



# Classification des cardiopathies congénitales

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IcarP Cardiology, Institut Hospitalo-Universitaire IMAGINE

Centre de Référence Maladies Rares  
**Malformations Cardiaques Congénitales Complexes-M3C**

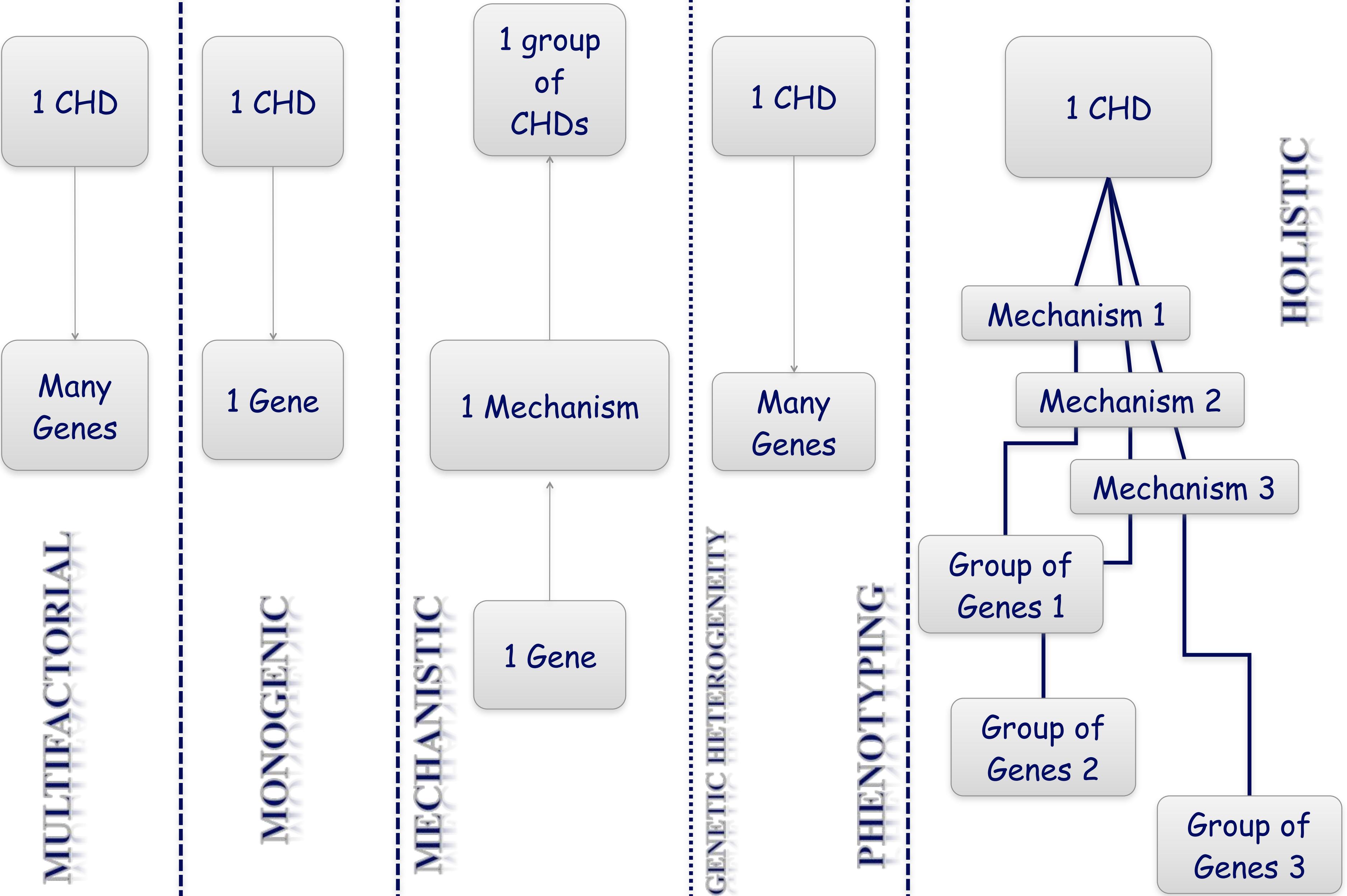
Centre de Référence Maladies Rares  
**Maladies Cardiaques Héréditaires- CARDIOGEN**



European Reference Network  
for rare or low prevalence complex diseases  
Network Respiratory Diseases (ERN-LUNG)



# Classification embryologique ou mécanistique des cardiopathies congénitales

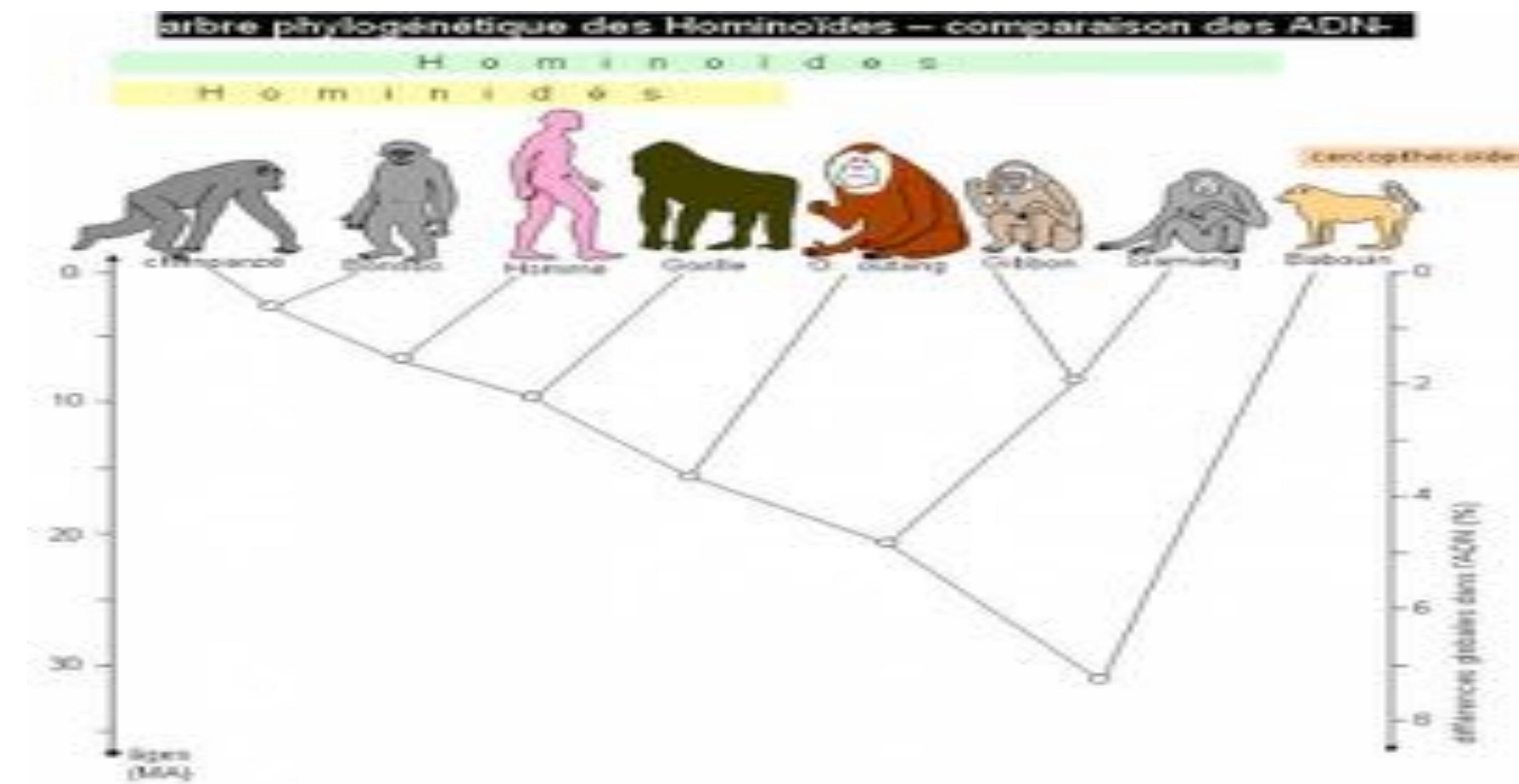


# Phylogeny

*Darwin*

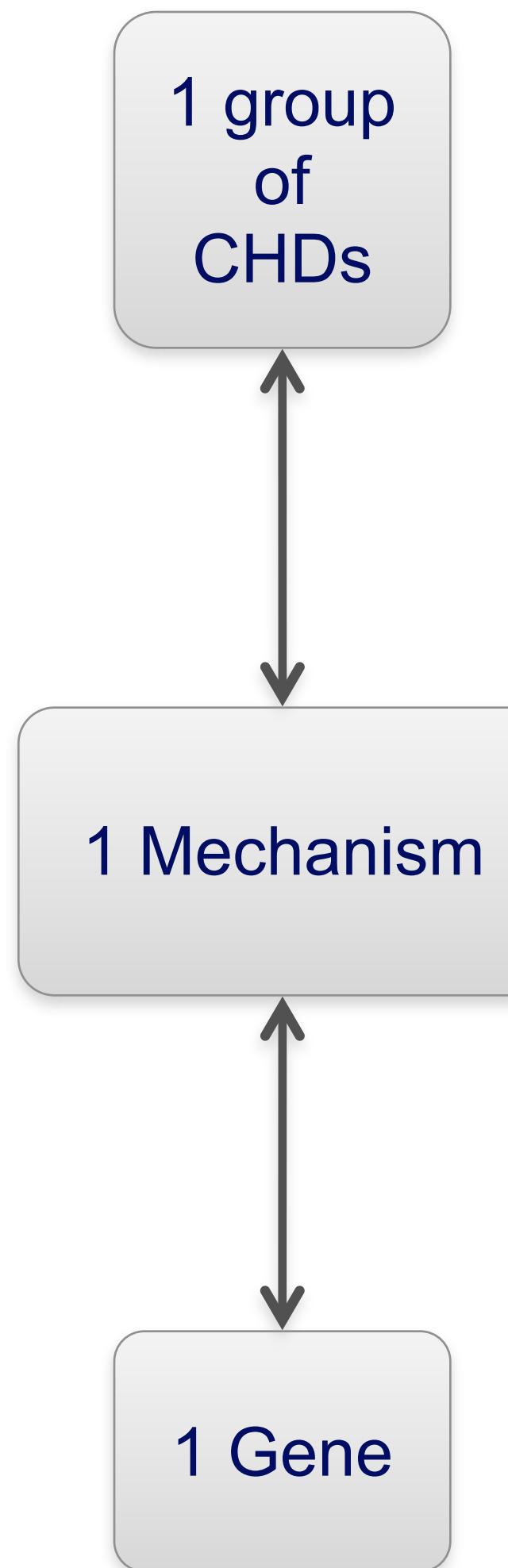
Based on the notion of common ancestor

Phylogenetic groups - phylum



# Mechanistic classification

- Neural crest cell migration defects  
*Conotruncal malformations*
- Flow defects  
*Hypoplastic left heart*
- Targeted developmental defects  
*TAPVR*
- Extracellular matrix defects  
*Ventricular Septal Defects*
- Endocardial cushions defects  
*Atrioventricular septal defects*
- Looping anomalies-laterality defects  
*Heterotaxia*

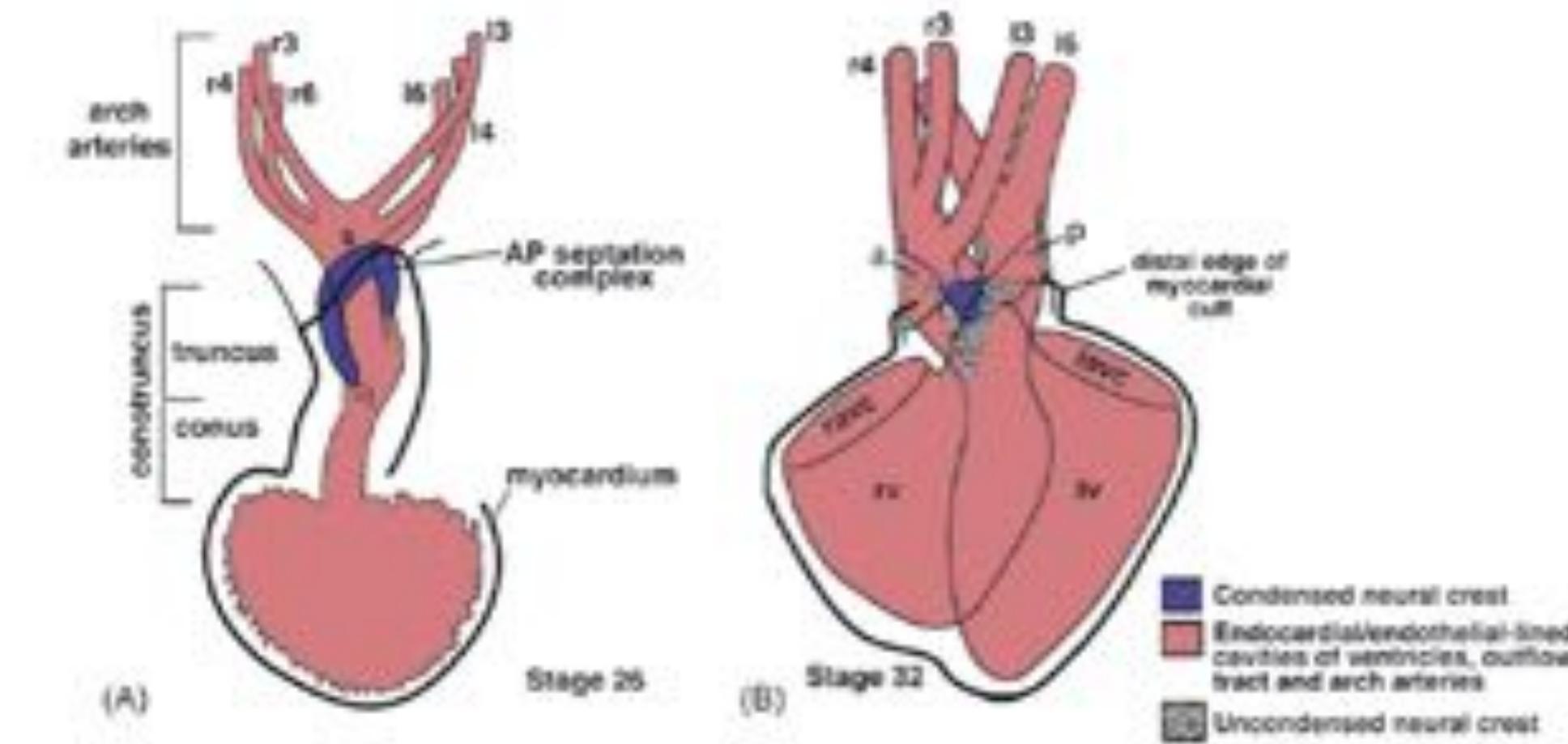
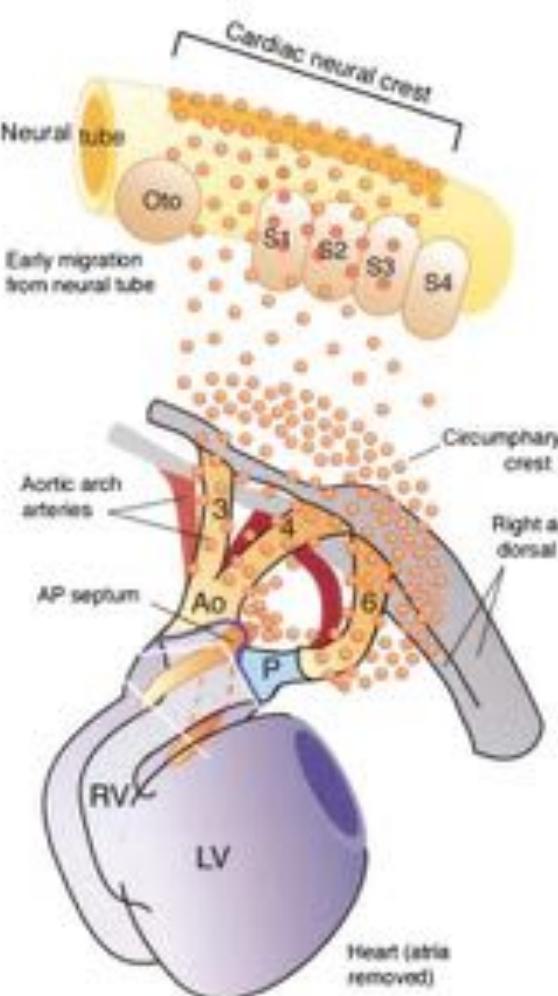


# Rôle des cellules de la crête neurale

## Migration dans la voie efférente

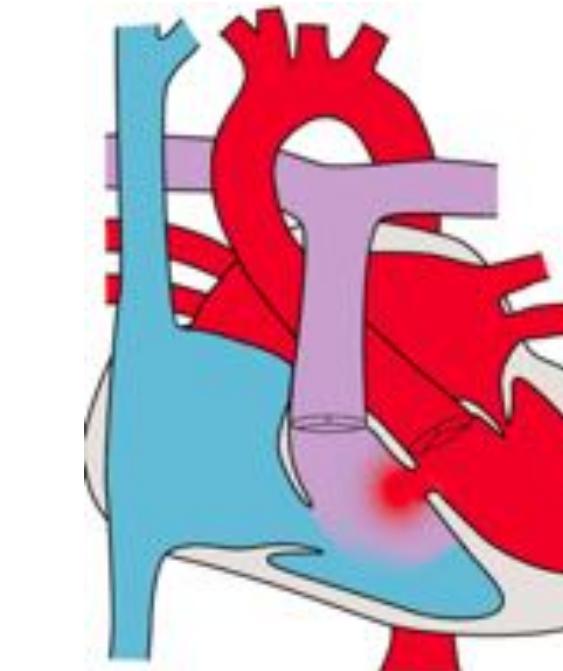
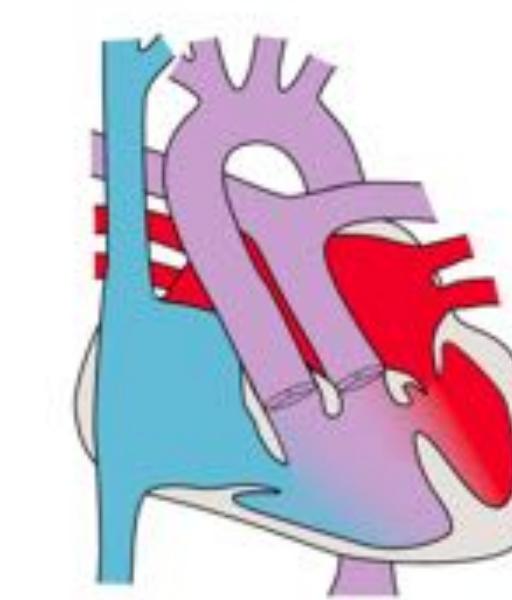
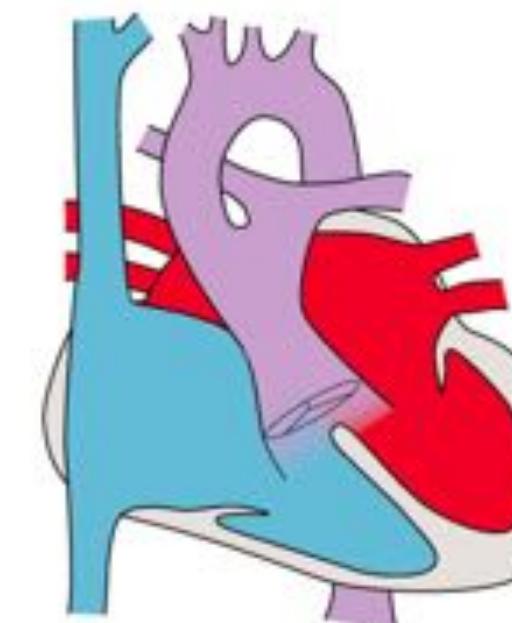
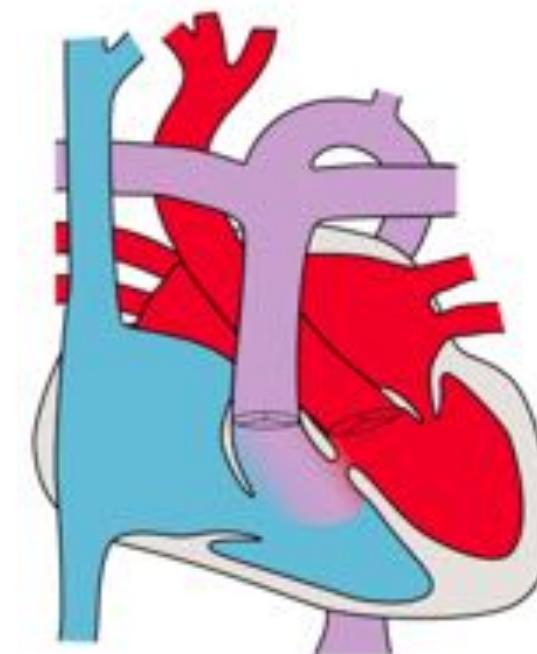
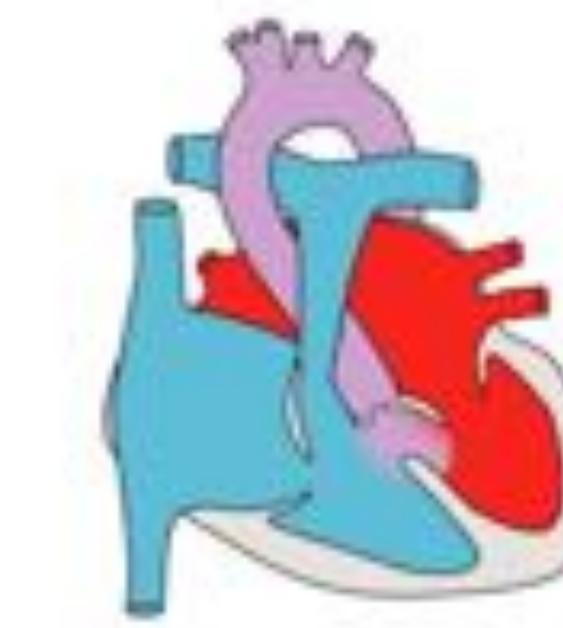
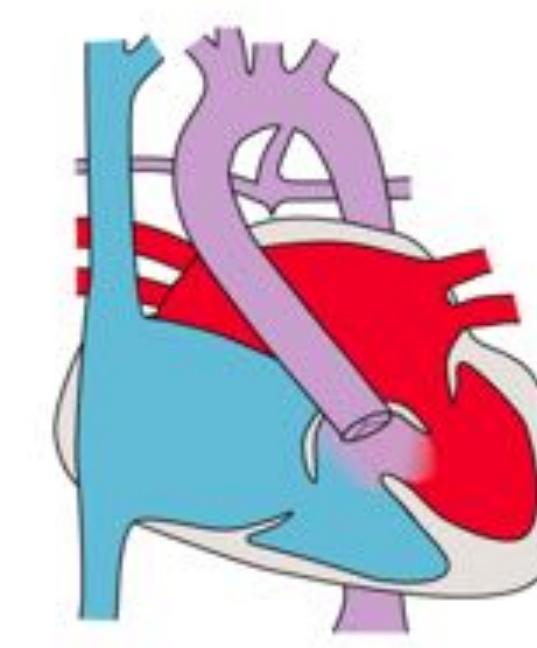
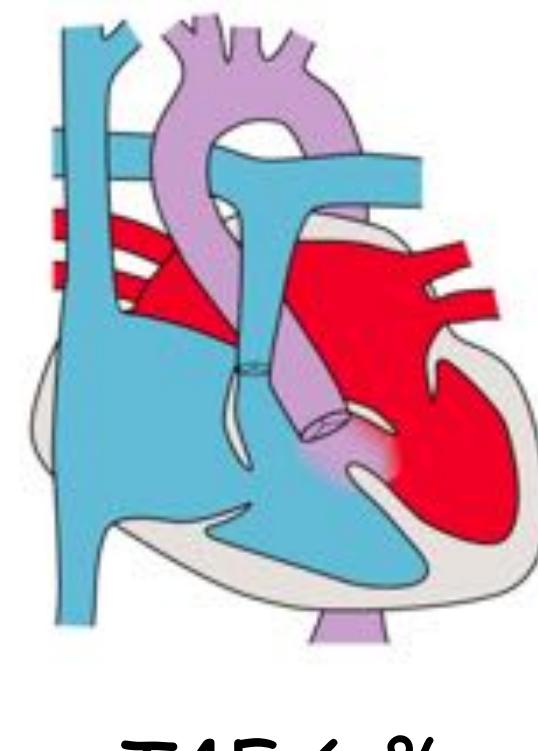
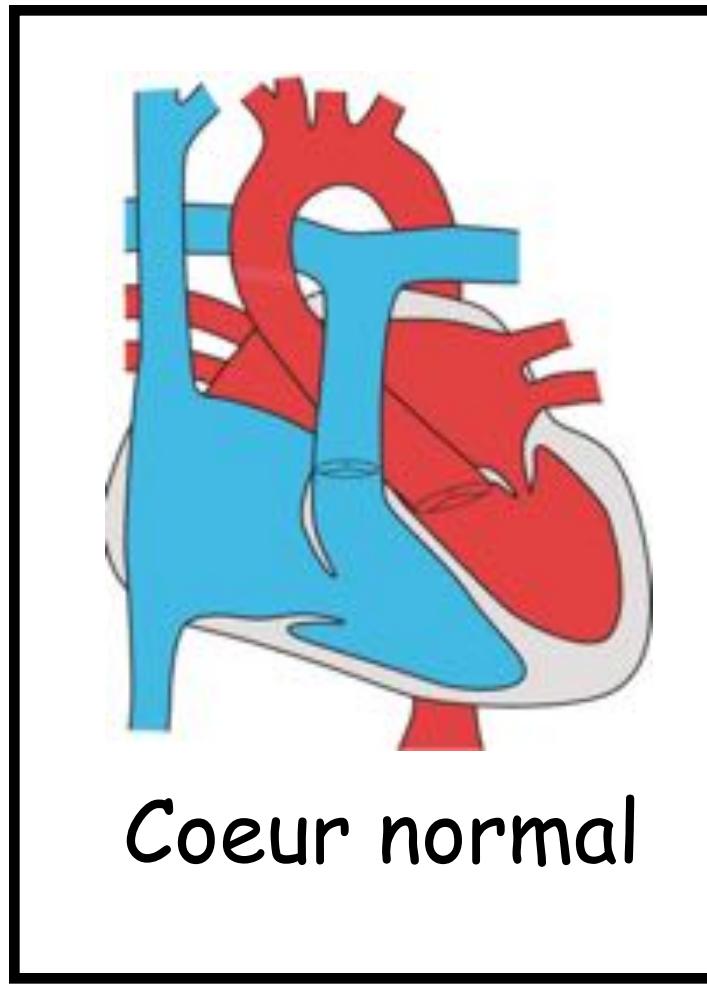
### Expériences d'ablation de CCN chez le poulet

- *totale* : absence de septation de la voie d'éjection (tronc artériel commun)
- *partielle* : malalignement au niveau du conus (VDDI, tétralogie de Fallot, APSO, dextroposition aortique)
- anomalies des arcs aortiques toujours associées





# Cardiopathies conotroncales



# Hypothesis confirmed in the 22q11 deletion

Randomised phenotype

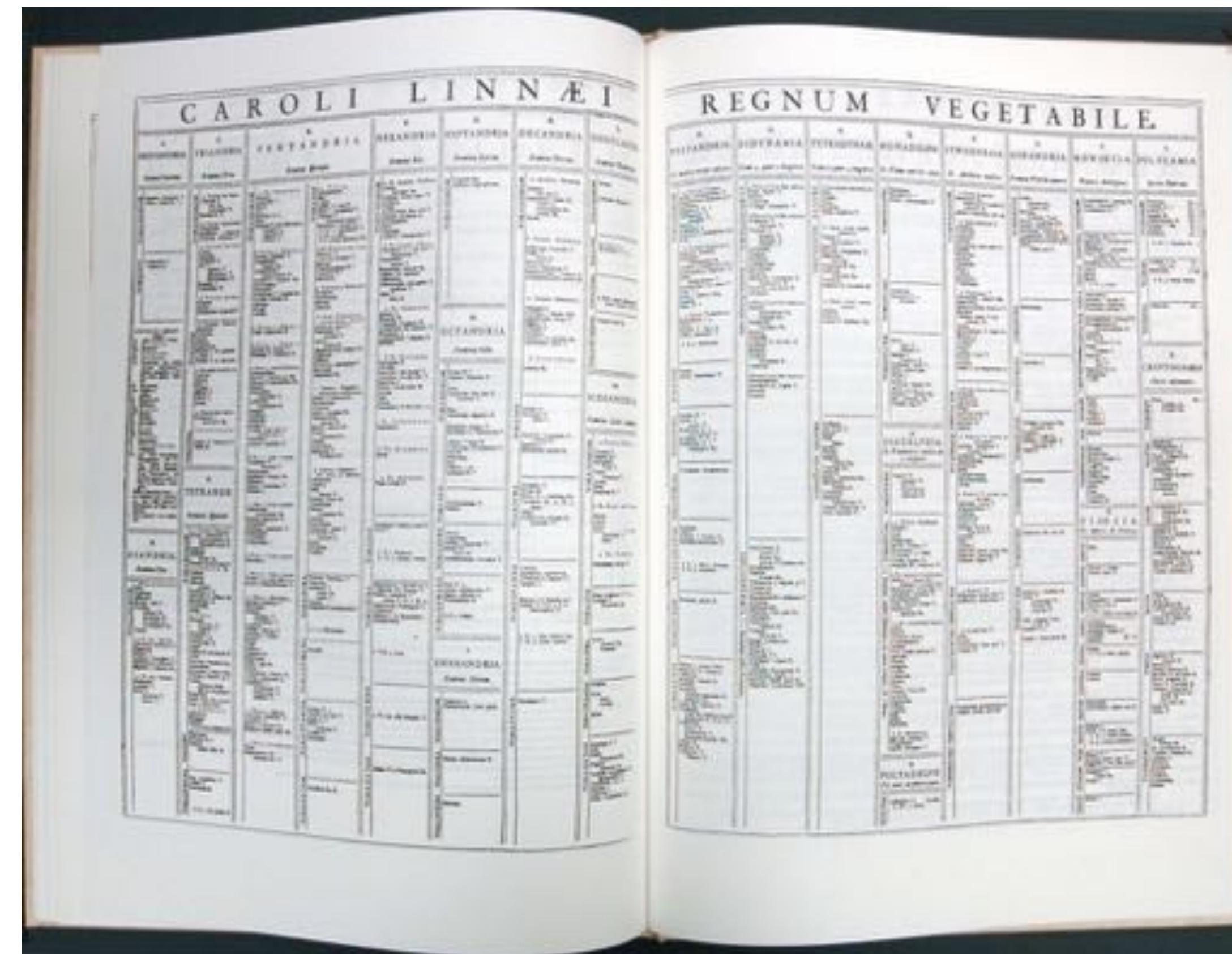


	%
Tetralogy of Fallot	22.2
PA-VSD	10.8
Interrupted aortic arch	26
Truncus arteriosus	11.4
Infundibular VSD	15.5
Aortic arch anomalies	13.9

