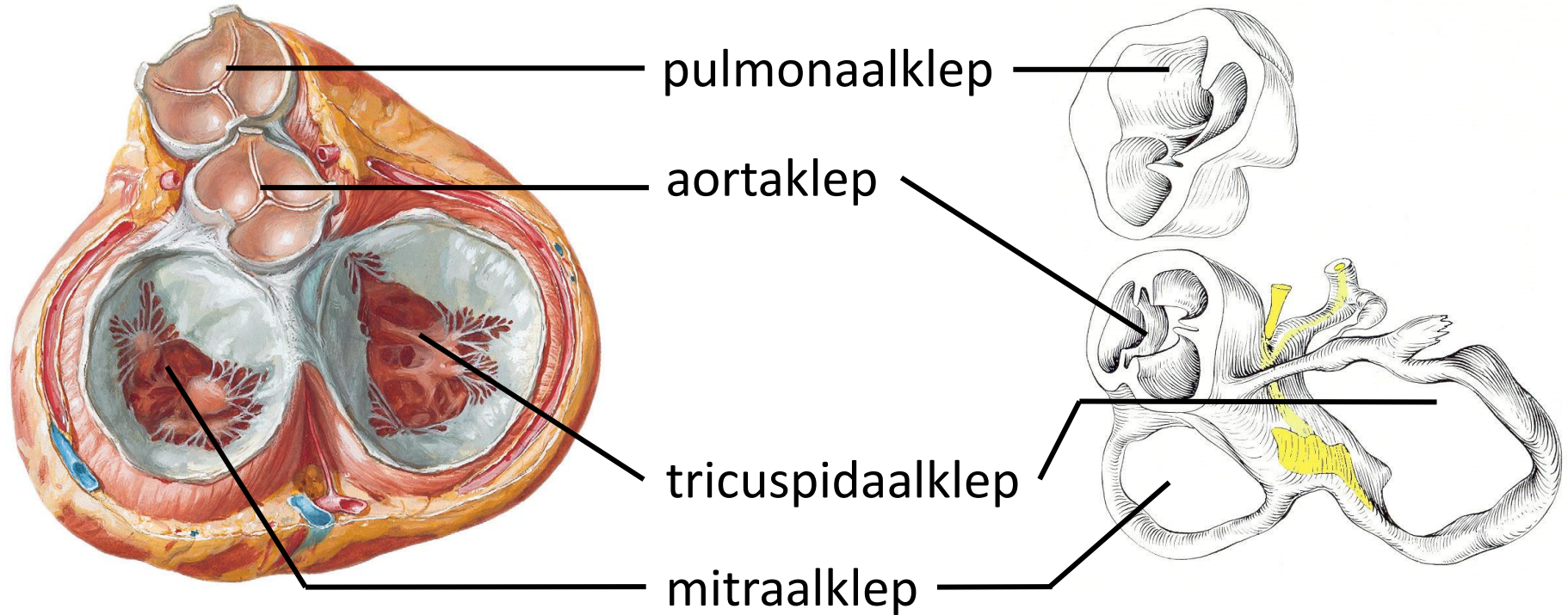
De centrale plaats van het atrioventriculaire septum; 4 kamerbeeld

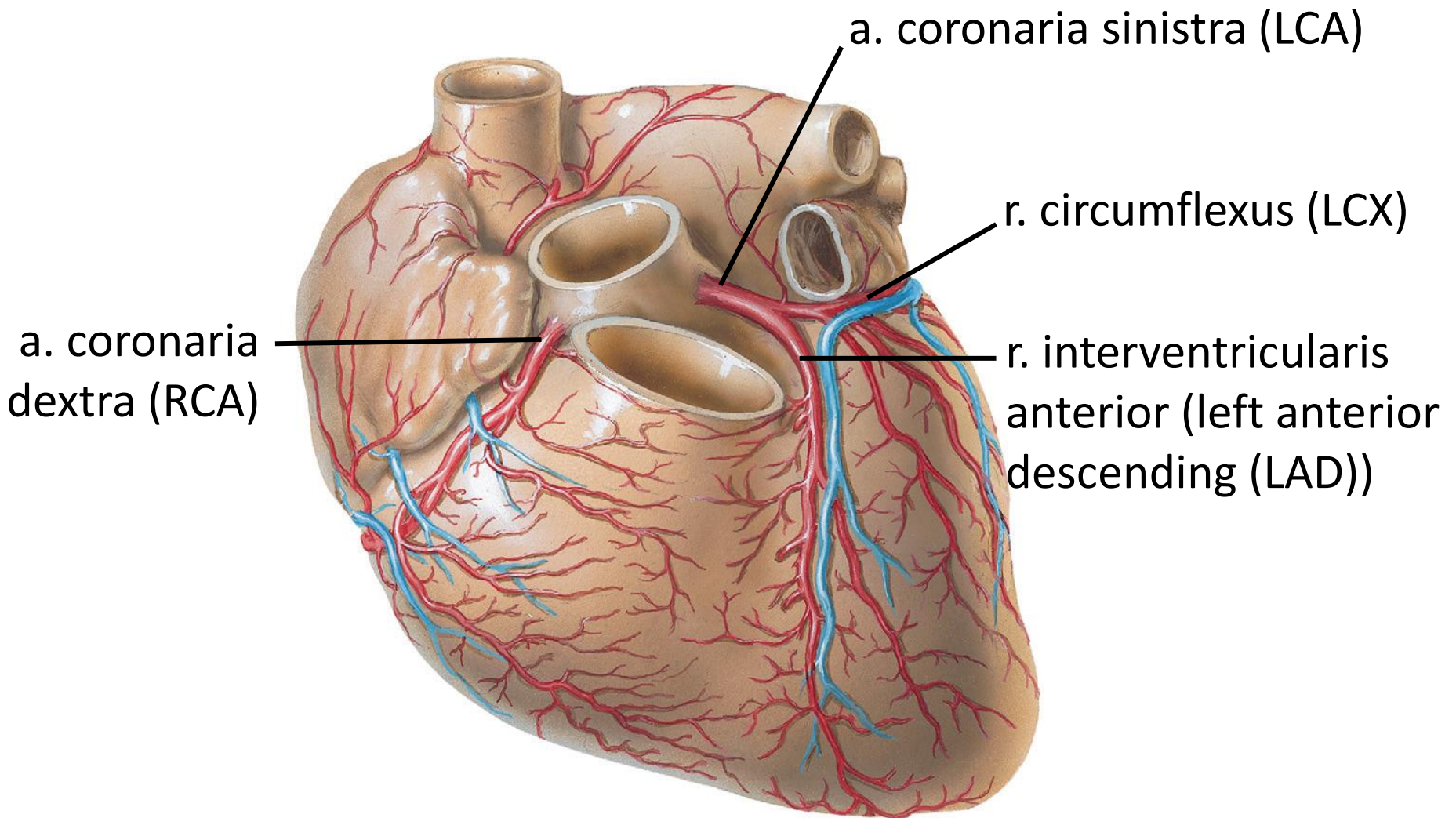
Atrioventricular septum



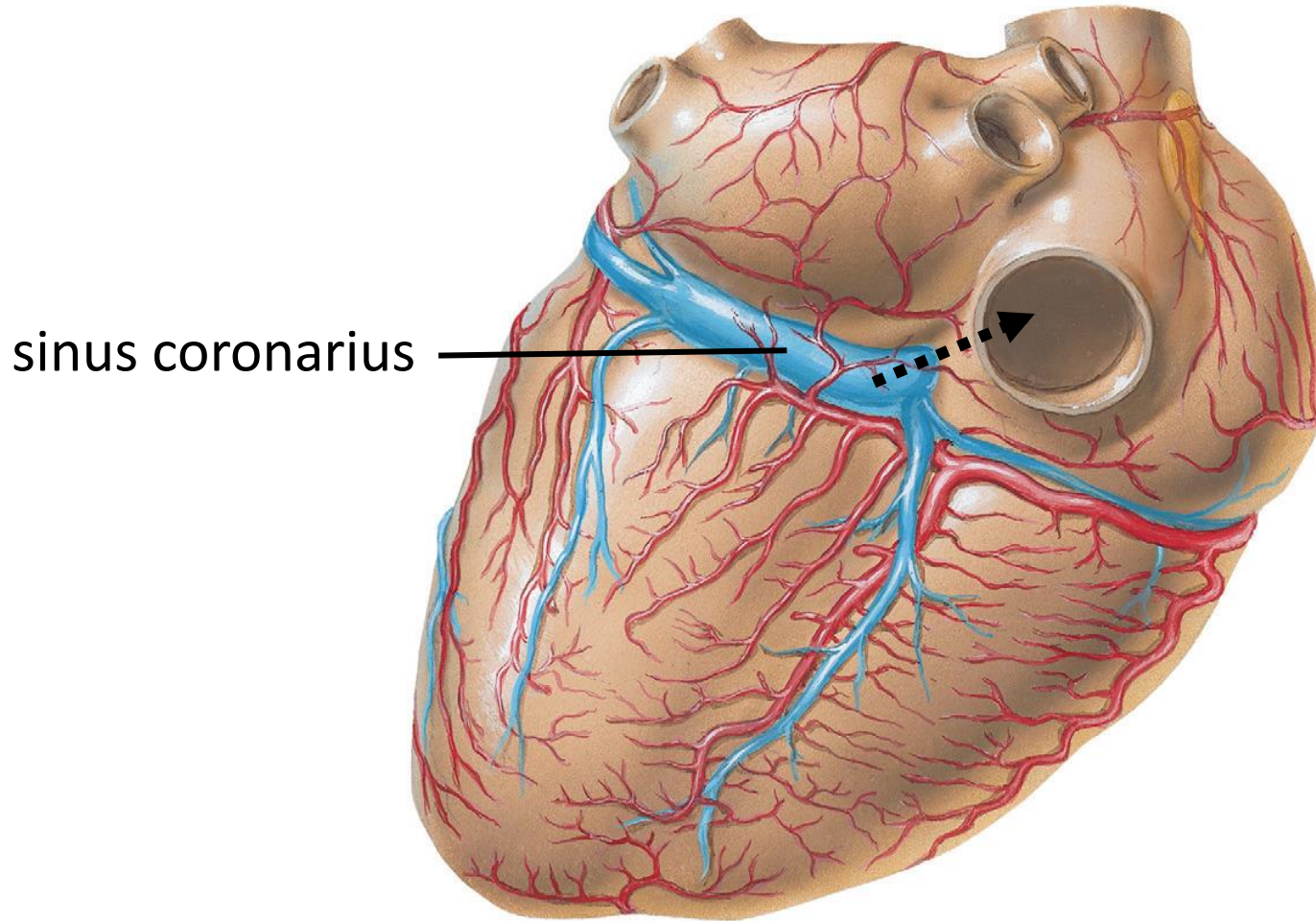
Membranous septum







vooraanzicht

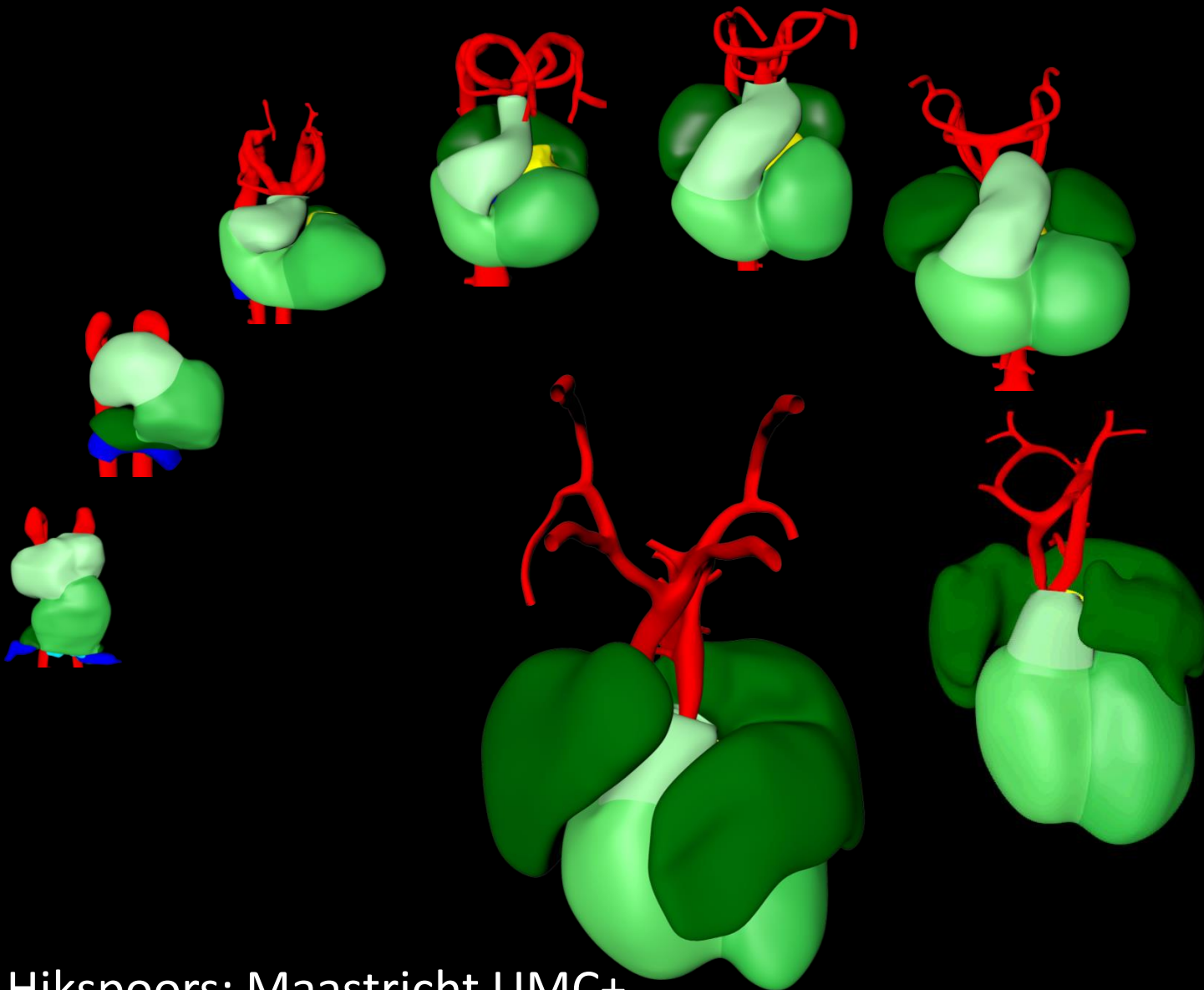


achteraanzicht

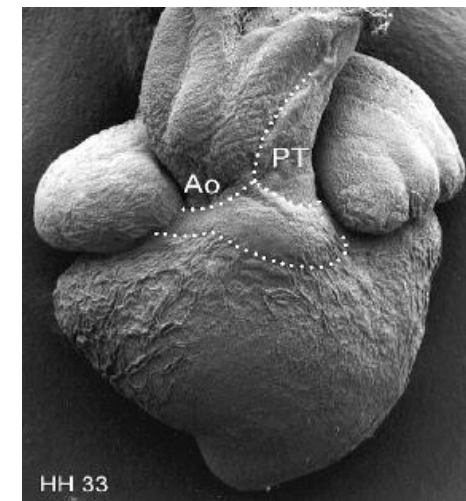
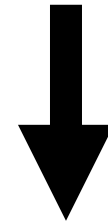
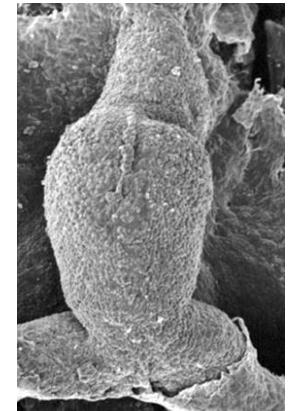
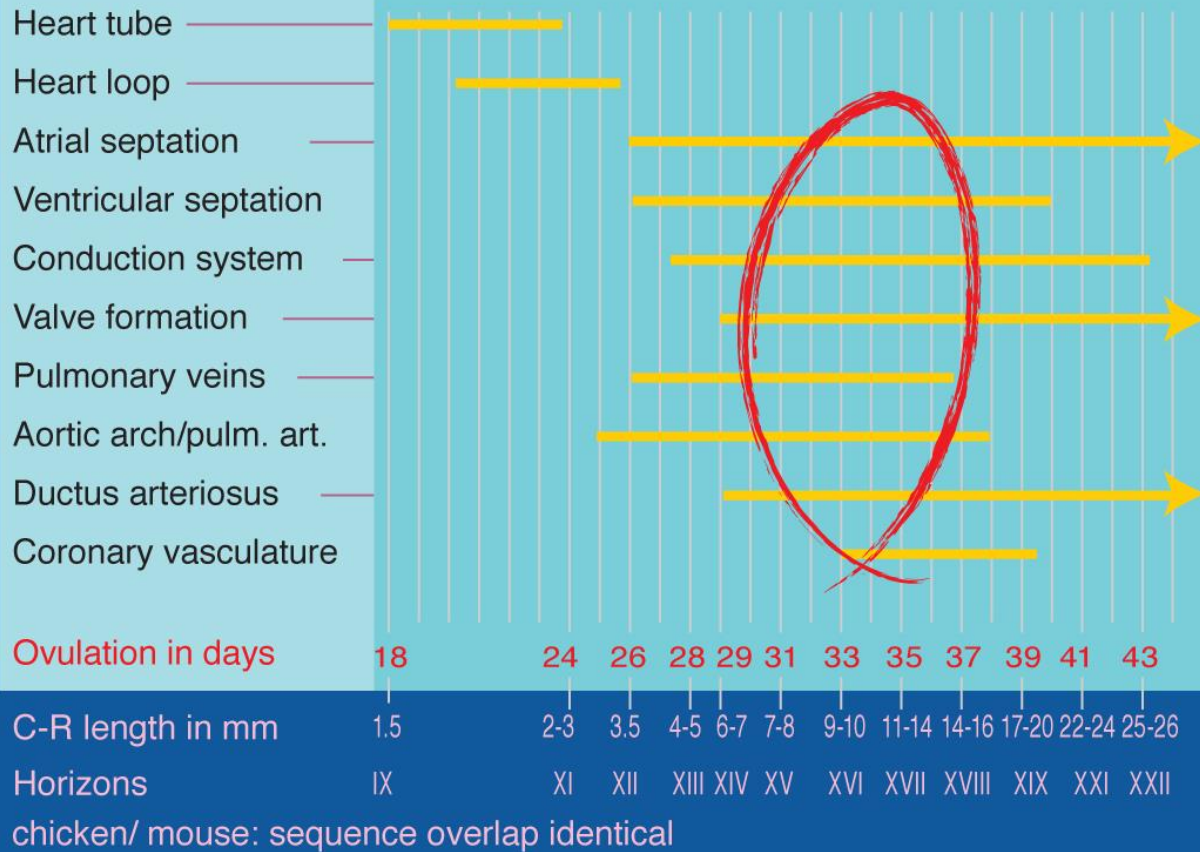
2. KUNNEN WE DEZE MORFOLOGIE EMBRYOLOGISCH VERKLAREN?