# Classical approach

*Carl von Linné*

Based on morphological characteristics  
(based on the fact that organisms resemble one another)





*Papuina pulcherrima*, with a dextral shell



Predator snakes with teeth and mandible that are adapted to dextral snails, resulting in positive selection for sinistrality





# Five chirality-related genes in snails

*Nodal,*

*Bone Morphogenetic Protein 4,*

*Fibroblast Growth Factor 8,*

*Inversin,*

*Left-Right Dynein*

have their homologous counterparts

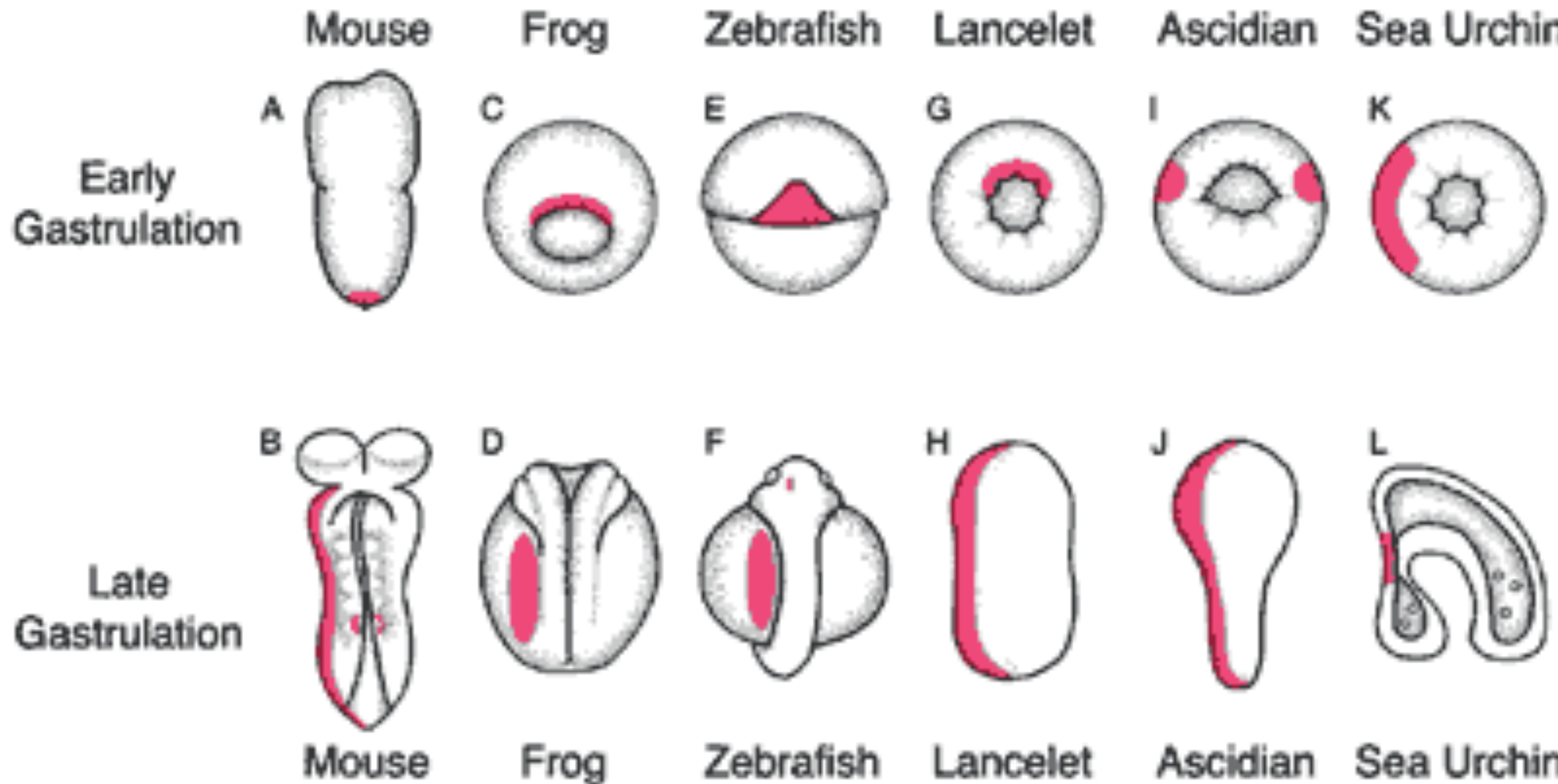
in vertebrates' .. left-right asymmetry

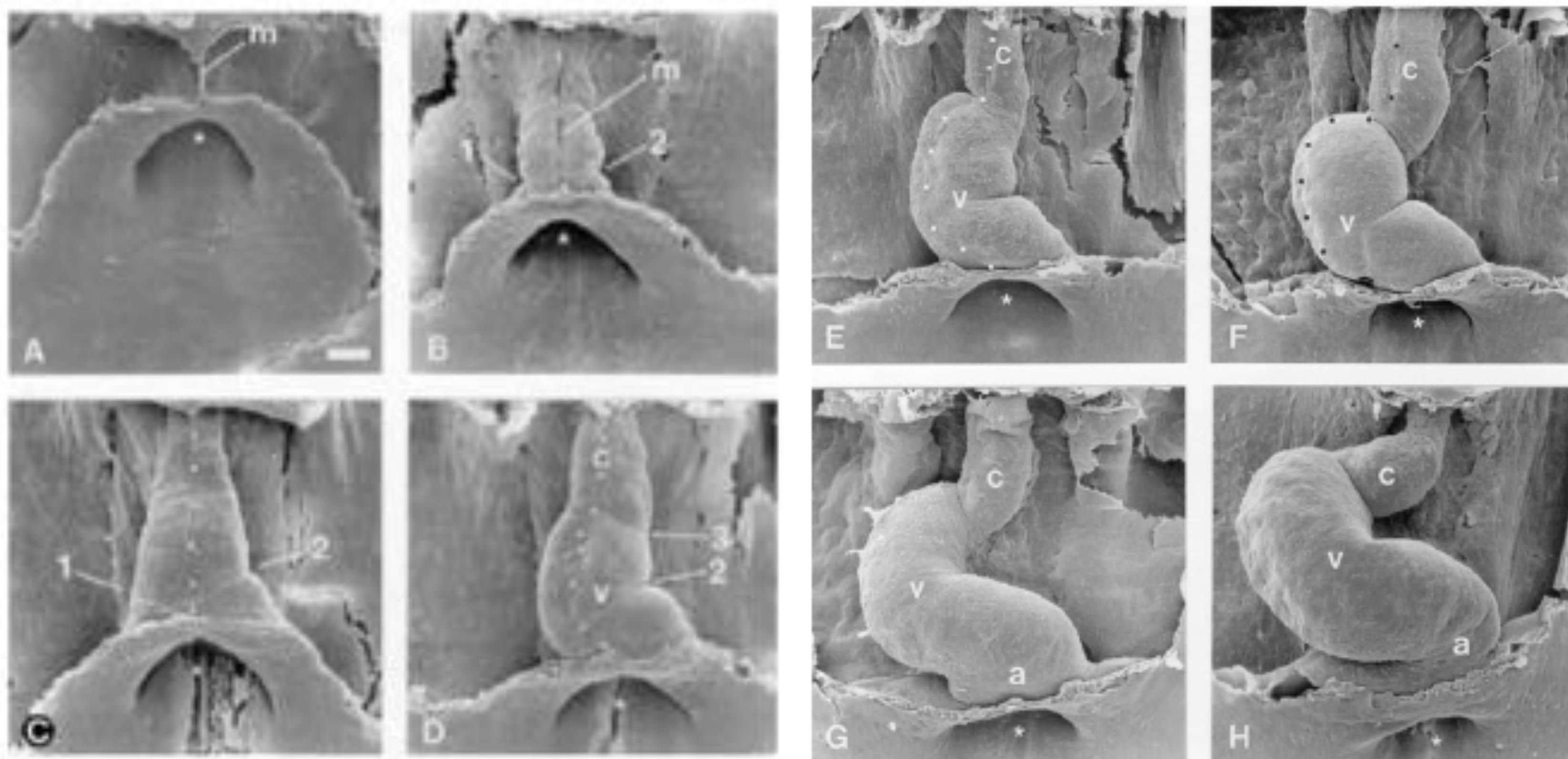
Cristina Grande & Nipam H. Patel, 2008

Nature Online, December 2008. Nodal signaling is involved in left-right asymmetry in snails

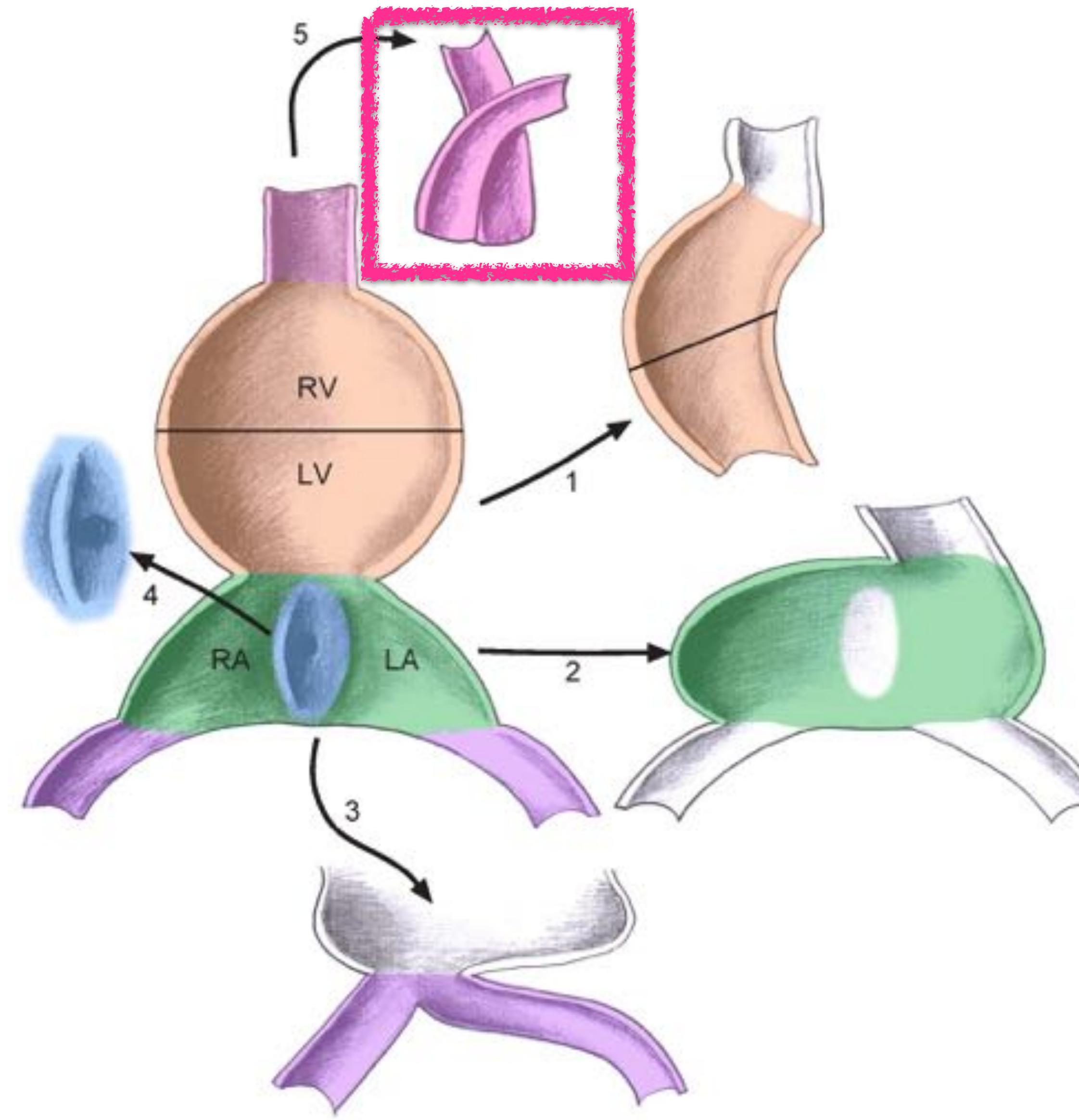
[“Here we report the first evidence for a Nodal orthologue ..”]

# Nodal expression is on the left side

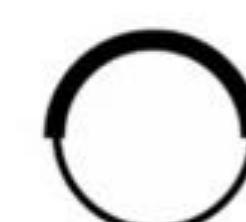
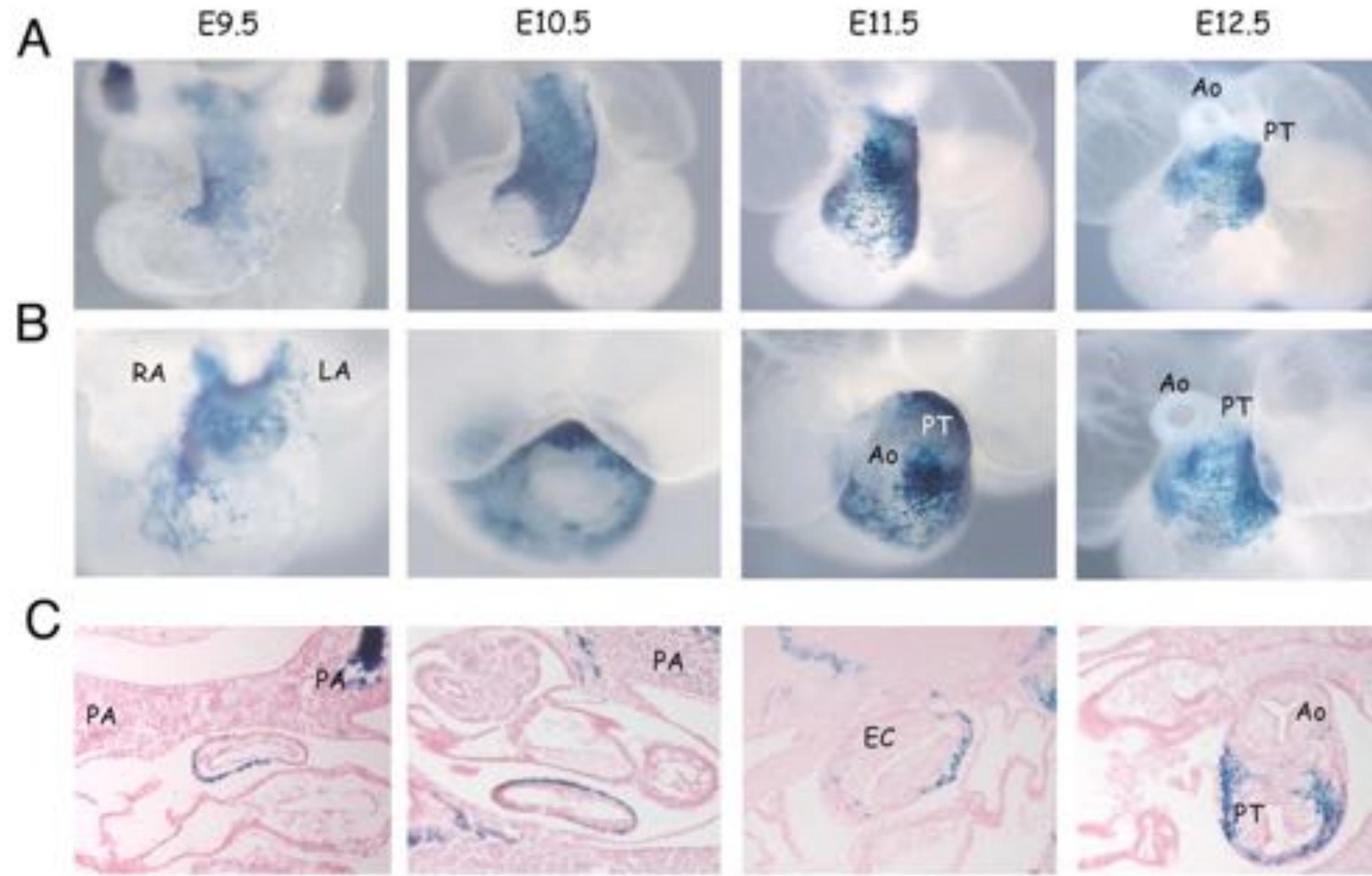




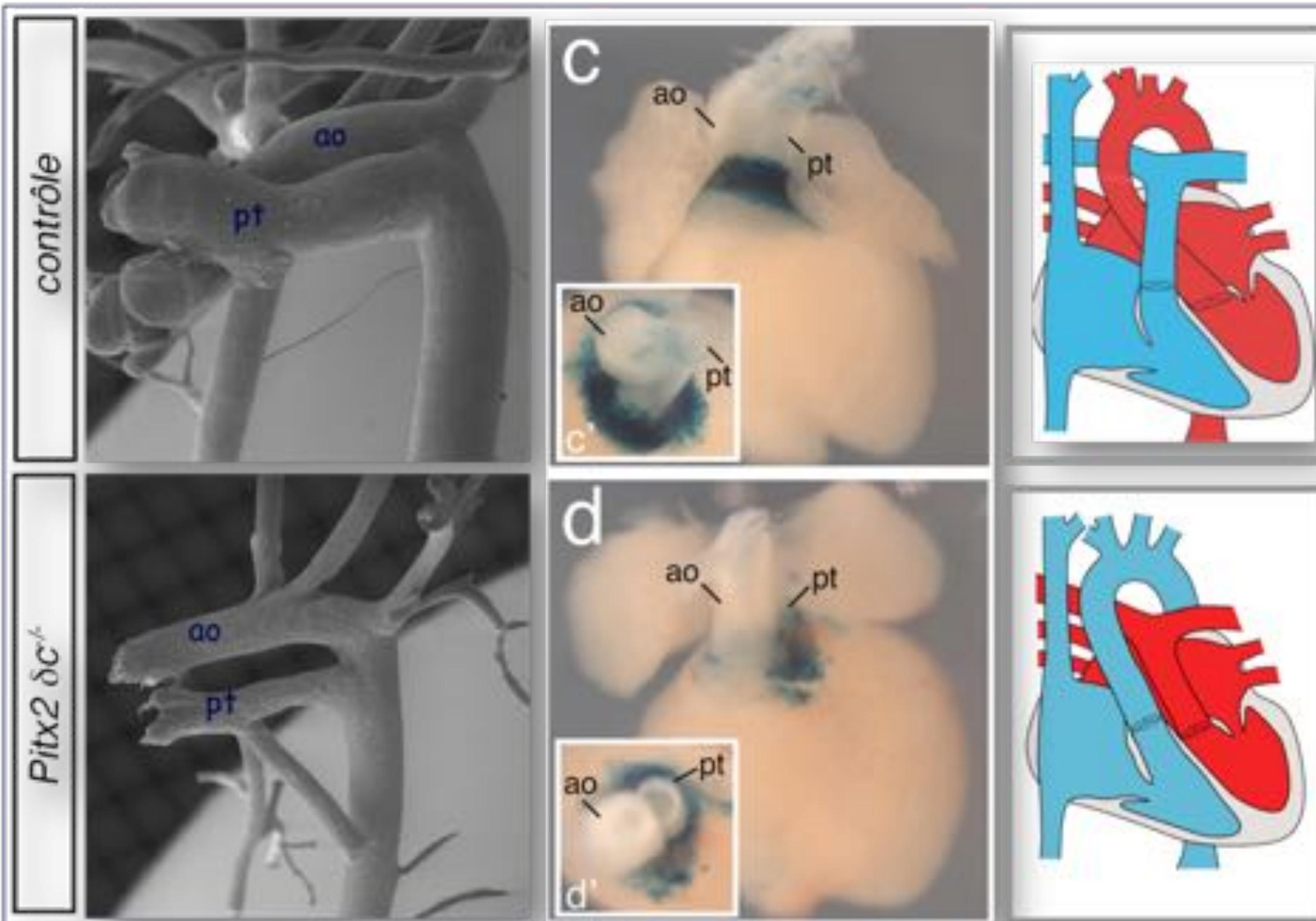
# 5 levels of asymmetry in the developing heart



# Cardiosensor mouse : 96-16



# 96-16 expression in Pitx2 $\delta$ c heart with TGA



- Transposition of the great arteries with a rotation defect
- Normal septation and normal neural crest cell migration
- Defect of left-right signalling

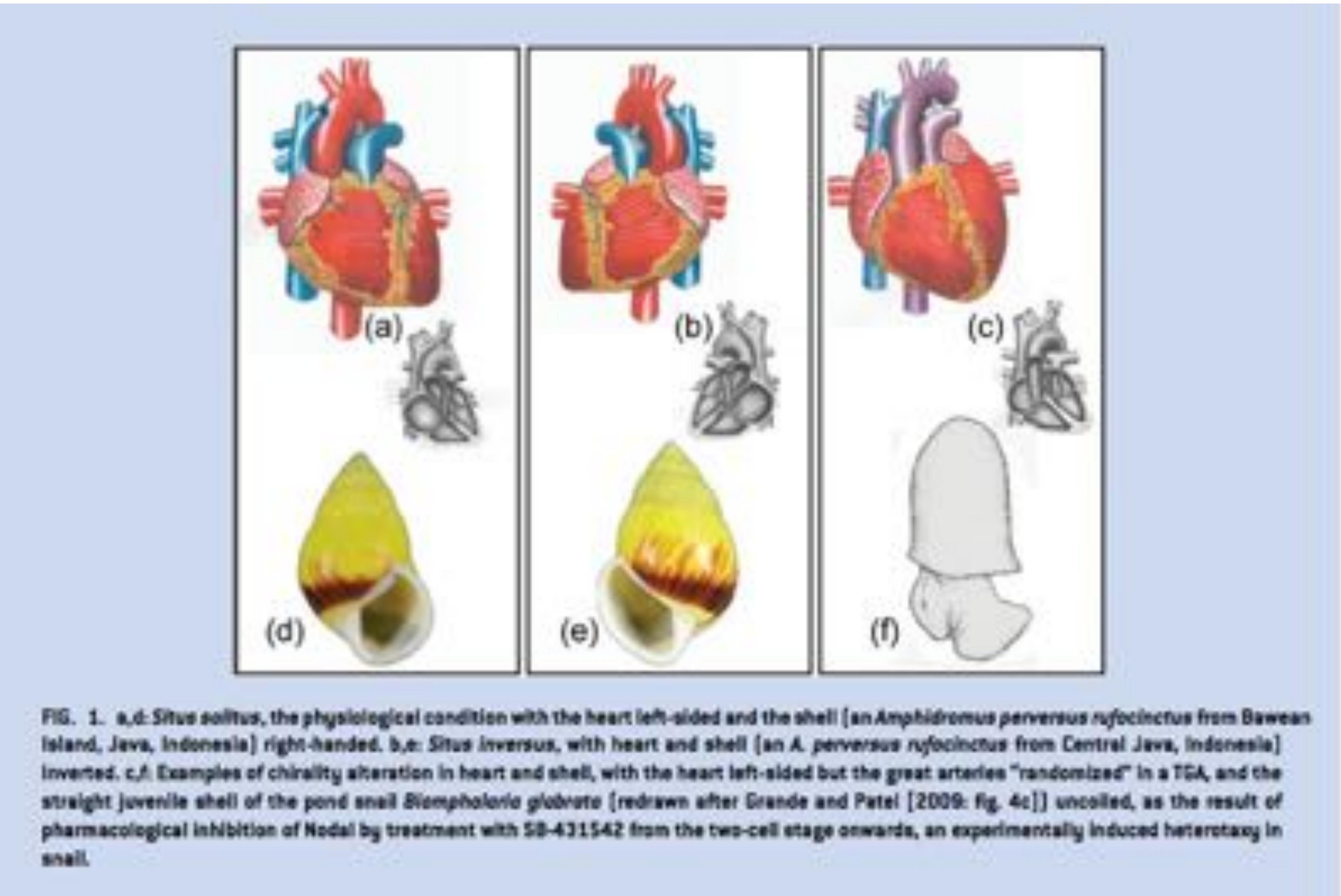


FIG. 1. a,d: *Situs solitus*, the physiological condition with the heart left-sided and the shell (*Anodonta perversus rufocinctus* from Bawean Island, Java, Indonesia) right-handed. b,e: *Situs inversus*, with heart and shell (*A. perversus rufocinctus* from Central Java, Indonesia) inverted. c,f: Examples of chirality alteration in heart and shell, with the heart left-sided but the great arteries “randomized” in a TGA, and the straight juvenile shell of the pond snail *Biomphalaria glabrata* (redrawn after Grande and Patel [2009: fig. 4c]) uncoiled, as the result of pharmacological inhibition of Nodal by treatment with SB-431542 from the two-cell stage onwards, an experimentally induced heterotaxy in snail.