Van hartbuis tot 4 kamerhart

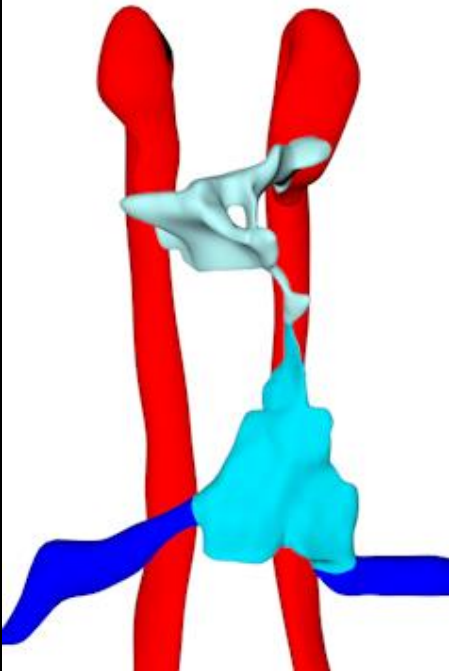


Cardiale ontwikkeling



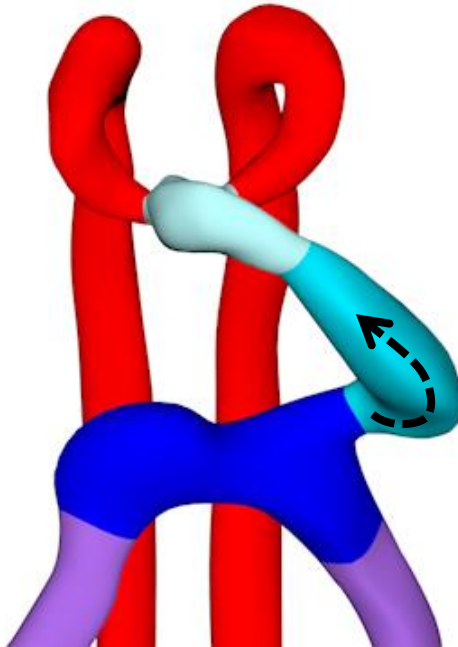
Hartontwikkeling: 4 fasen

CS10 28 dagen



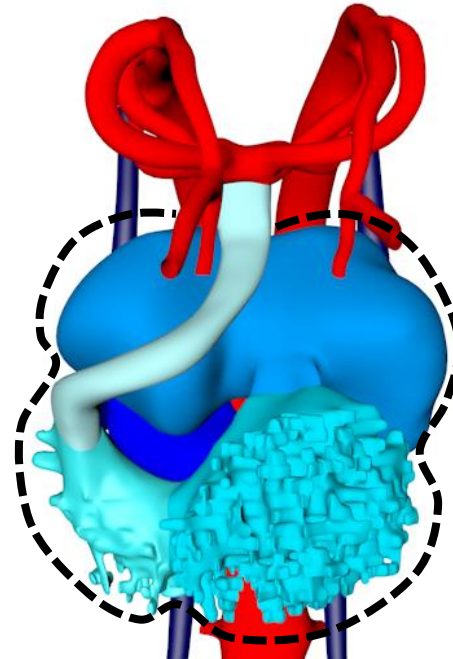
1. hartbuis

CS11 29 dagen



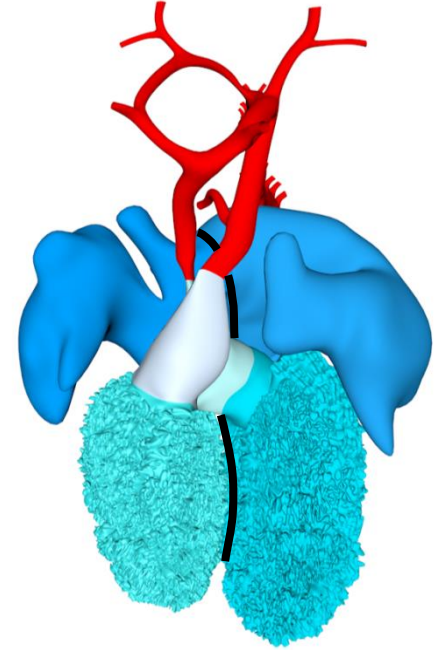
2. looping

CS13 32 dagen



3. ballooning

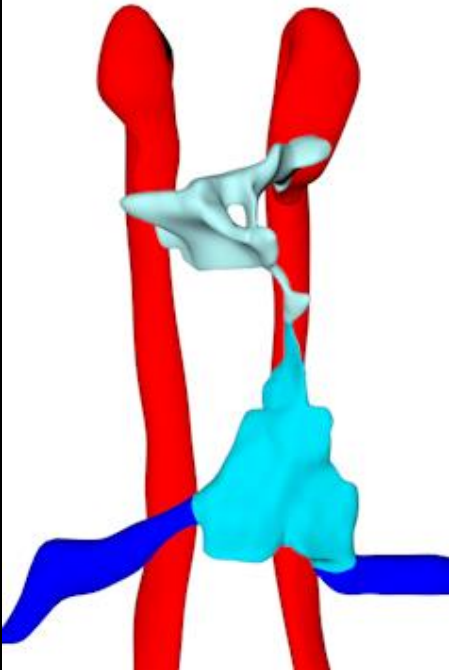
CS18 44 dagen



4. septatie

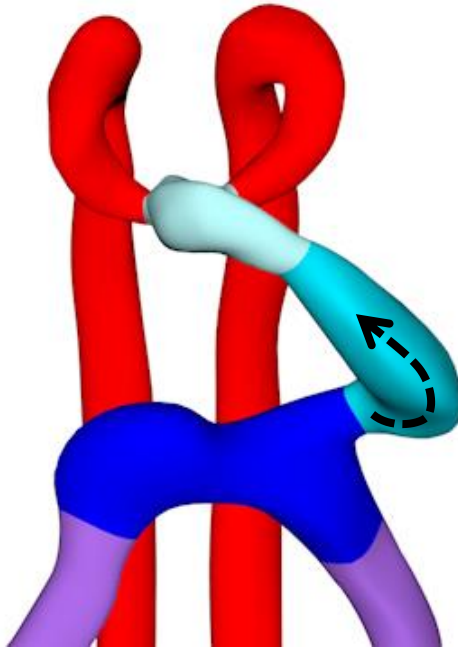
hartontwikkeling: 4 fasen

CS10 28



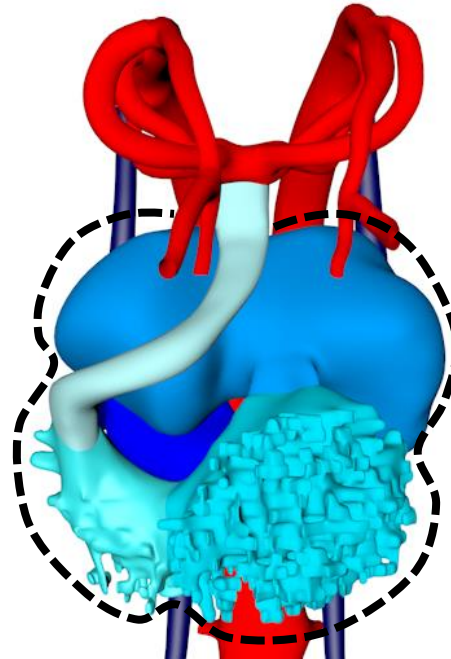
1. hartbuis

CS11 29 dagen



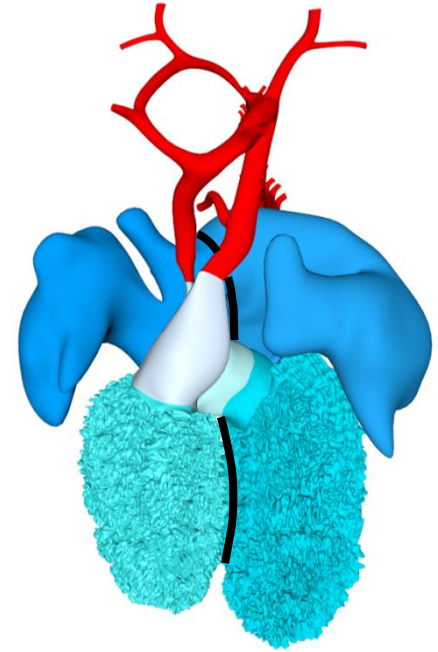
2. looping

CS13 32 dagen



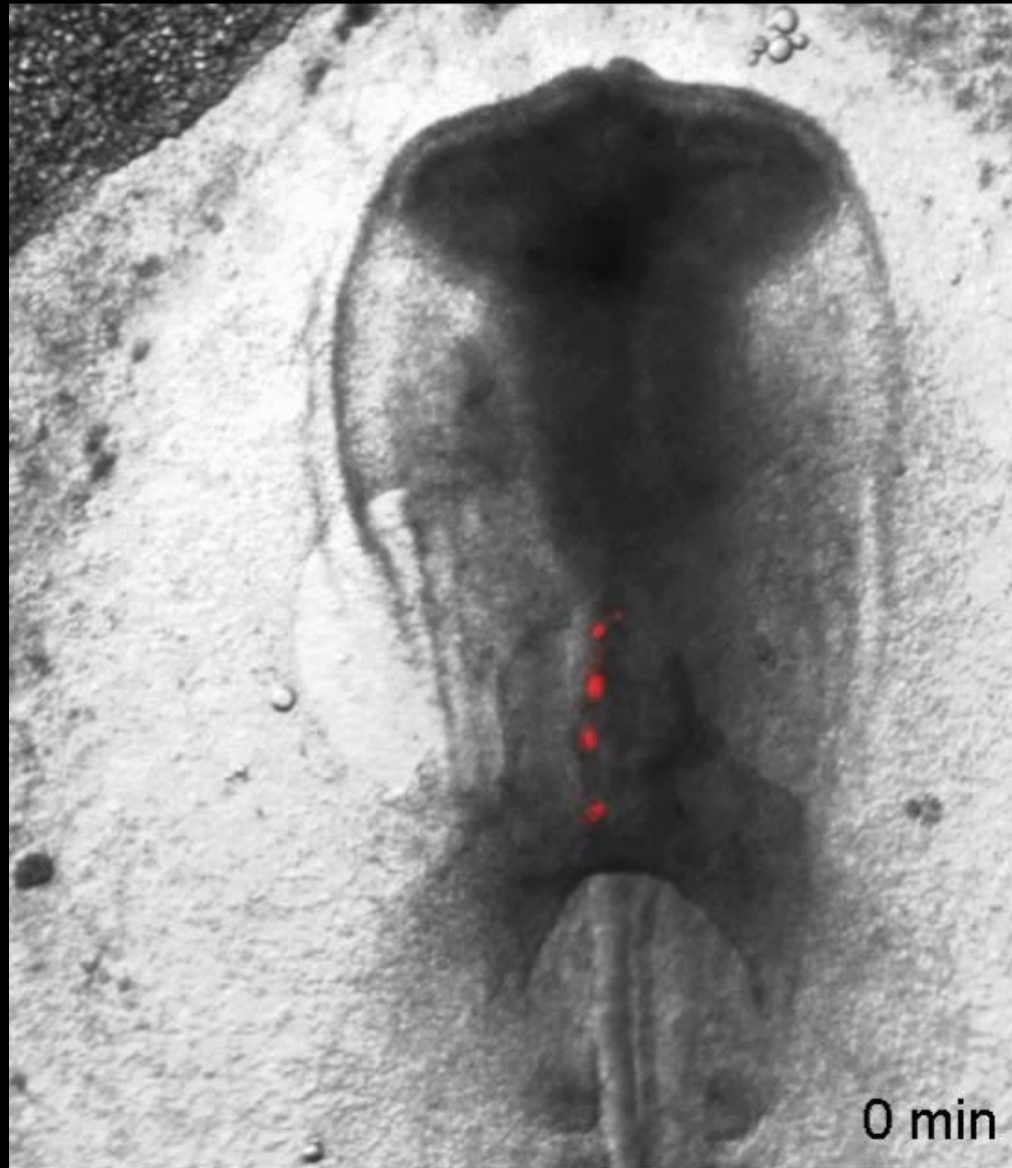
3. ballooning

CS18 44 dagen

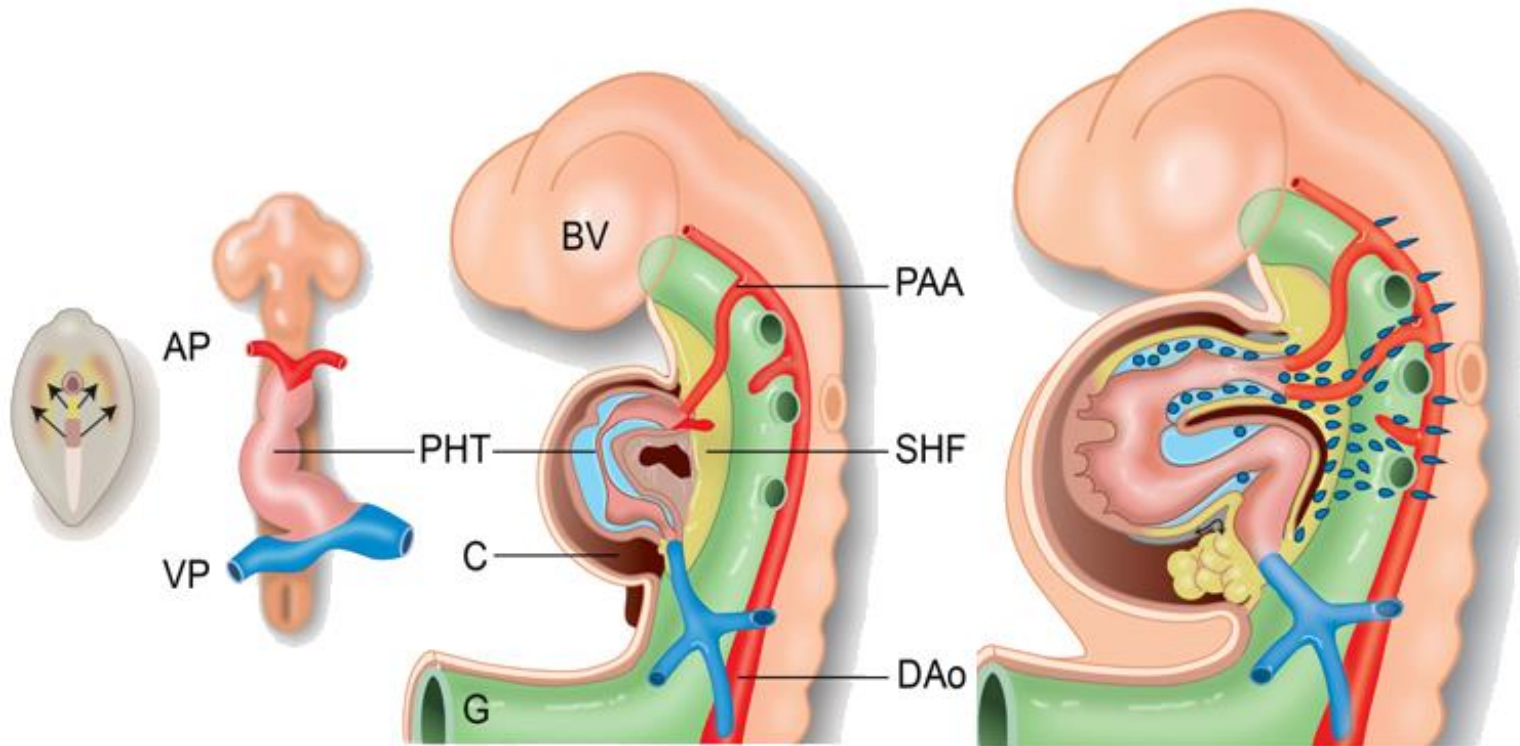


4. septatie

Hartbuis draait om lengte-as



Extracardiale cellulaire bijdragen aan het hart zijn voorwaardelijk voor juiste looping en septatie



First heart field

**Second heart field, epicard en
neurale lijst**

Primaire hartbuisafwijkingen †

Aangeboren hartafwijkingen

Plaatsen van meest voorkomende aangeboren hartafwijkingen

Segmenten en connecties

Veneus systeem

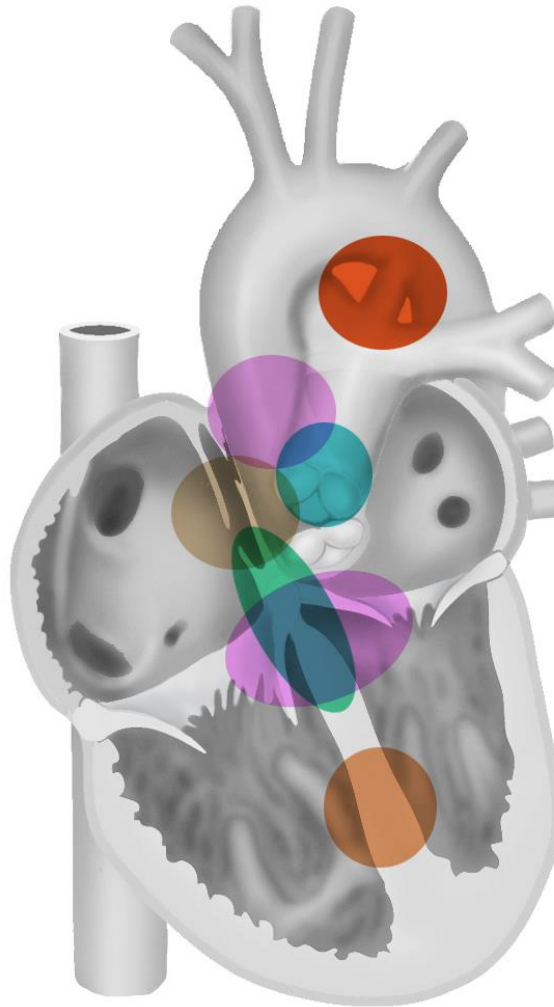
Atrium

Ventrikel

Ventriculaire inflow

Ventriculaire outflow

Arteriele pool



Structuren

Atrium septum

AV septum

Ventriculair septum

AV-kleppen

Arteriële kleppen

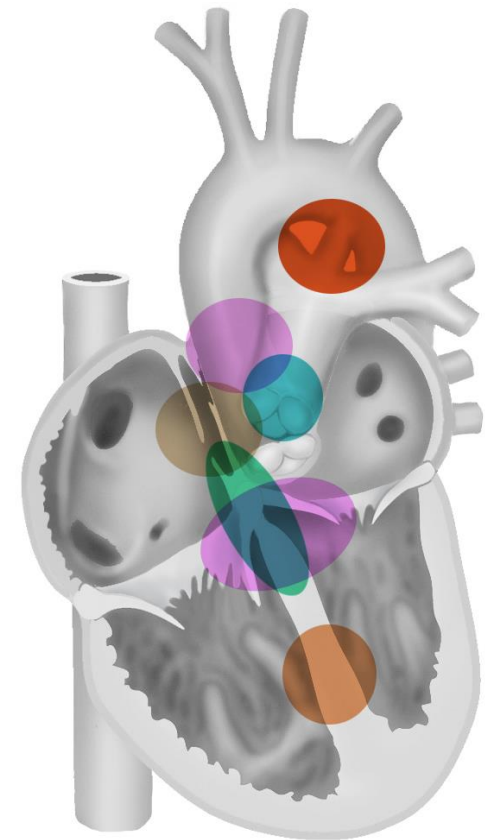
Geleidingssysteem

Myocard

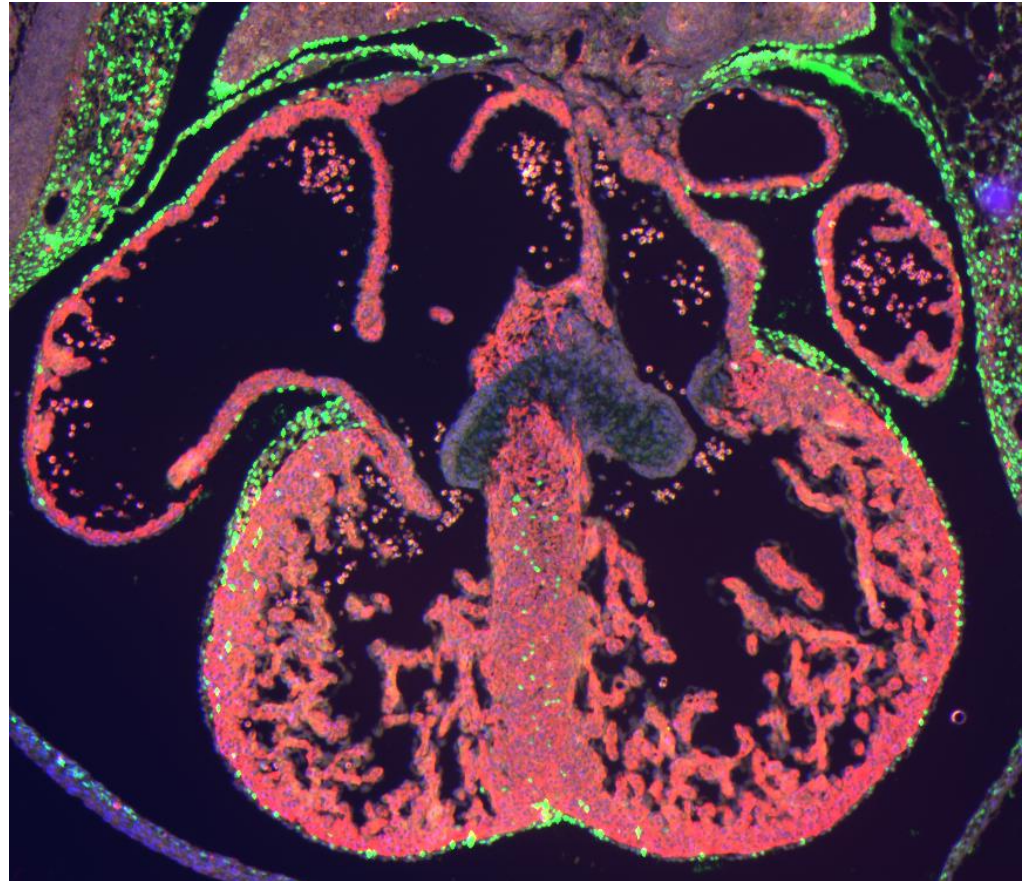
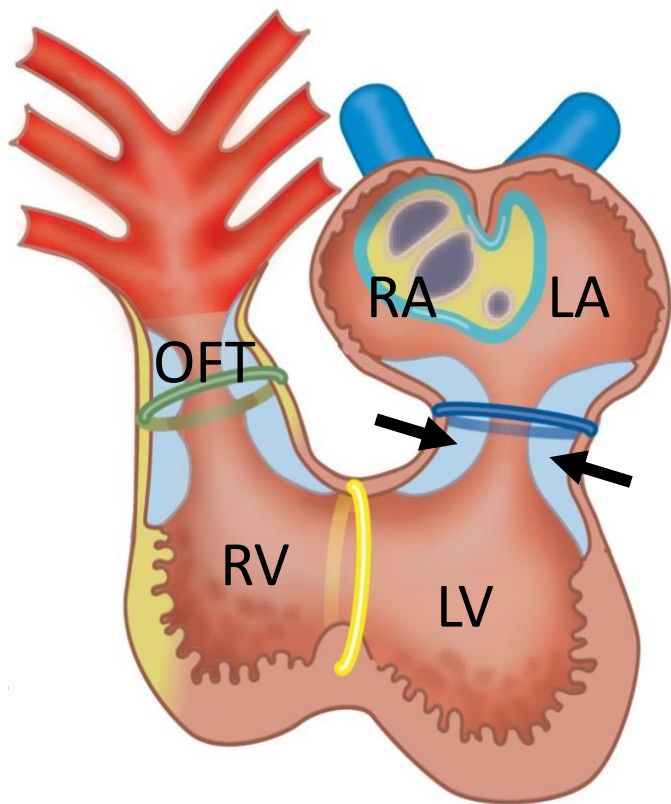
Incidentie van aangeboren hartafwijkingen

10 per 1000 levend geboren

- Ventrikel Septum Defecten (VSD) 31 %
- Atrium Septum Defecten (ASD) 12 %
- Atrium-Ventrikel Septum Defecten (AVSD) 2 %

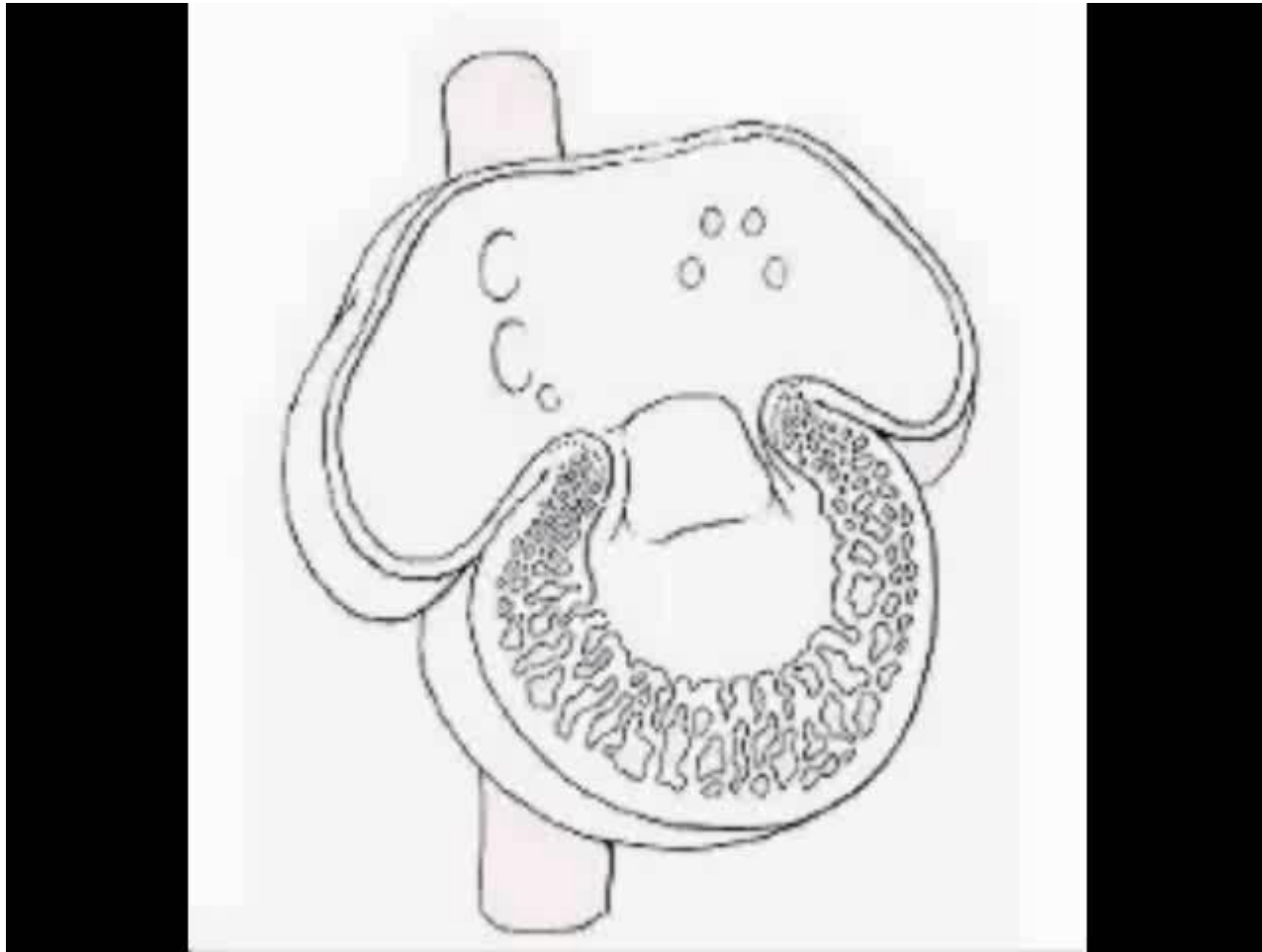


Van gekromde buis naar 4 kamerhart



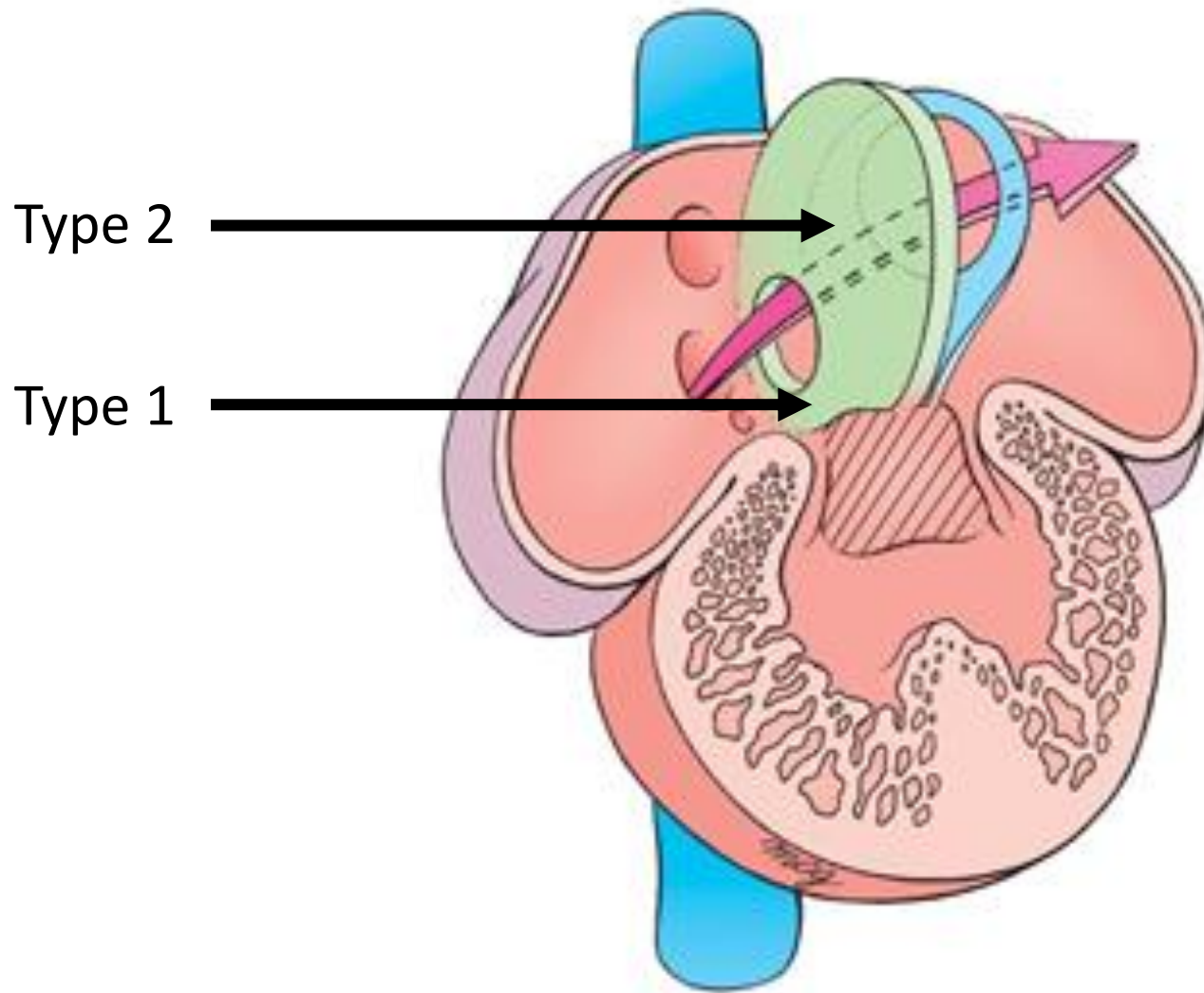
Van gekromde buis naar 4 kamerhart

atriumseptatie



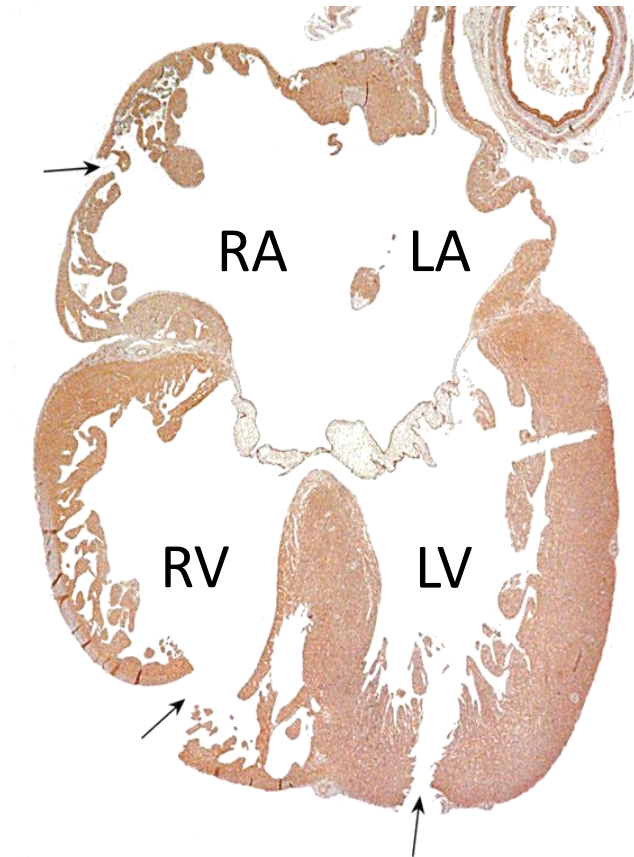
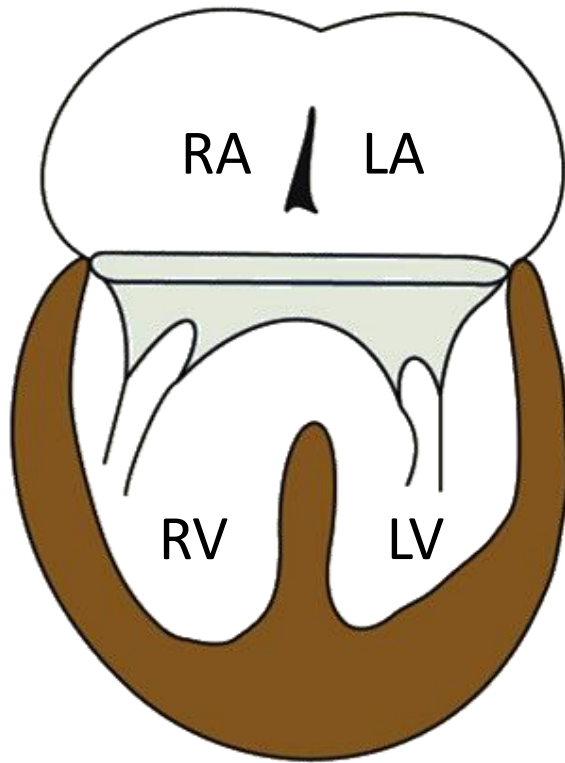
Van gekromde buis naar 4 kamerhart

Atrium Septum defect type 1 en type 2



Van gekromde buis naar 4 kamerhart

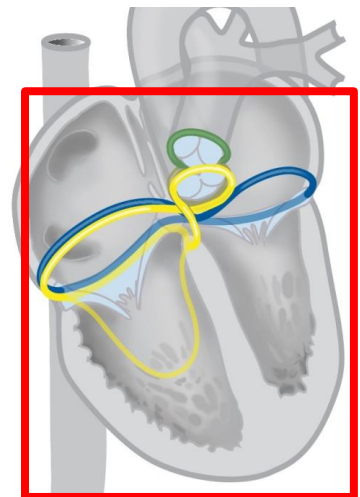
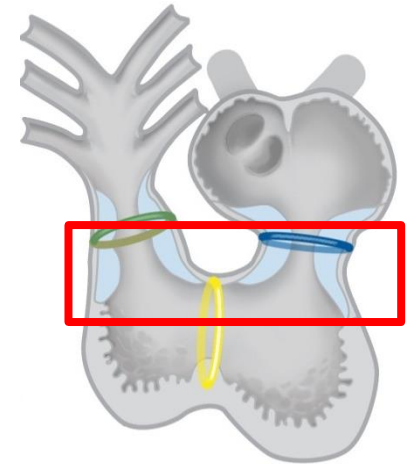
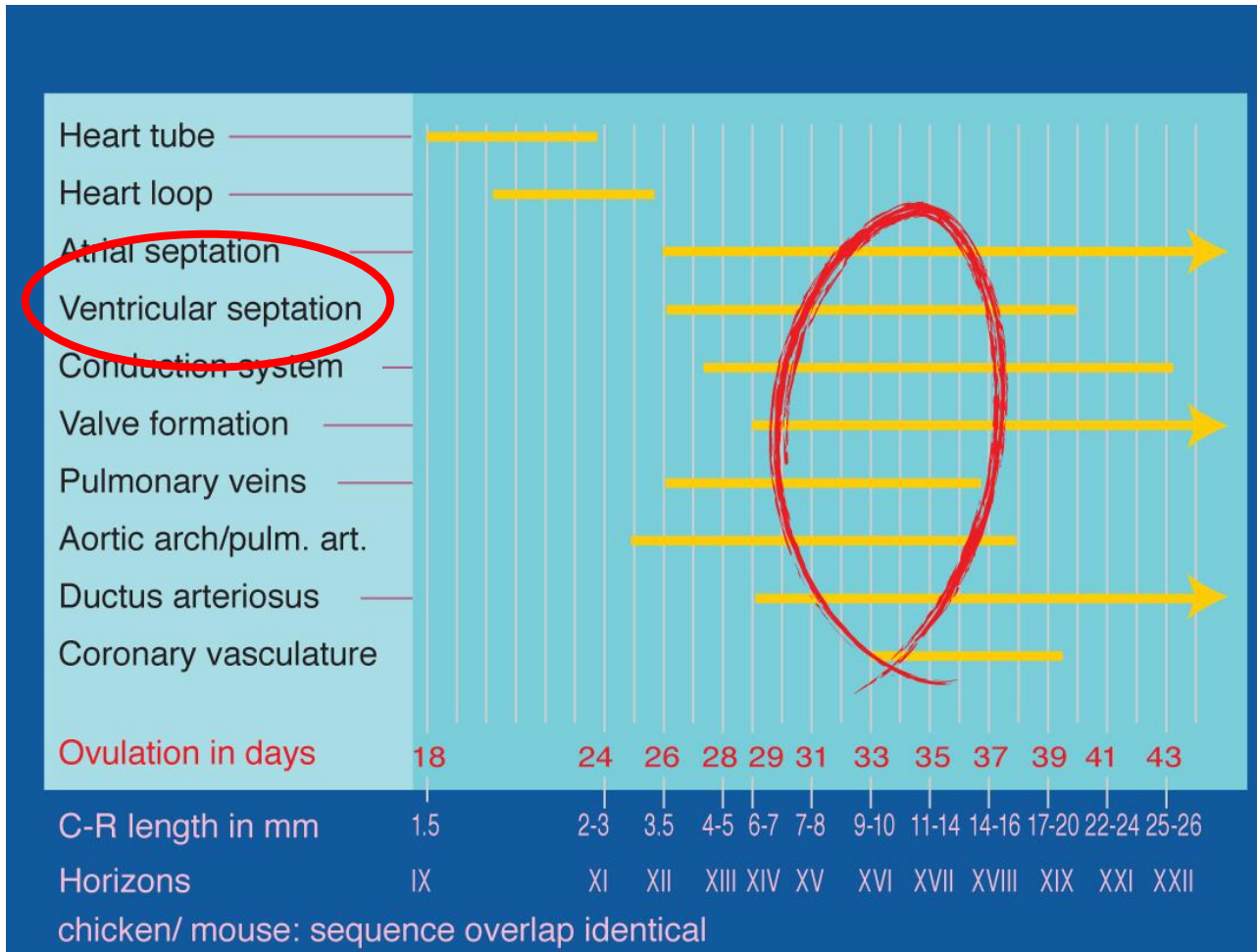
Atrium-Ventrikel Septum Defect (AVSD)



Gemeenschappelijke
Atrioventriculaire klep

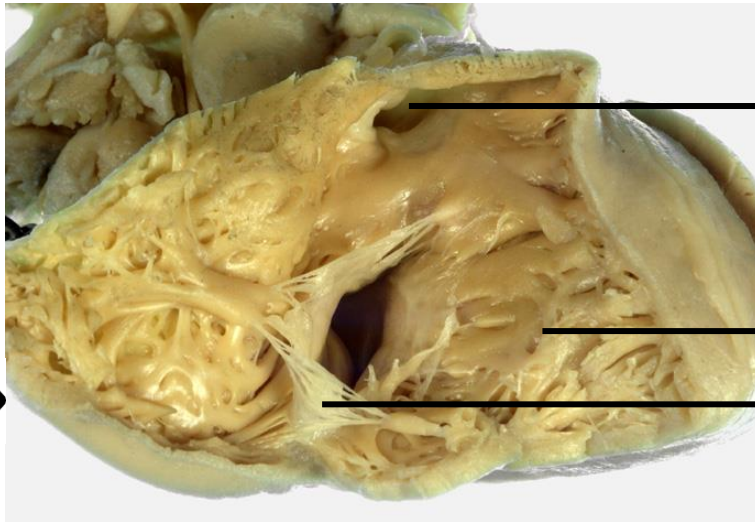
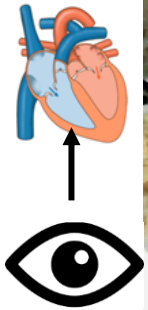
Van gekromde buis naar 4 kamerhart

Ventrikelseptatie



Van gekromde buis naar 4 kamerhart

Ventrikel Septum Defect

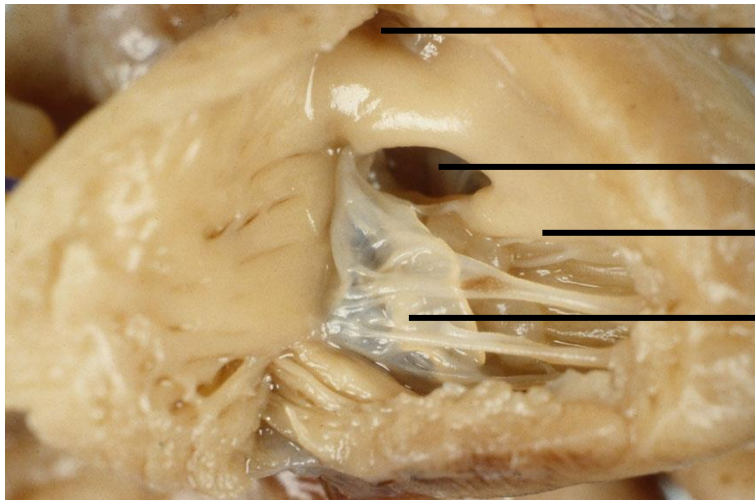


normaal

pulmonaalklep

ventrikelseptum

tricuspidaalklep



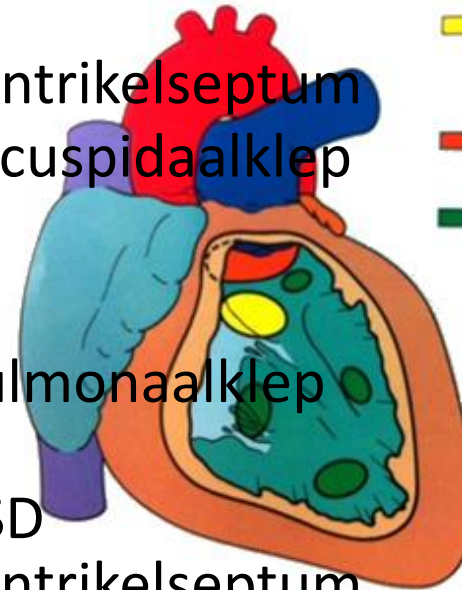
abnormaal

pulmonaalklep

VSD

ventrikelseptum

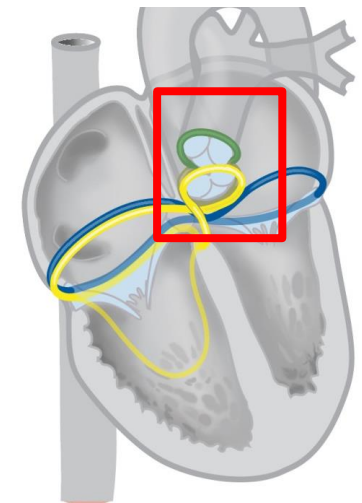
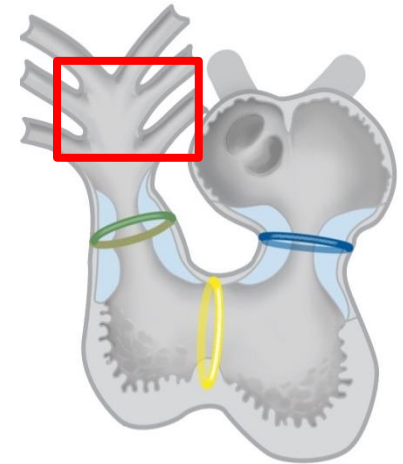
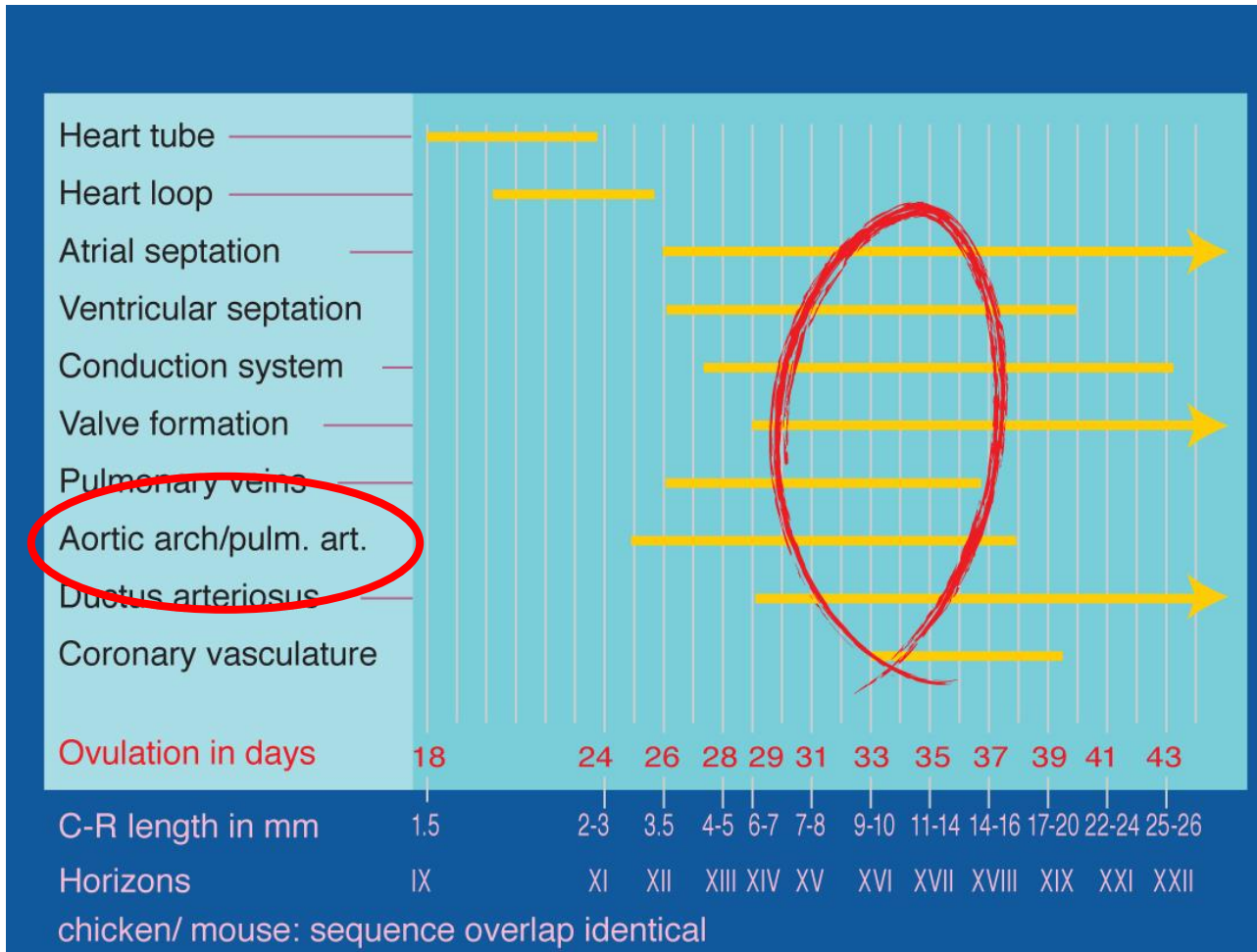
tricuspidaalklep

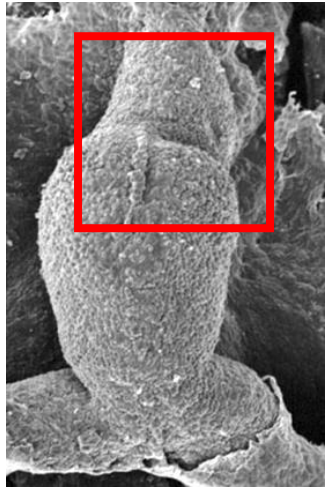


- Perimembranous defects
 - *subaortic
 - *abut onto CFB
- Subarterial defects
 - *beneath AoV and PV
- Muscular defects
 - *entirely enclosed in muscular septum

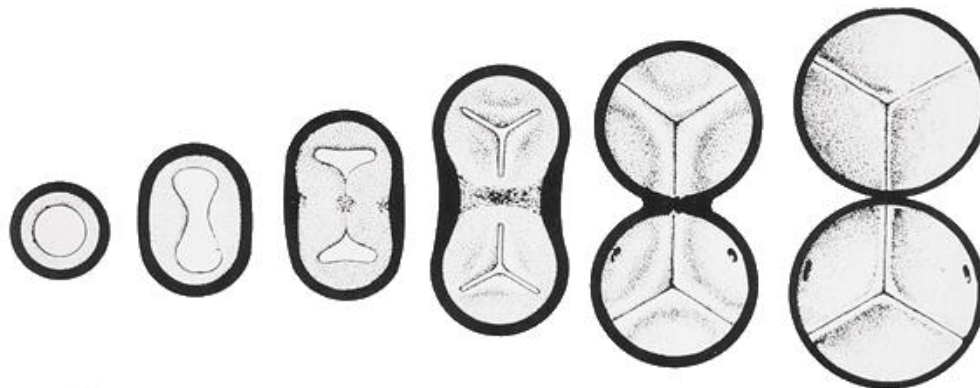
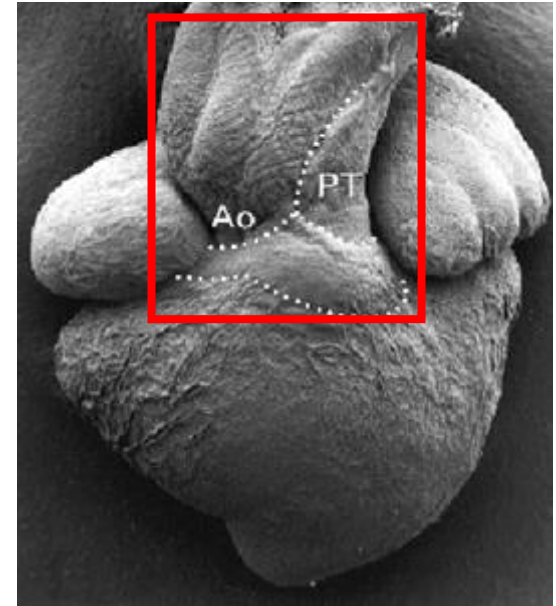
Van gekromde buis naar 4 kamerhart

Uitstroomseptatie





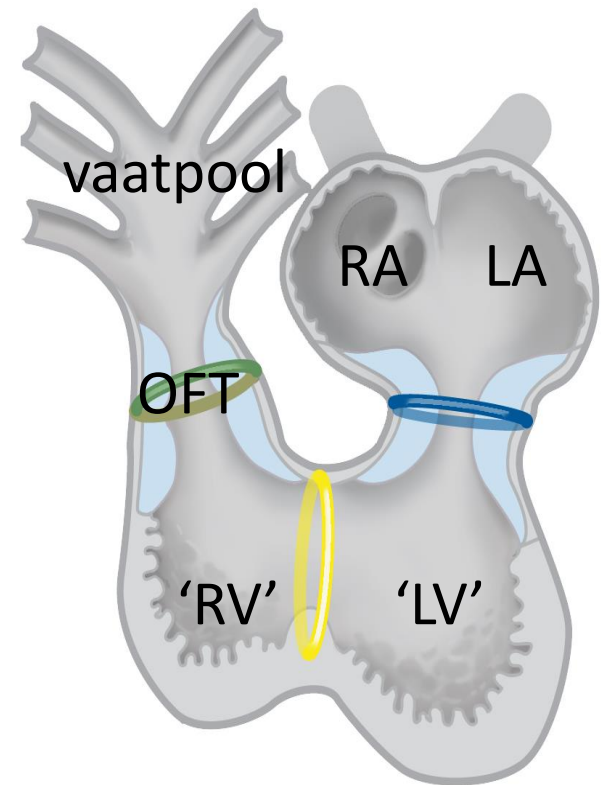
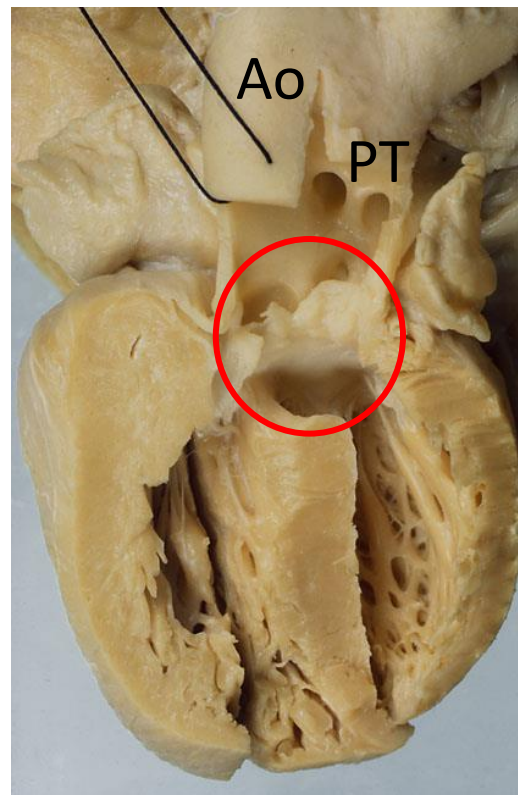
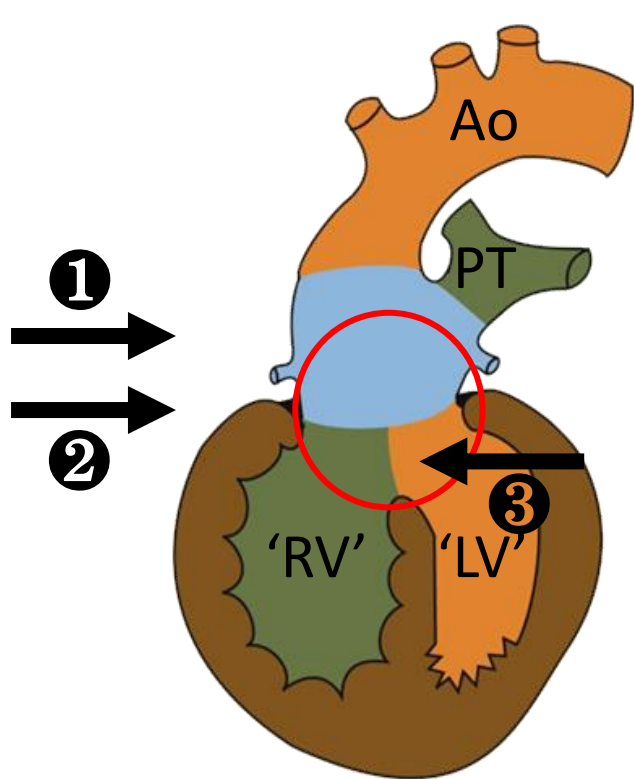
Belangrijke rol voor neurale lijst



Abnormale septatie uitstroom

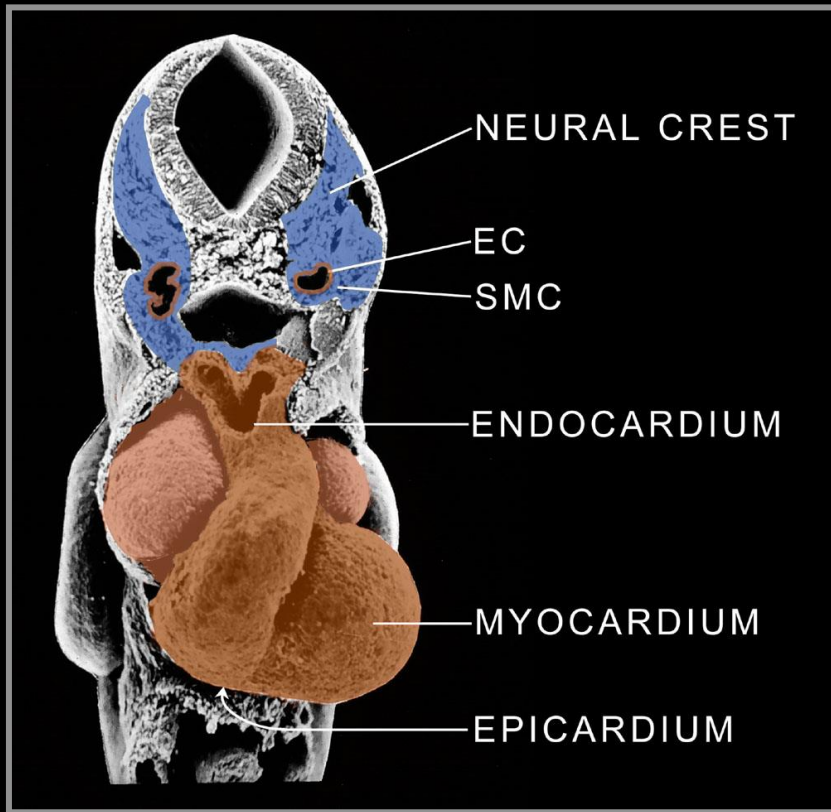
Defect op 3 niveaus

1. grote vaten (aorta en truncus pulmonalis)
2. niveau van kleppen
3. rechter en linker outflow tract

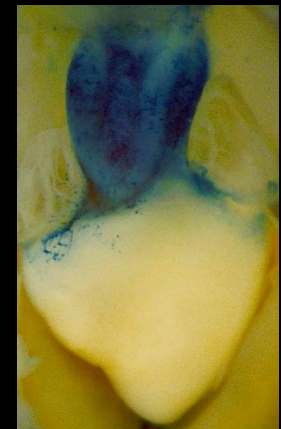
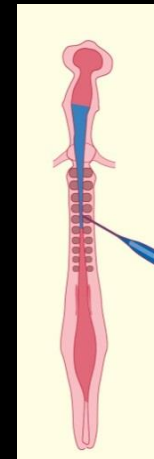
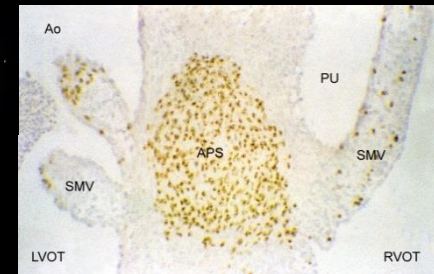
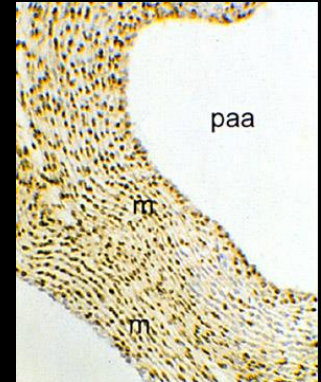