# TGA is a laterality defect

It is not a conotruncal defect

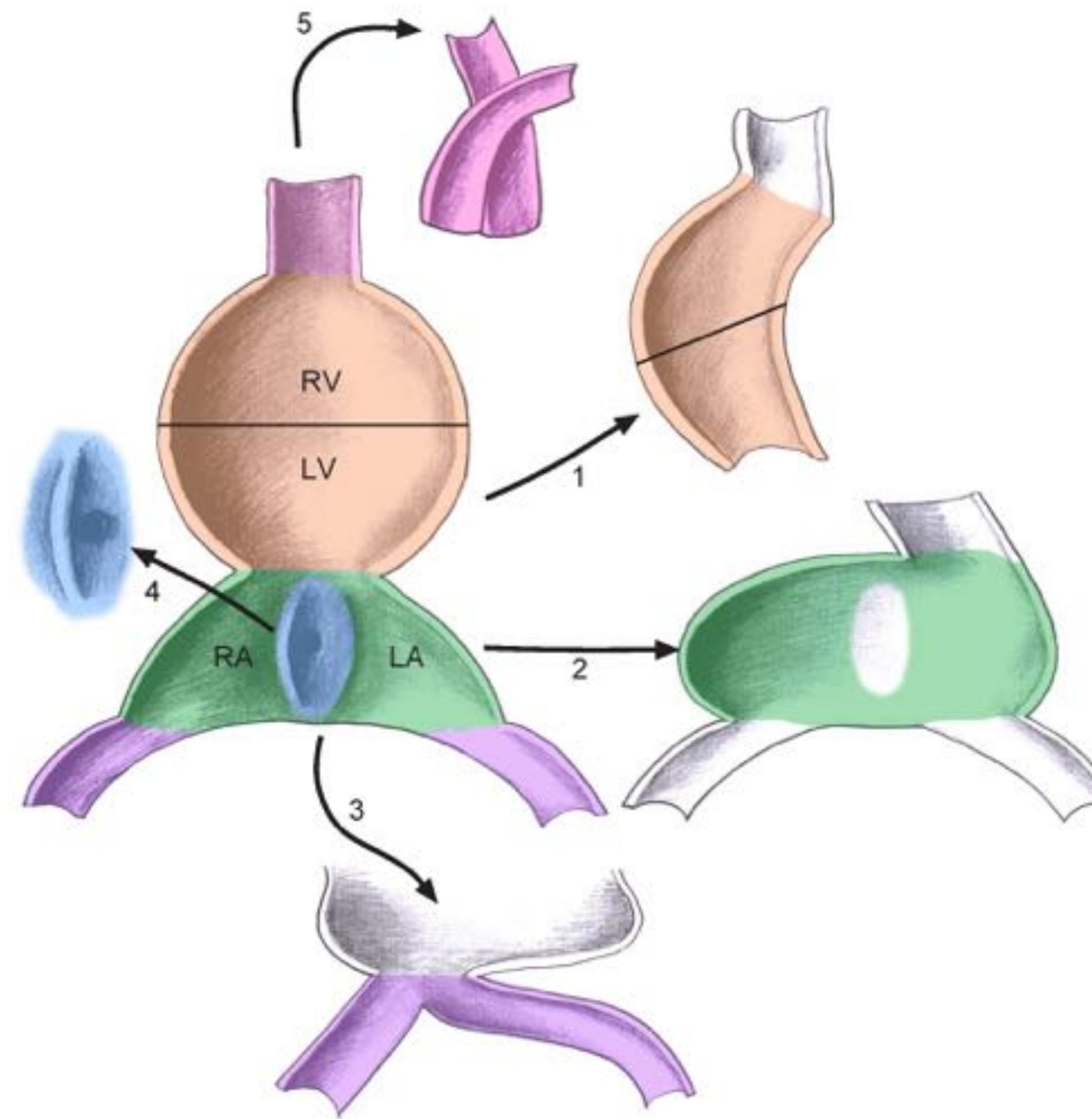
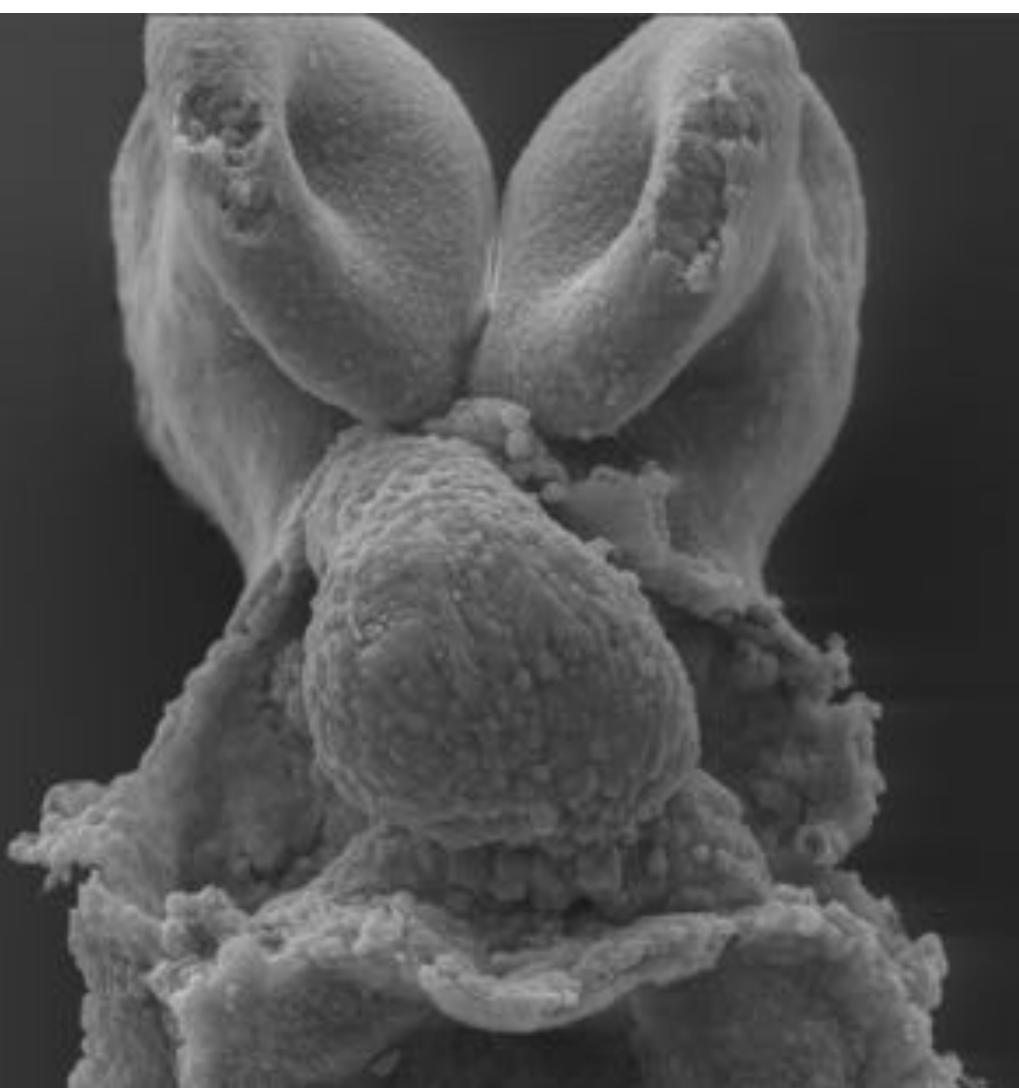
It is a laterality (rotation) restricted to a single segment of the developing heart

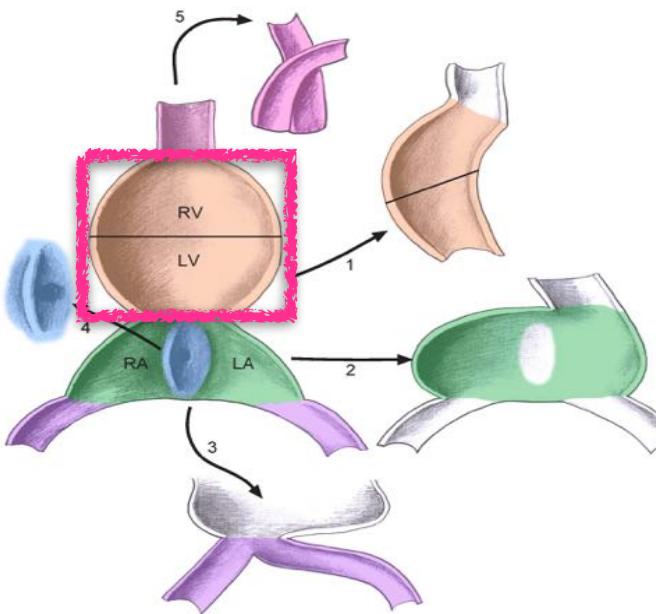
Familial transposition of the great arteries caused by multiple mutations in laterality genes

Alessandro De Luca,<sup>1</sup> Anna Sarkozy,<sup>1,6</sup> Federica Consoli,<sup>1</sup> Rosangela Ferese,<sup>1</sup> Valentina Guida,<sup>1</sup> Maria Lisa Dentici,<sup>1</sup> Rita Mingarelli,<sup>1</sup> Emanuele Bellacchio,<sup>1</sup> Giulia Tuo,<sup>2</sup> Giuseppe Limongelli,<sup>3</sup> Maria Cristina Digilio,<sup>4</sup> Bruno Marino,<sup>5</sup> Bruno Dallapiccola<sup>1</sup>

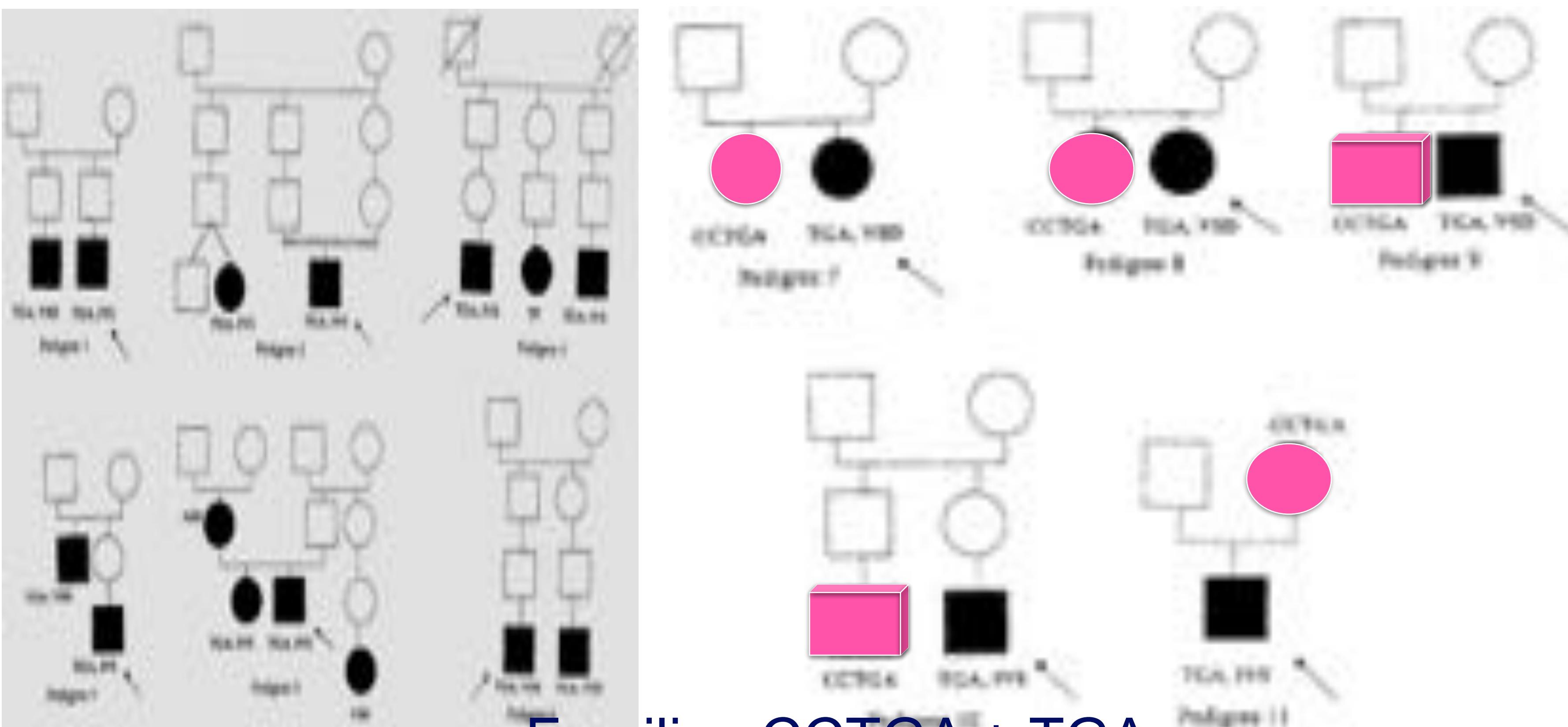
Heart 2010;96:673–677.

# 5 levels of asymmetry in the developing heart



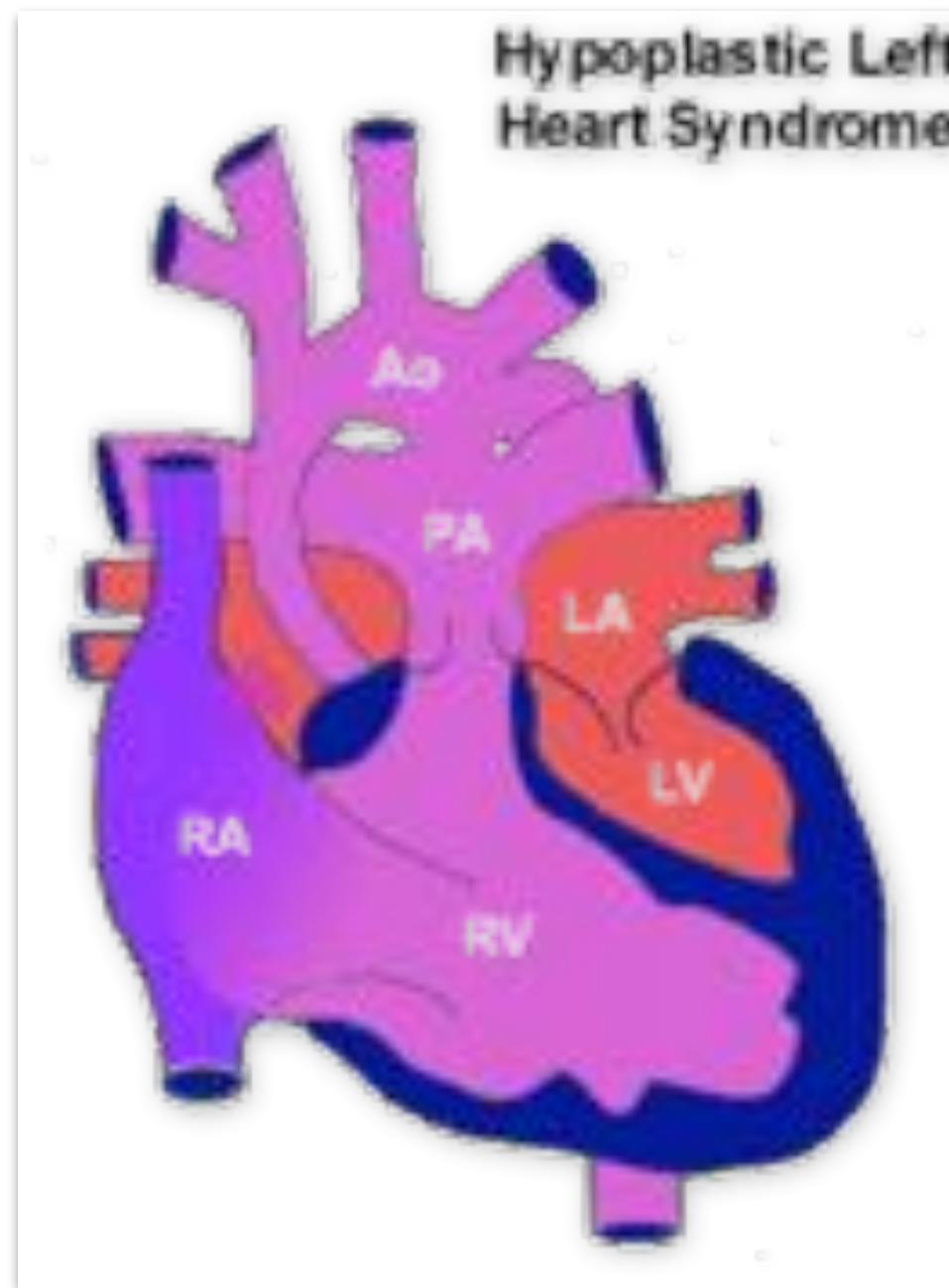


# Families TGA & CC-TGA

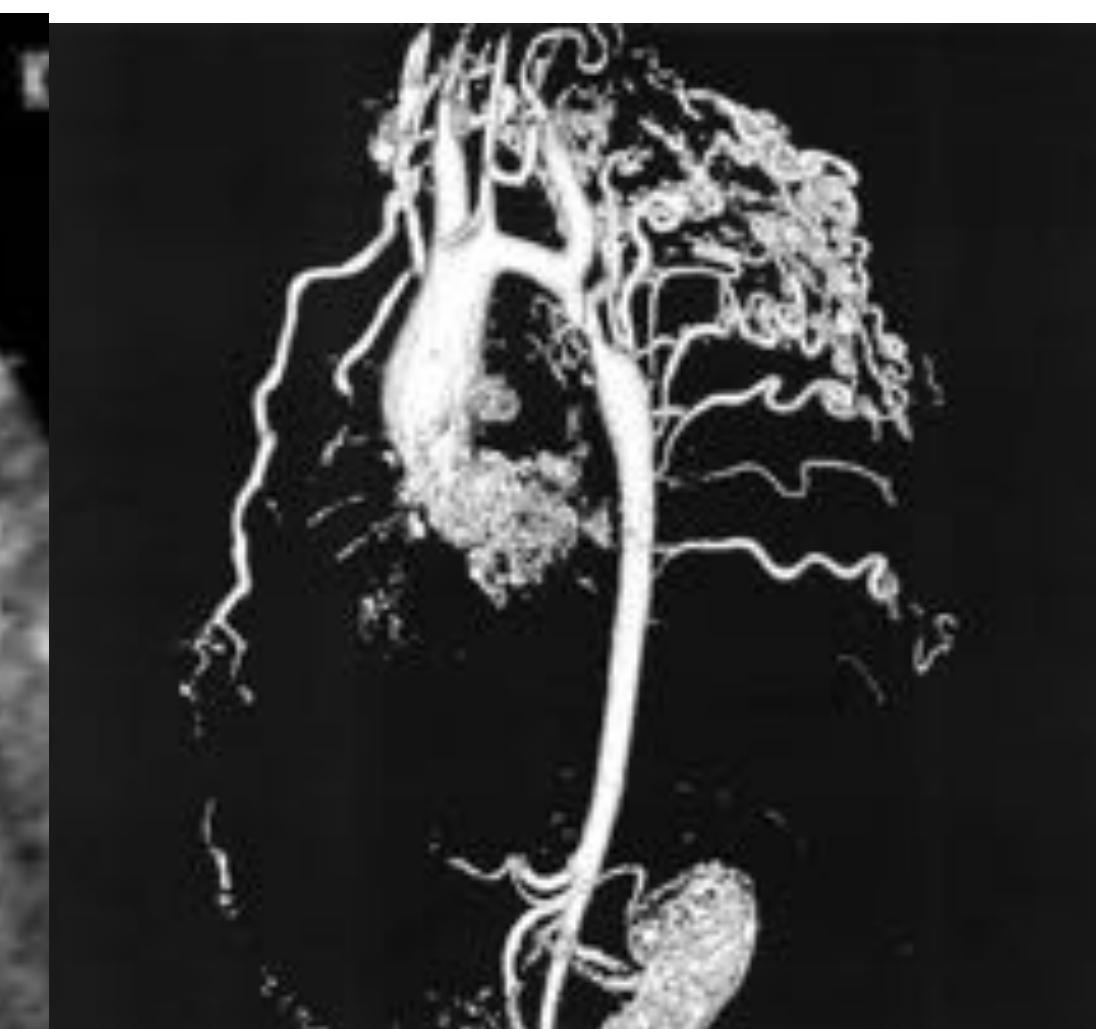
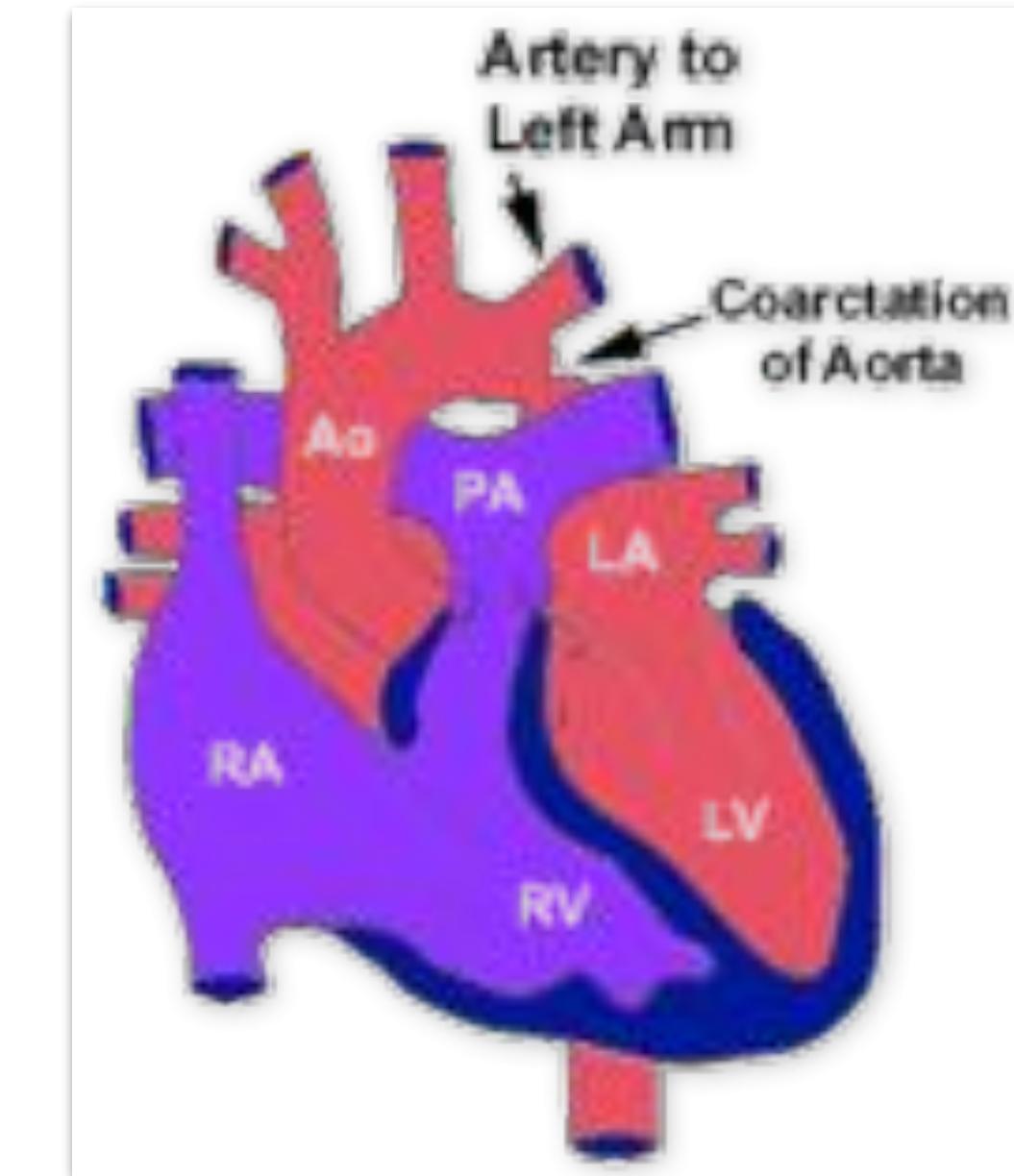


# Families CCTGA + TGA

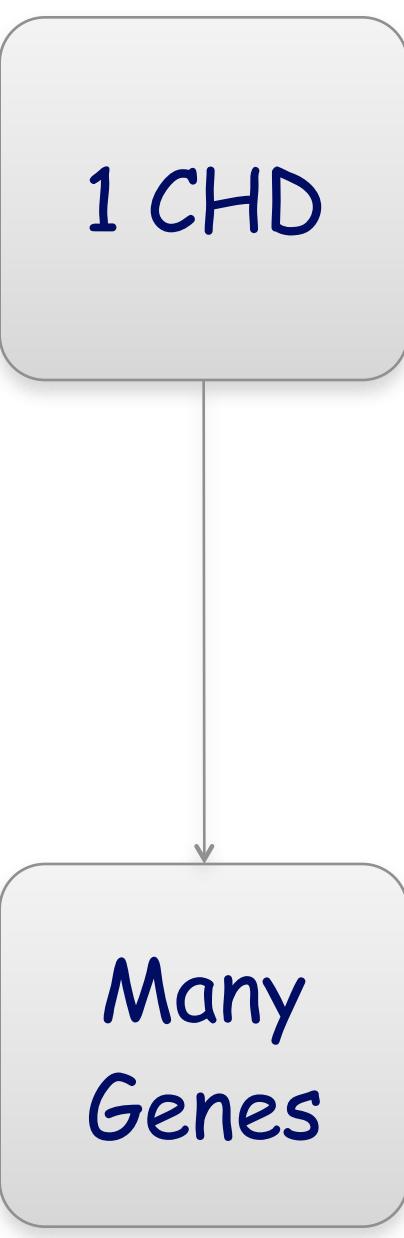
# Phenotypic continuum



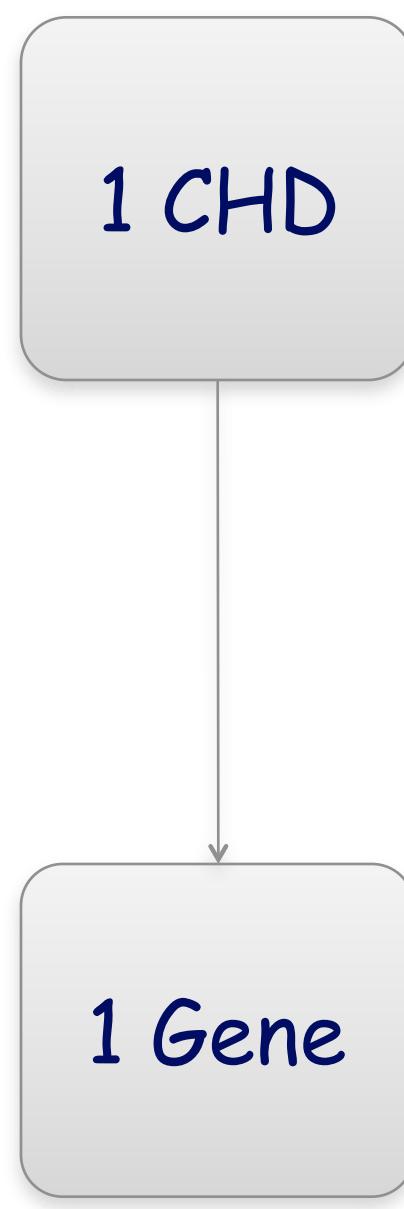
Recurrences inside  
the phenotypic continuum



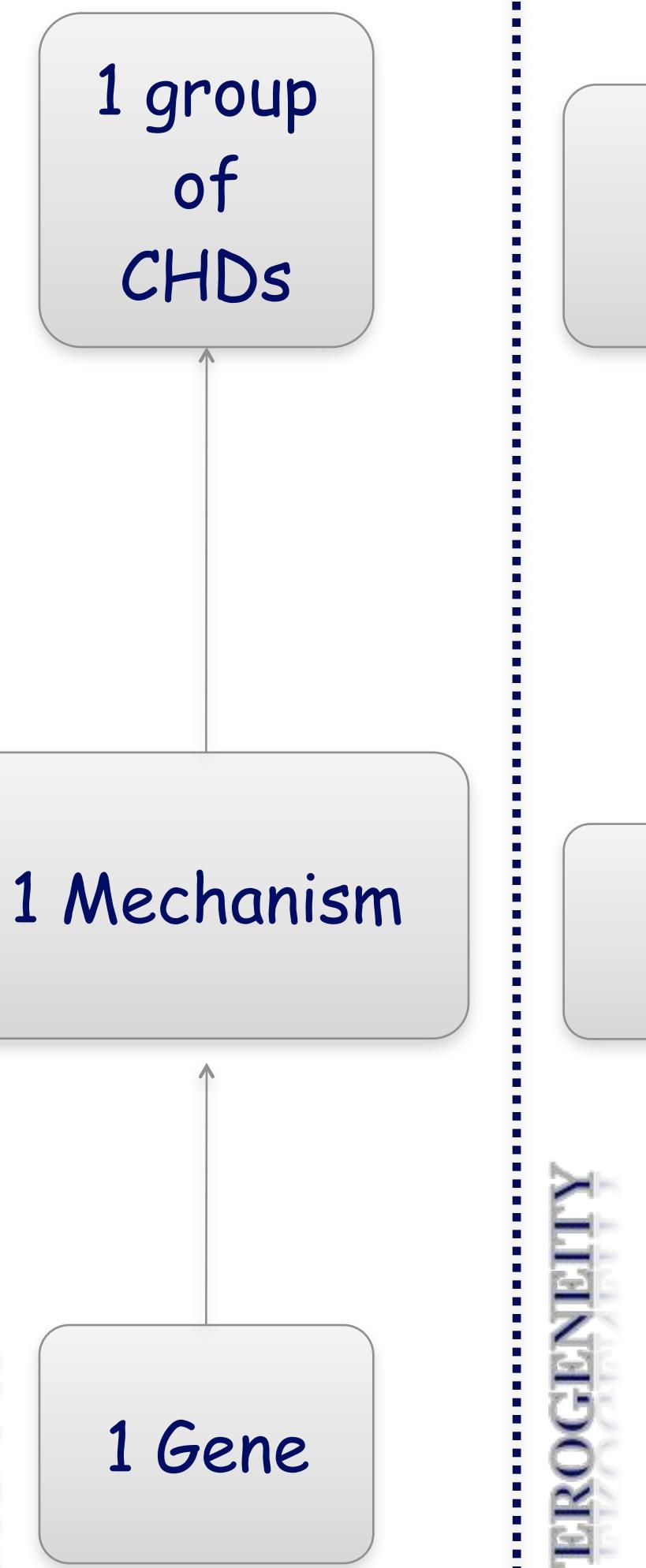
## MULTIFACTORIAL



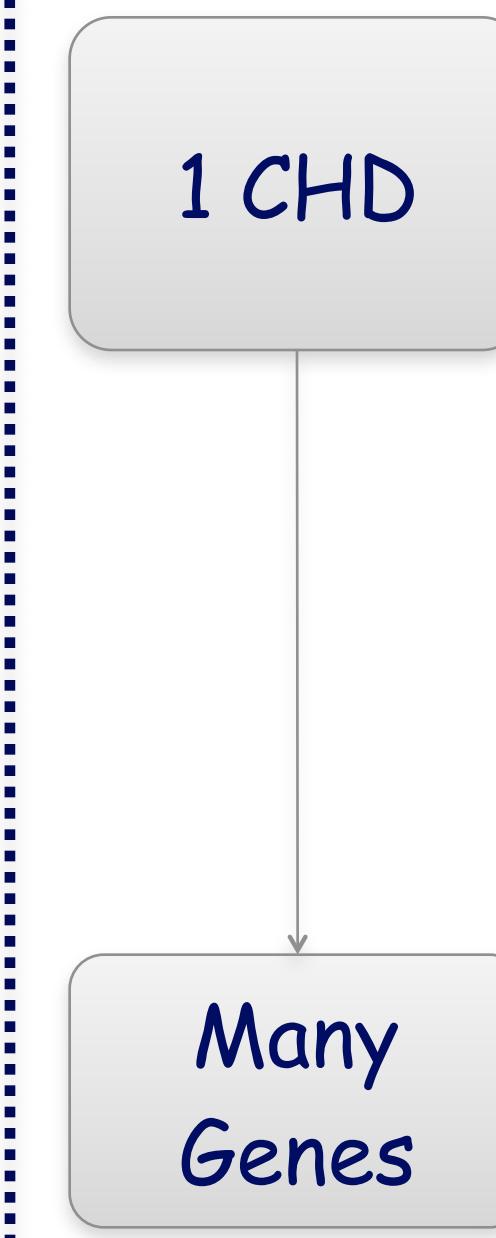
## MONOGENIC



## MECHANISTIC

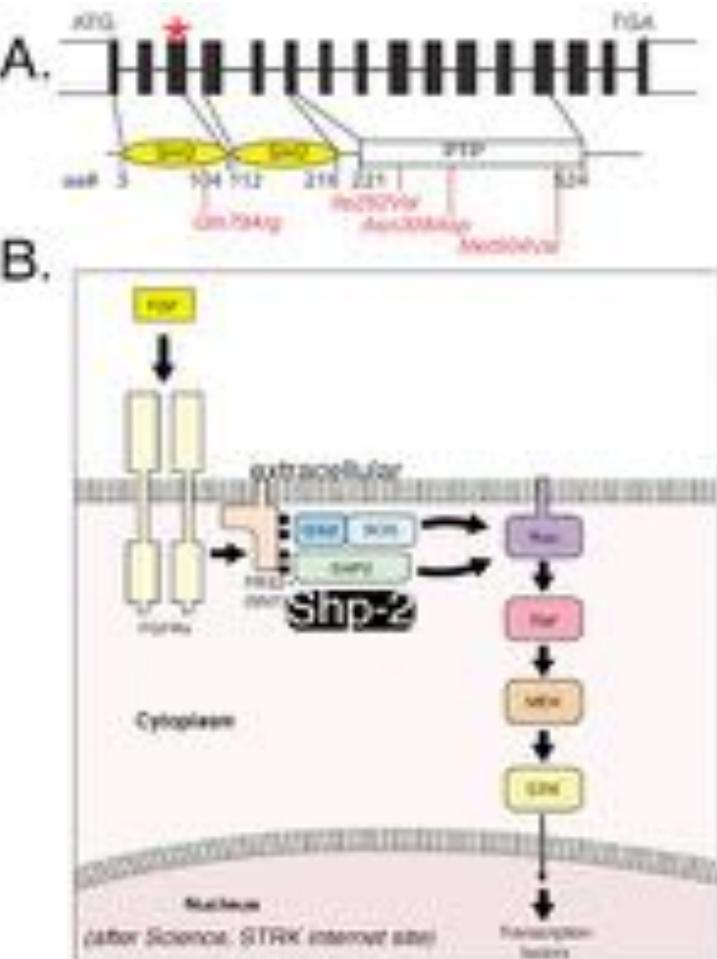
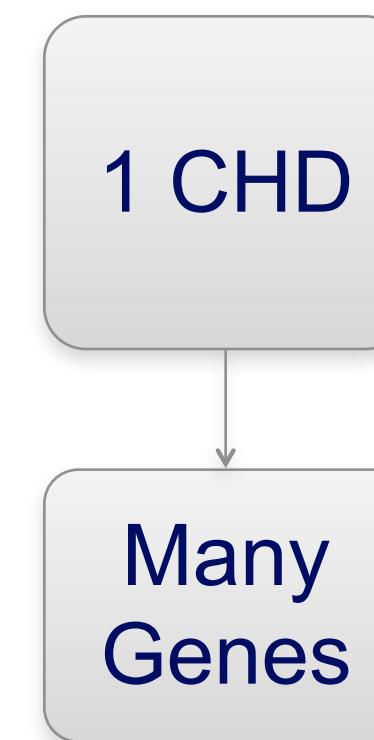