3. Hoe bestuderen we de ontwikkeling van het hart?

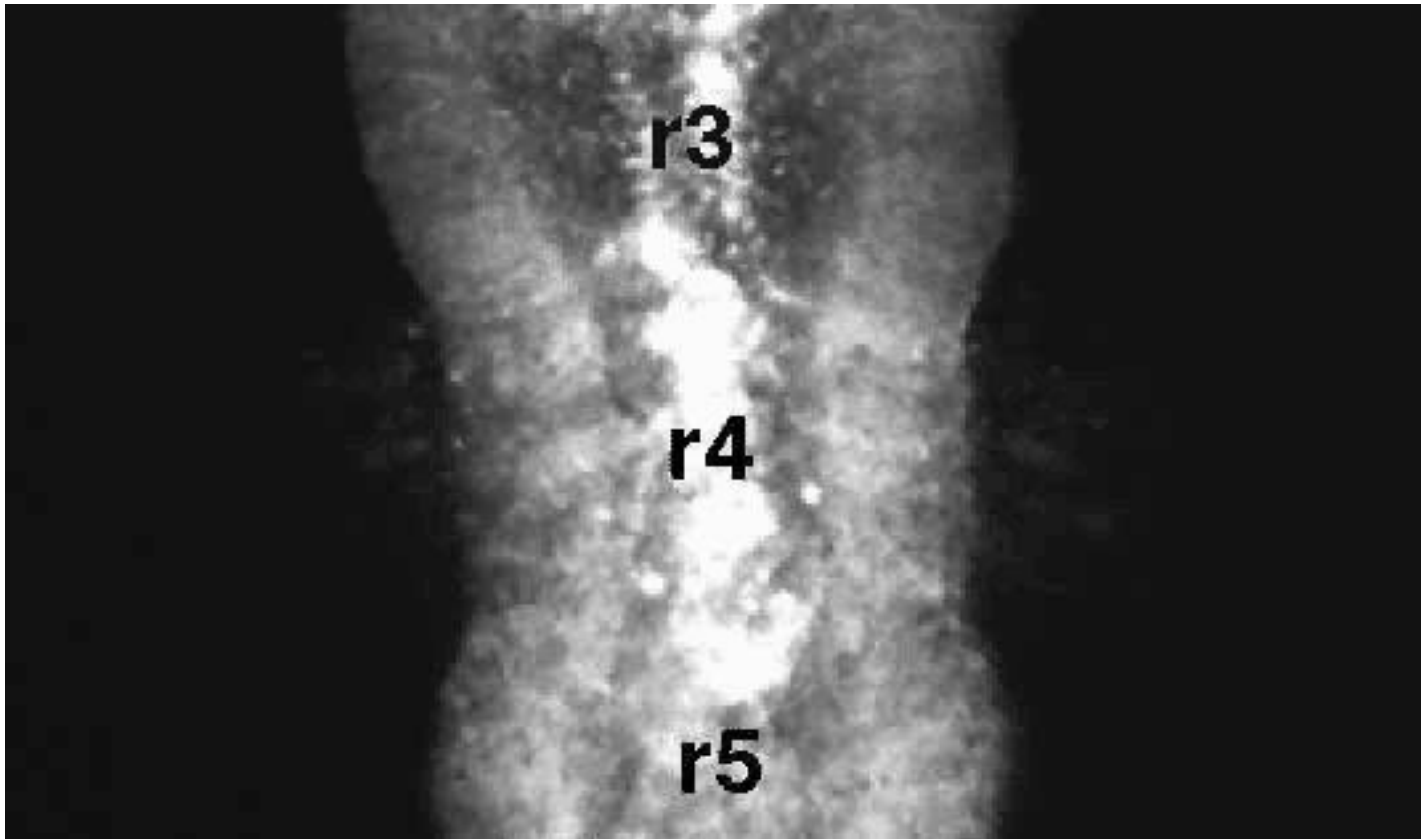
Cell fate; cell lineage studies



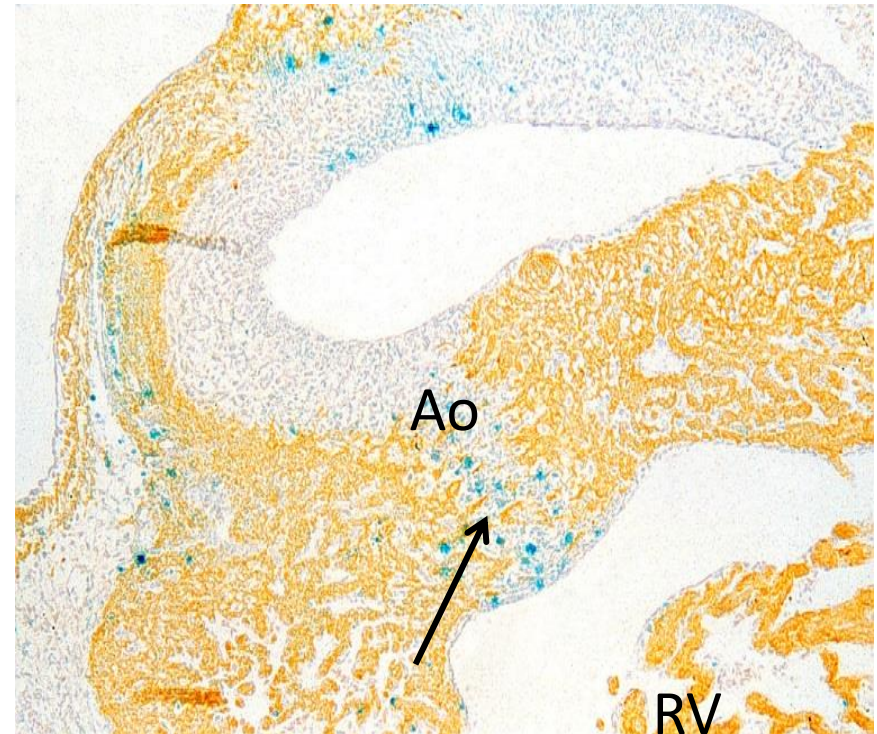
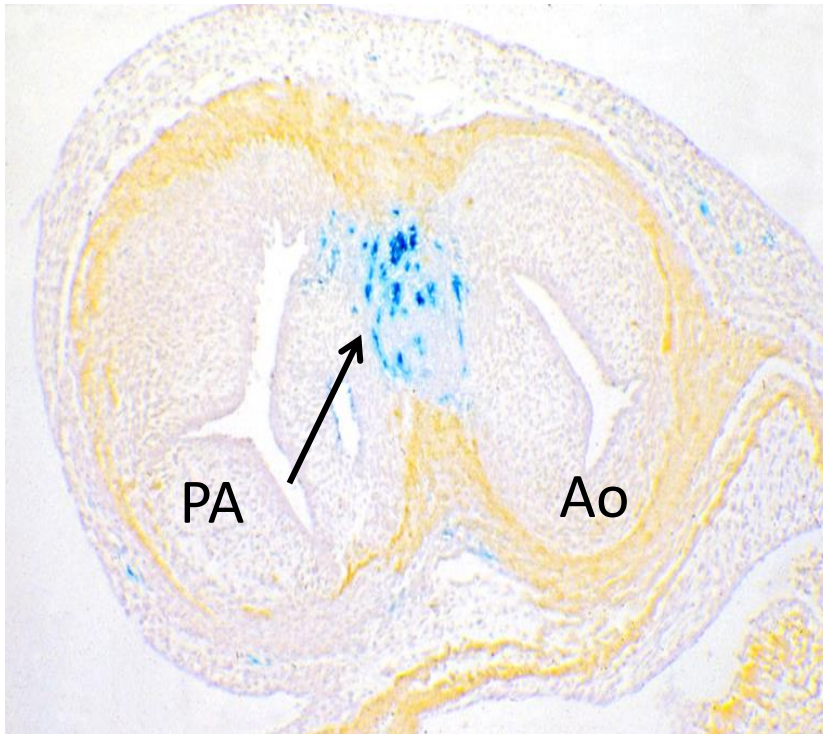
QUAIL-CHICKEN CHIMERA

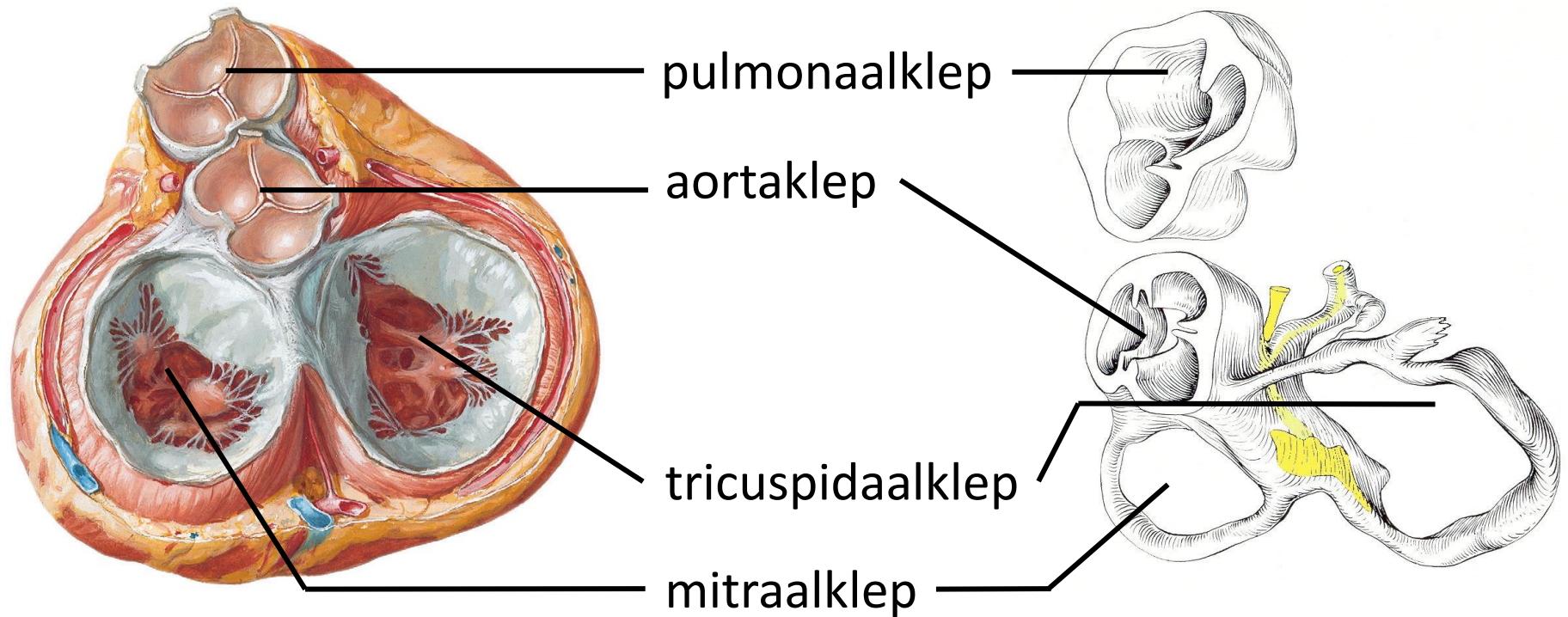


Migratie neurale lijst cellen uit rhombencephalon

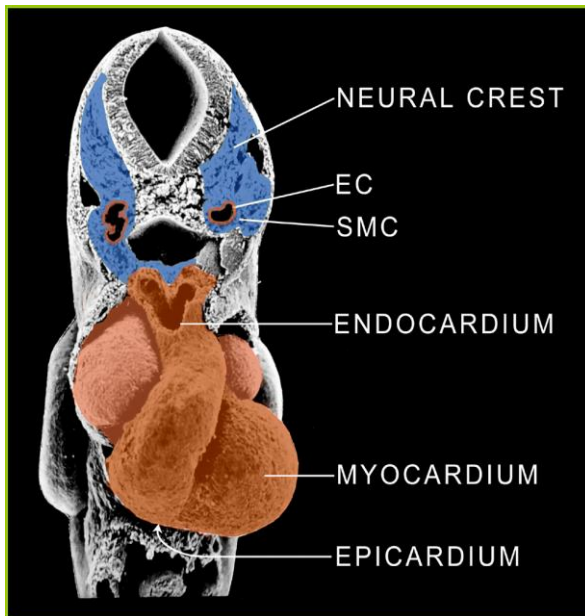


Tracing van neurale lijst in kip

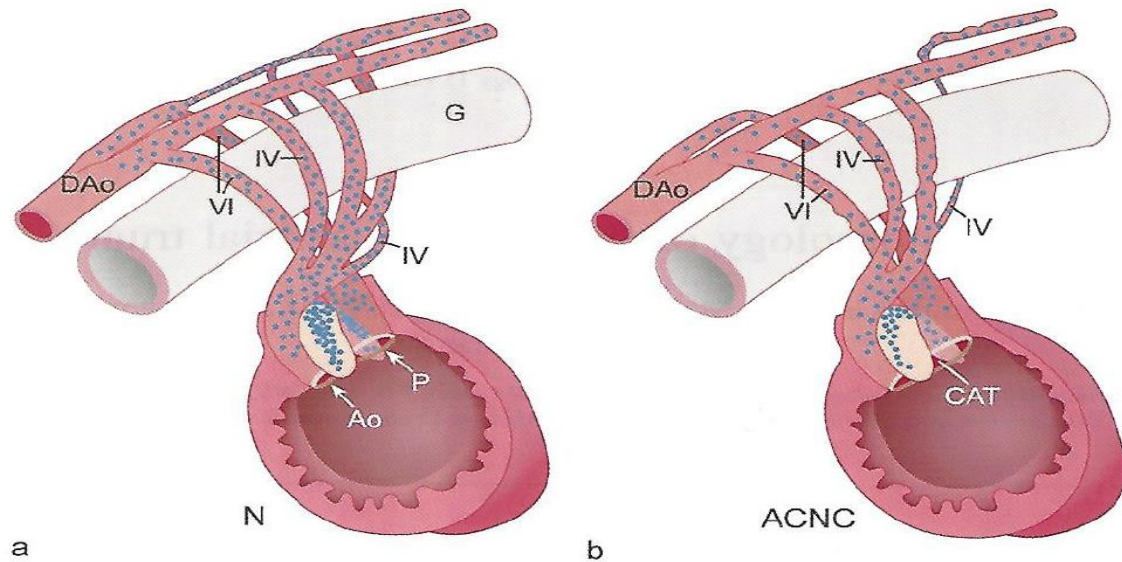




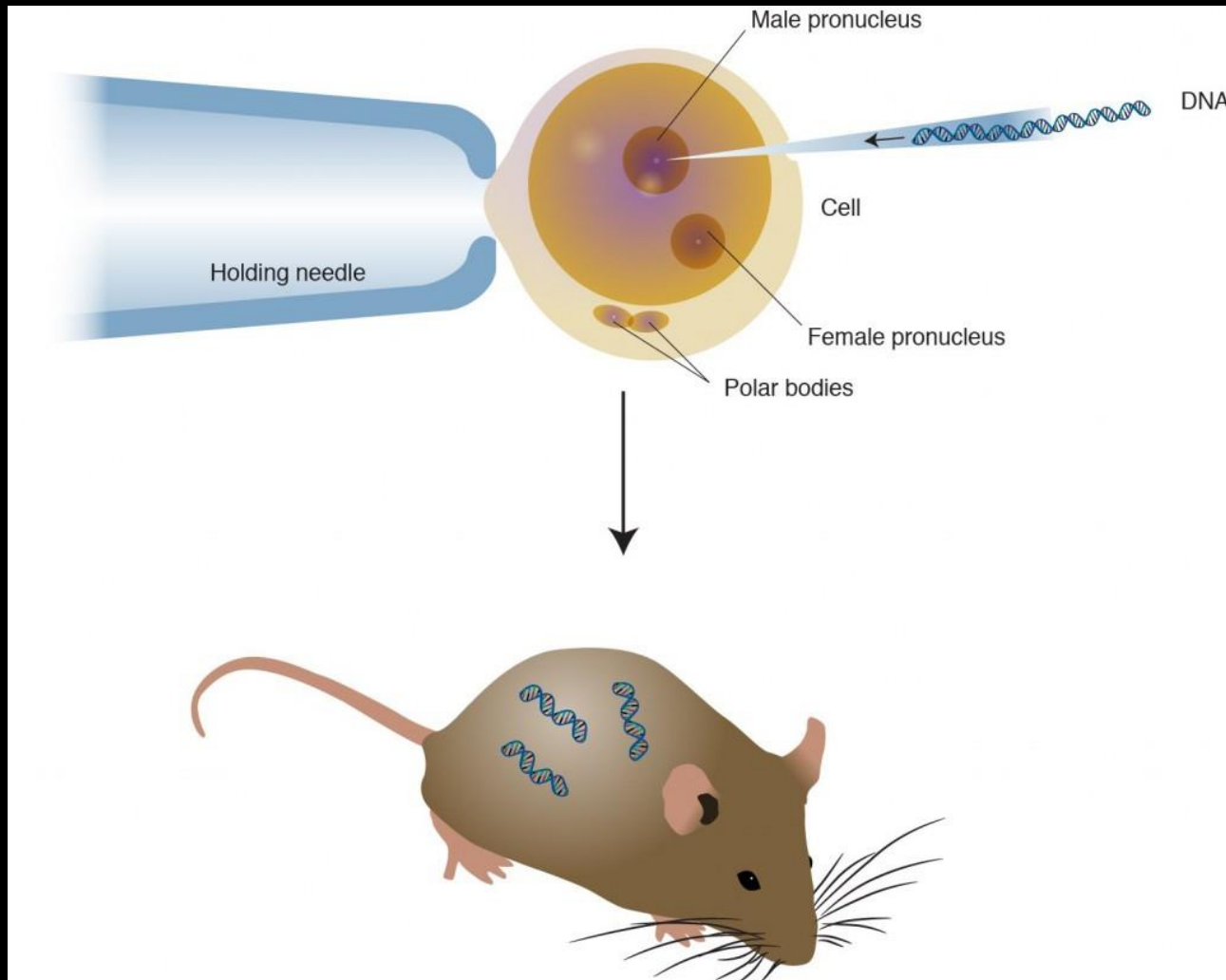
Neural crest ablatie in kippeëmbryo's resulteert in een persisterende truncus arteriosus



A.C. Gittenberger-de Groot et al. / *Progress in Pediatric Cardiology* 15 (2002) 1–8

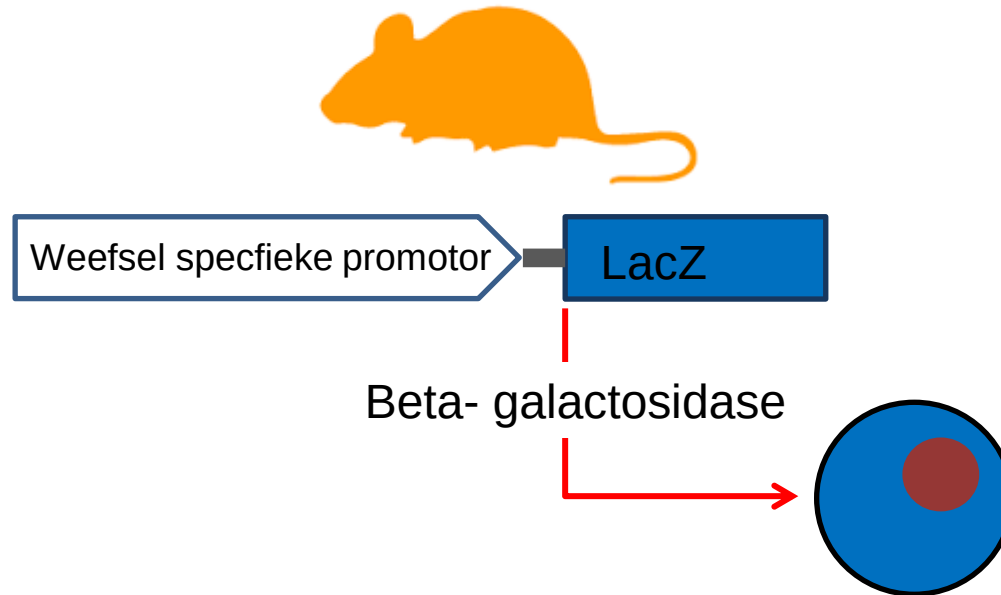


Transgenic mice technology



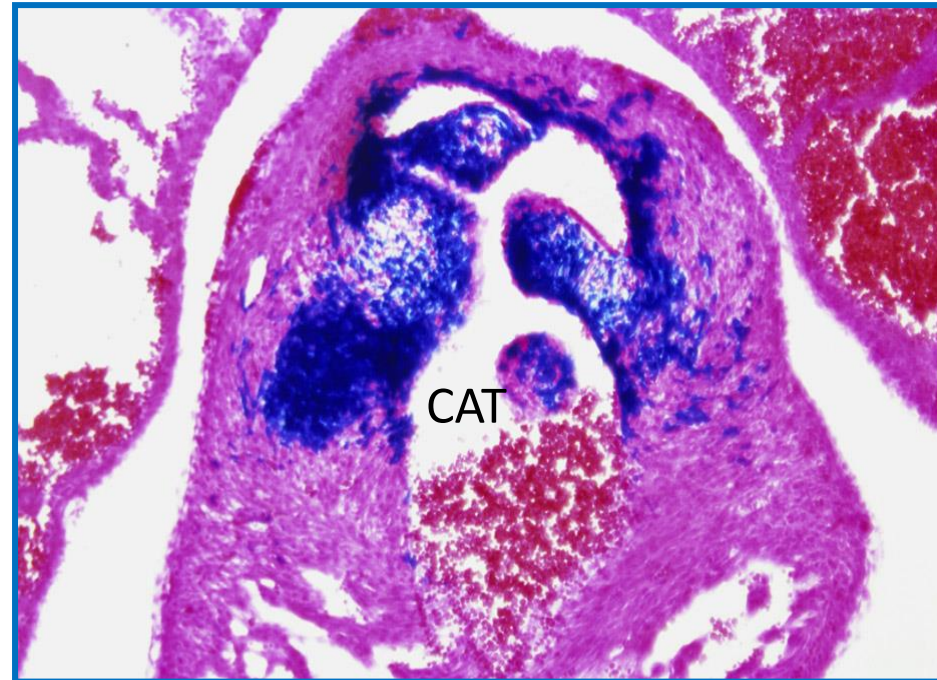
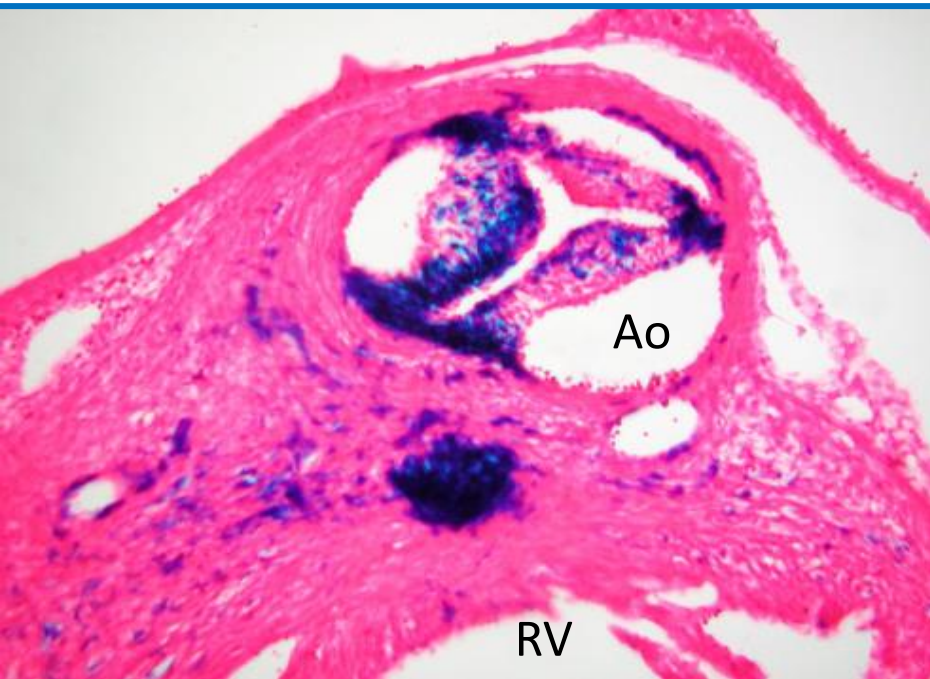
Genetic cell lineage study in mouse embryos

Expressie van een marker in cellen met specifieke eiwitexpressie



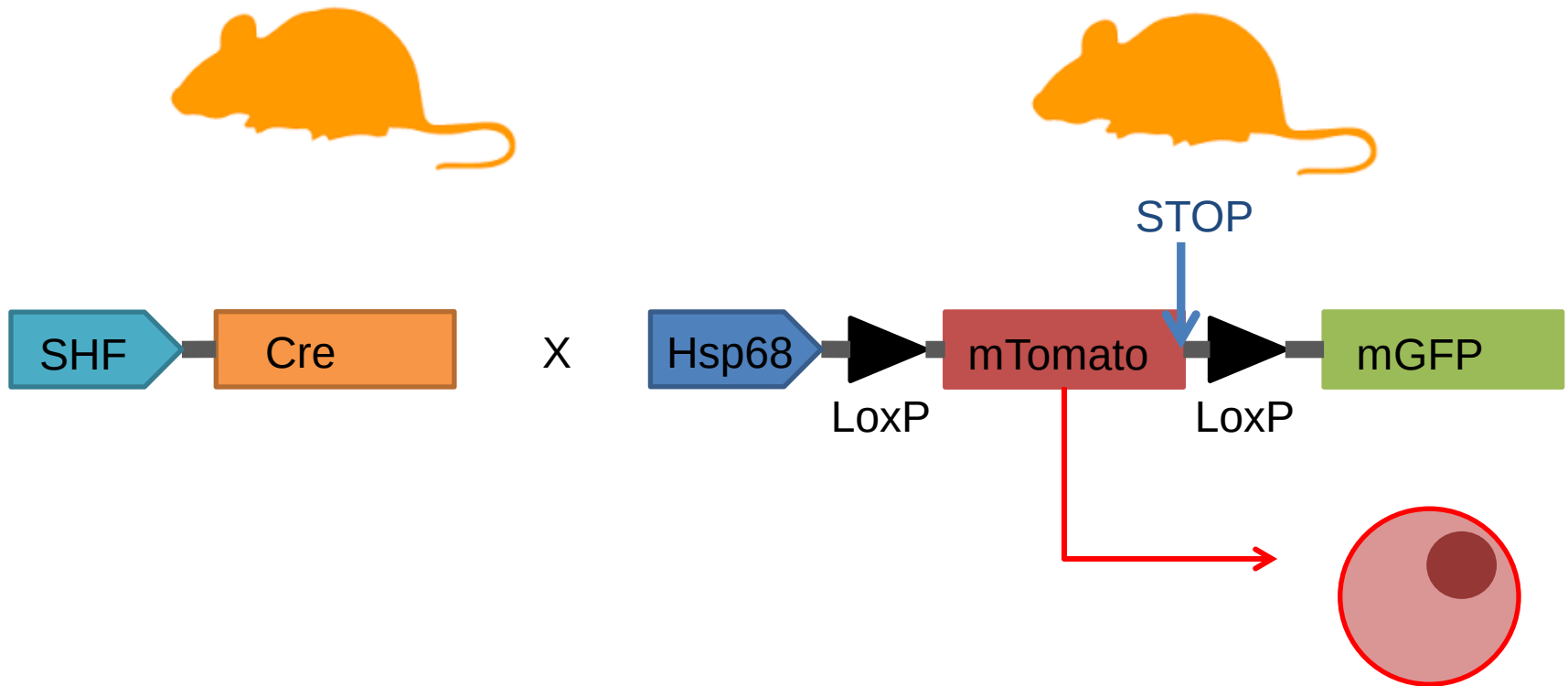
Nadeel: marker verdwijnt indien promotor afgeschakeld wordt

Cell lineage tracing van neural crest in wild type en TGFB2 deficiente muizeëmbryo's