## GENETIC HETEROGENEITY



# Genetic heterogeneity

## One CHD- many genes



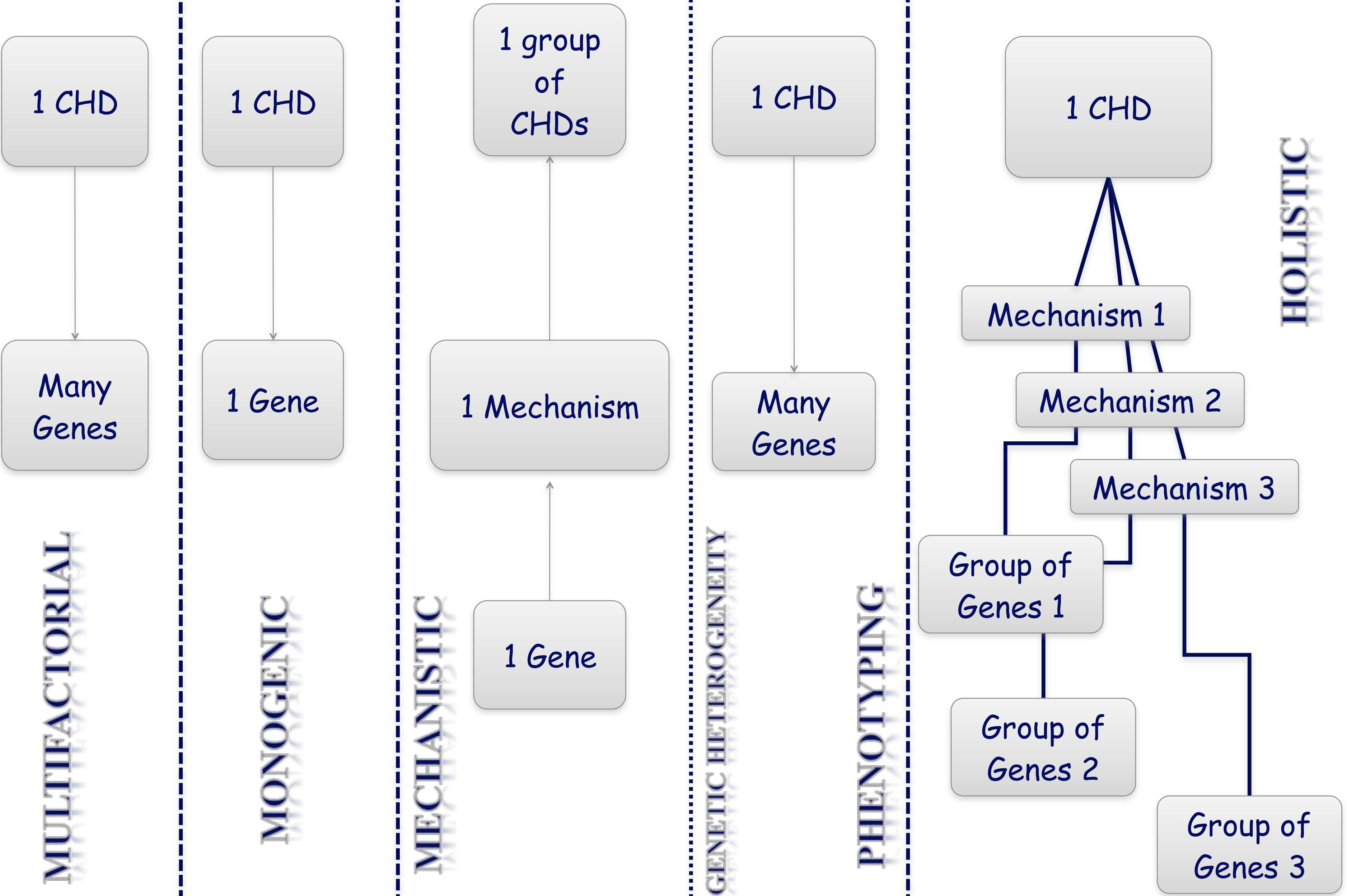
# Tetralogy of Fallot :

*TBX1, Fog2, Gata4, NkX2.5,  
CDH7, PAX3, JAGGED1...*

# AVSD :

*Trisomie 21, Ellis van Creveld,  
Noonan, del8p23, ...*

# TGA : ZIC3, PROSIT, Cryptic...

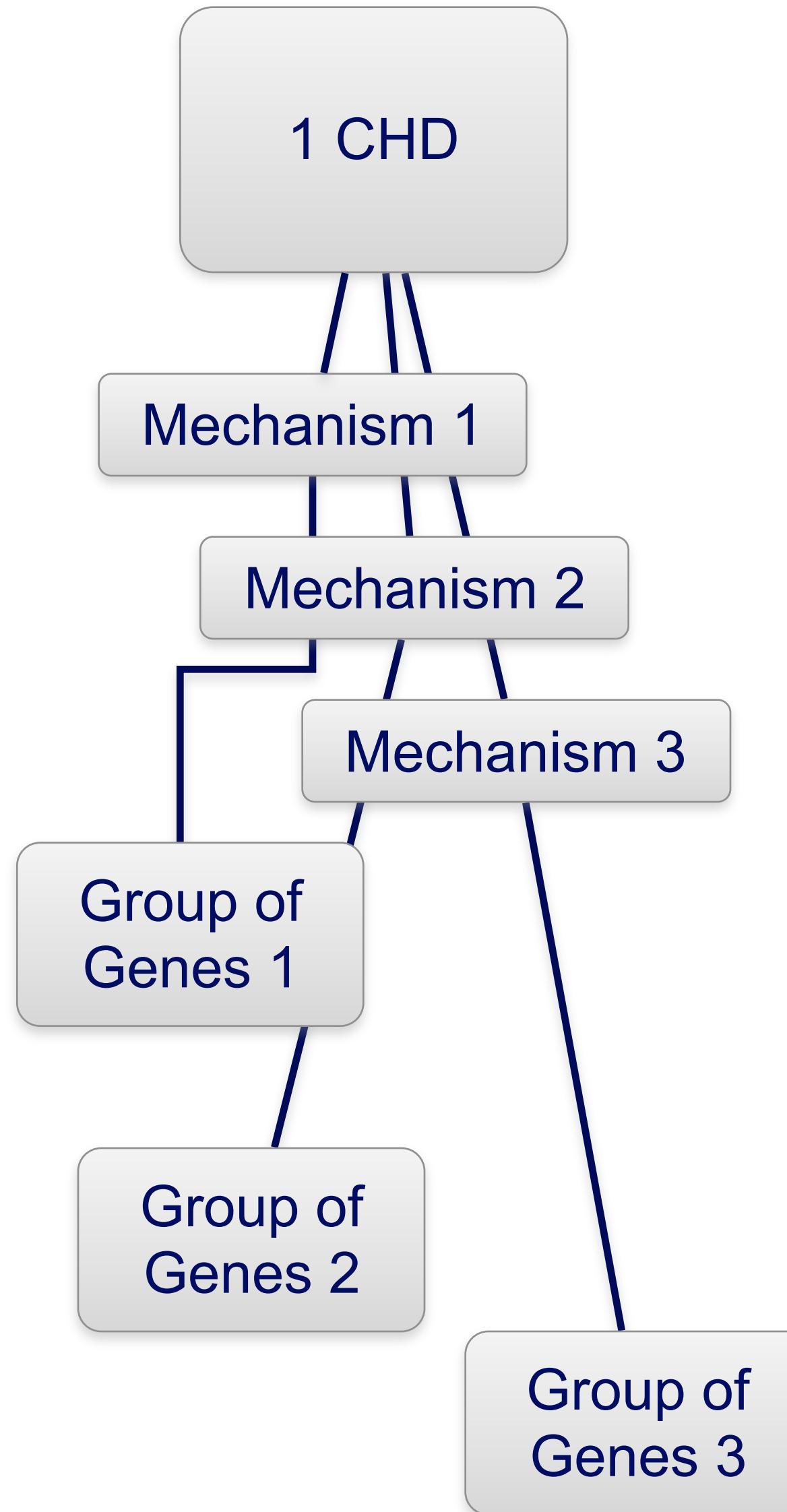




# Coarctation of the aorta

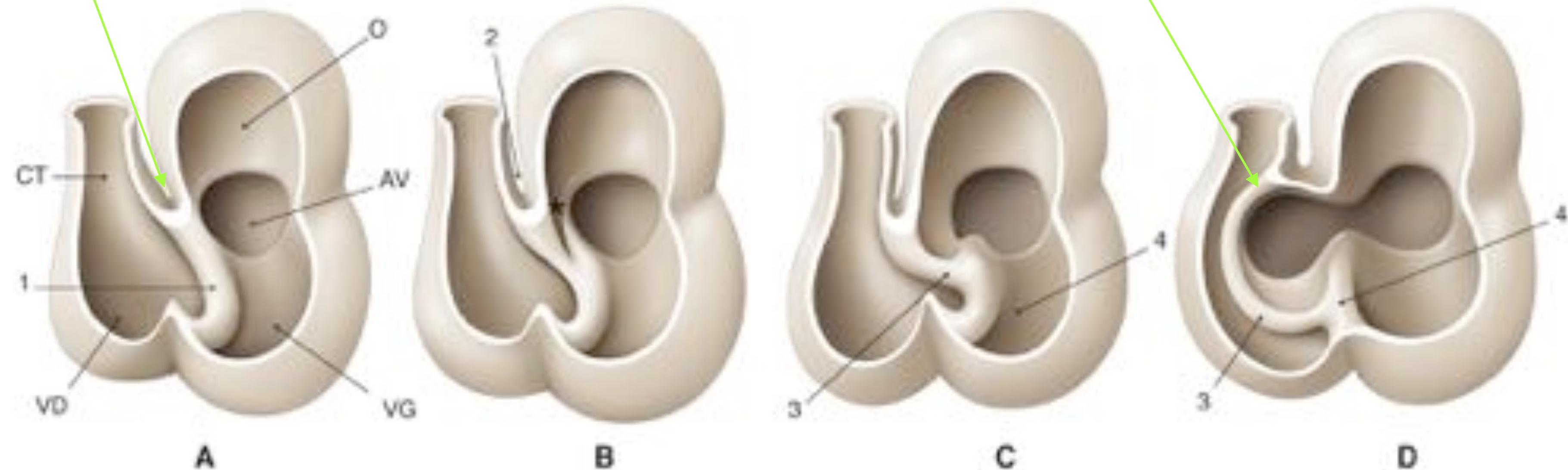
1 CHD various mechanisms

- Disease of the aortic isthmus
- Flow defect : spectrum of HLHS
- Conotruncal defect
  - Interrupted aortic arch
  - Conoventricular VSD
- Laterality defect with persisting LSCV



Les arrêts du développement embryonnaire,  
les coeurs qui n'existent jamais,  
et les algorithmes.

Courbure  
interne



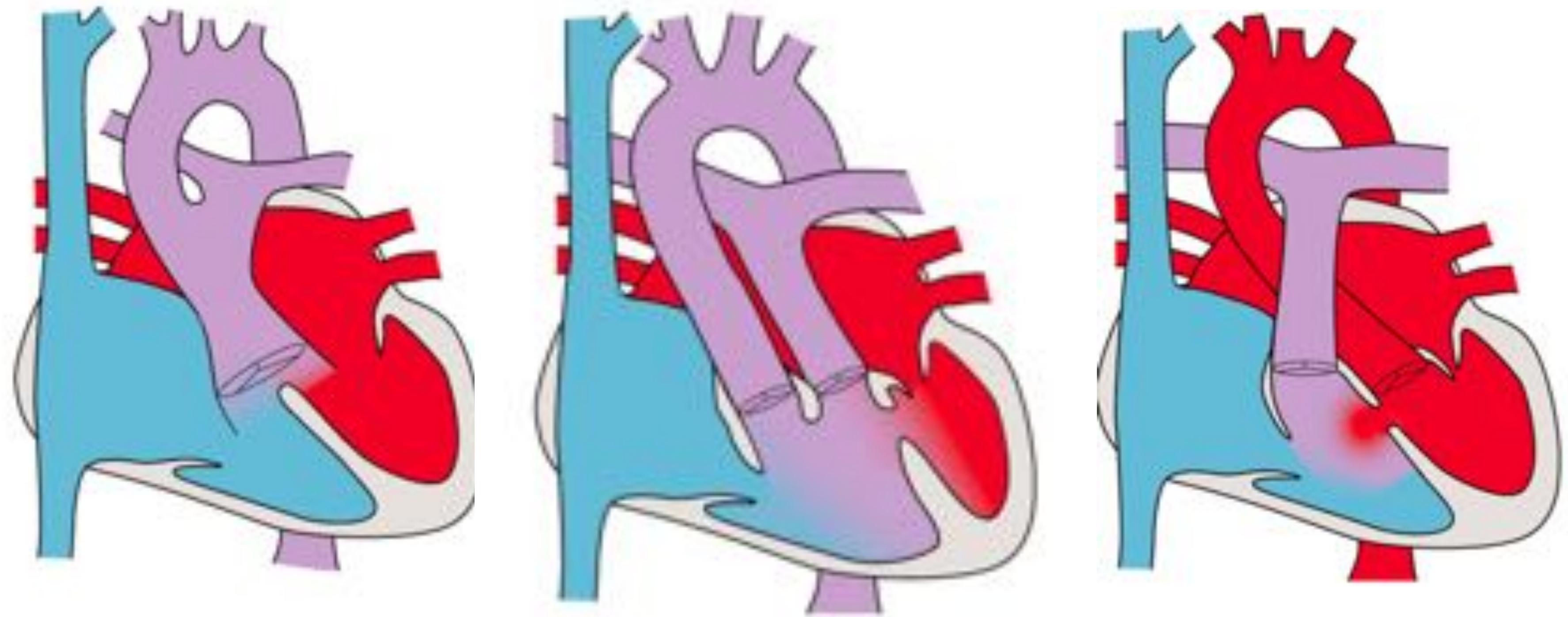
Primary fold  
(anneau primitif)

Bande pariétale (ventriculo-infundibular fold)

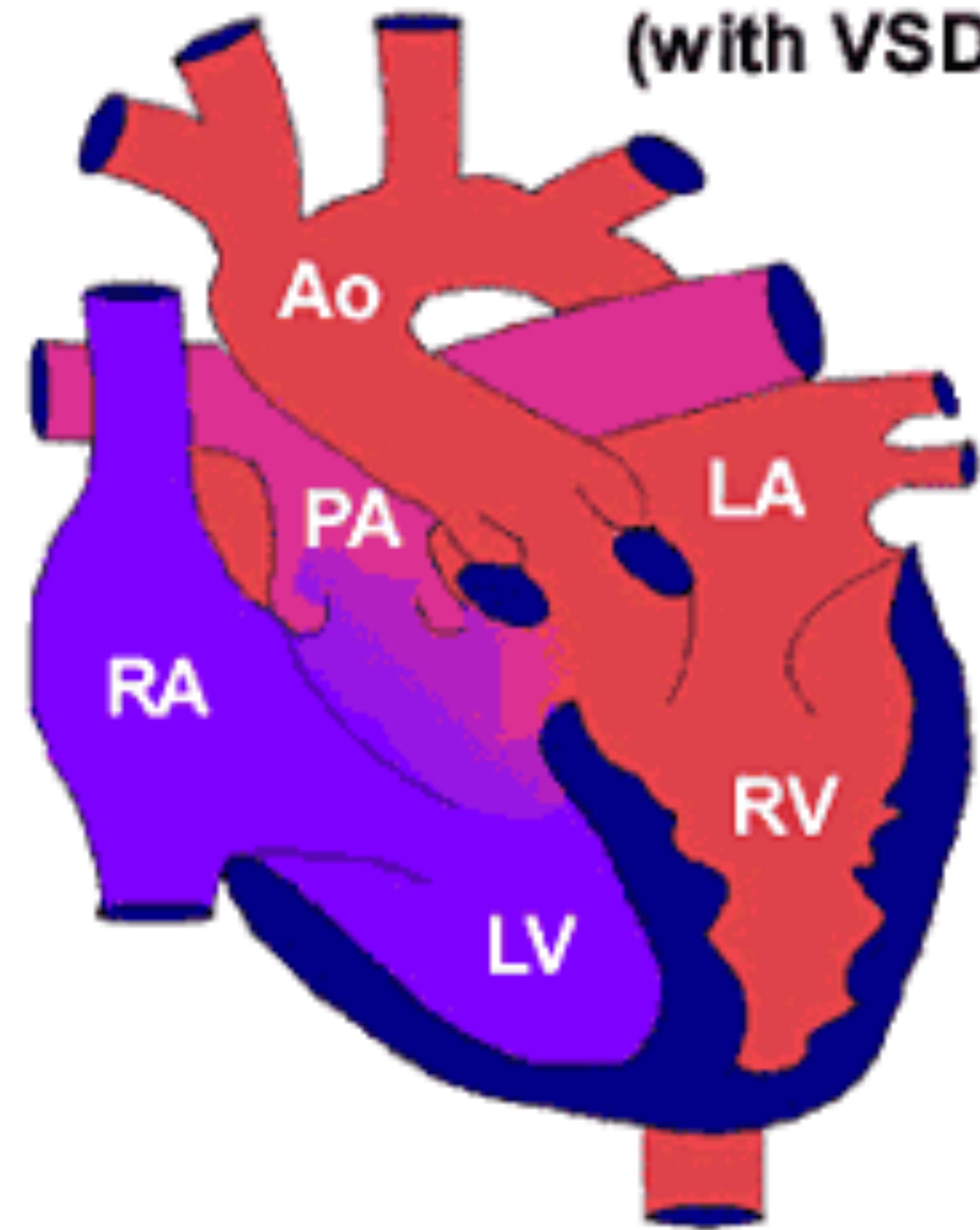
Entonnoir  
tricuspidien

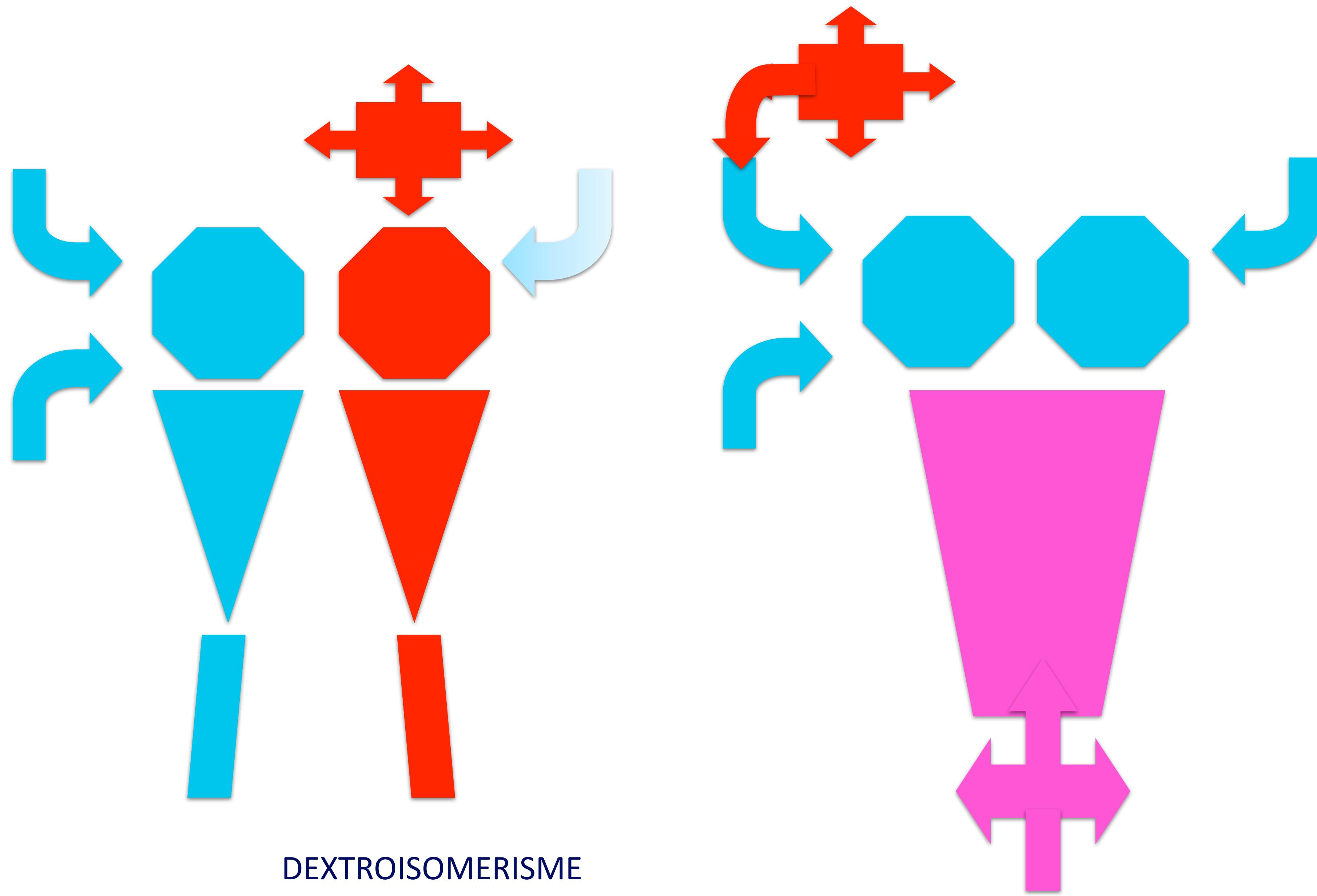
+

Bande modératrice  
Bande septale



**'Corrected' Transposition  
(with VSD)**





# Classifications anatomiques des cardiopathies congénitales

# Purpose of nomenclature

- Convey information
  - diagnosis to clinician, surgeon
- Collect data
  - incidence, outcomes
- Further understanding
  - development, causes

# **Characteristics of the different classifications**

- Descriptive
  - the name conveys a picture
- Unambiguous
  - 1:1 correspondence between name and entity
- Inclusive
  - no large ‘other’ category
- Consistent
  - but capable of evolution

# **Diagnostic Approach of congenital heart diseases**

- Cardiac position
- Segmental situs
- Segmental alignments/connections
- Associated defects
- Physiology

# **Cardiac Position**

- **Levocardia**
  - heart in left chest, apex to left
- **Mesocardia**
  - midline heart, apex inferior
- **Dextrocardia**
  - heart in right chest, apex to right
- **Ectopia Cordis**
  - heart partially or completely out of chest