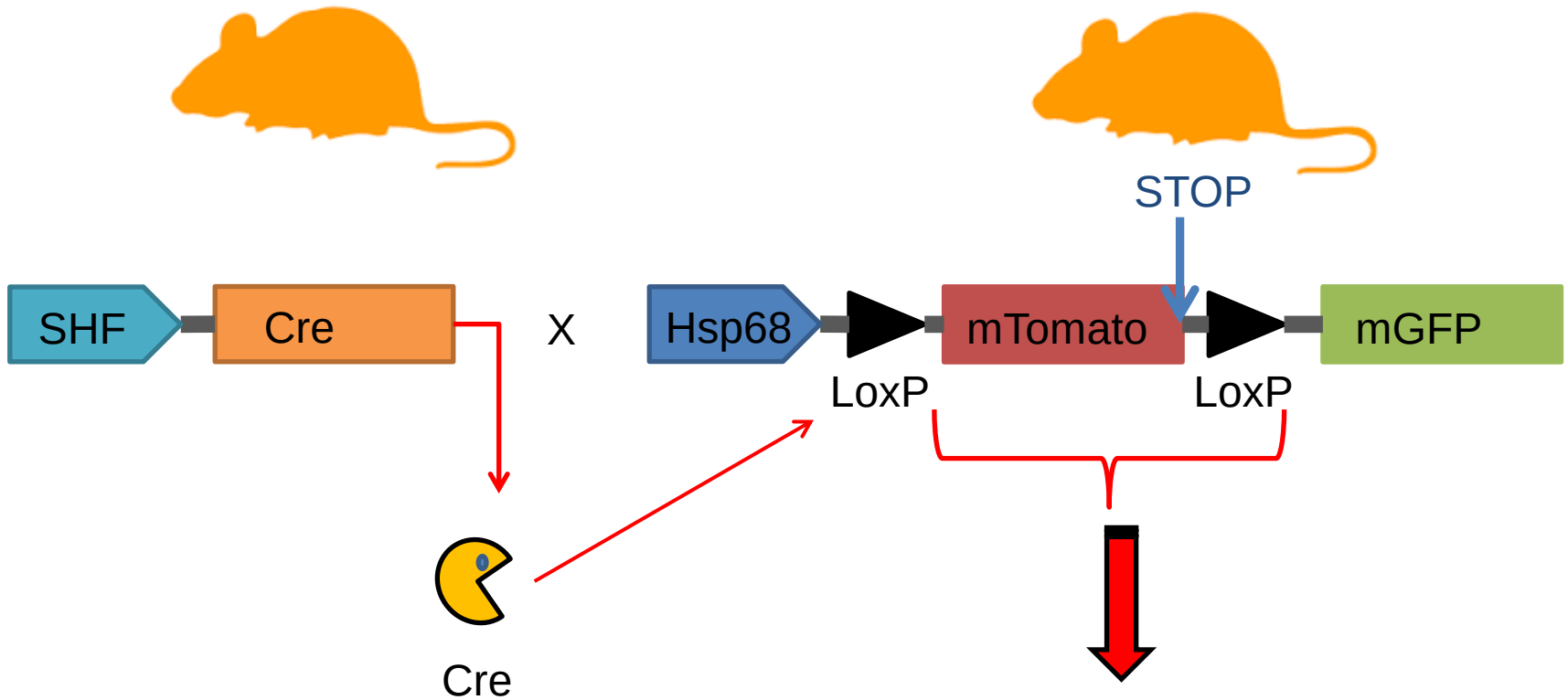


Molin et al. Circ Res 2004;
Gittenberger-de Groot et al 2002

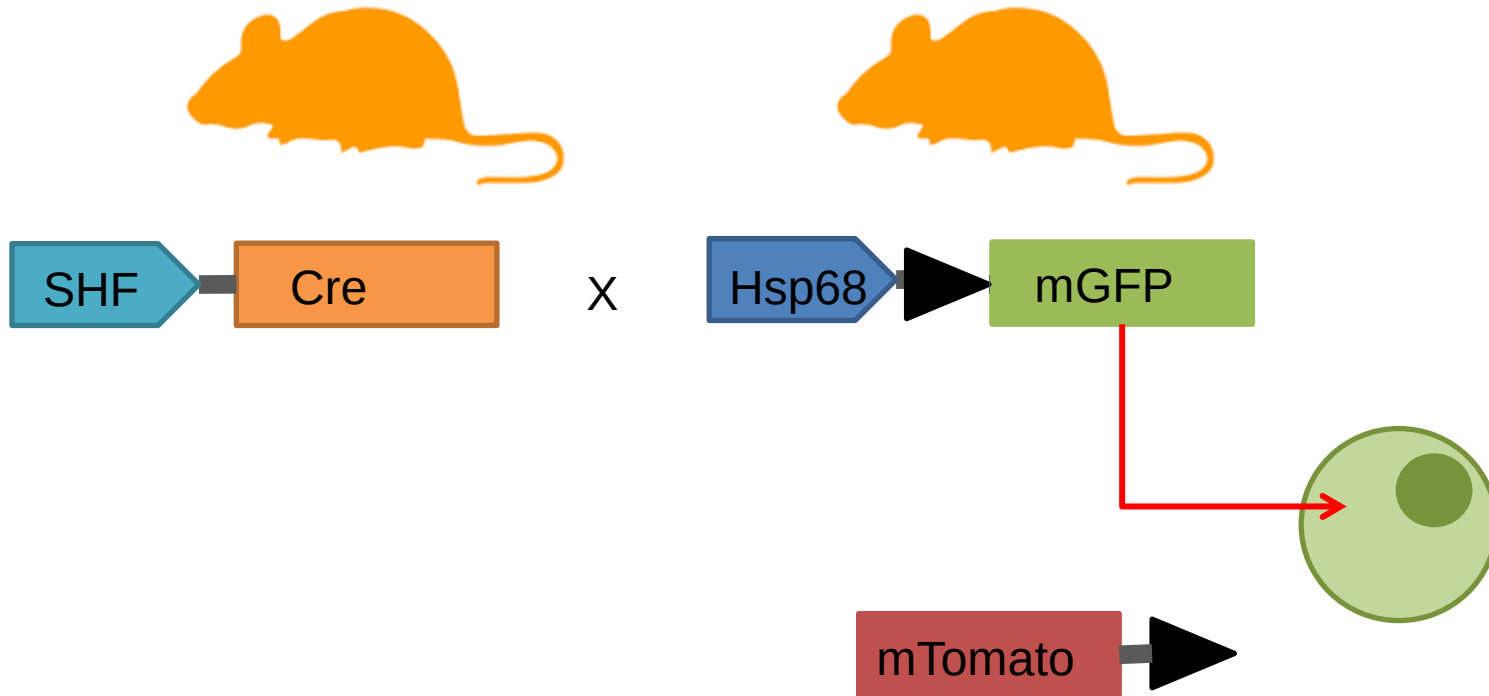
Second Heart Field lineage study in mouse embryos



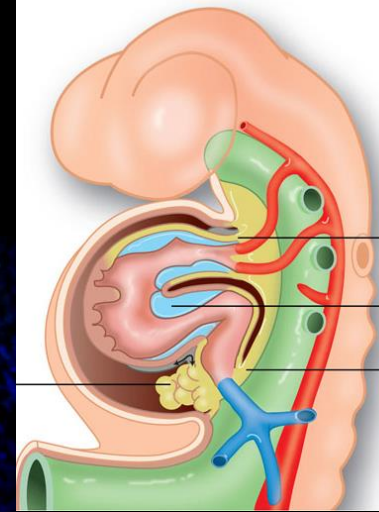
Second Heart Field lineage study in mouse embryos



Second Heart Field lineage study in mouse embryos



Second Heart Field Lineage study: Right ventricle E14,5; Mef2c-Cre x mTmG



Right Ventricle

Left Ventricle

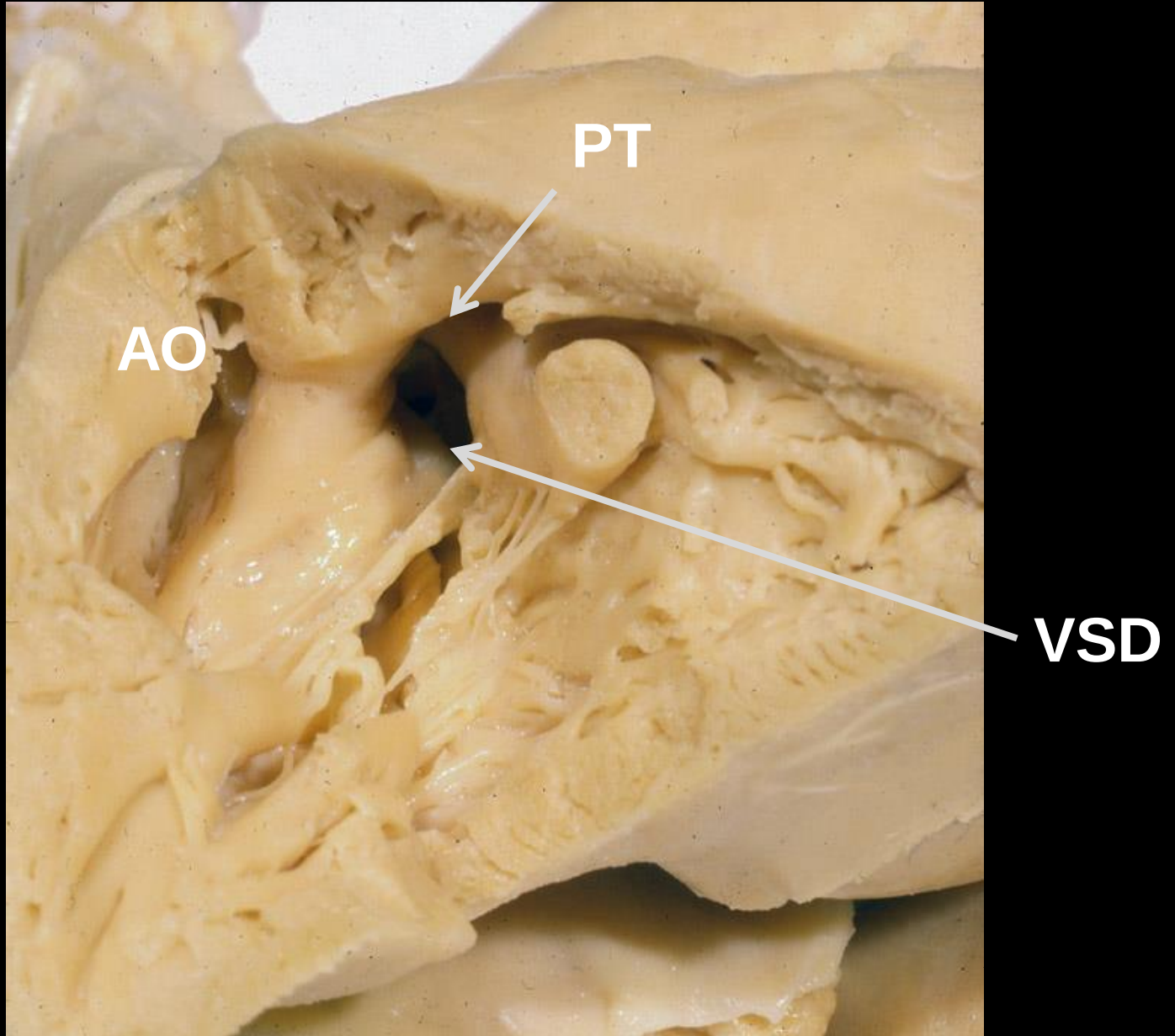
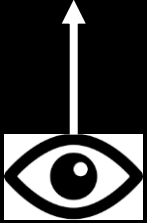
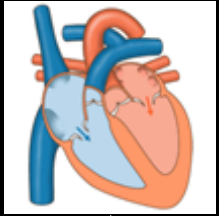
Ventricular Septum

Asymmetrische contribution van Second Heart aan de linker en rechter uitstroom:

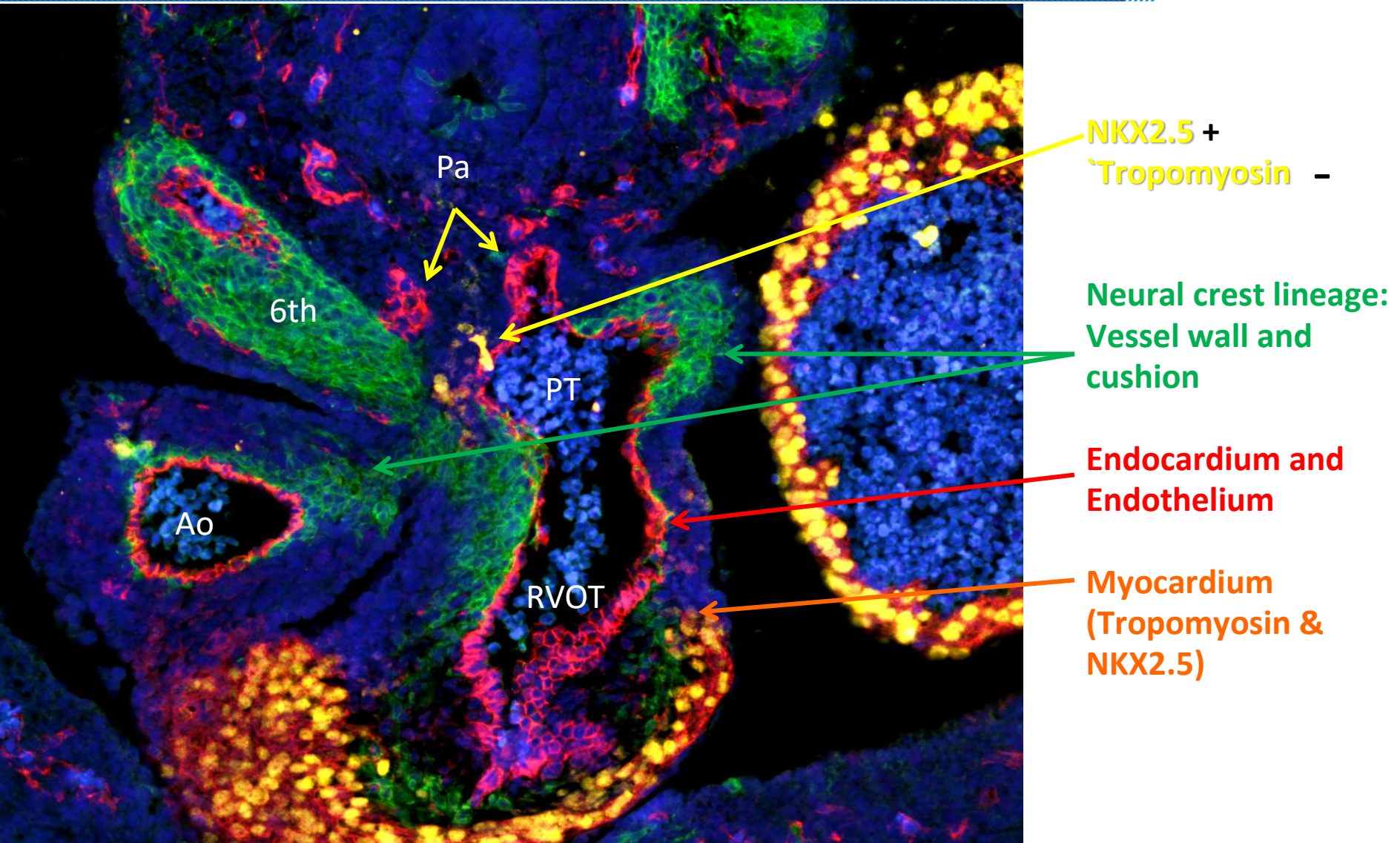
“Pulmonary Push”



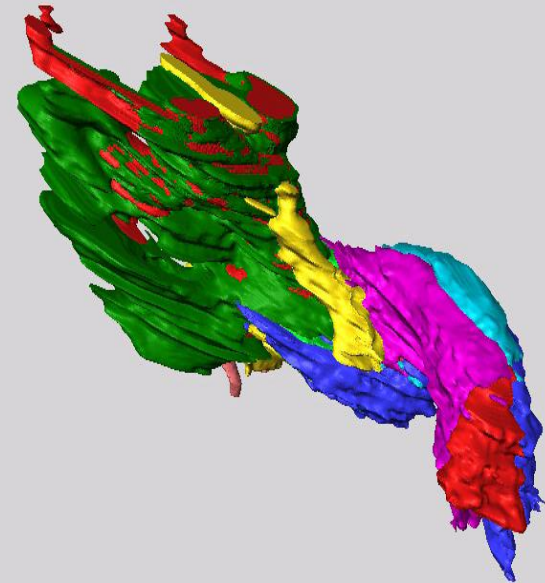
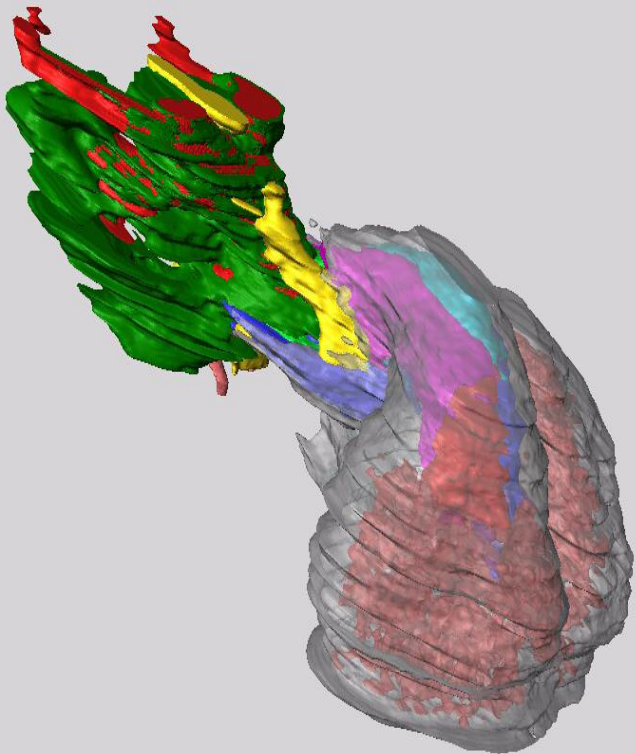
Double outlet right ventricle



Neural Crest (*wntcre x mtmg*) and Second Heart Field (*nkx2.5*) contribution to the cardiovascular outflow tract

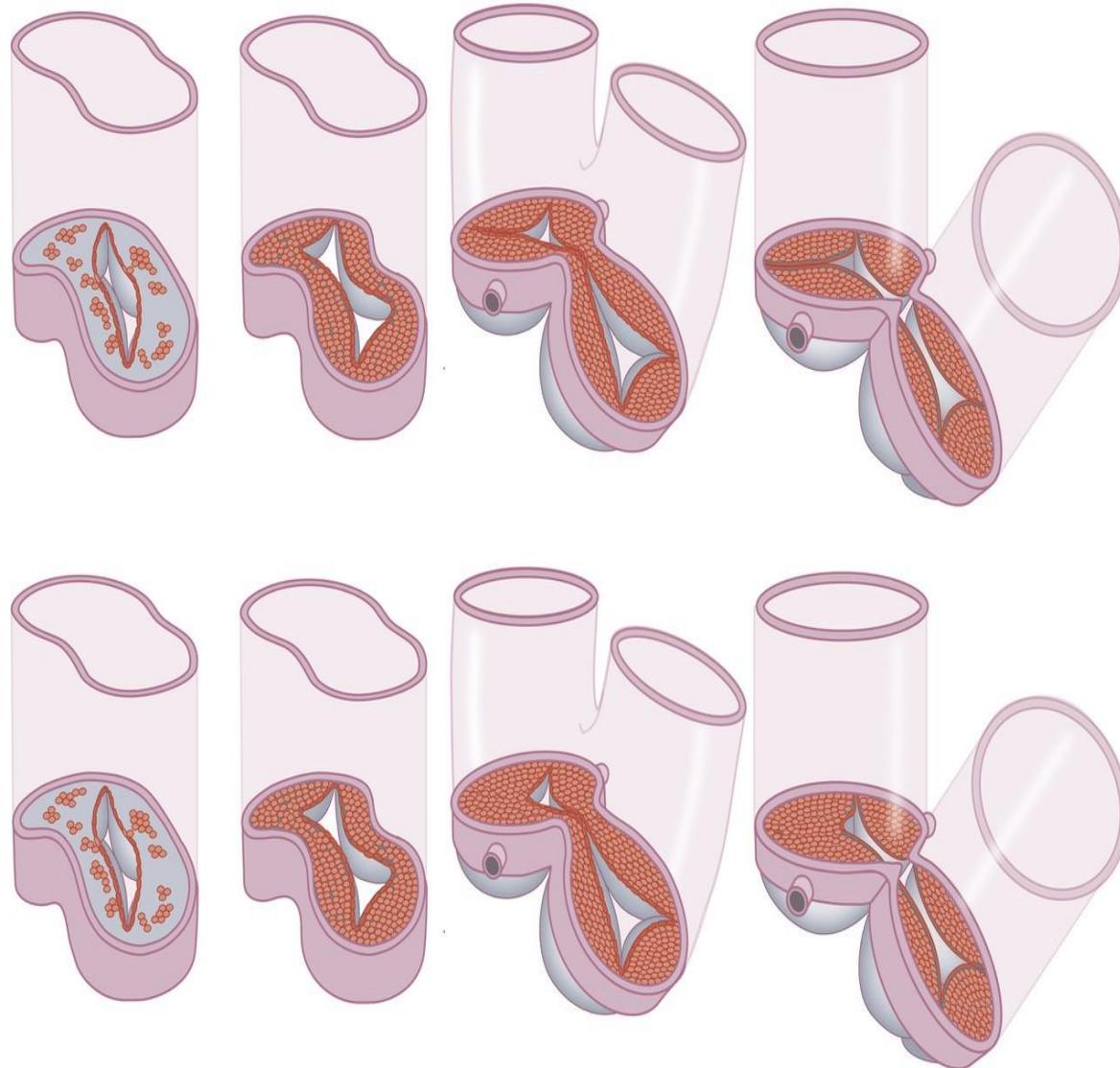


Neural Crest (**wntcre x mtmg**) and Second Heart Field (**nkx2.5**) contribution to the cardiovascular outflow tract

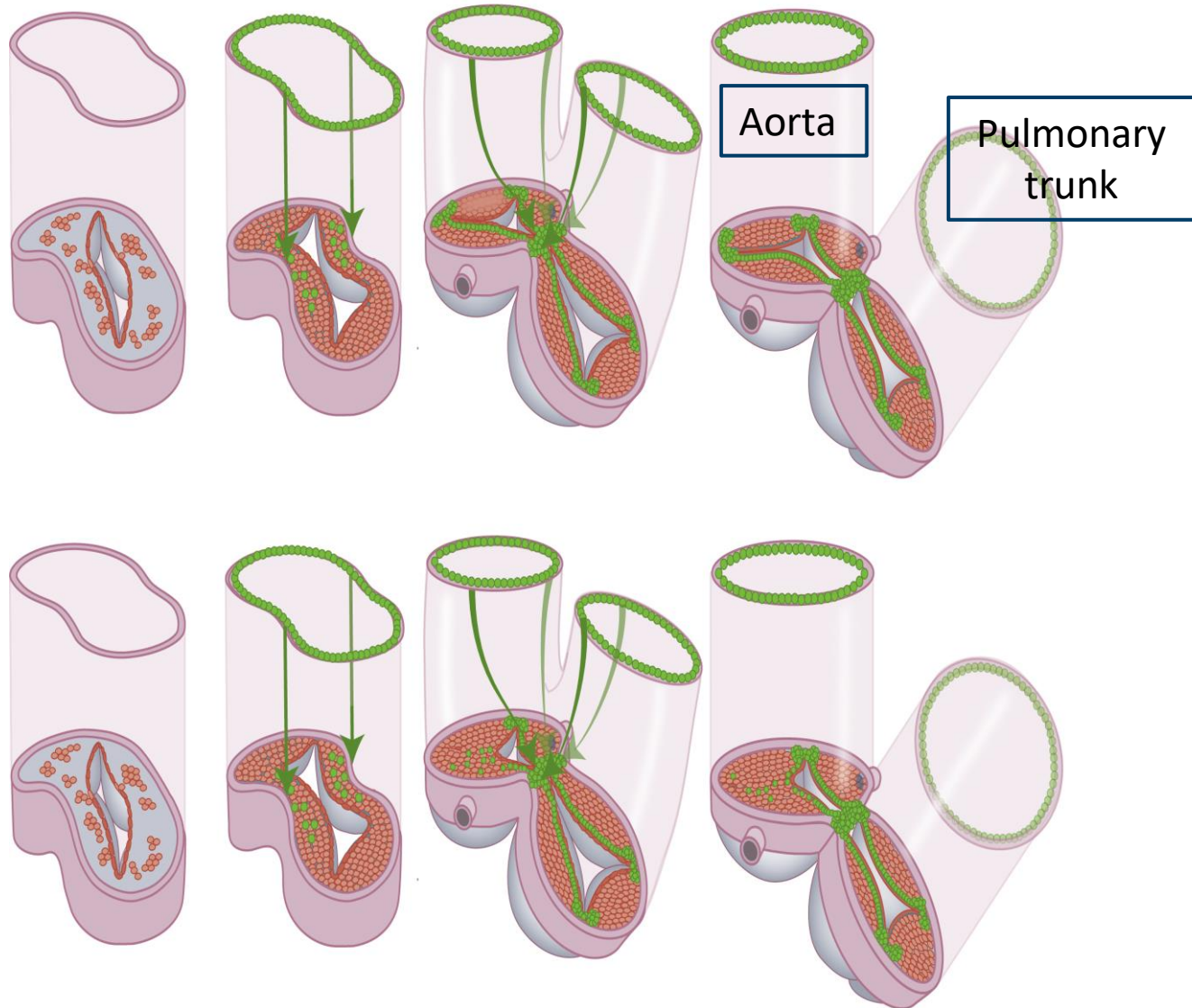


Parietal cushion
Septal cushion
Transitional zone
Neural crest
Second Heart Field
Endothelium
Myocardium

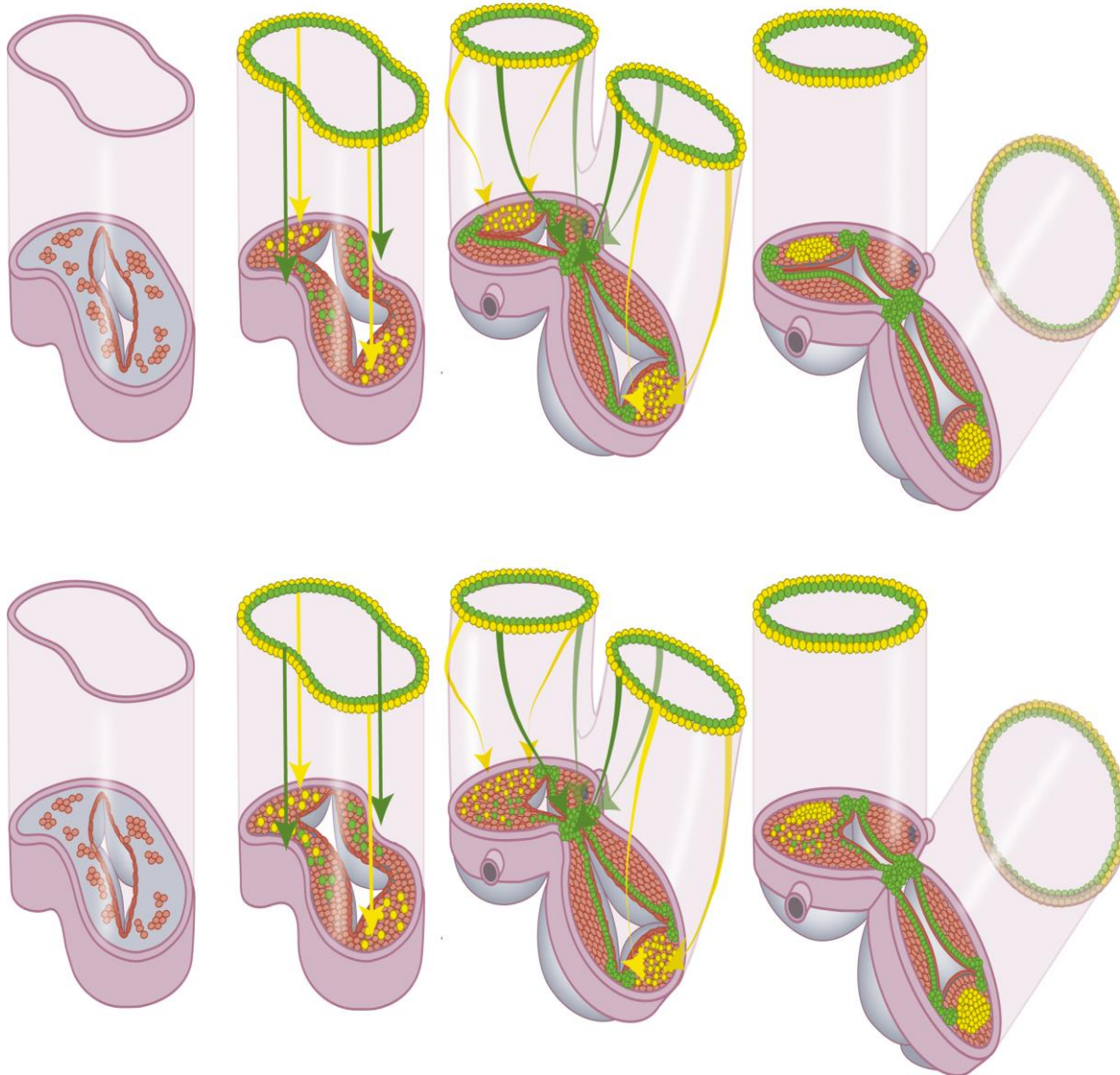
The outflow tract cushions of both aortic and pulmonary valves are formed by epithelial mesenchymal transformation



Neural Crest homes mainly to the left and right leaflets
SHF homes to the non-coronary/non-facing leaflets



Neural Crest homes mainly to the left and right leaflets
SHF homes to the non-coronary/non-facing leaflets



Anatomie van de tricuspide en bicuspide aortaklep

Een verworven of congenitale hartziekte?

Adult



Left (coronary) leaflet
Right (coronary) leaflet
Non-facing leaflet
(posterior or non-coronary)

Adult



L-R (coronary) leaflet fusion
Complete commissure

Newborn



L-R (coronary) leaflet fusion
with a raphe

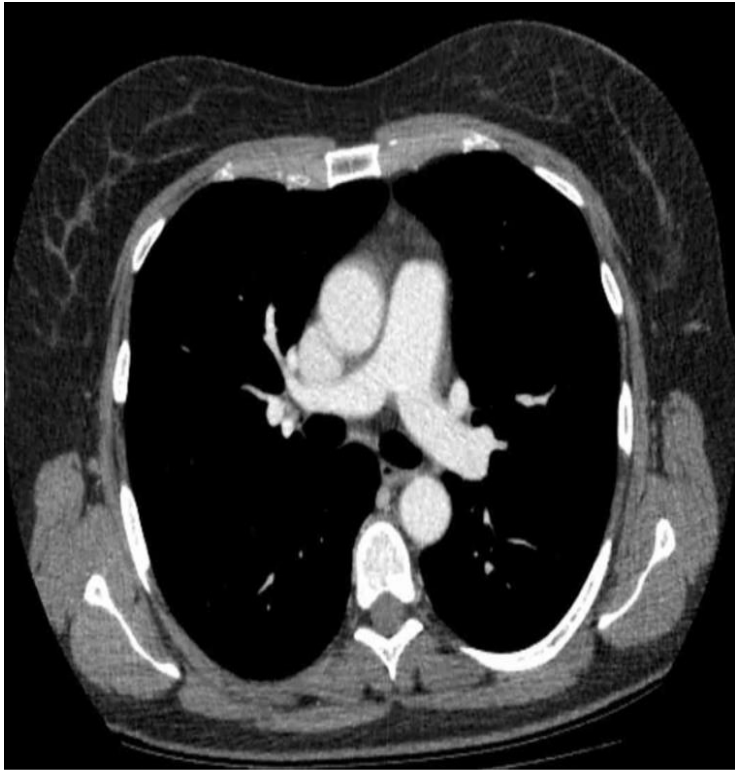
Newborn



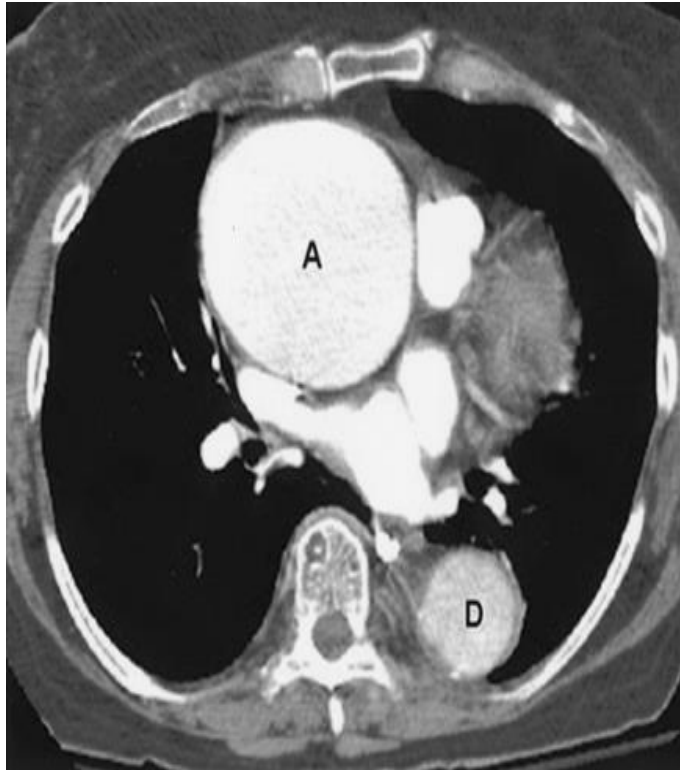
R-N or L-N leaflet fusion
without a raphe

Superior view of the aortic valve

Bicuspid Aorta klep (BAV): *hoge incidentie van Thoracale Aorta Aneurysmata (TAA)*



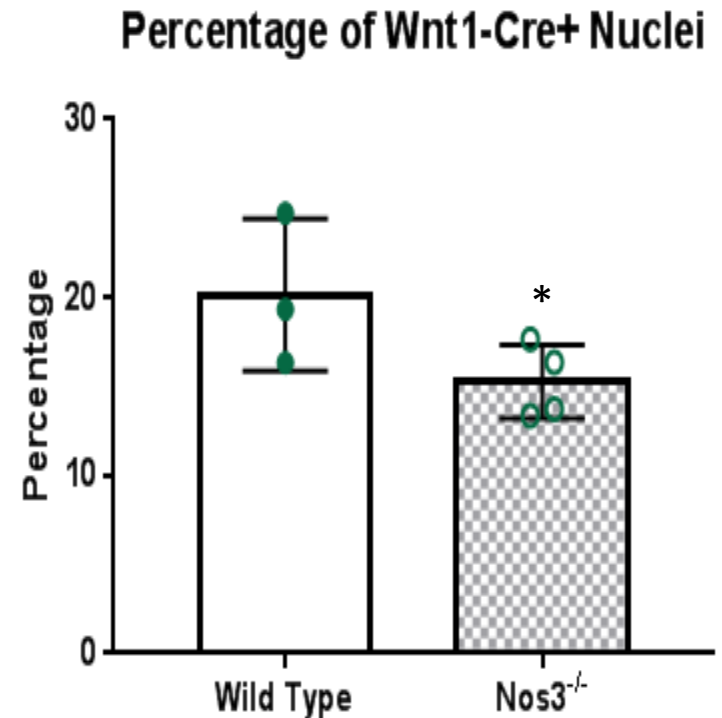
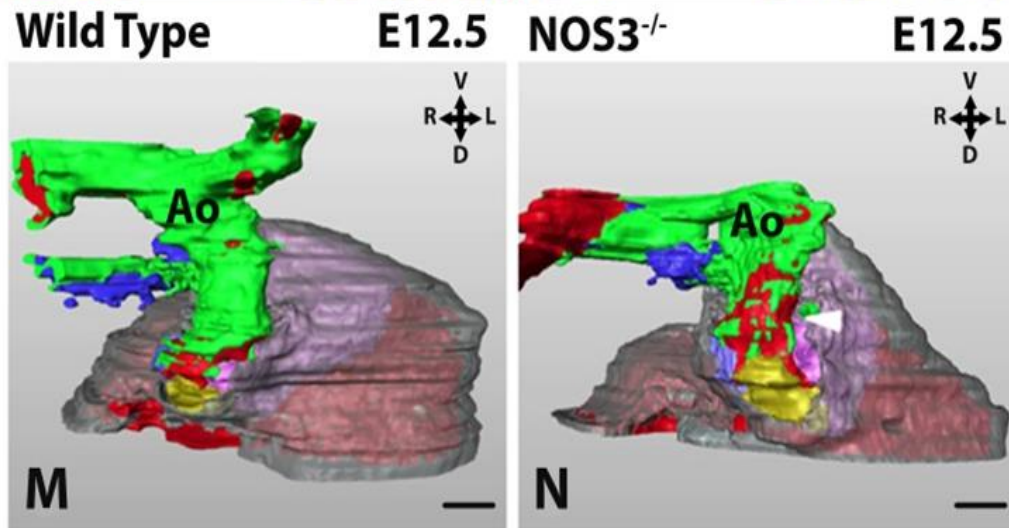
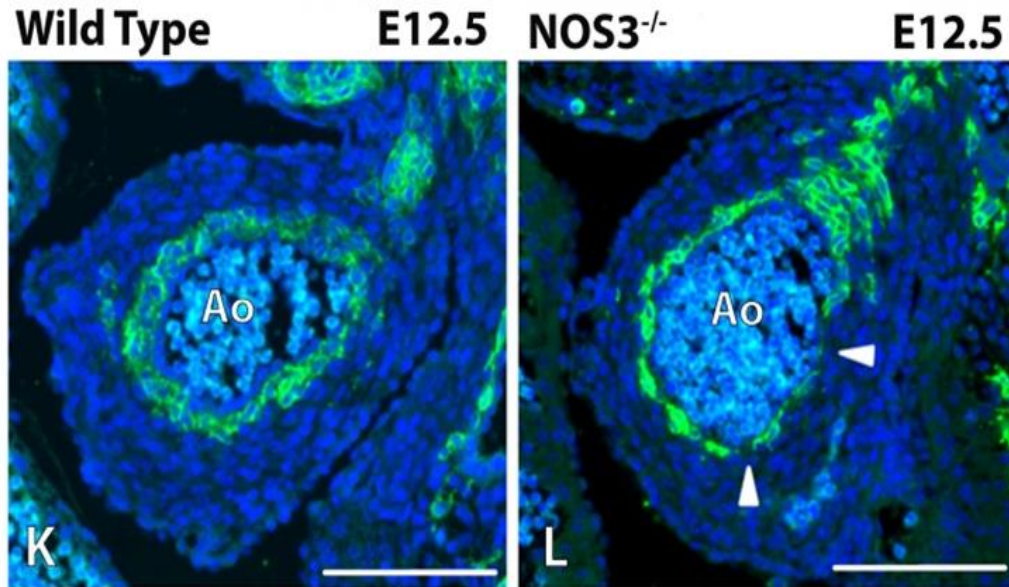
Control



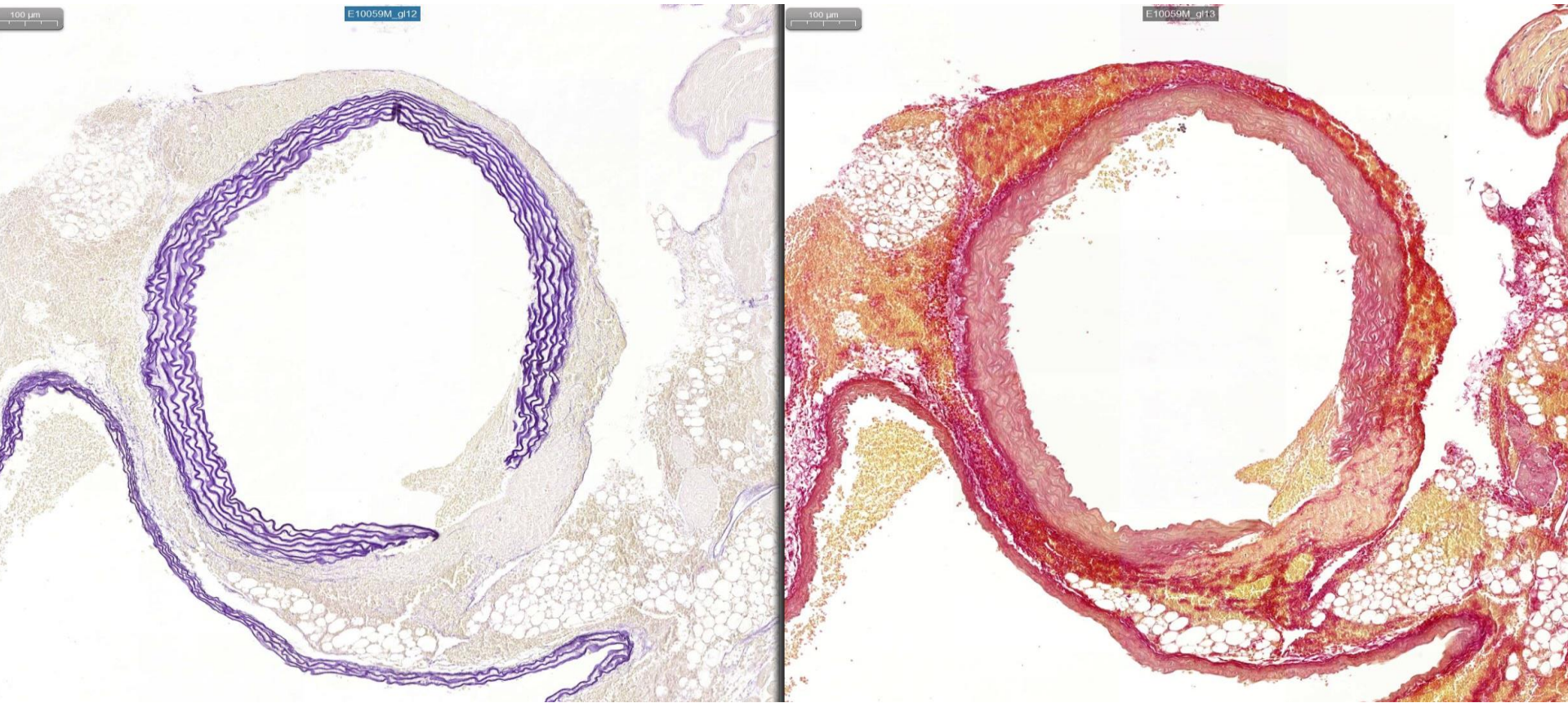
Patient



Een reductie van neurale lijst afkomstige cellen in de aorta of NO-synthase $-/-$ embryos op E12.5

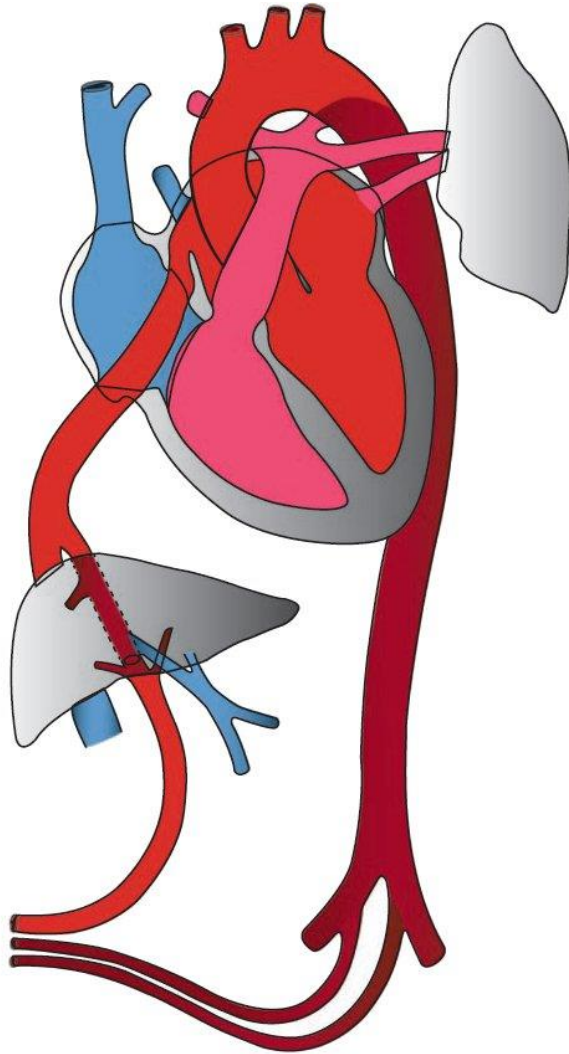


20% van de adulte muizen knock out voor NO-synthase heeft een dissectie van de aorta

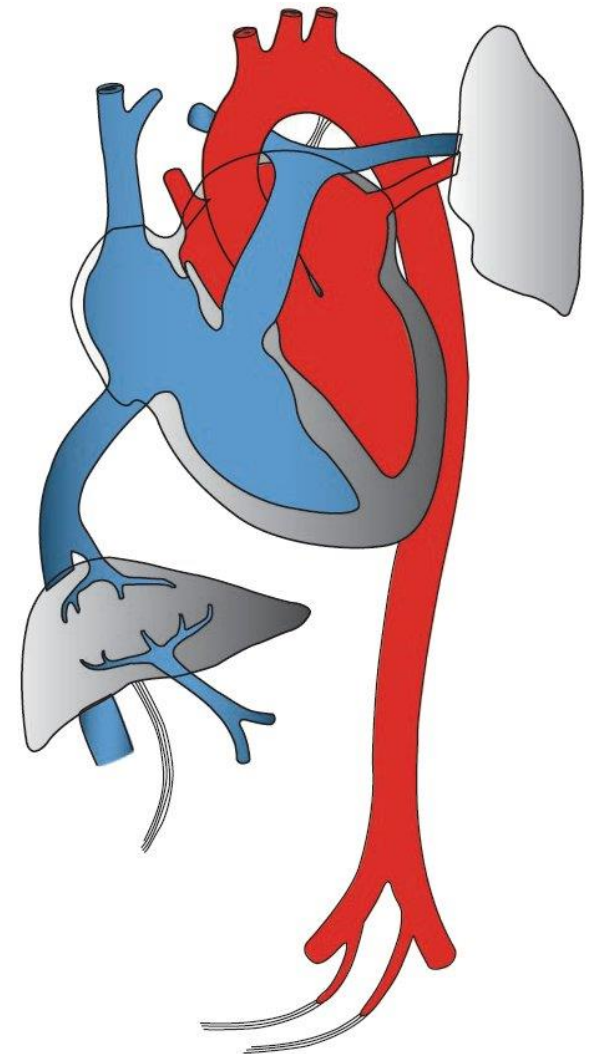


4. Waarom zijn de meeste hartafwijkingen na de geboorte schadelijk? Foetale versus volwassen circulatie

prenataal



postnataal



Larsen's Human Embryology, 5th ed., 2014

Gevolgen aangeboren hartafwijkingen

Het normale hart

aorta

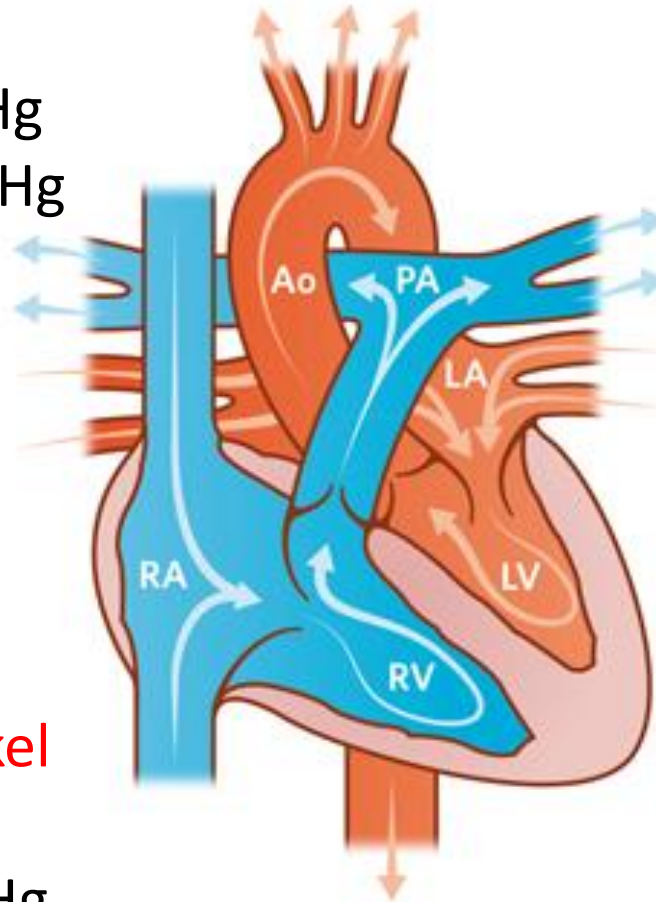
DP 60-80 mm Hg
SP 90-150 mm Hg

rechter atrium

MP 2-6 mm Hg

rechter ventrikel

DP 2-6 mm Hg
SP 20-30 mm Hg



pulmonaal art.

DP 8-12 mm Hg
SP 20-30 mm Hg

linker atrium

MP 6-12 mm Hg

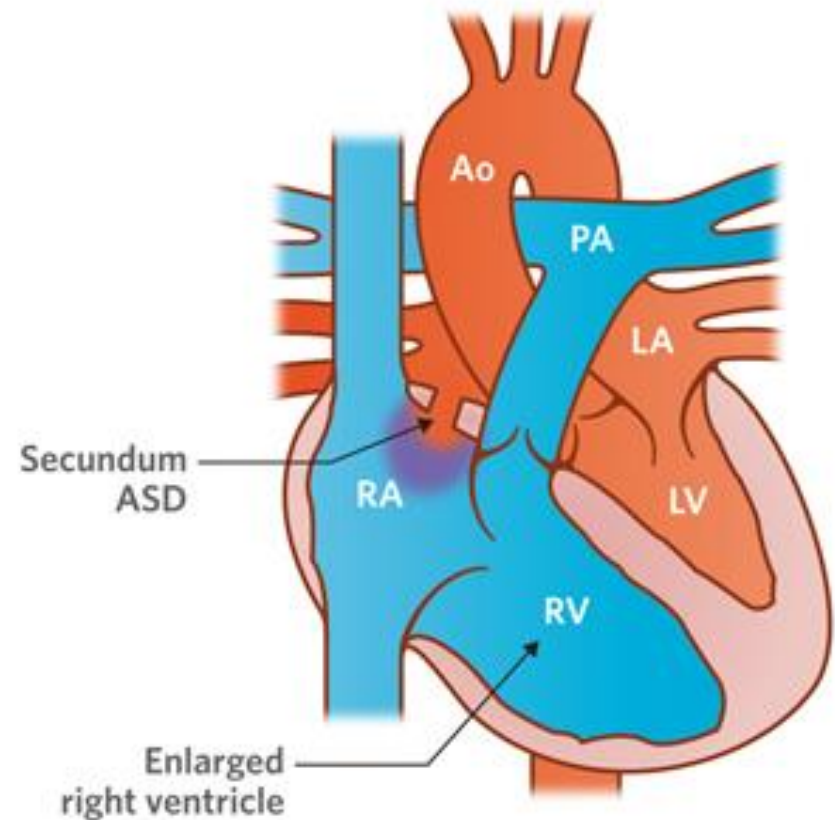
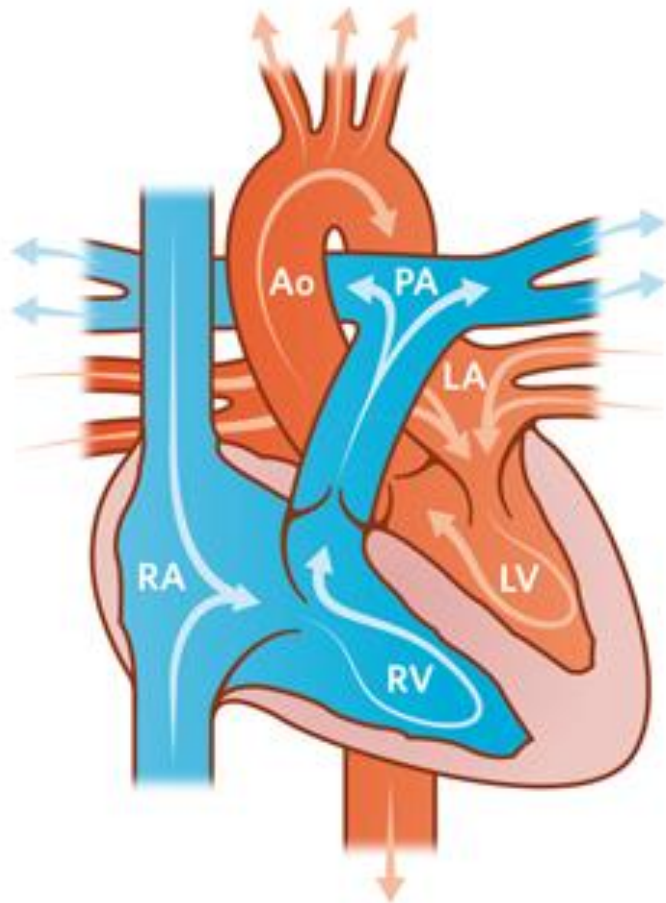
linker ventrikel