## Cardiac Position

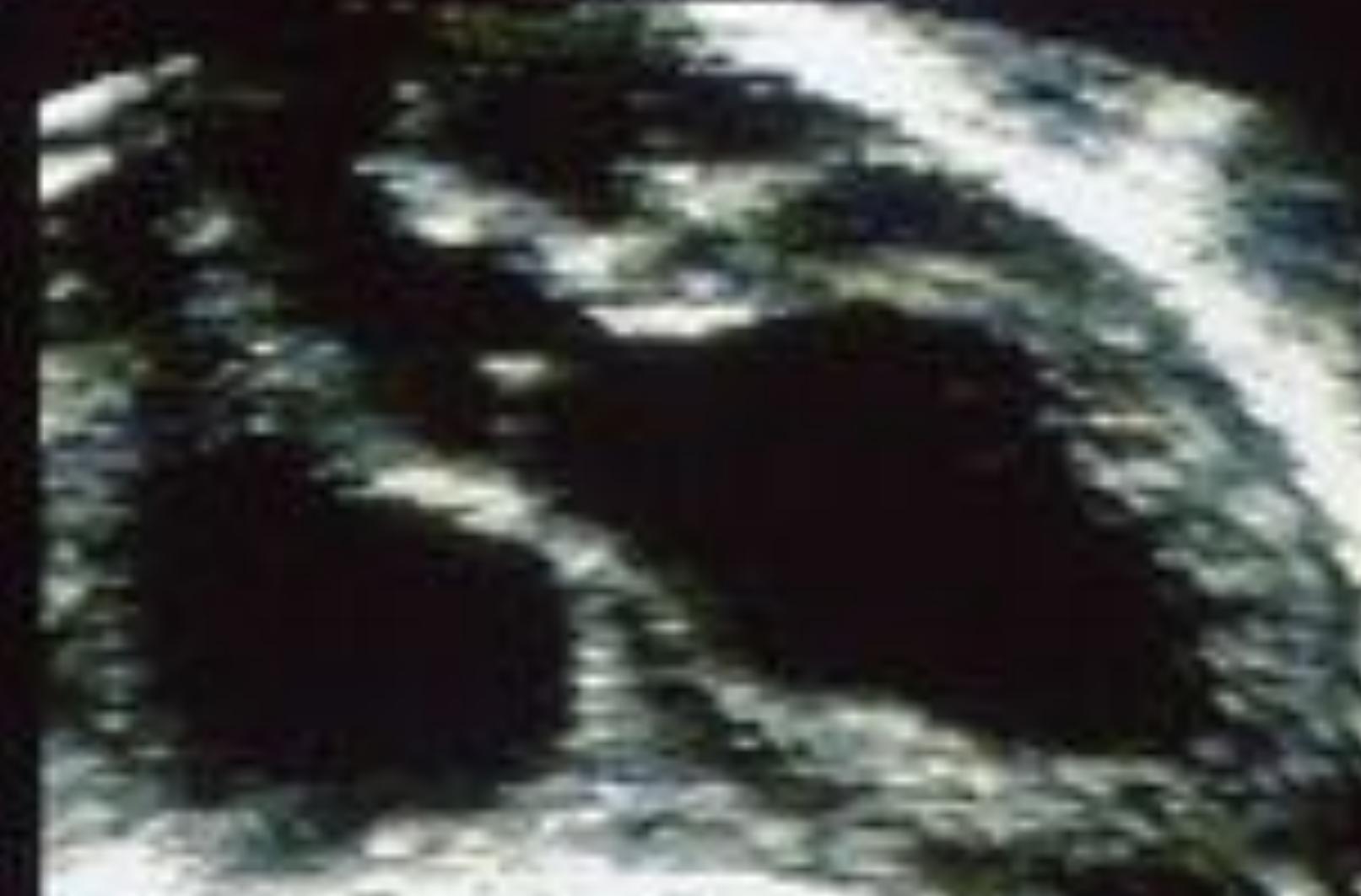
Mesocardia



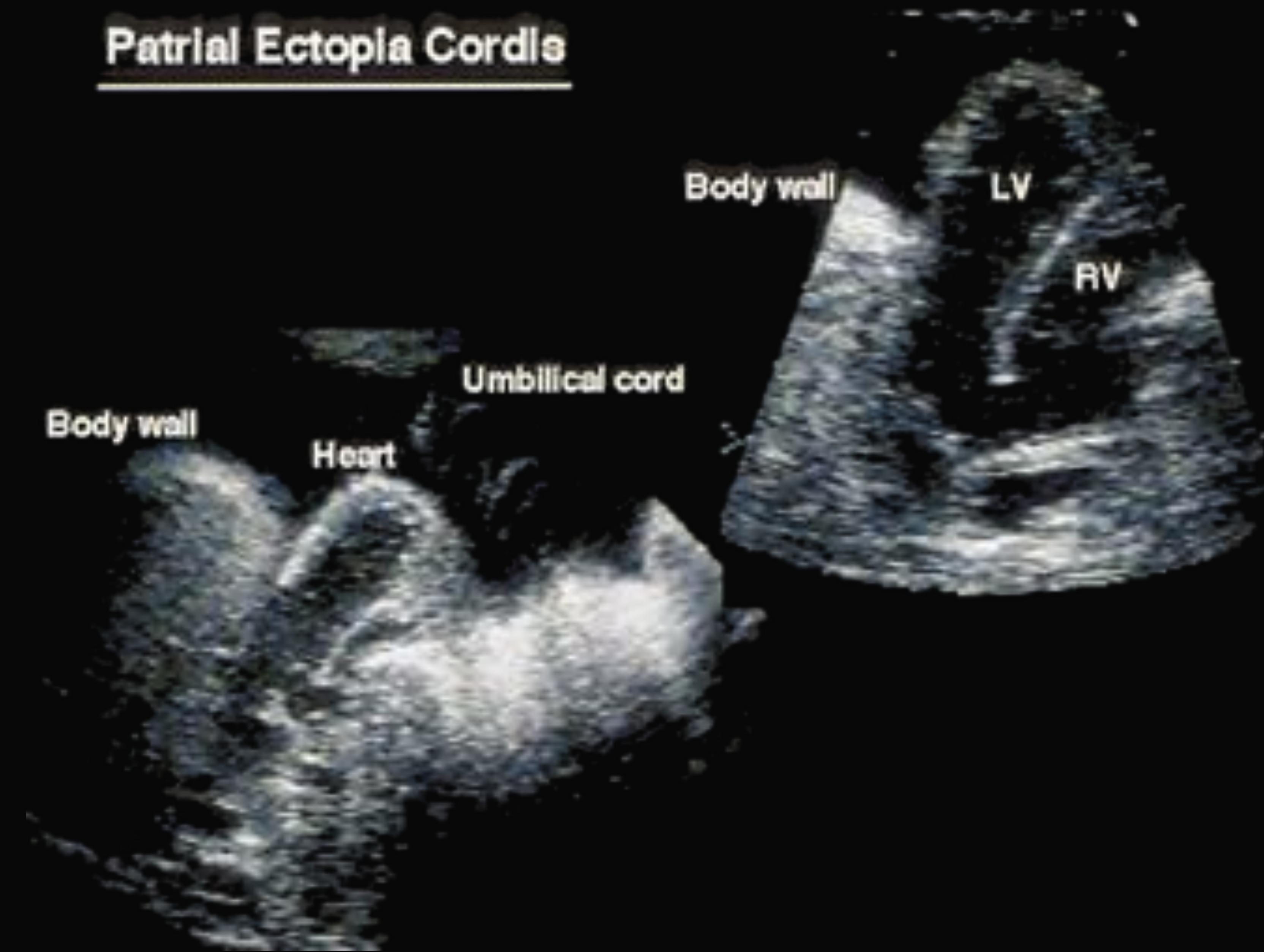
Dextrocardia



Levocardia



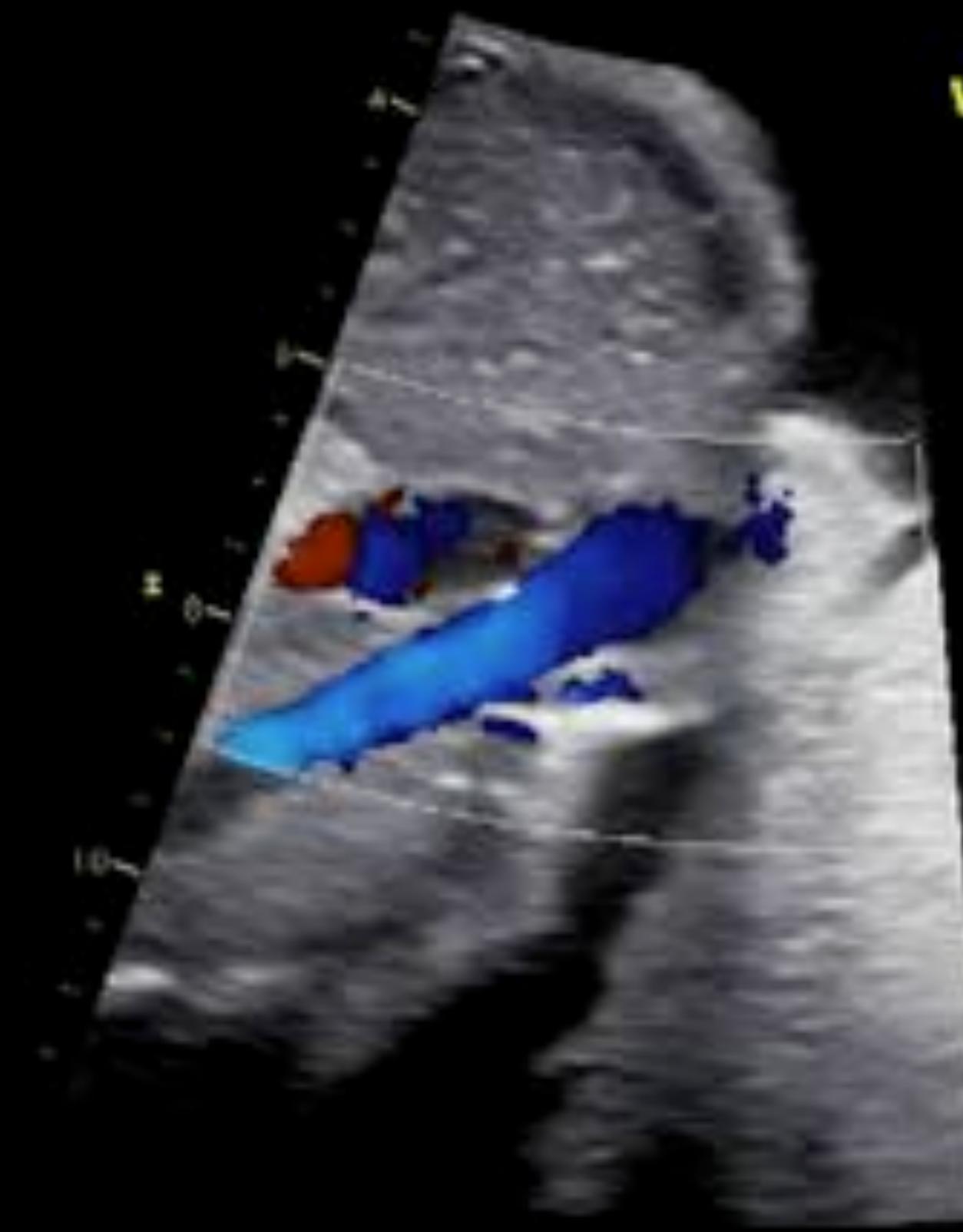
## Patral Ectopia Cordis



# Complete ectopia cordis



# Ectopia cordis and univentricular heart



# Dextroposition



# Why segmental analysis?

- Facilitates understanding of complex defects
  - Divide heart into manageable segments
  - Analyze each segment
  - Formulate comprehensive diagnosis

# Cardiac Segments

Atria

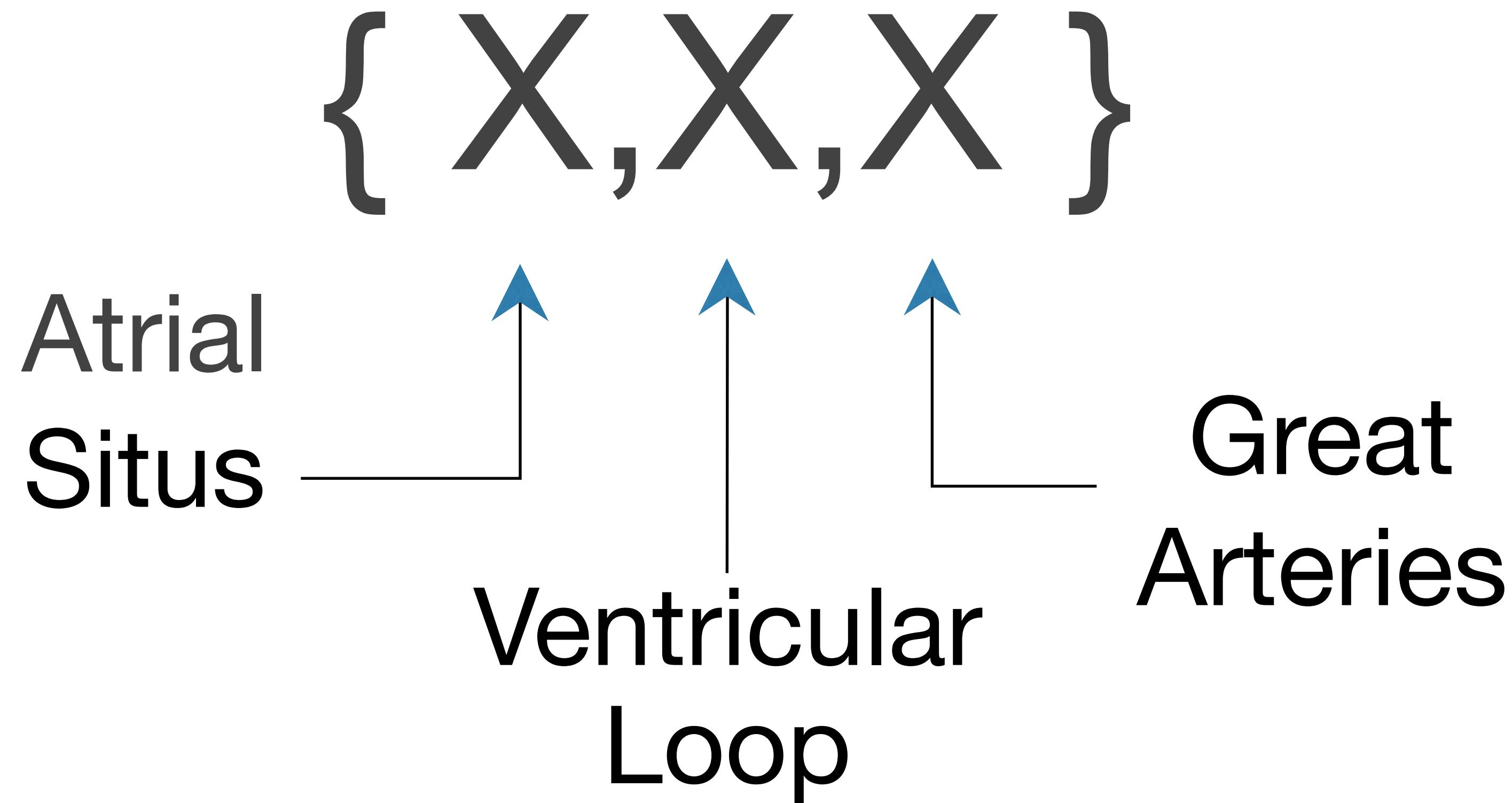
AV Canal

Ventricles

Conus

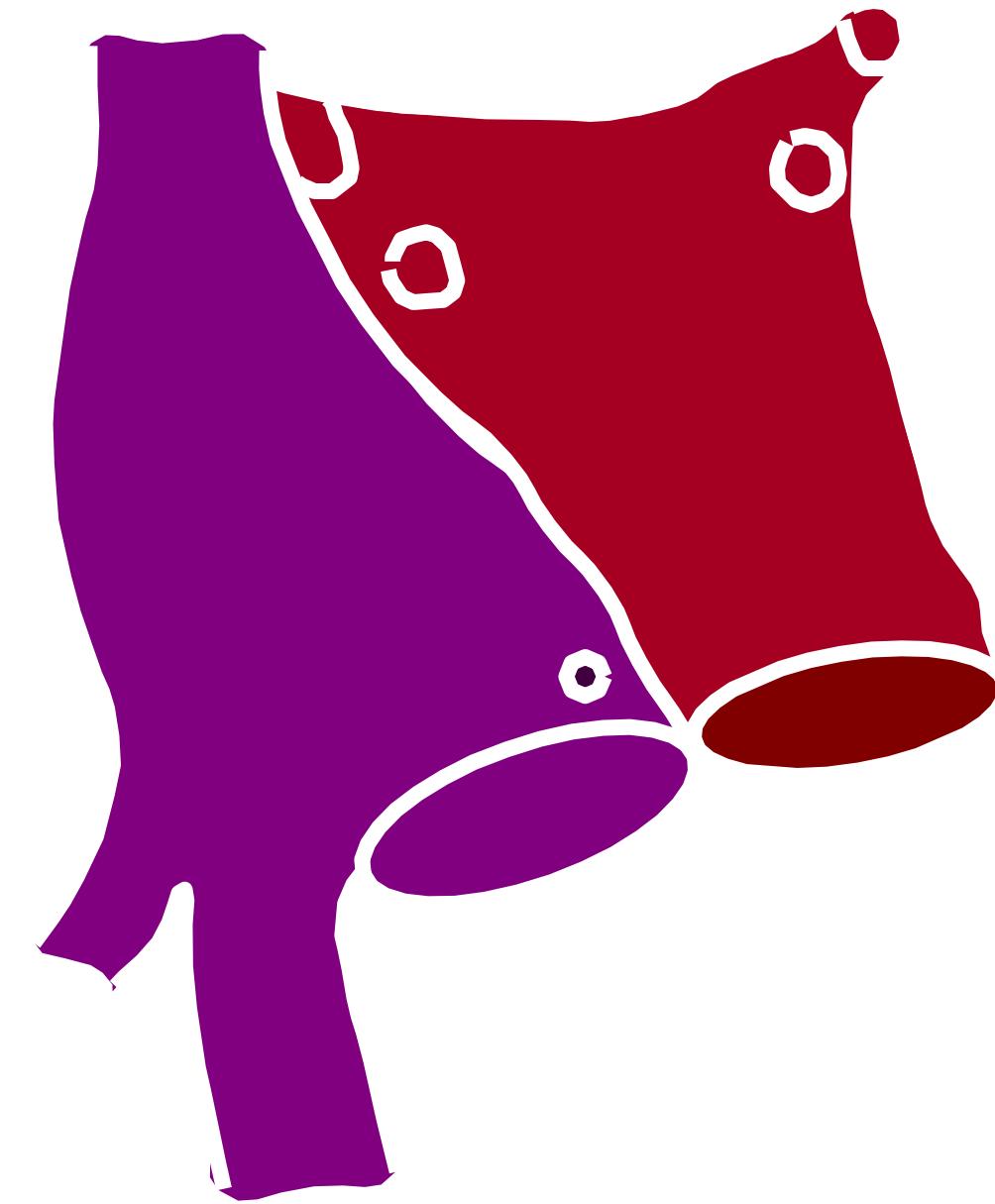
Great Arteries

# Segmental Set

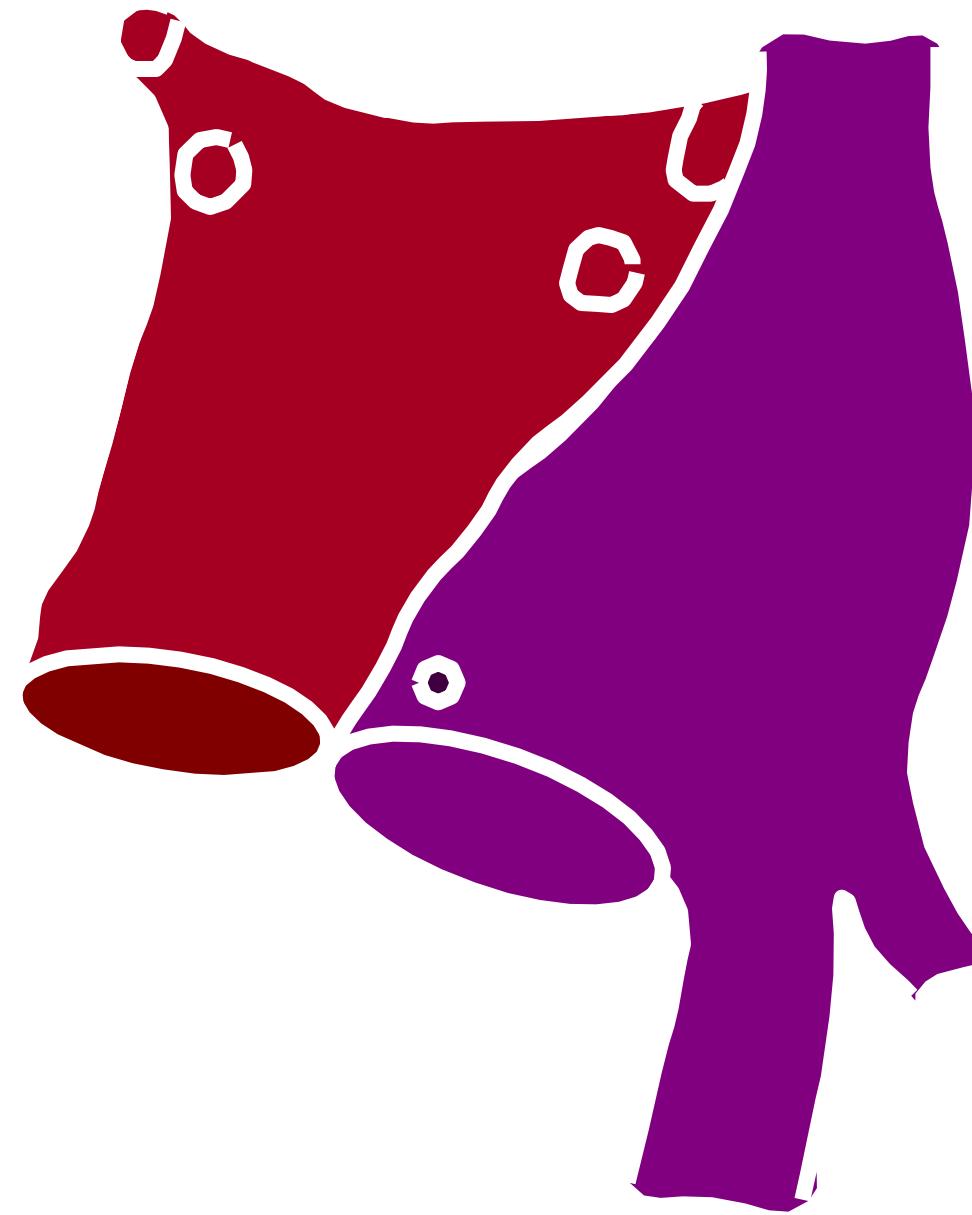


# Veno-atrial Segment

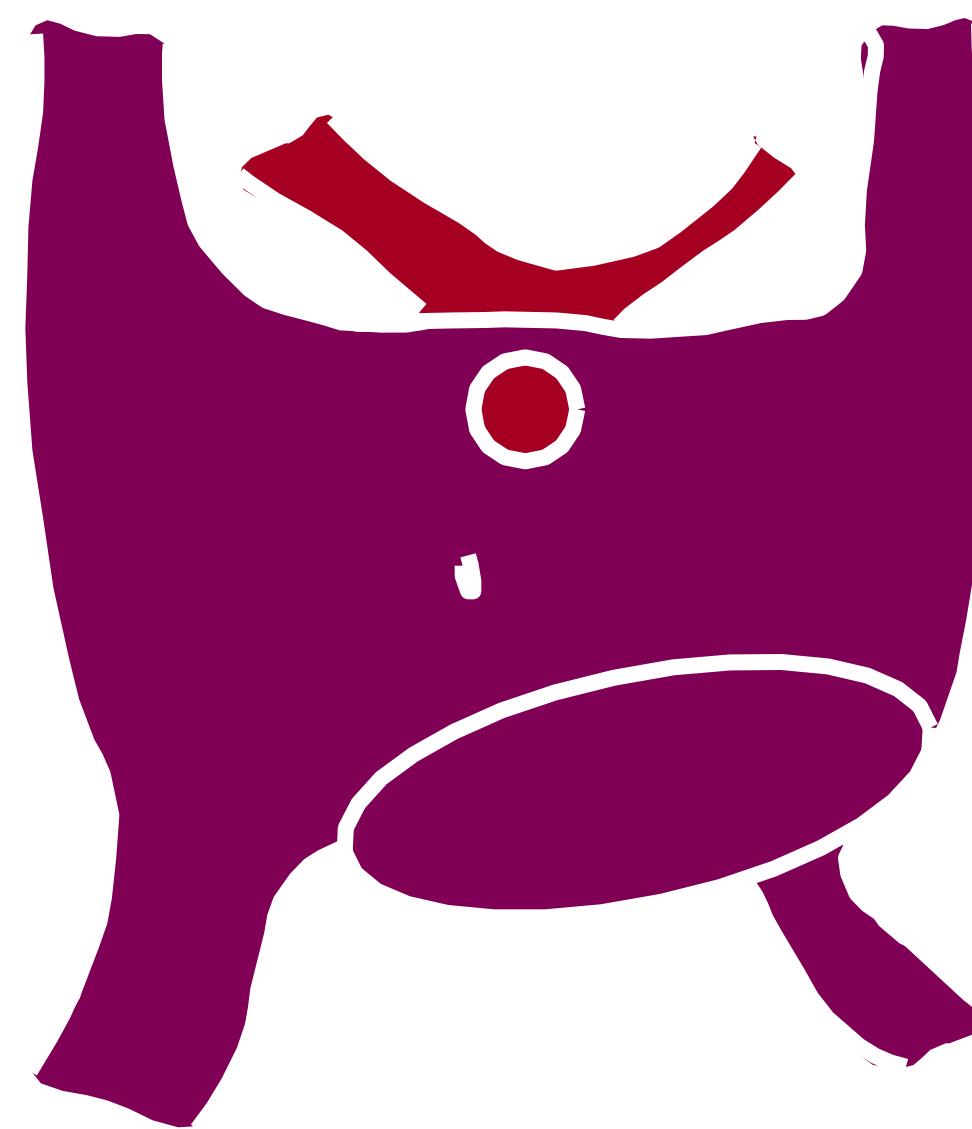
Situs Solitus (S)



Situs Inversus (I)



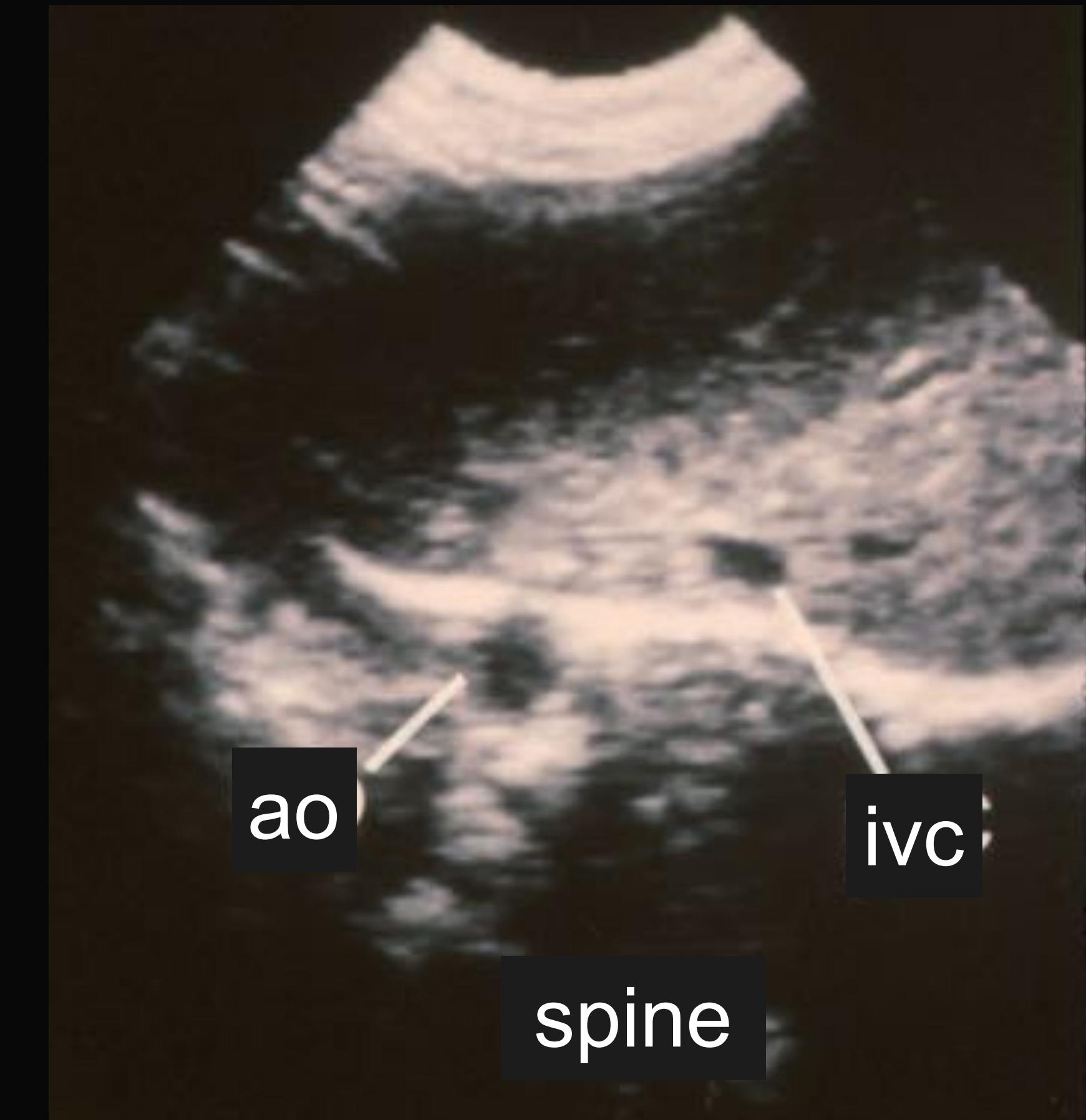
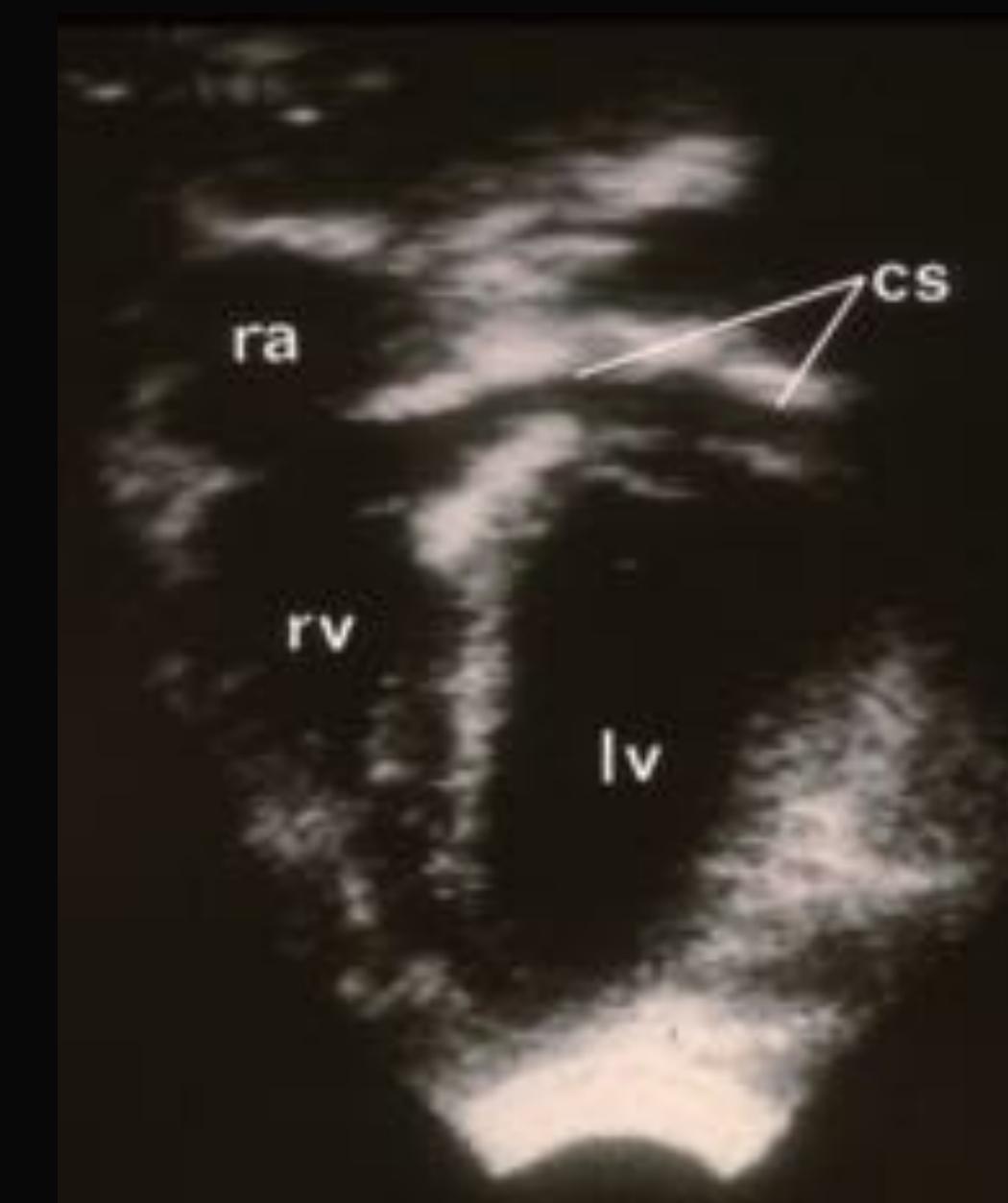
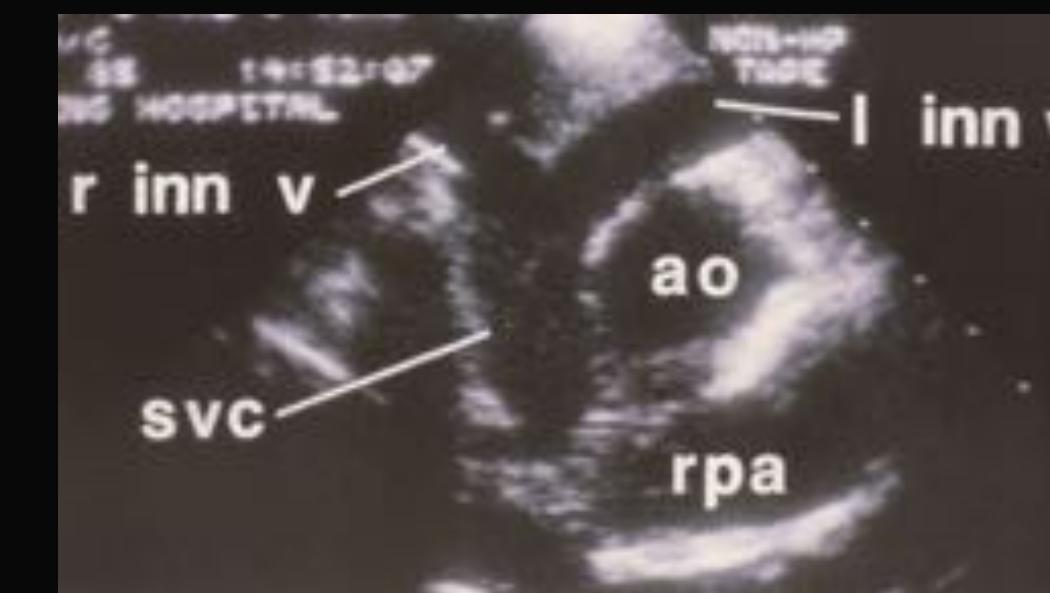
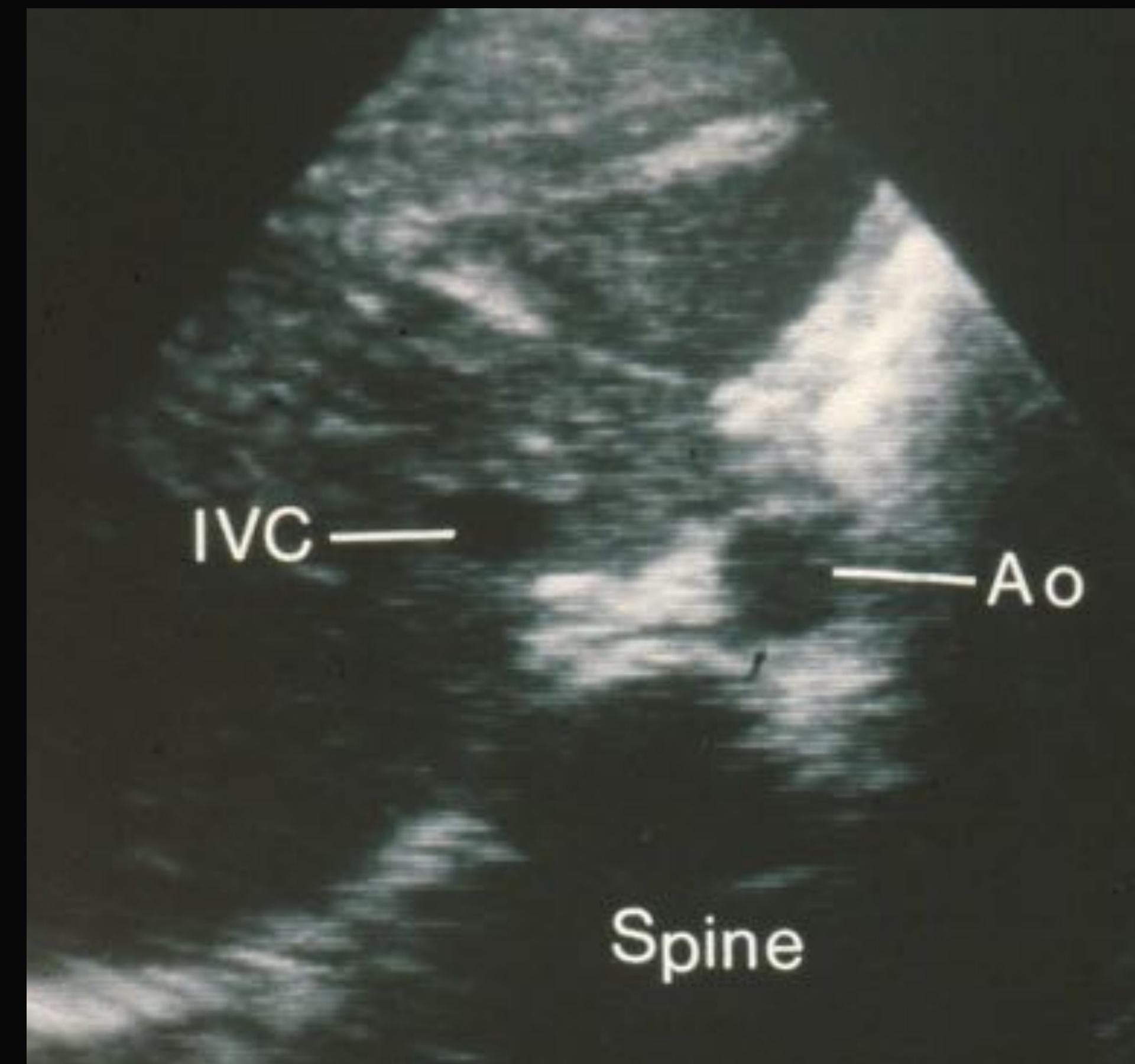
Situs Ambiguus (A)