DP 6-12 mm Hg
SP 90-150 mm Hg

normaal

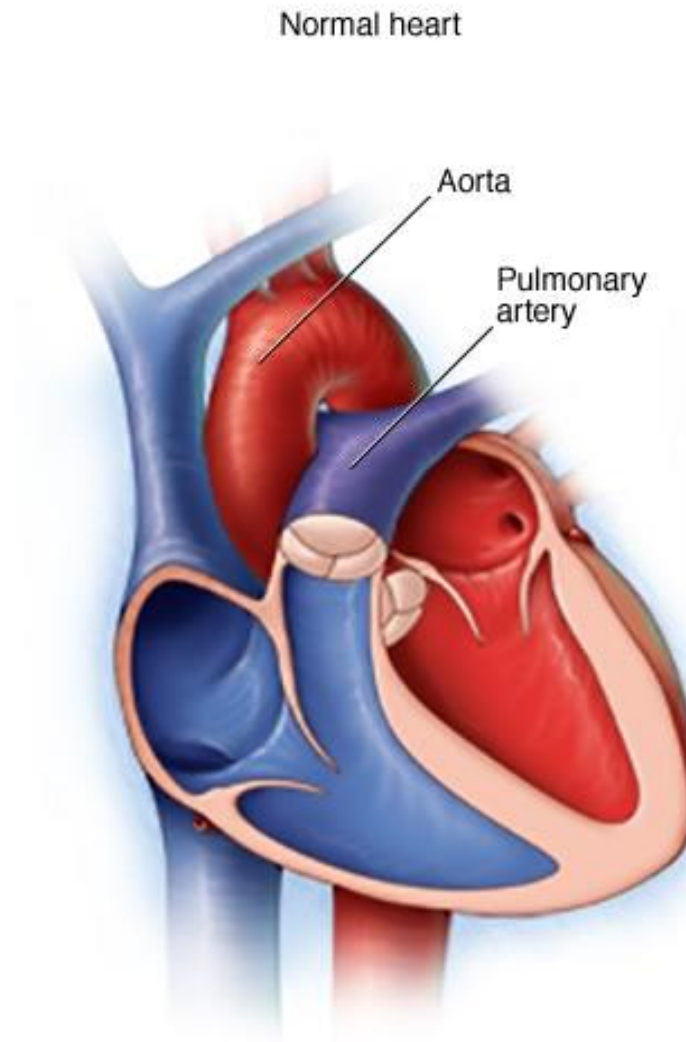
Gevolgen aangeboren hartafwijkingen

Atrium Septum Defect (type 2)



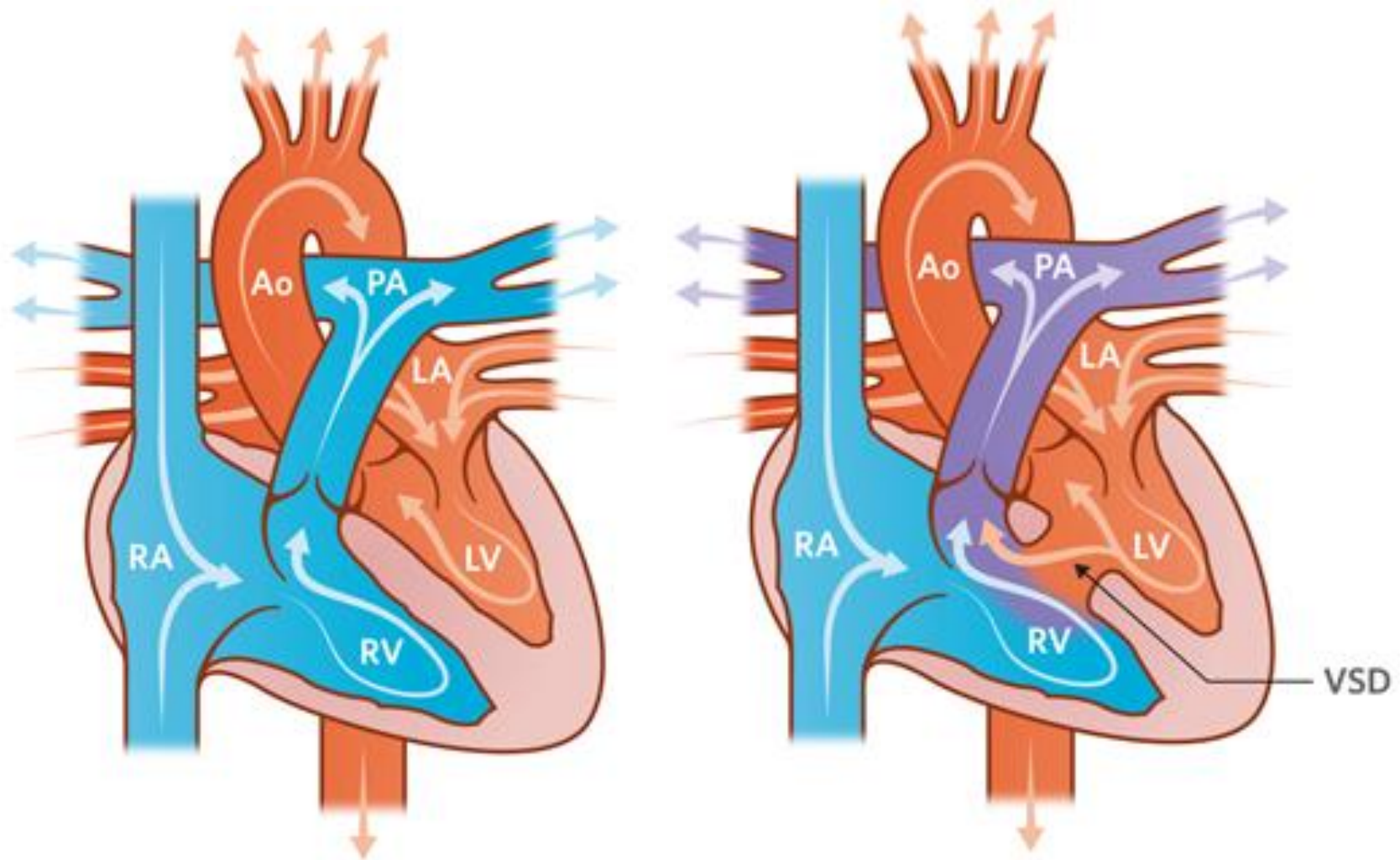
Gevolgen aangeboren hartafwijkingen

transpositie van de grote arteriën



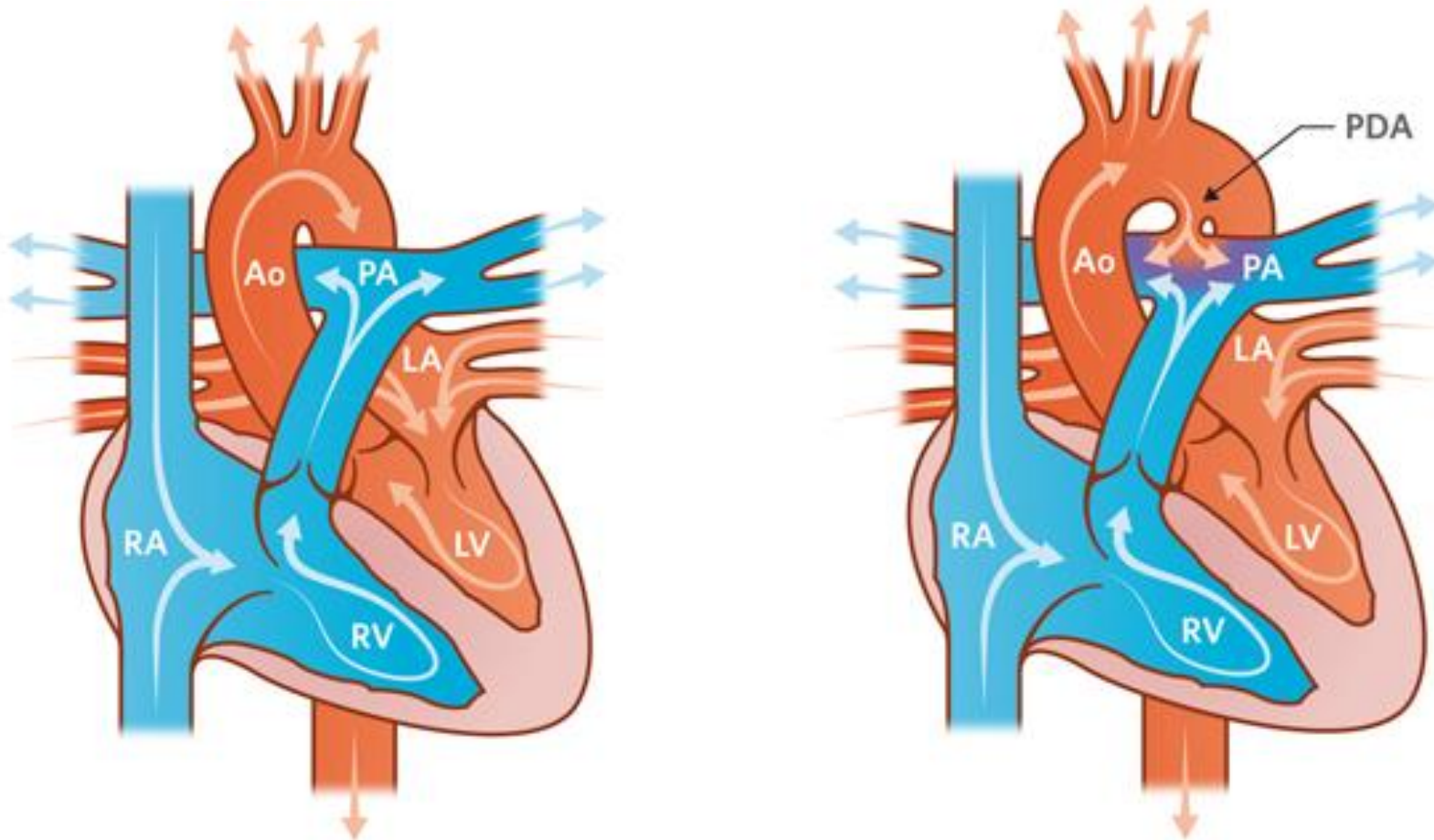
© MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH. ALL

Gevolgen aangeboren hartafwijkingen (groot) Ventriculair Septum Defect



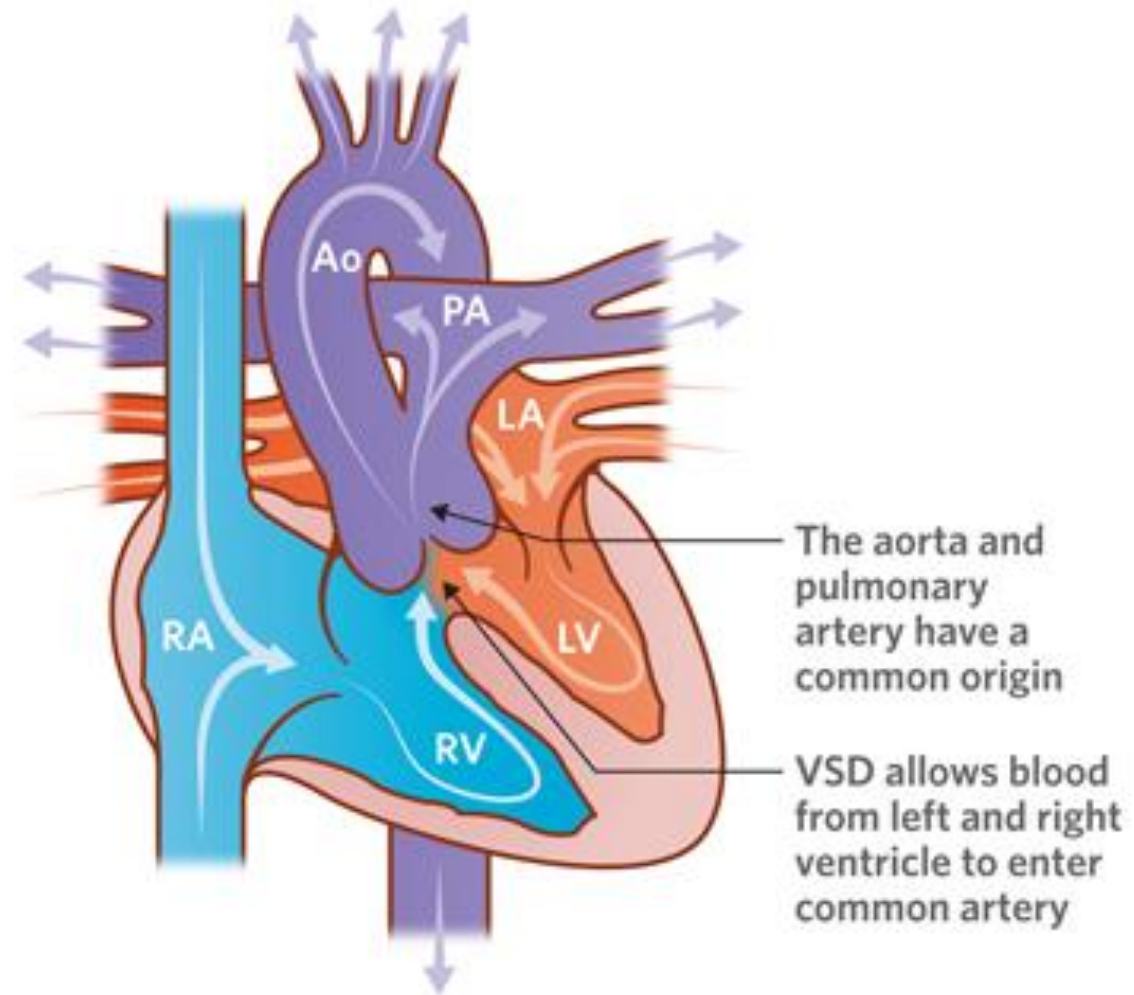
Gevolgen aangeboren hartafwijkingen

persisterende ductus arteriosus



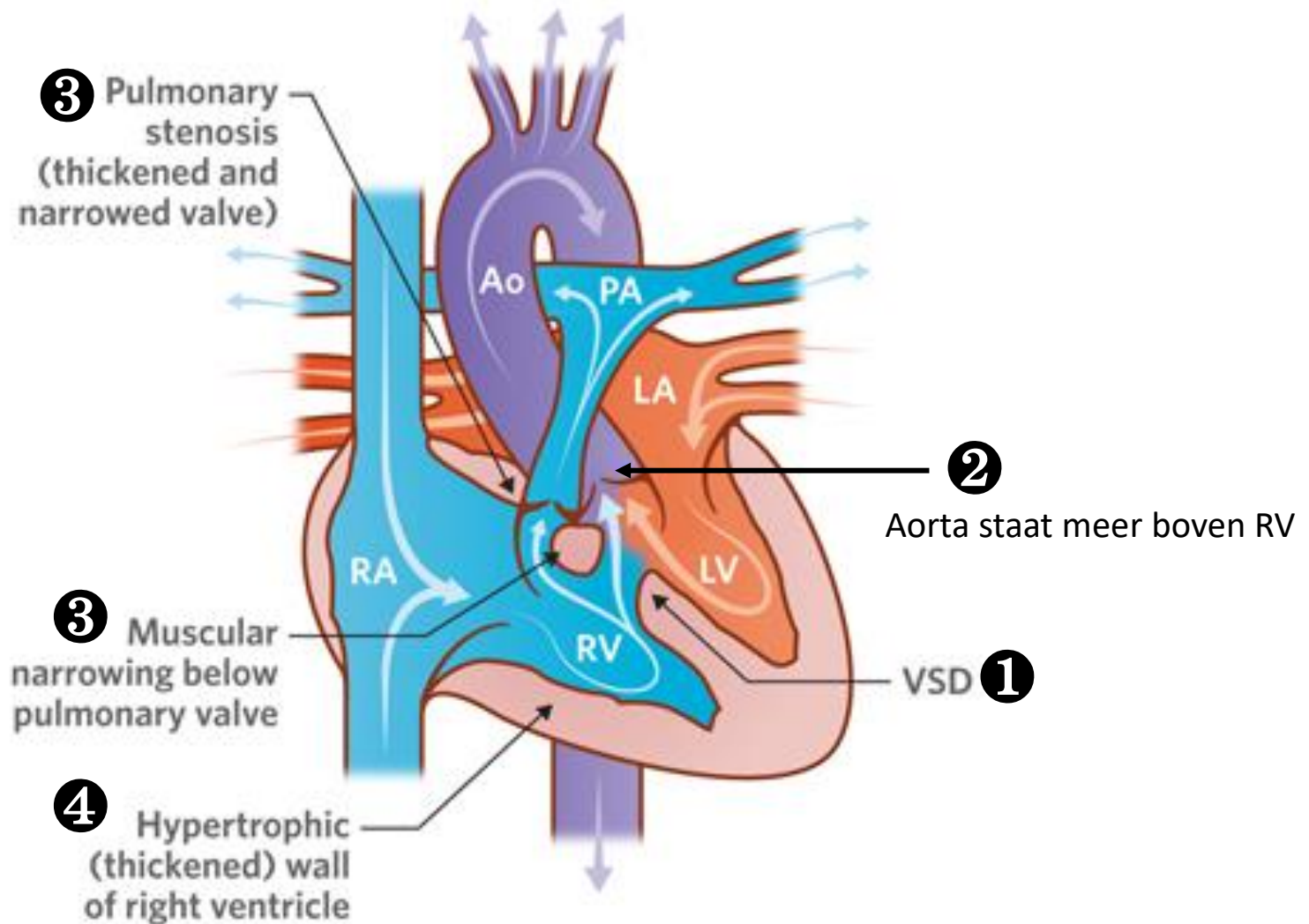
Gevolgen aangeboren hartafwijkingen

persisterende truncus arteriosus

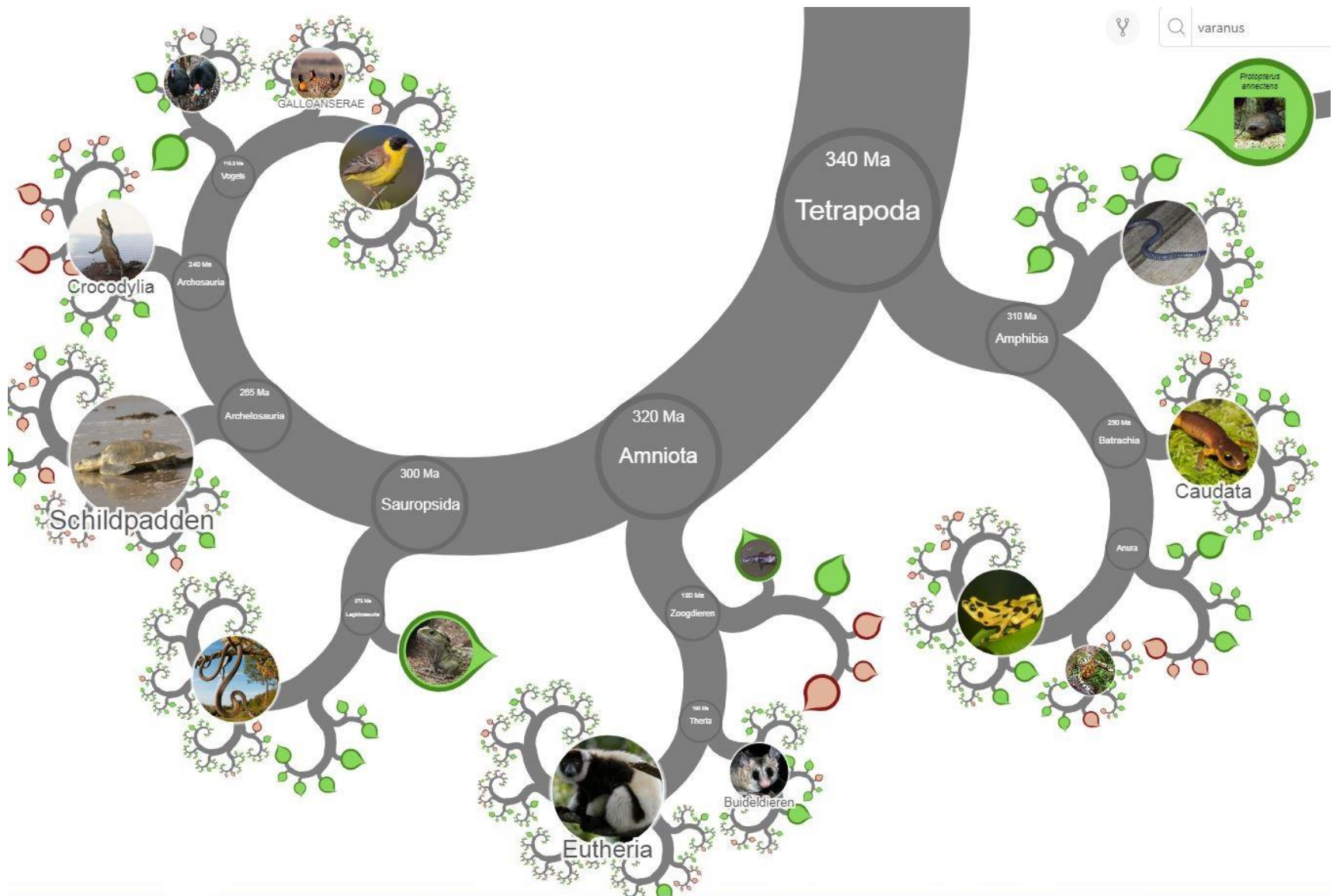


Gevolgen aangeboren hartafwijkingen

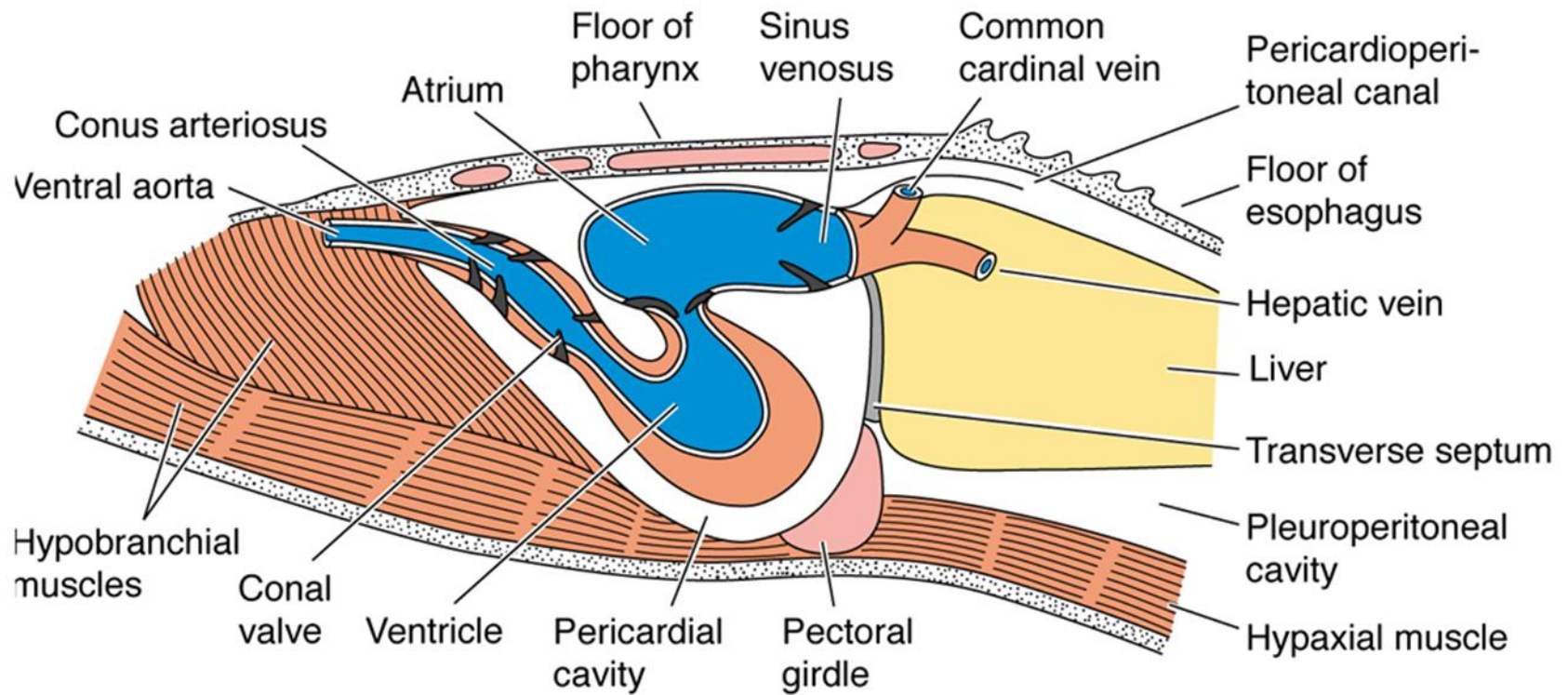
Tetralogie van Fallot



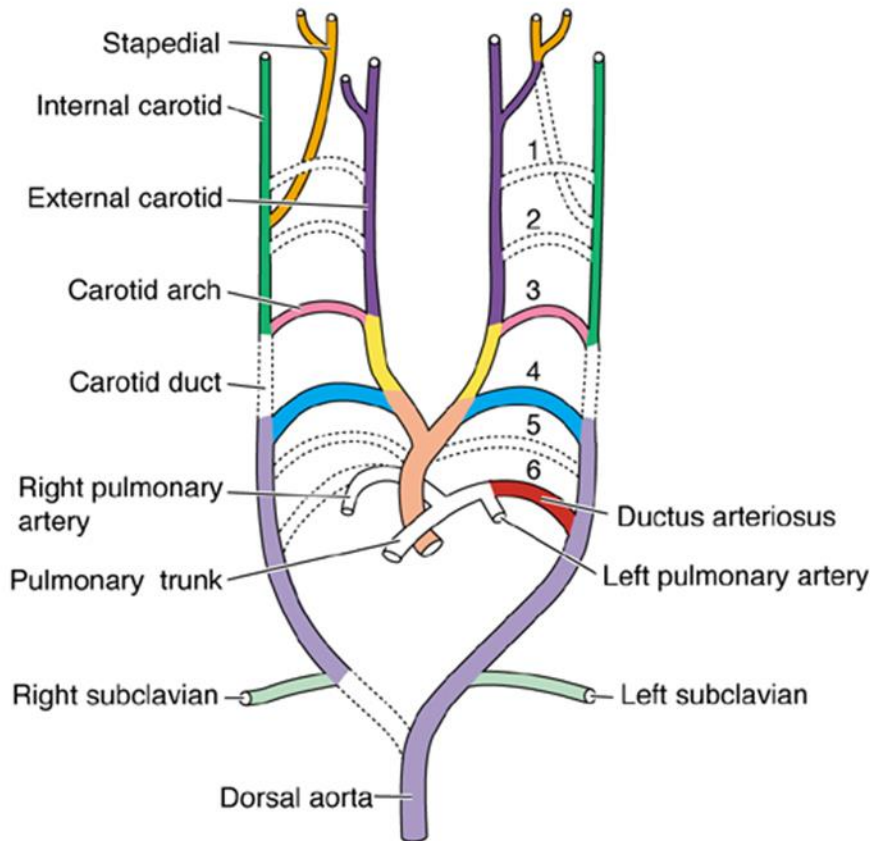
5. Wat leren de harten van andere tetrapoden ons?