# Atrial Morphology

- Right atrium
  - receives coronary sinus
  - pectinate muscles extend to vestibule of AV valve
  - receives IVC
  - septum secundum on septal surface
  - broad, triangular appendage

# Right atrium



## Right atrium

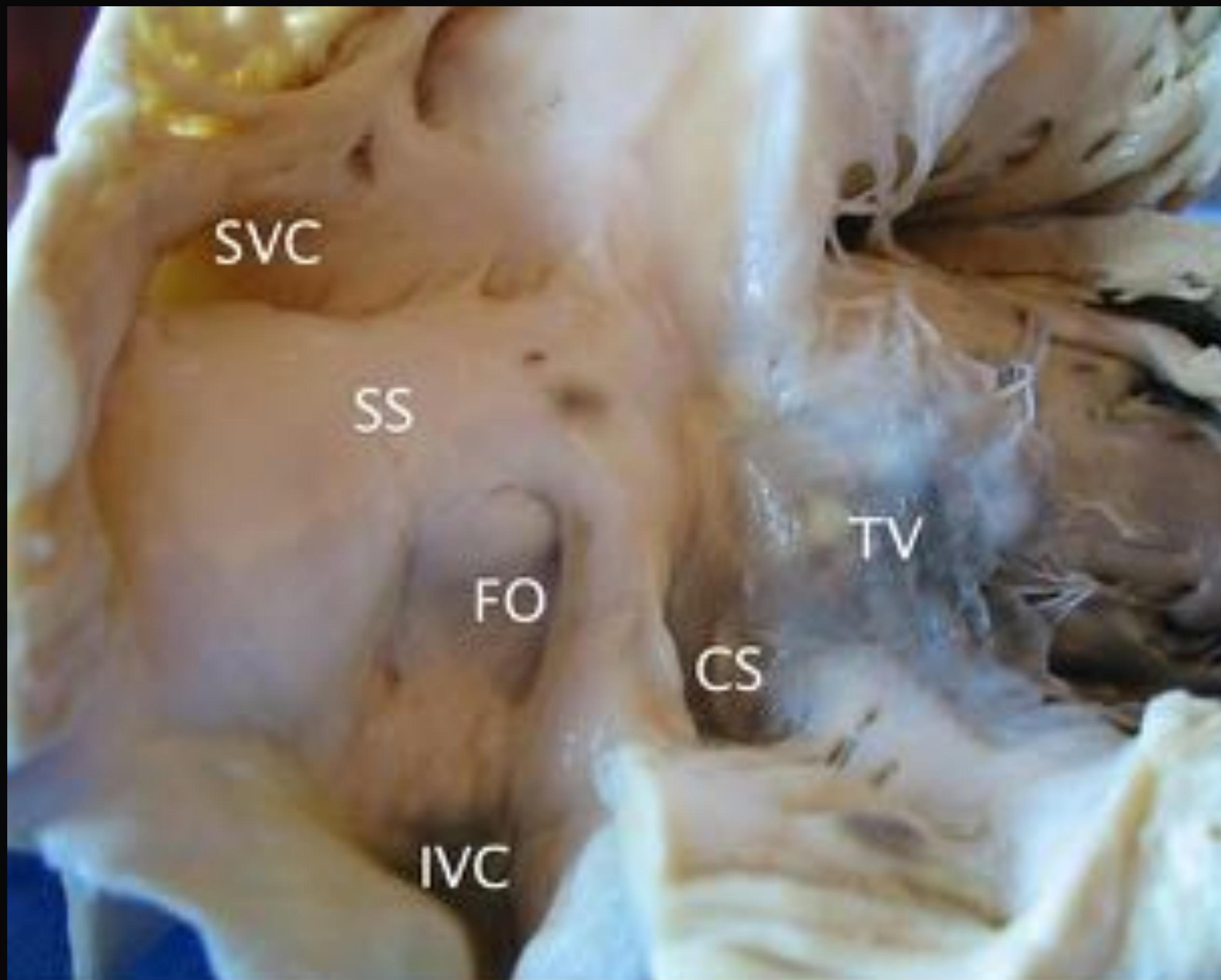
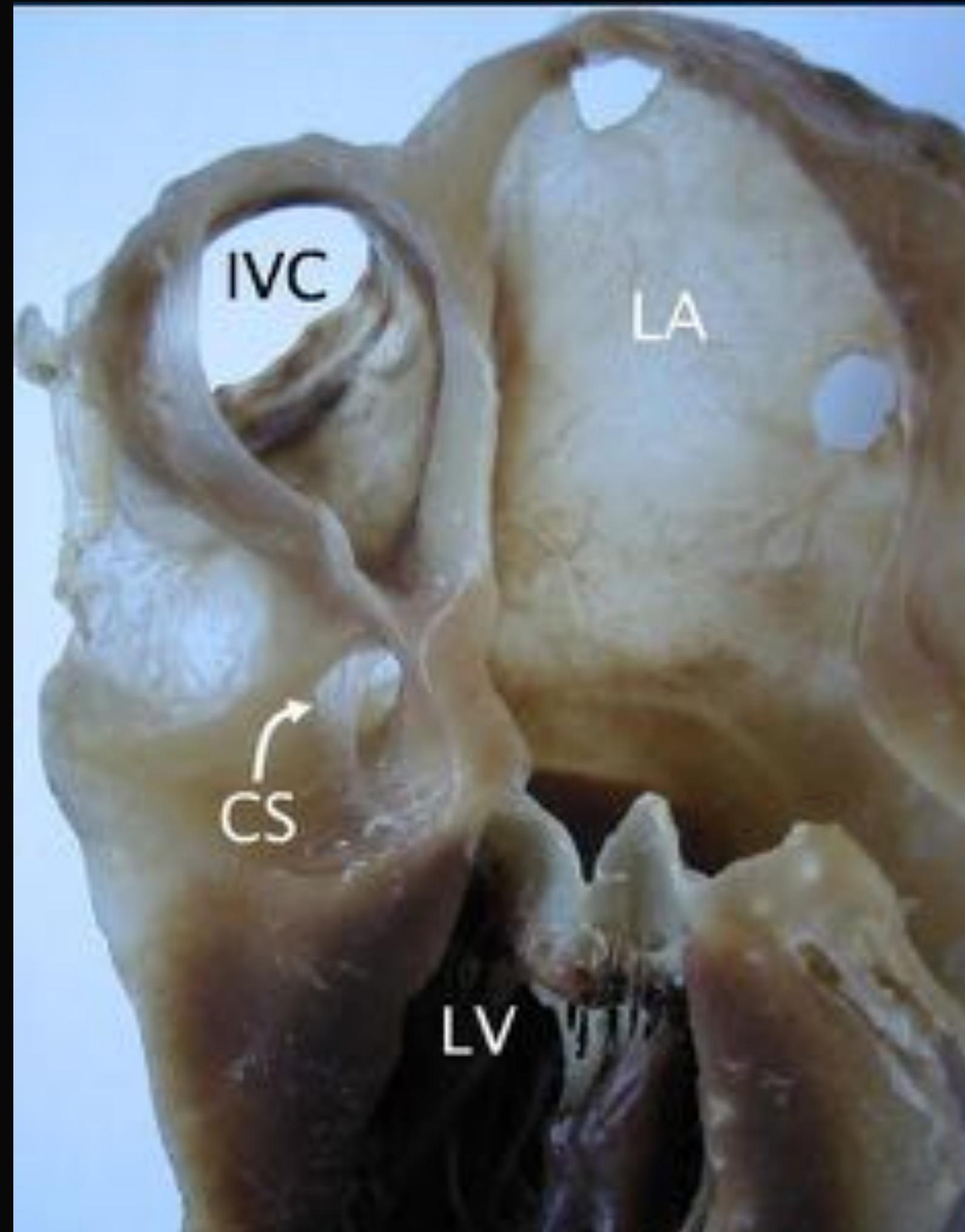


Fig 10. The specimen has been opened to show the right atrium. Note septum secundum (SS) on the septal surface above the fossa ovalis (FO). The superior vena cava (SVC), inferior vena cava (IVC) and coronary sinus (CS) enter the right atrium.



## Right atrium

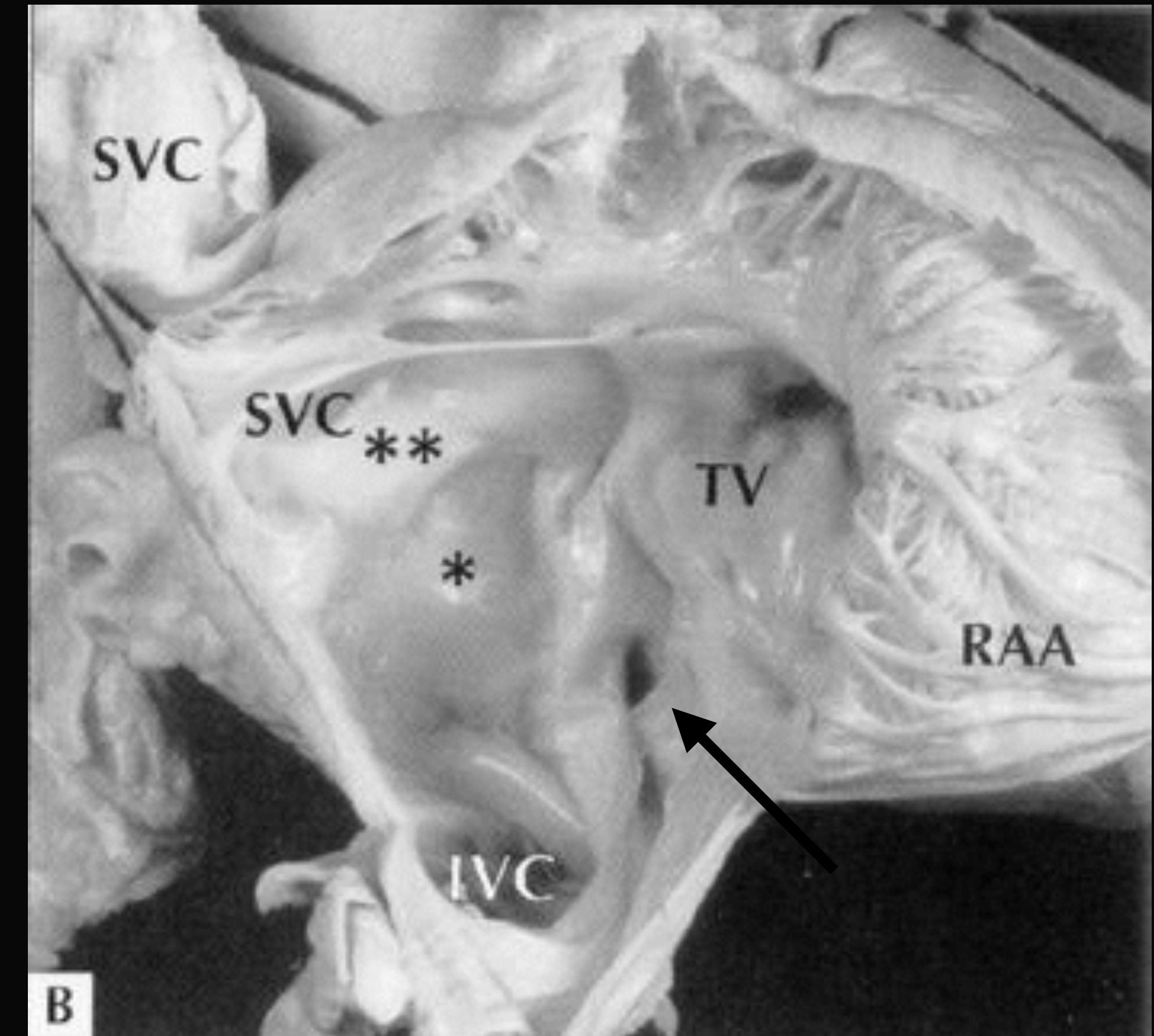


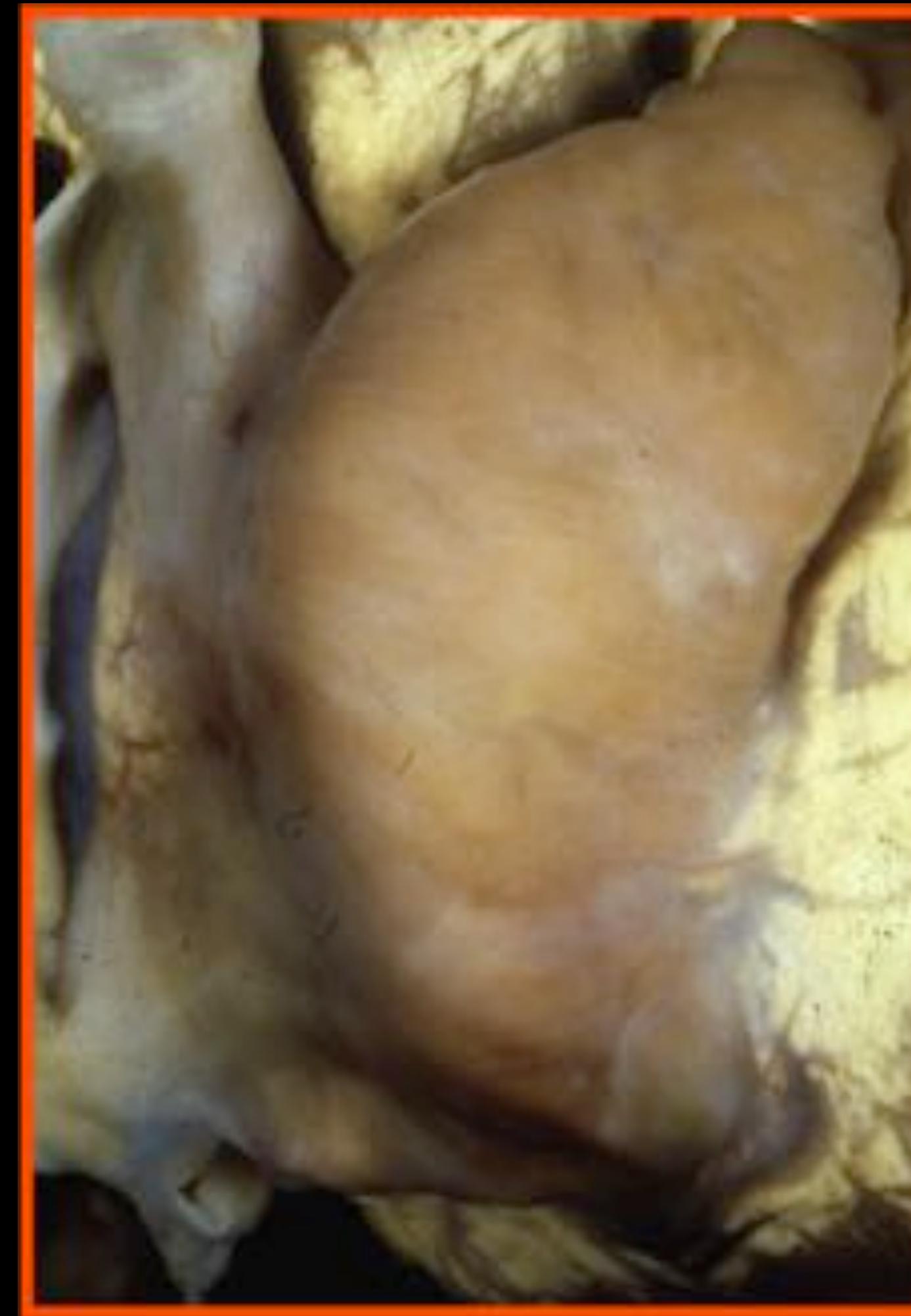
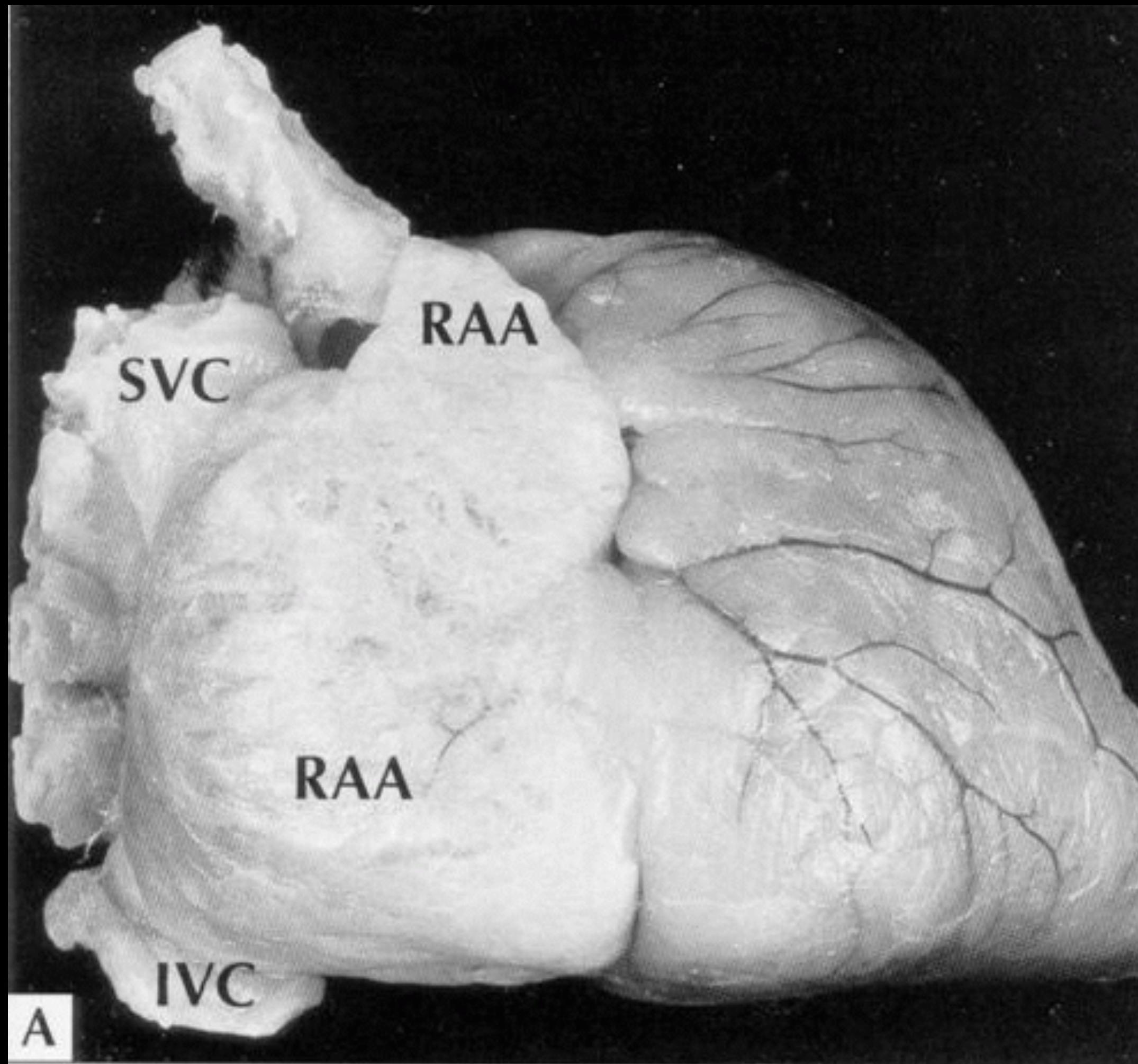
Fig 8. The coronary sinus is the most reliable marker for the right atrium and is seen entering the right atrium in a waxed specimen (left) and in an apical echo angled posteriorly. The inferior vena cava also connects with the right atrium (left)

# Right atrial appendage

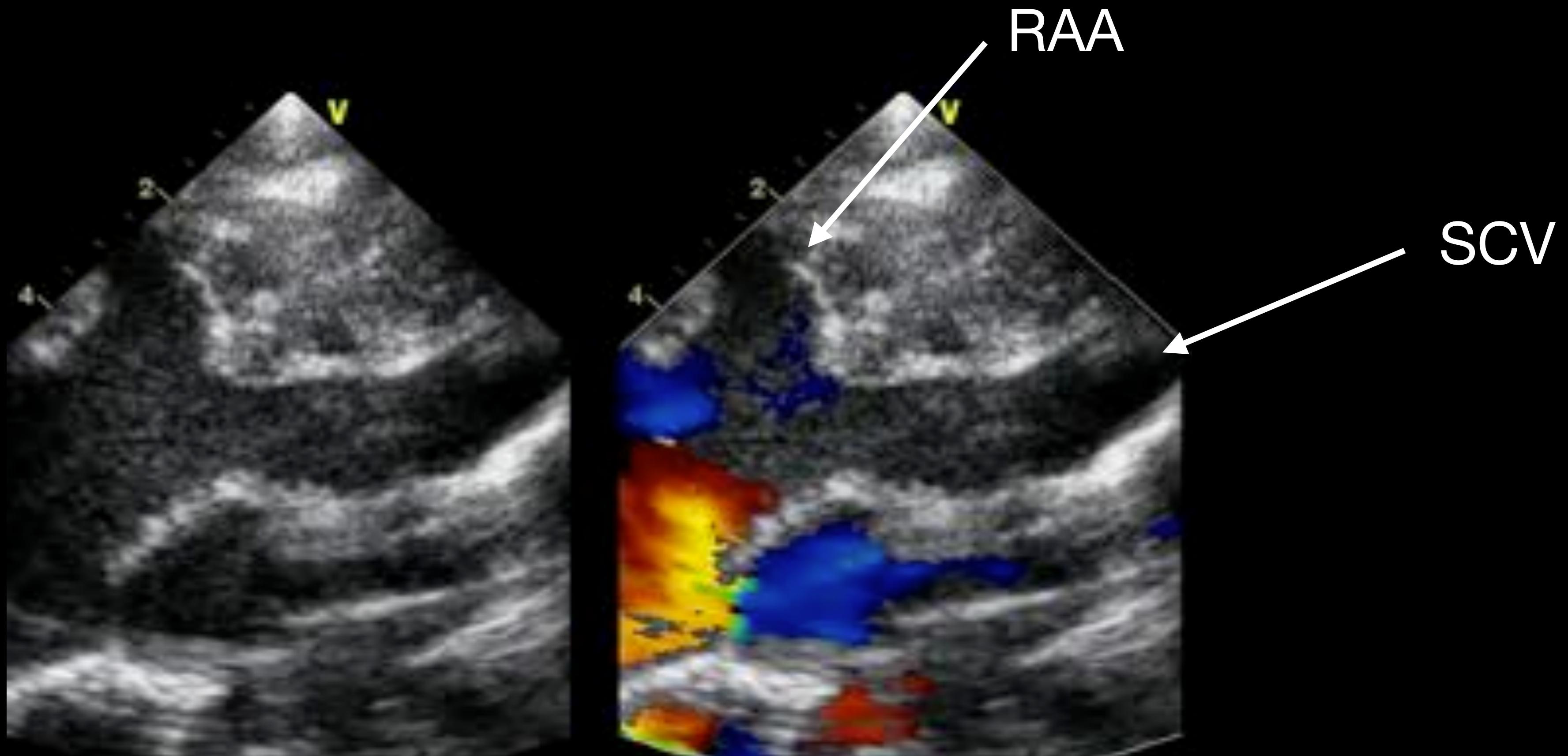


Fig 9. The specimen (left) has been opened to show the right atrium and ventricle with the atrioventricular junction. The pectinate muscles (PM) of the right atrium extend to the tricuspid valve (TV) annulus. The waxed specimen (right) shows the large right atrial appendage (RAA) with a broad opening into the right atrium.

# Right atrial appendage



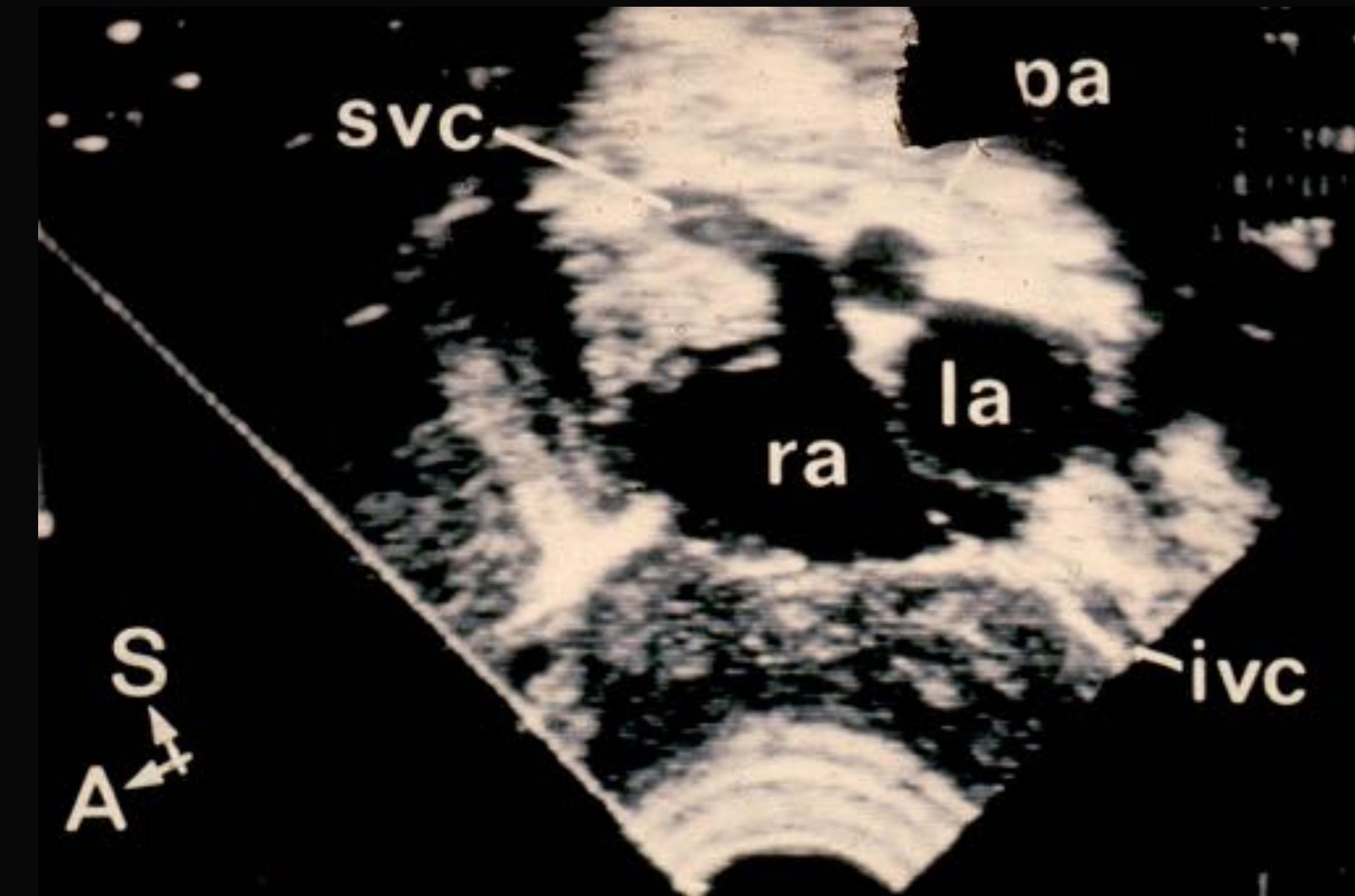
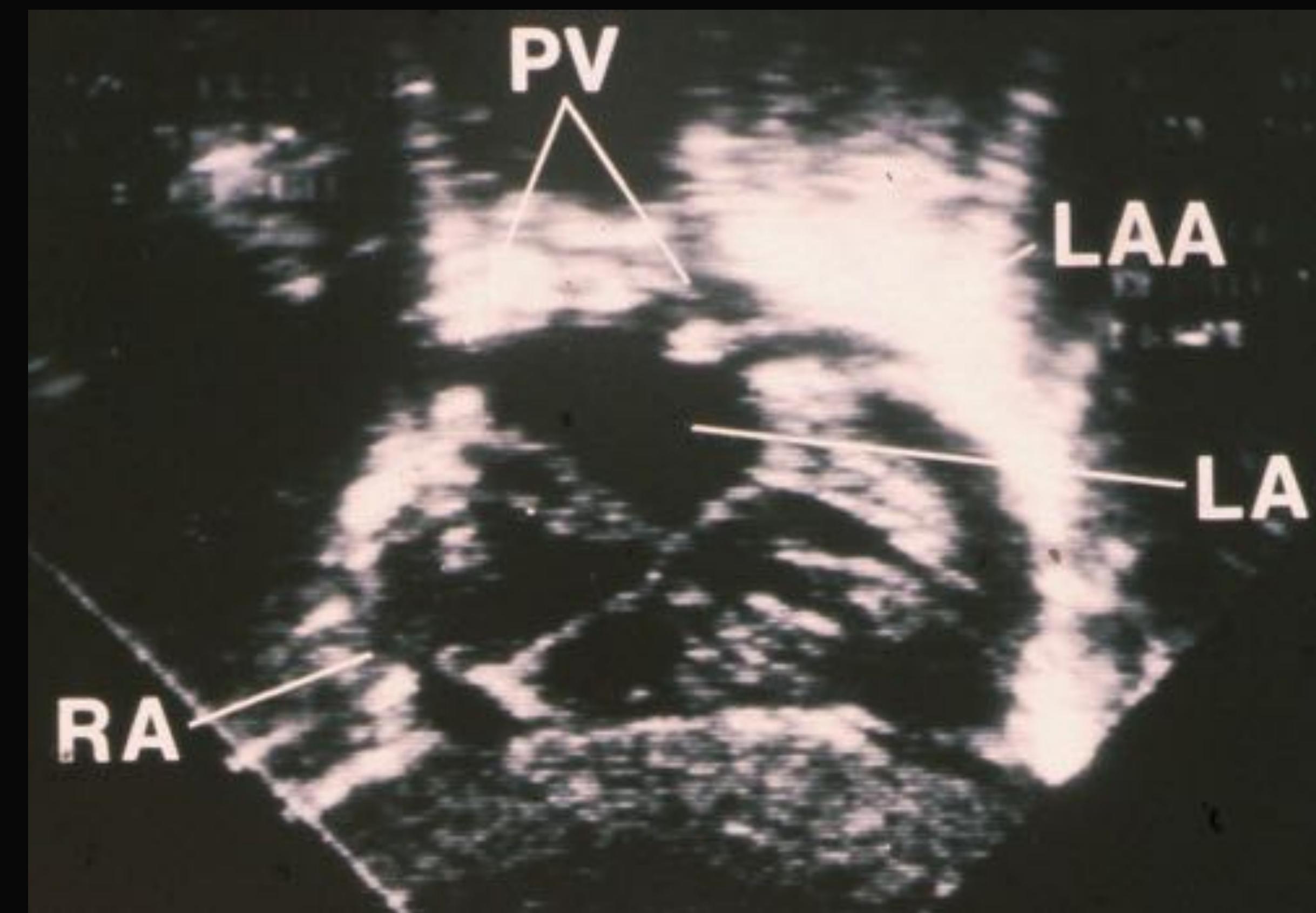
# Right atrial appendage



## Atrial Morphology

- Left atrium
  - pectinate muscles confined to appendage
  - septum primum on septal surface
  - small, finger-like appendage

# Left atrium



# Left atrium

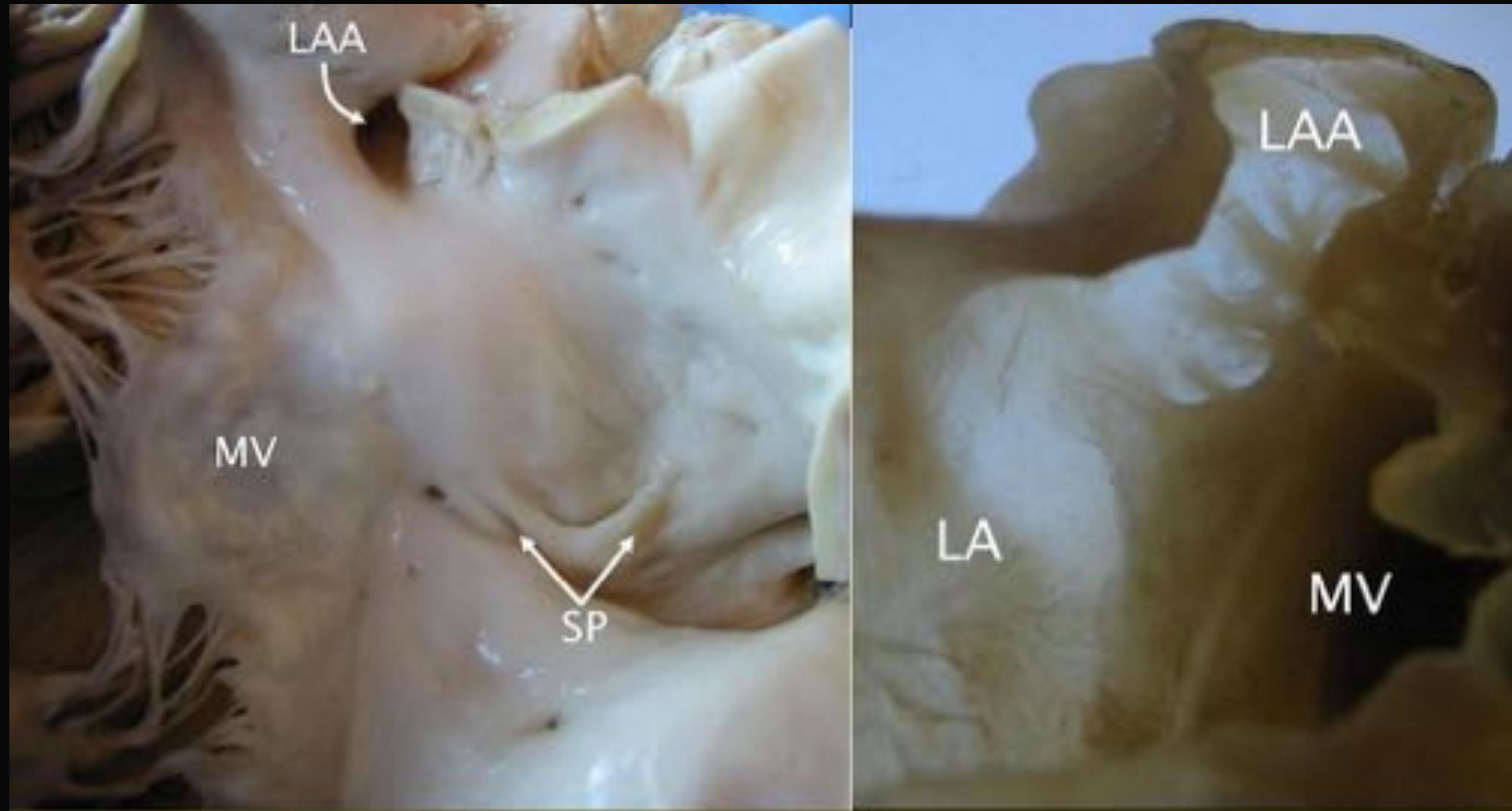


Fig 11. A specimen opened to show the left atrium (left). The left atrial appendage (LAA) is small with a restricted orifice. The pectinate muscles are confined to the appendage and do not extend to the vestibule of the mitral valve (MV). Septum primum (SP) is seen on the septal surface. The waxed specimen (right) shows the small left atrial appendage with pectinate muscles.

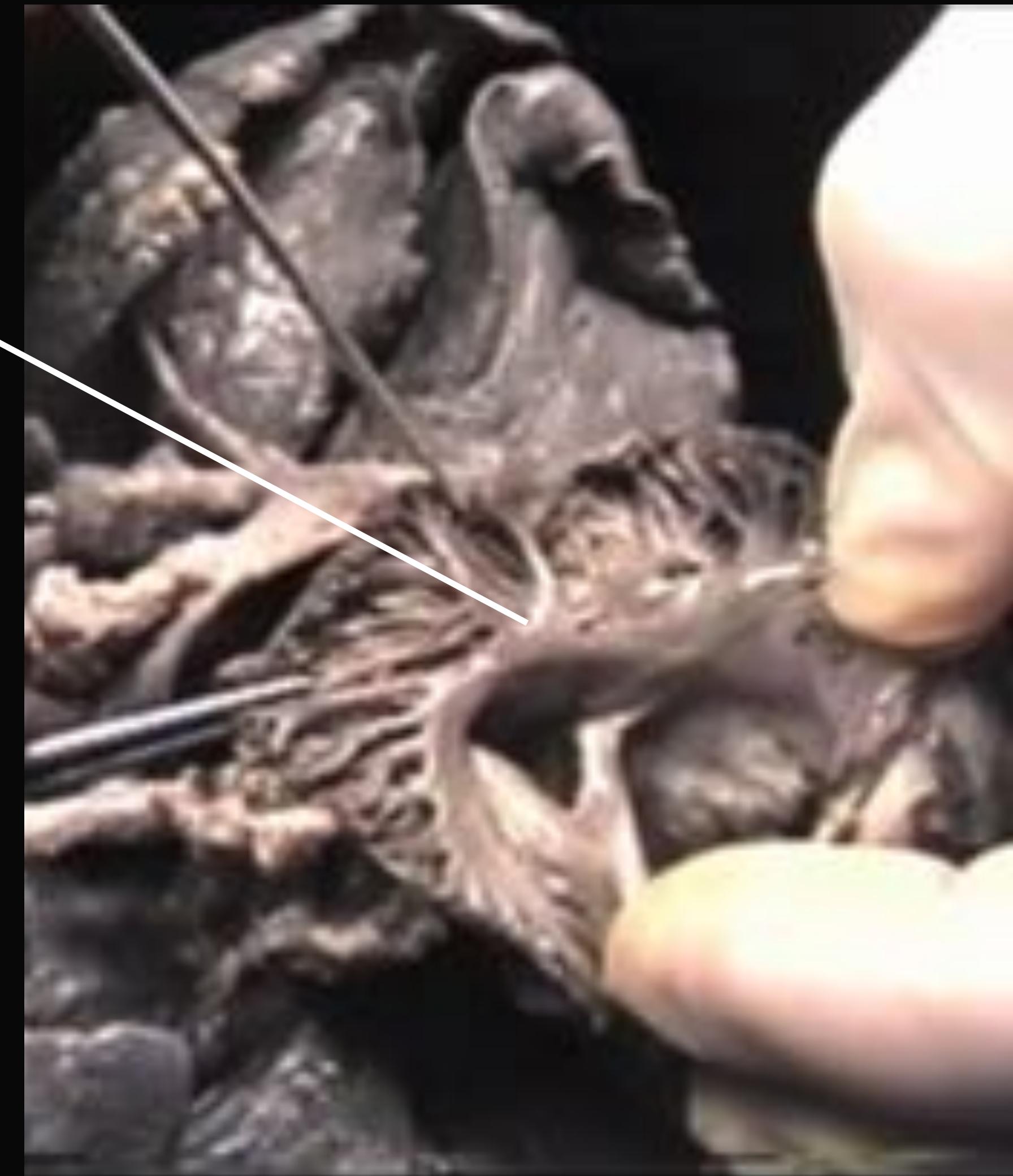
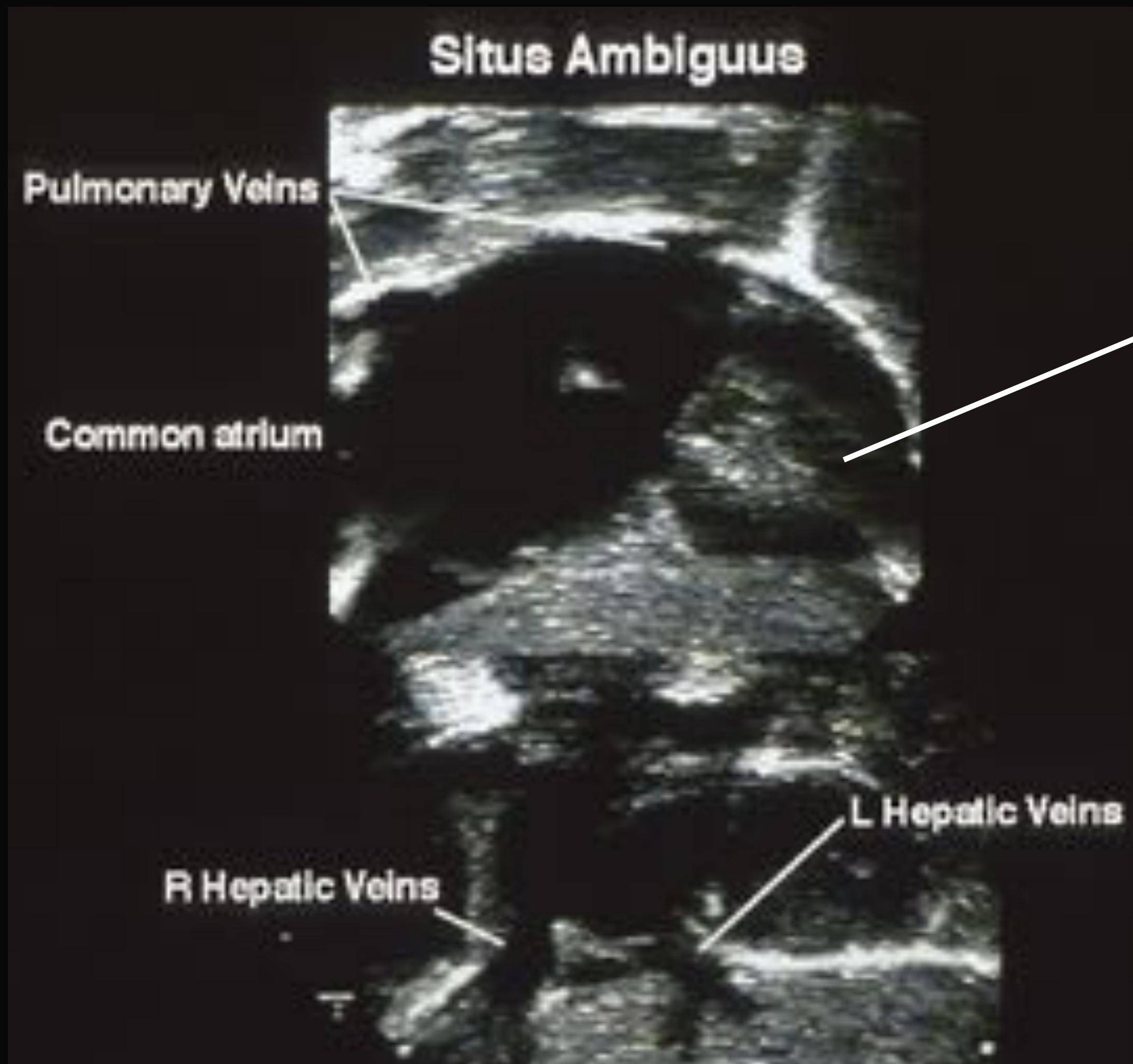
## Left atrial appendage



# Inversion

- Left-right reversal with no
  - antero-posterior or
  - supero-inferior change

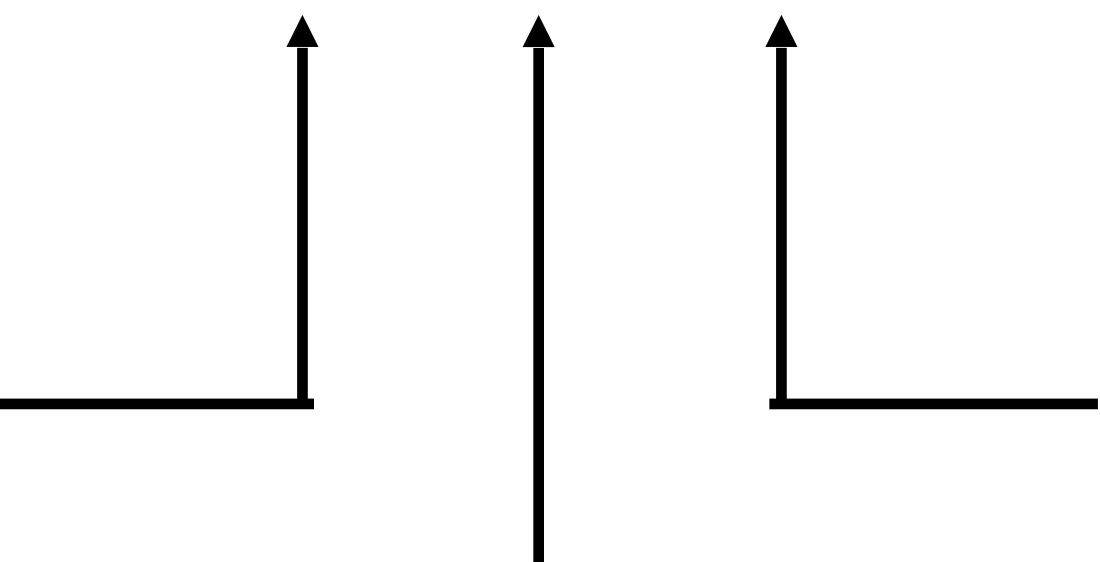
# Situs ambiguus



# **Segmental situs**

{ X, X, X }

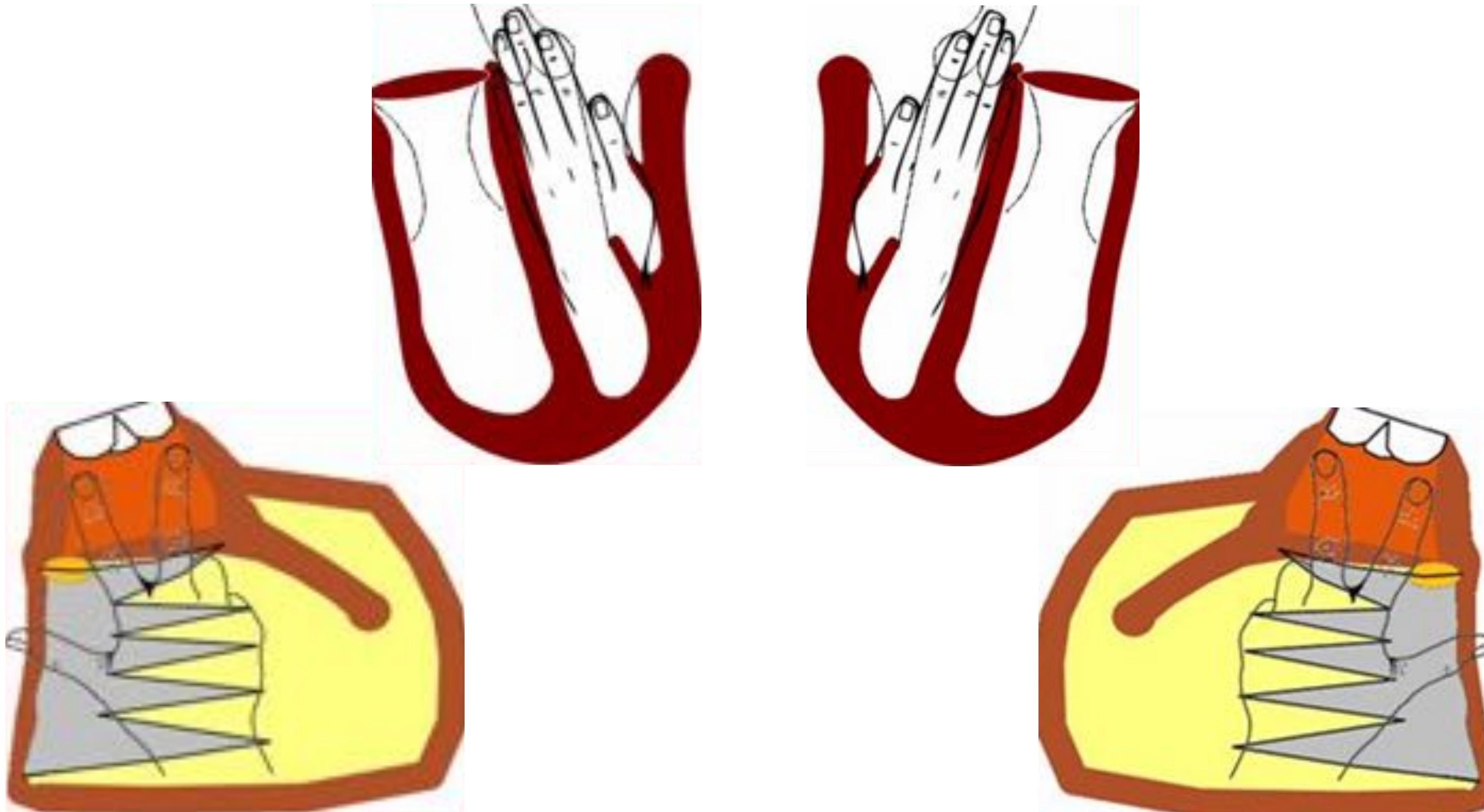
Atrial Situs  
(S,I,A)



Ventricular  
Loop  
(D,L)

Great Arteries  
(S,I  
D,L,A)

# Ventricles



Solitus or D-loop

Inversus or L-loop

# Ventricular Morphology

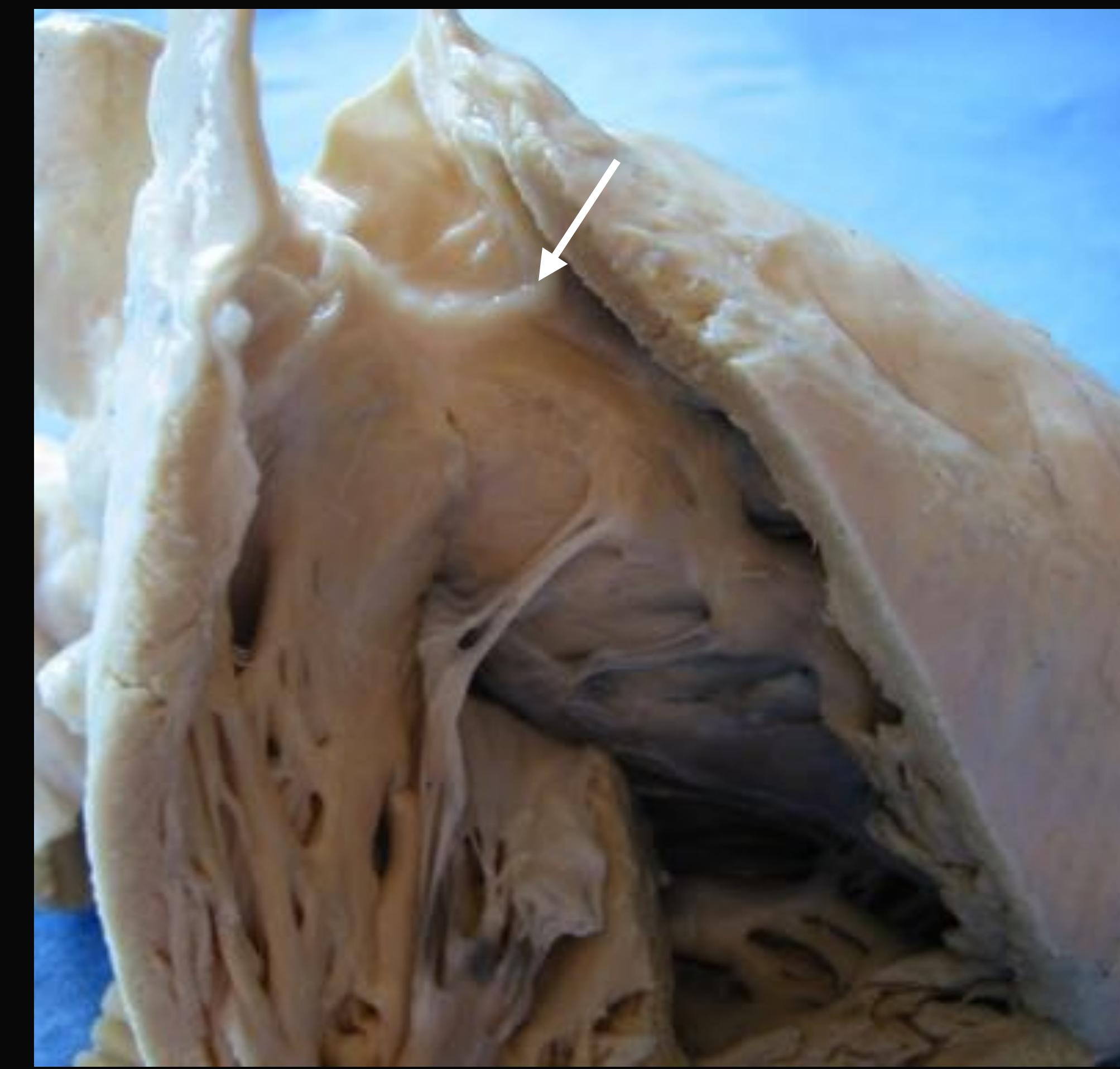
- Right ventricle
  - trapezoidal shape
  - coarsely trabeculated
  - 2 parts – body and outflow
  - tricuspid valve attached to septum

## Right ventricle



Fig 15. The right ventricle is trapizoidal in shape from a frontal view (left) and has coarse muscular trabeculations (right)

# Right ventricle



## Right ventricle

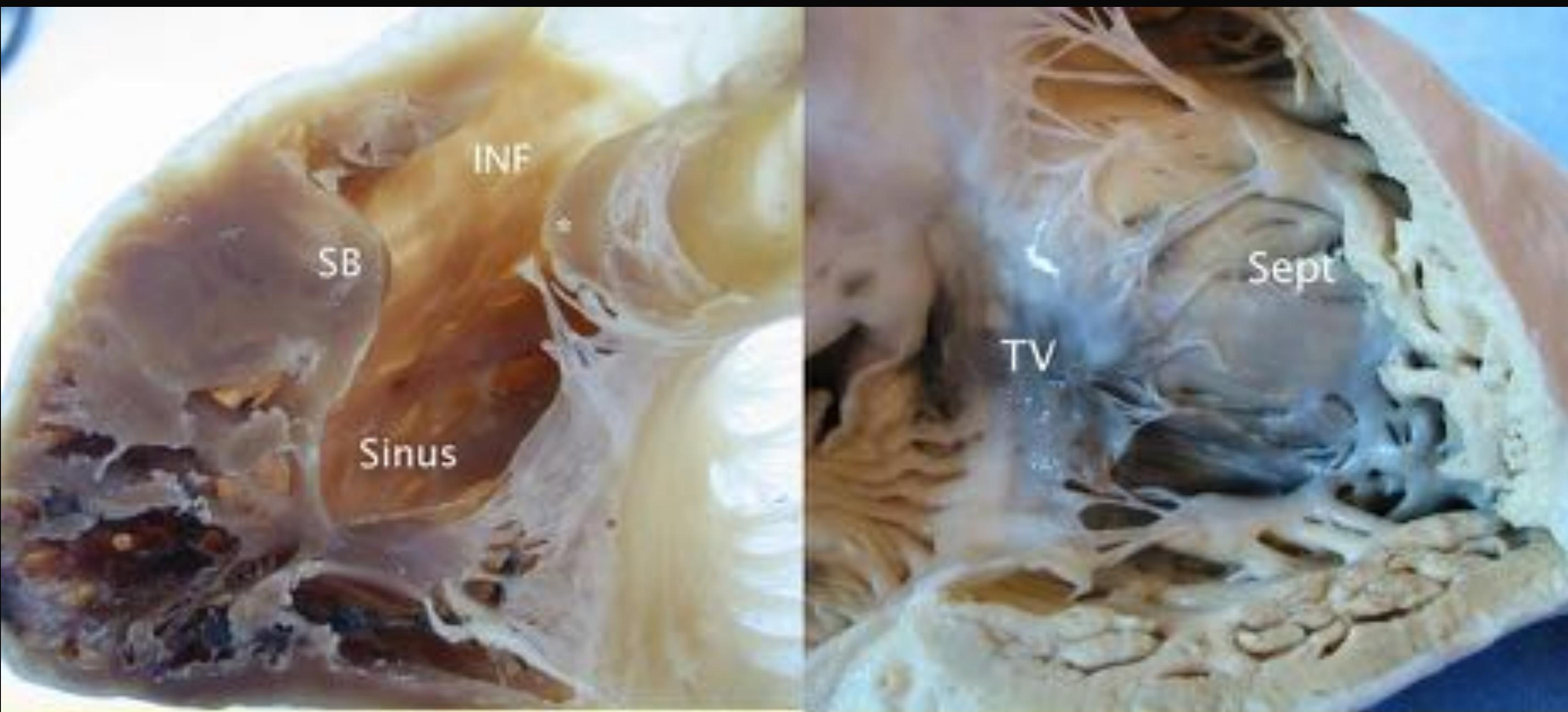


Fig 16. The opened right ventricle (left) viewed from posterior shows the sinus and infundibular (INF) parts separated by the septal (SB) and parietal (\*) bands. Right panel shows multiple insertions of the tricuspid valve (TV) onto the septum (Sept).