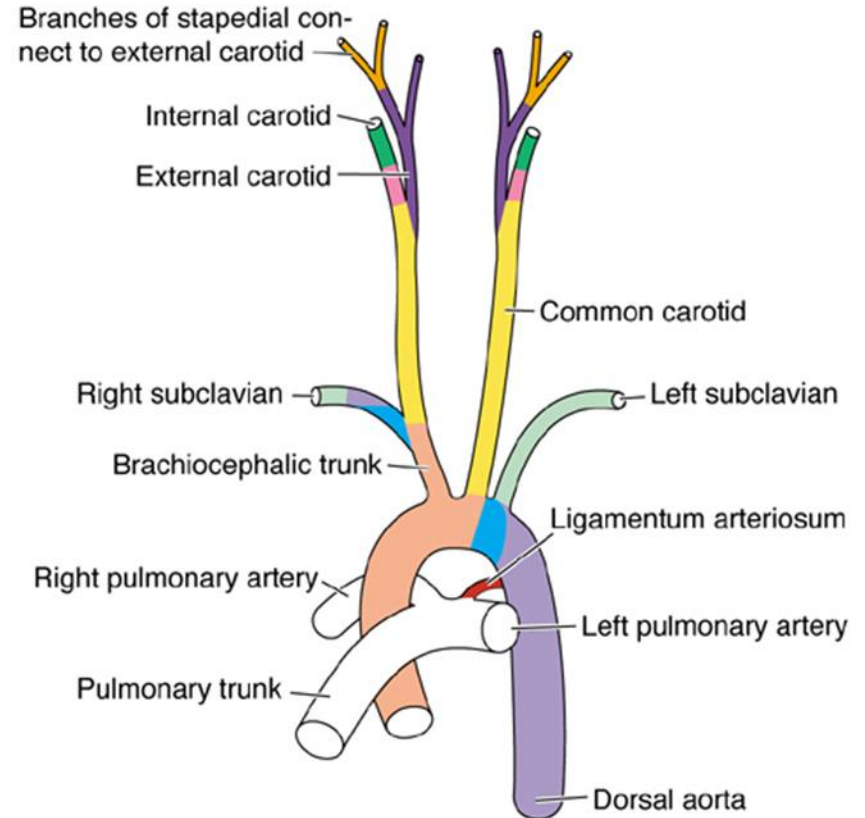
Tubular heart haai



Remodelling kieuwbogen in zoogdieren

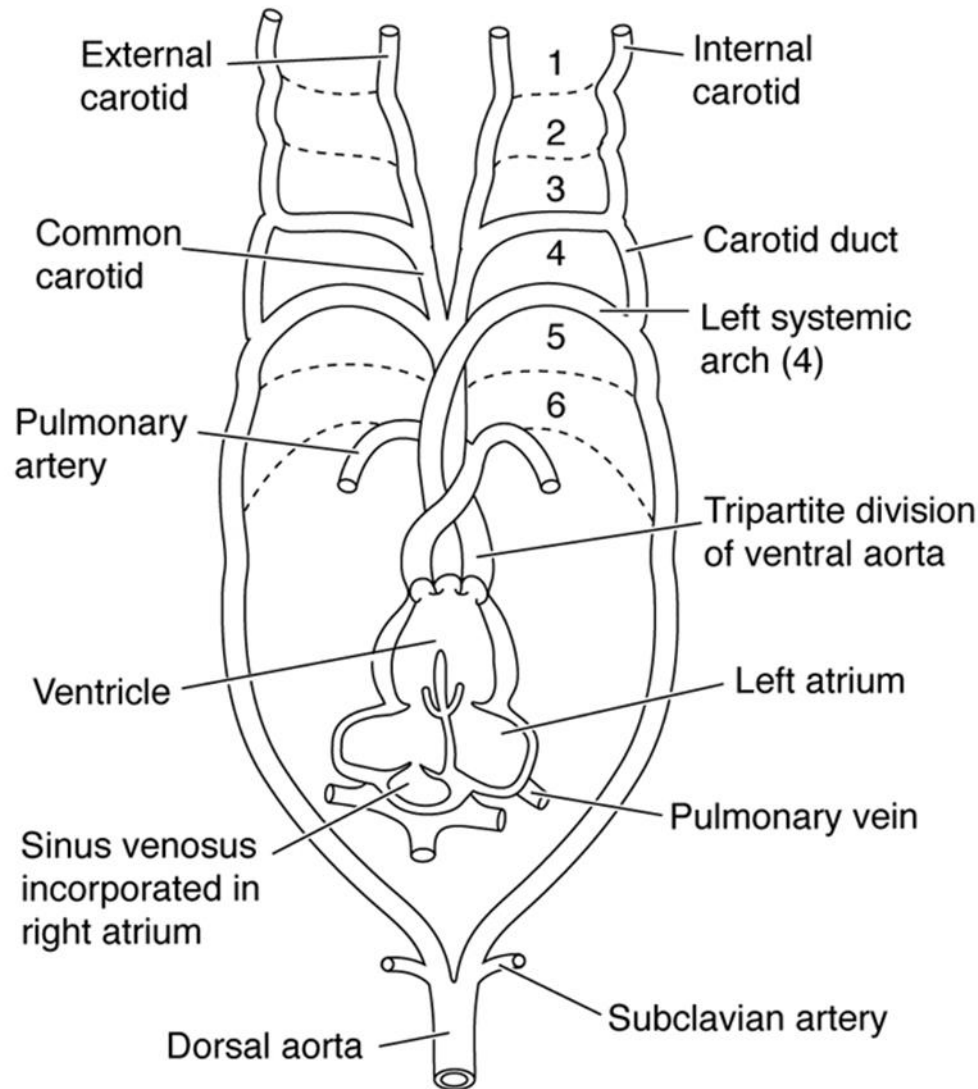


A. Early developmental stage



B. Adult human

Remodelling kieuwbogen in reptielen



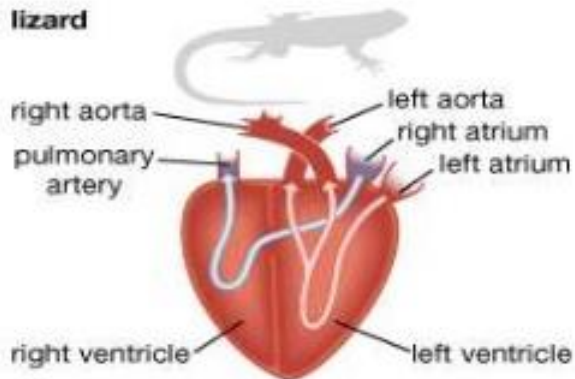
Partial
septation of
ventricle,

Complete
septation in
crocodile

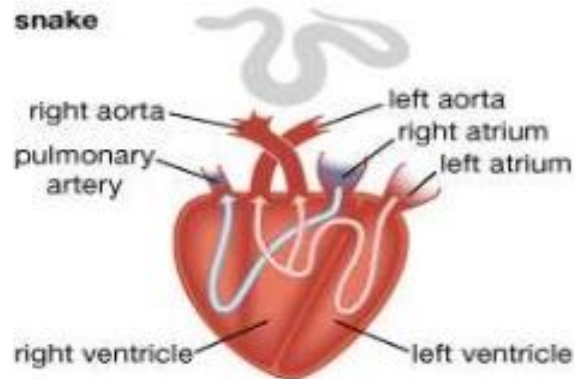
Left and
right aorta

+ Heart of Reptiles

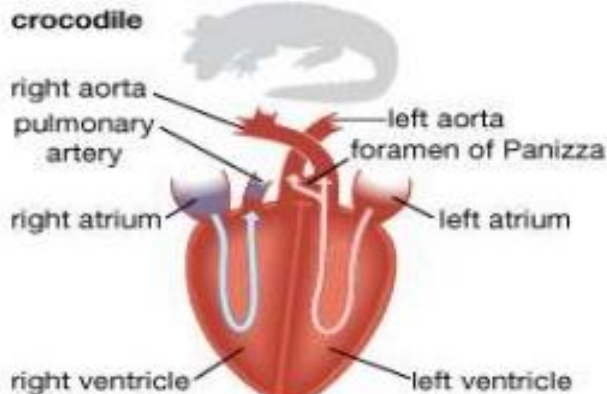
lizard



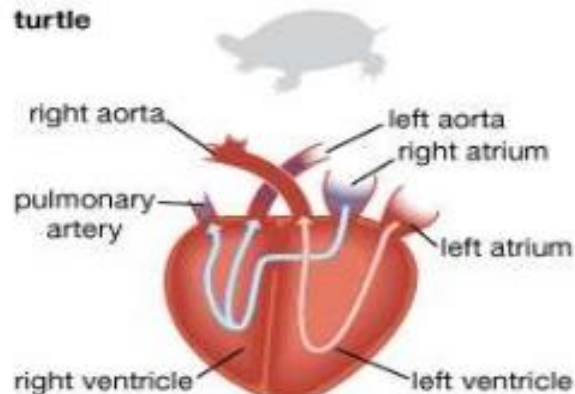
snake



crocodile



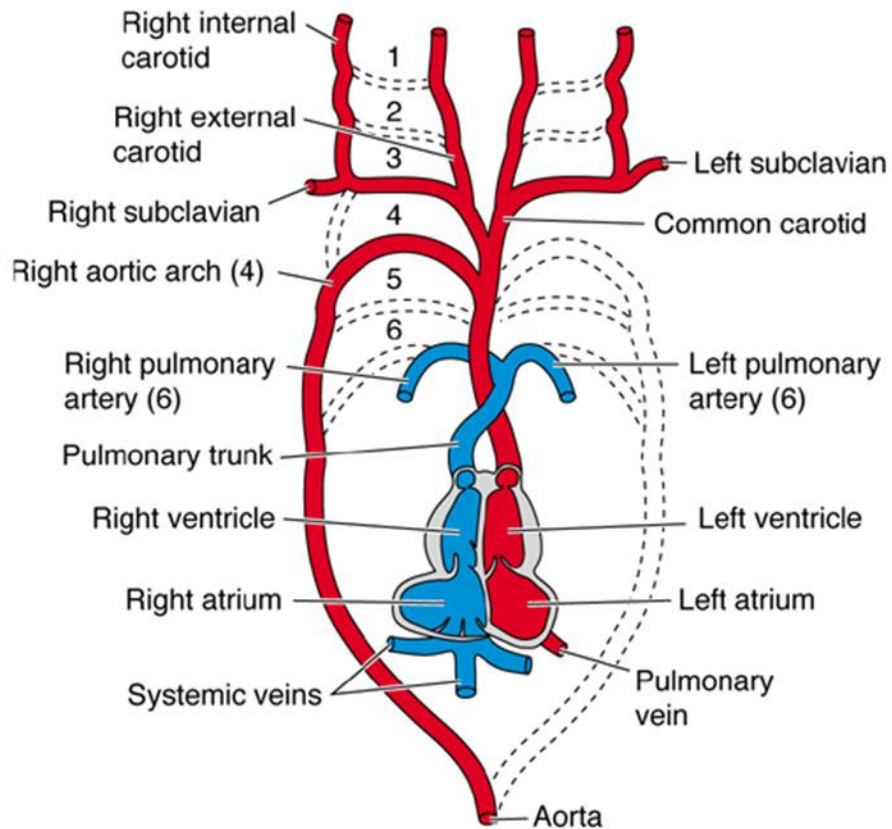
turtle



© 2008 Encyclopædia Britannica, Inc.

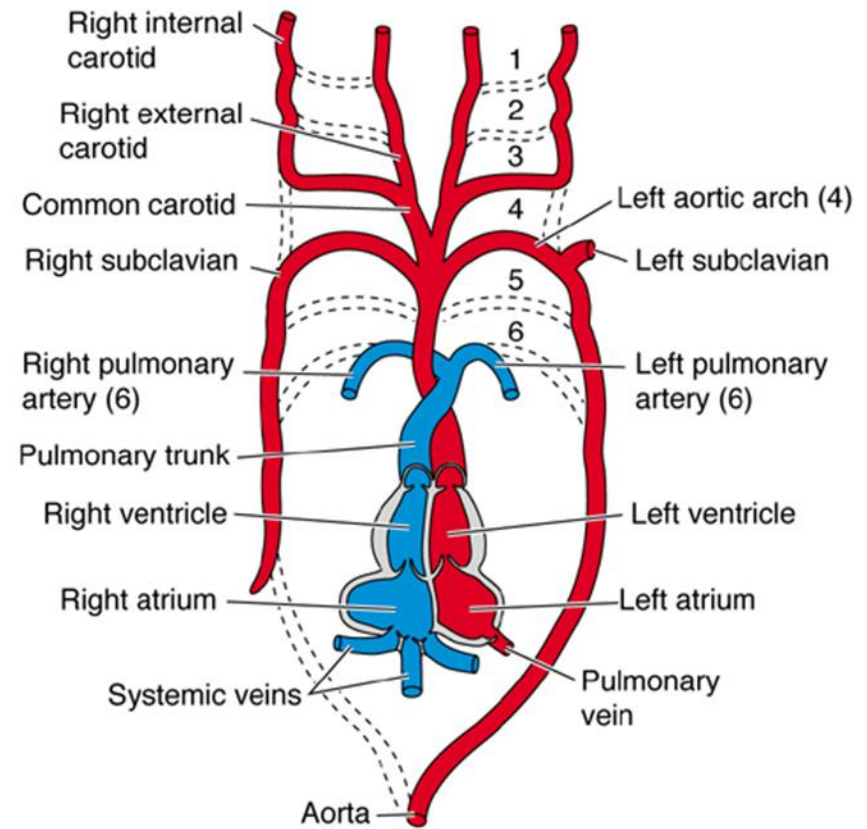
Varaan en python: ventriculair septum sluit bij contractie van de ventrikel op de uitstroom: hoge druk en lage kamer

Vogel (is een reptiel!), Zoogdier



A. Bird

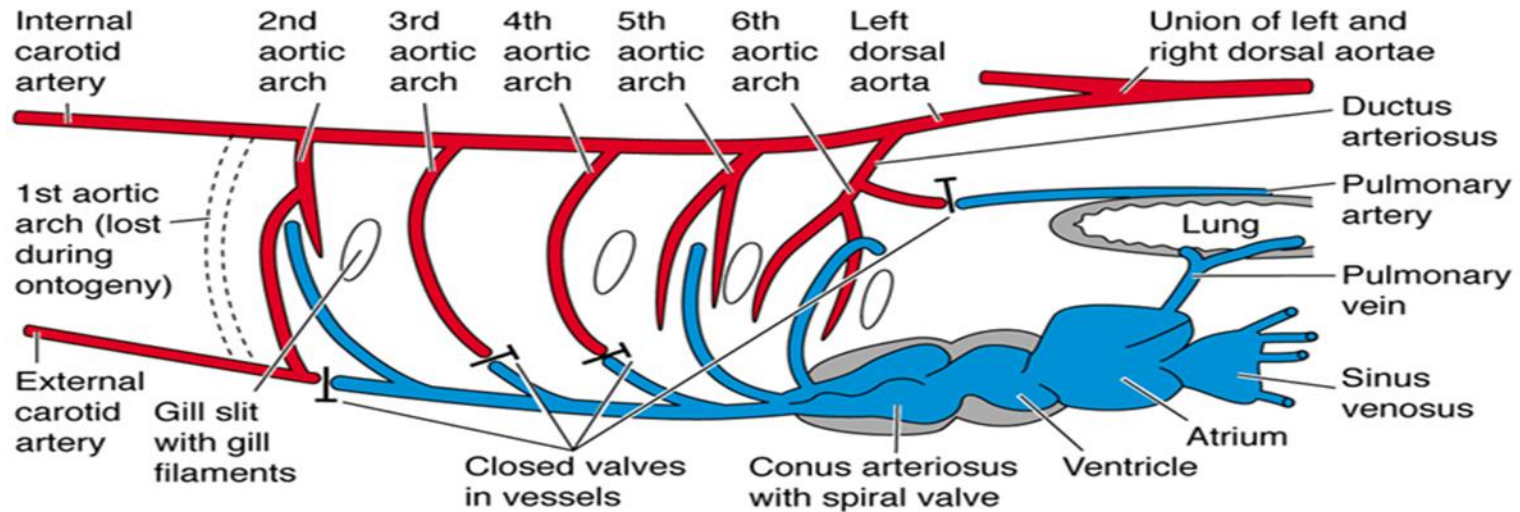
Complete septation
Left OR right aorta



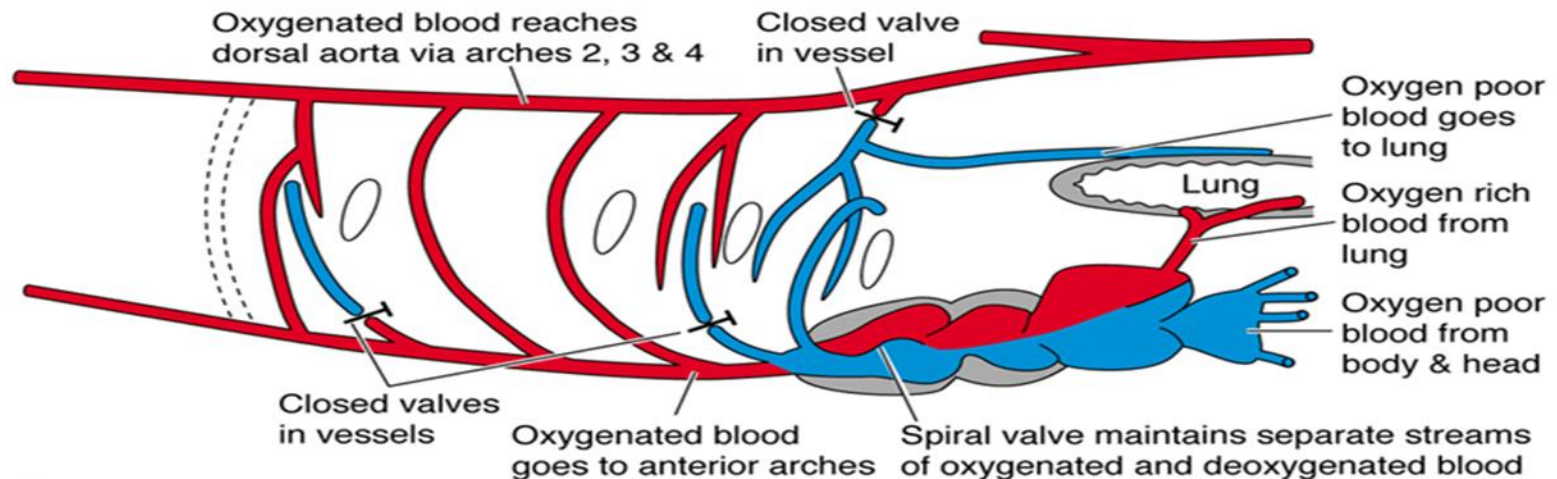
B. Mammal

High pressure and low pressure
compartment

Africaanse longvis: bimodale O₂ voorziening

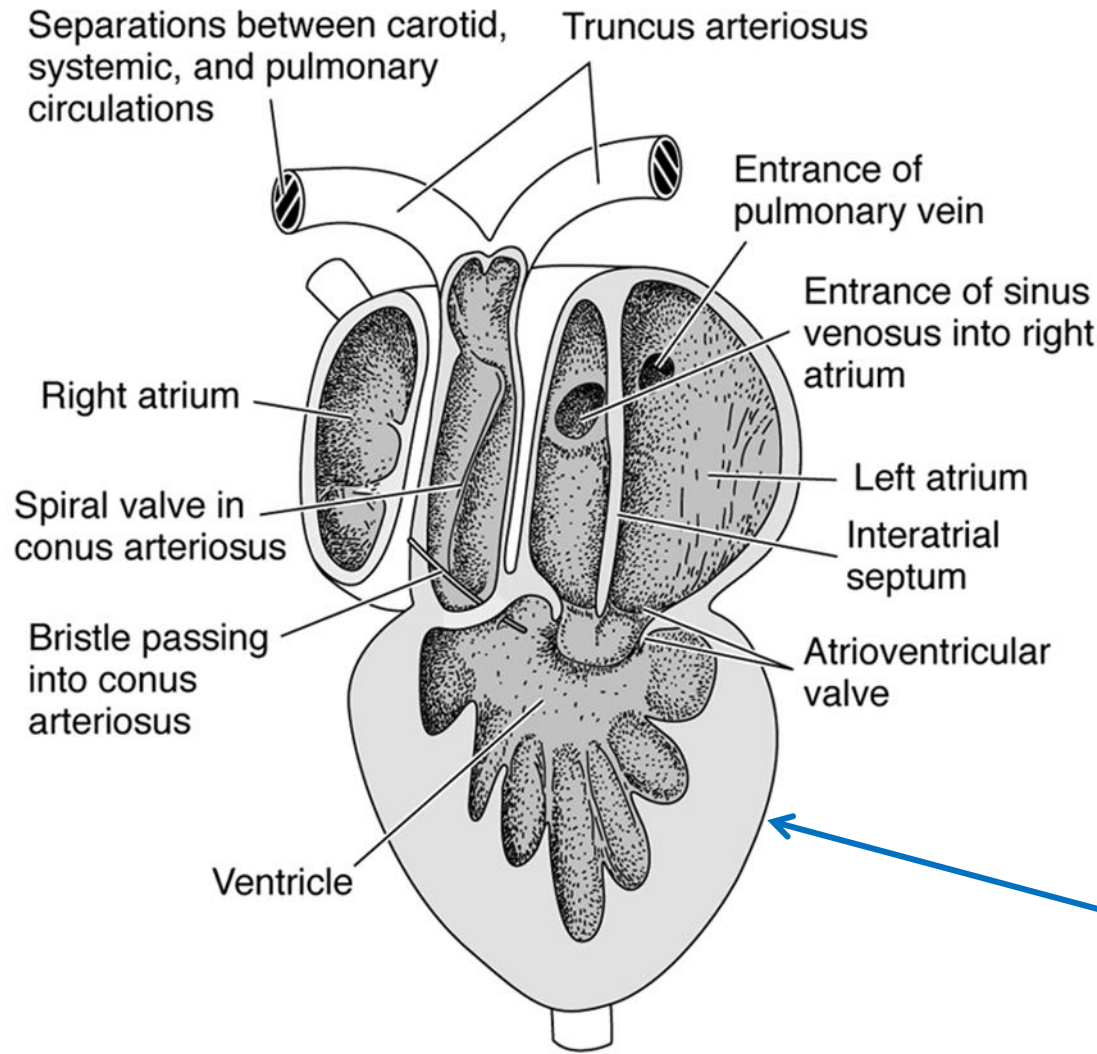


A. Aquatic breathing mode



B. Aerial breathing mode

Kikkerhart



Septatie van atrium,
maar niet van
ventrikel

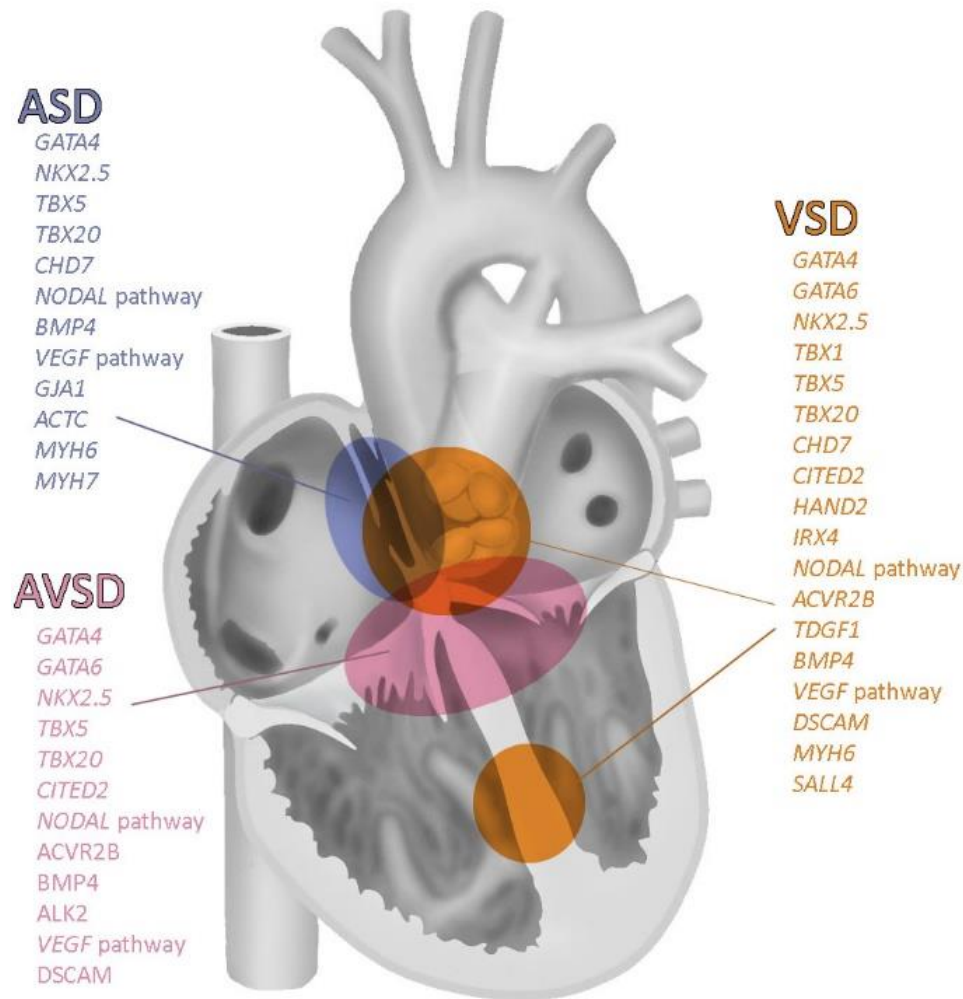
Linker en rechter
atrium
LET OP!!!

Univentrikel

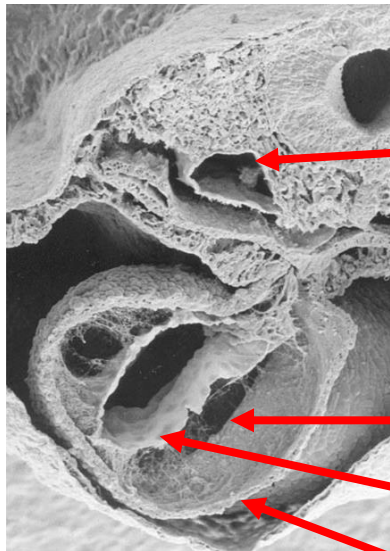
EINDE



Betrokken genen



Bijdrage van verschillende celgroepen



SMOOTH MUSCLE CELLS

ENDOTHELIAL CELLS

NEURAL CREST CELLS

**ENDOCARDIAL CUSHION
CELLS**

“CARDIAC JELLY”

ENDOCARDIUM

MYOCARDIUM

EPICARDIUM