# Ventricular Morphology

- Left ventricle
  - ellipsoidal shape
  - finely trabeculated
  - Adjacent inflow and outflow
  - 2 discrete free-wall papillary muscles
  - Mitral valve with no septal attachments

## Left ventricle



Fig 17. The left ventricle (LV) is elliptical as seen from posterior (left). The opened left ventricle (right) shows the smooth mid and basal septum (Sept) with fine apical trabeculations. The mitral valve (MV) has 2 free-wall papillary muscles (\*).

## Left ventricle

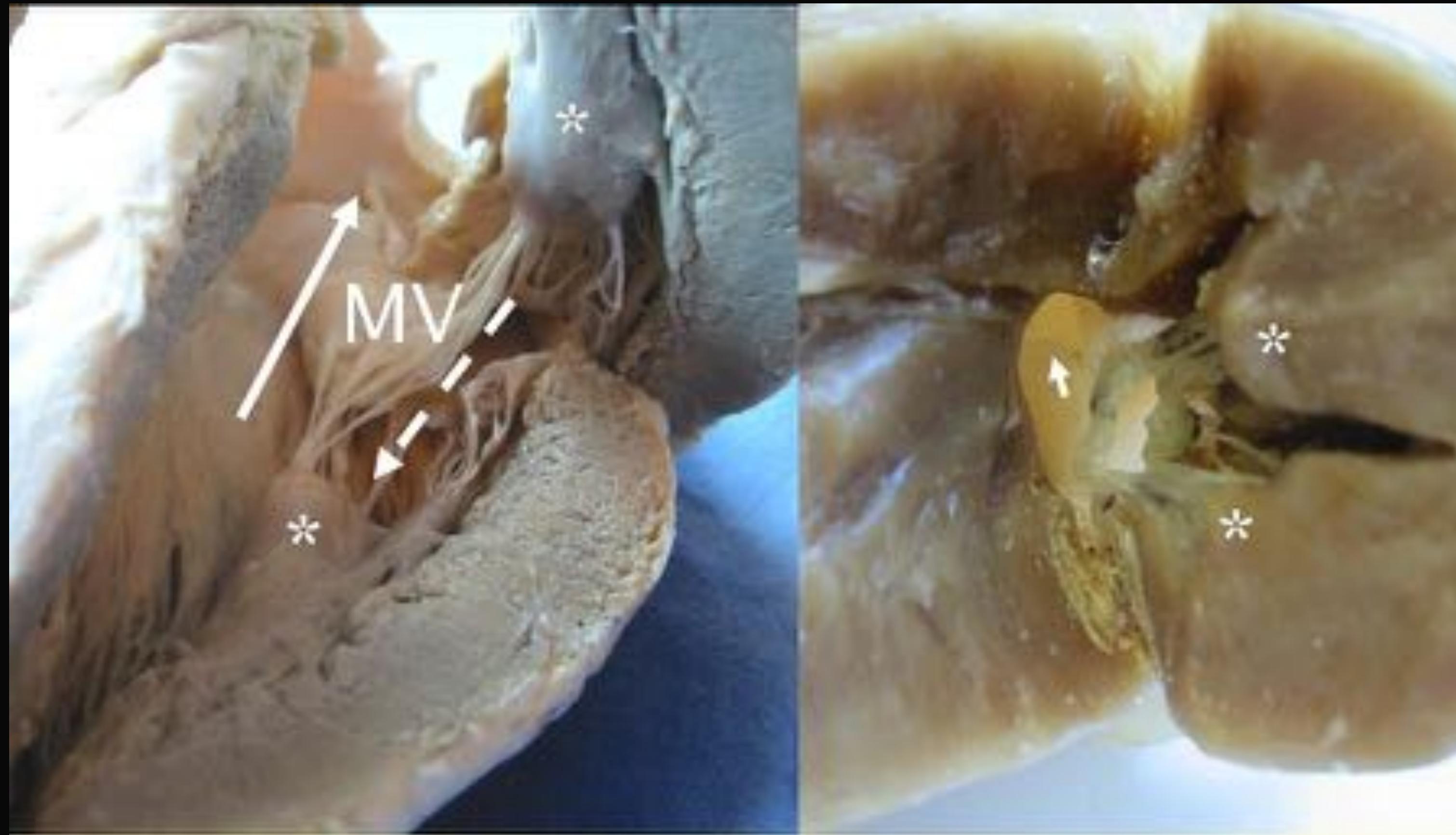
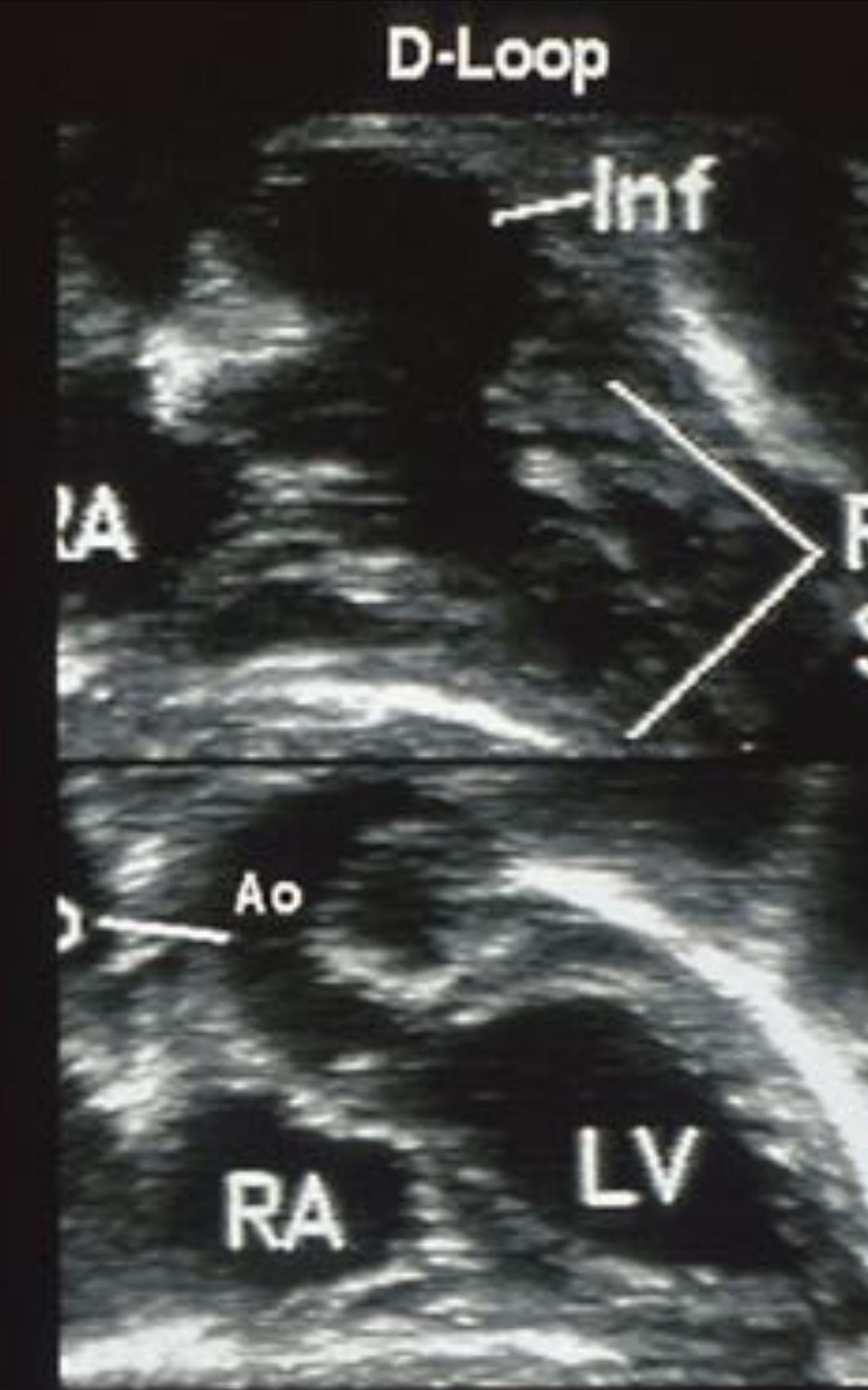
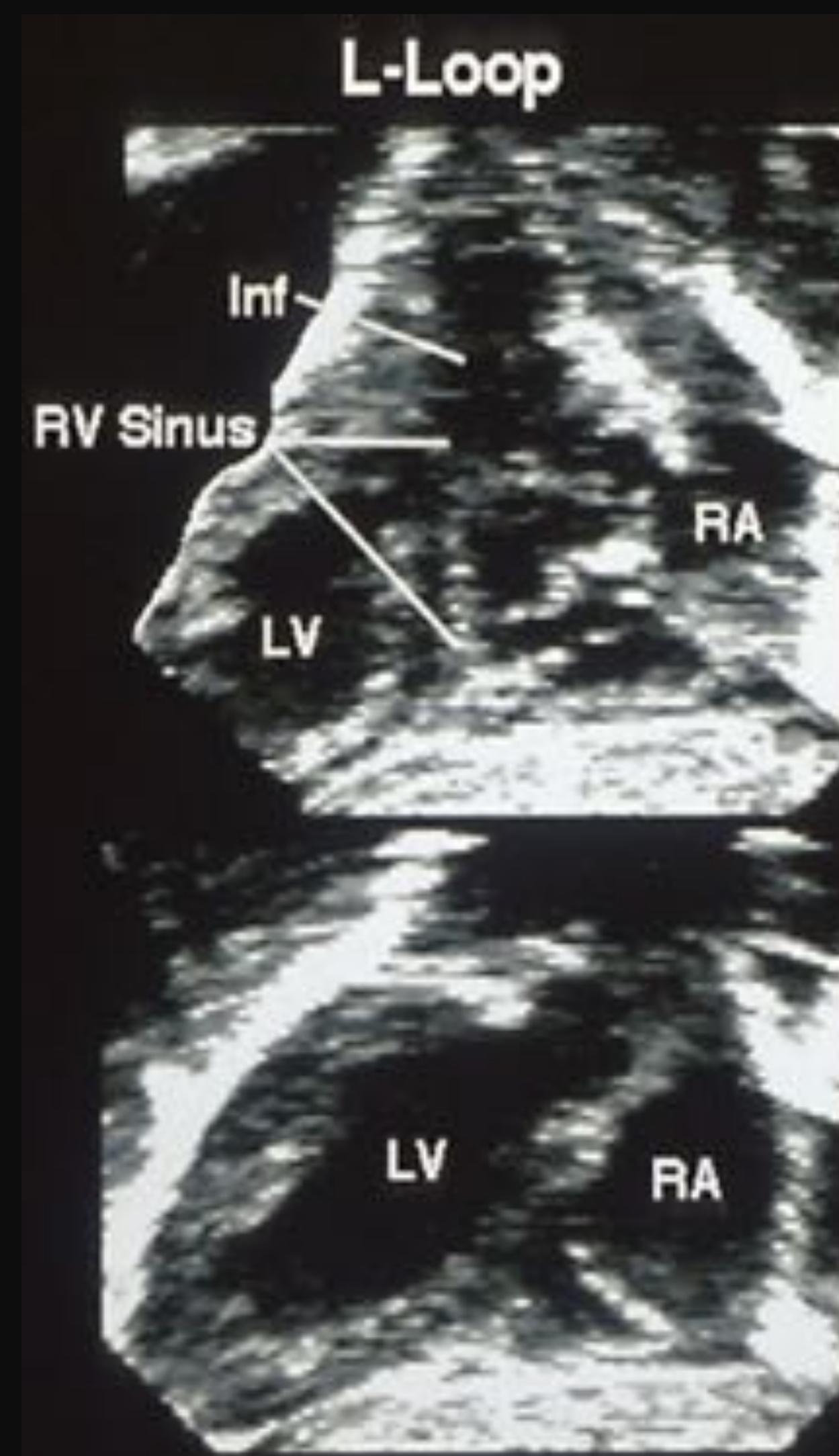


Fig 18. The left ventricle viewed from the apex shows the free wall papillary muscles (\*), the adjacent and nearly parallel inflow ( $\nearrow$ ) and outflow ( $\rightarrow$ ) tracts, and the outflow tract between the anterior mitral leaflet and the septum.

# Left ventricle



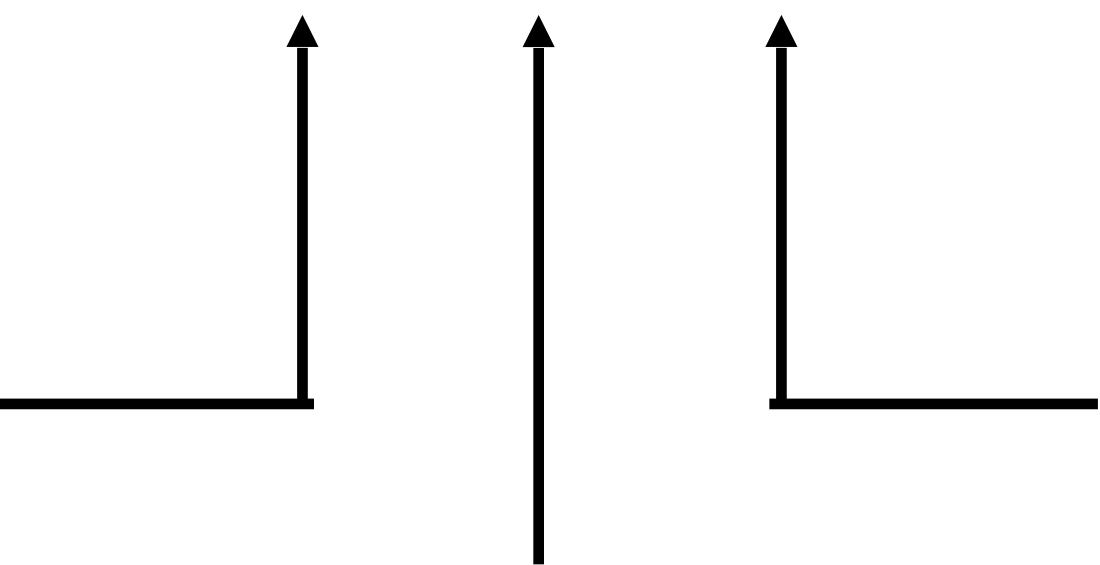
# Ventricular situs or loop



# **Segmental situs**

{ X, X, X }

Atrial Situs  
(S,I,A)



Ventricular  
Loop  
(D,L)

Great Arteries  
(S,I  
D,L,A)

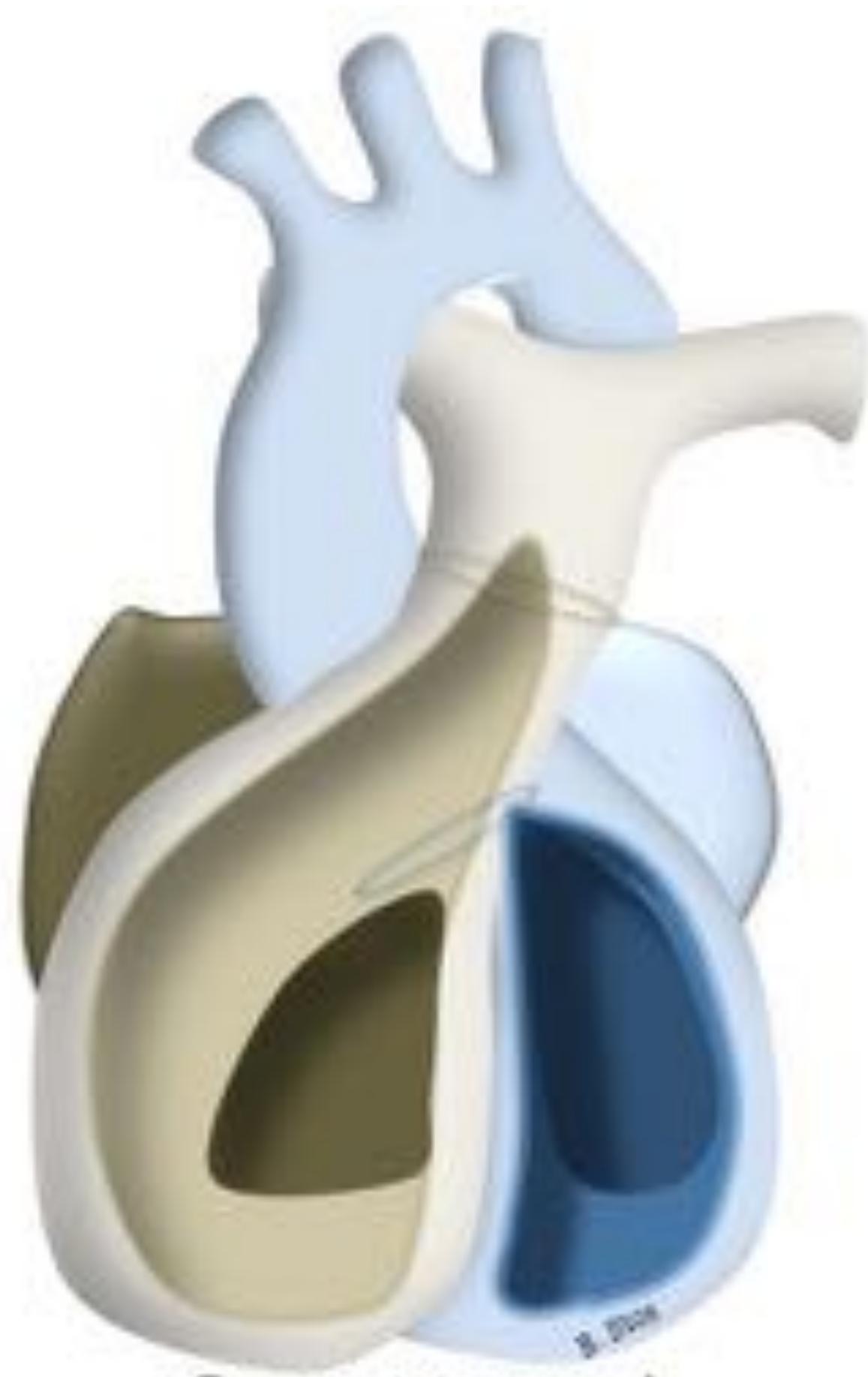
# Great Artery Morphology

- Aorta
  - forms arch
  - origin of at least some arch vessel
- Pulmonary artery
  - short trunk
  - bifurcates into right and left branches

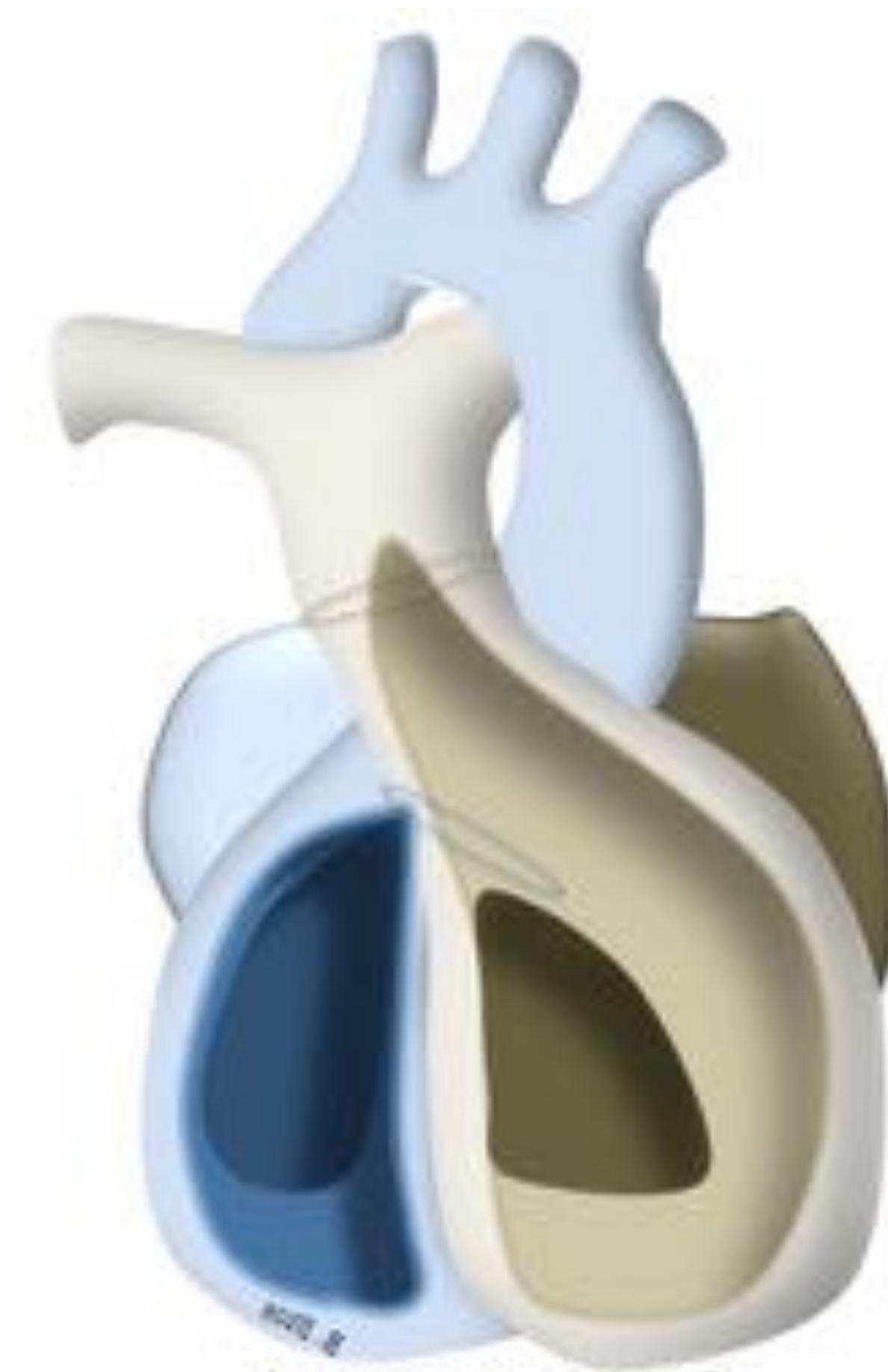
There are significant exceptions

# **Great Arteries**

## **Normally Related Great Arteries**

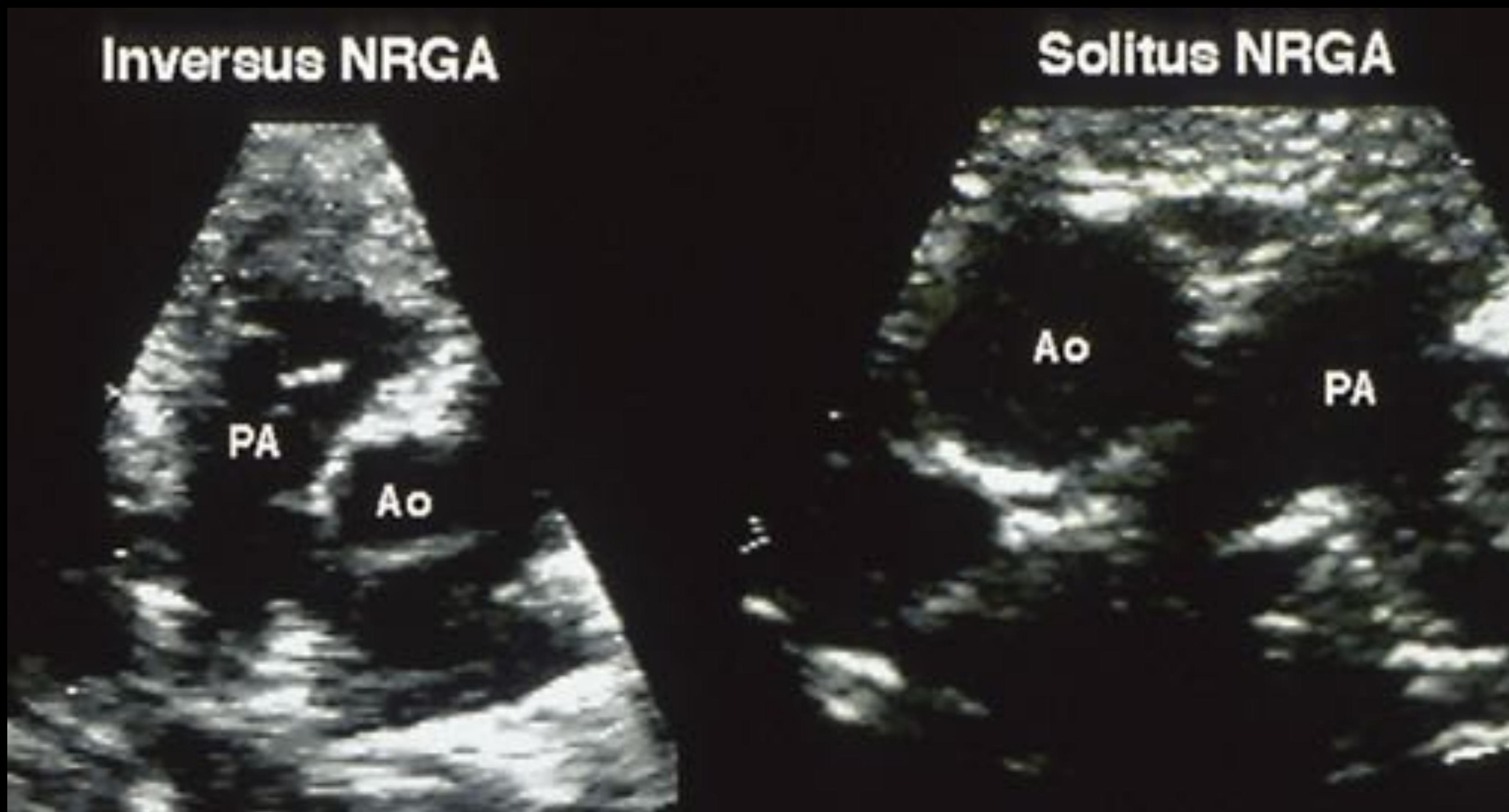


**Solitus (S)**

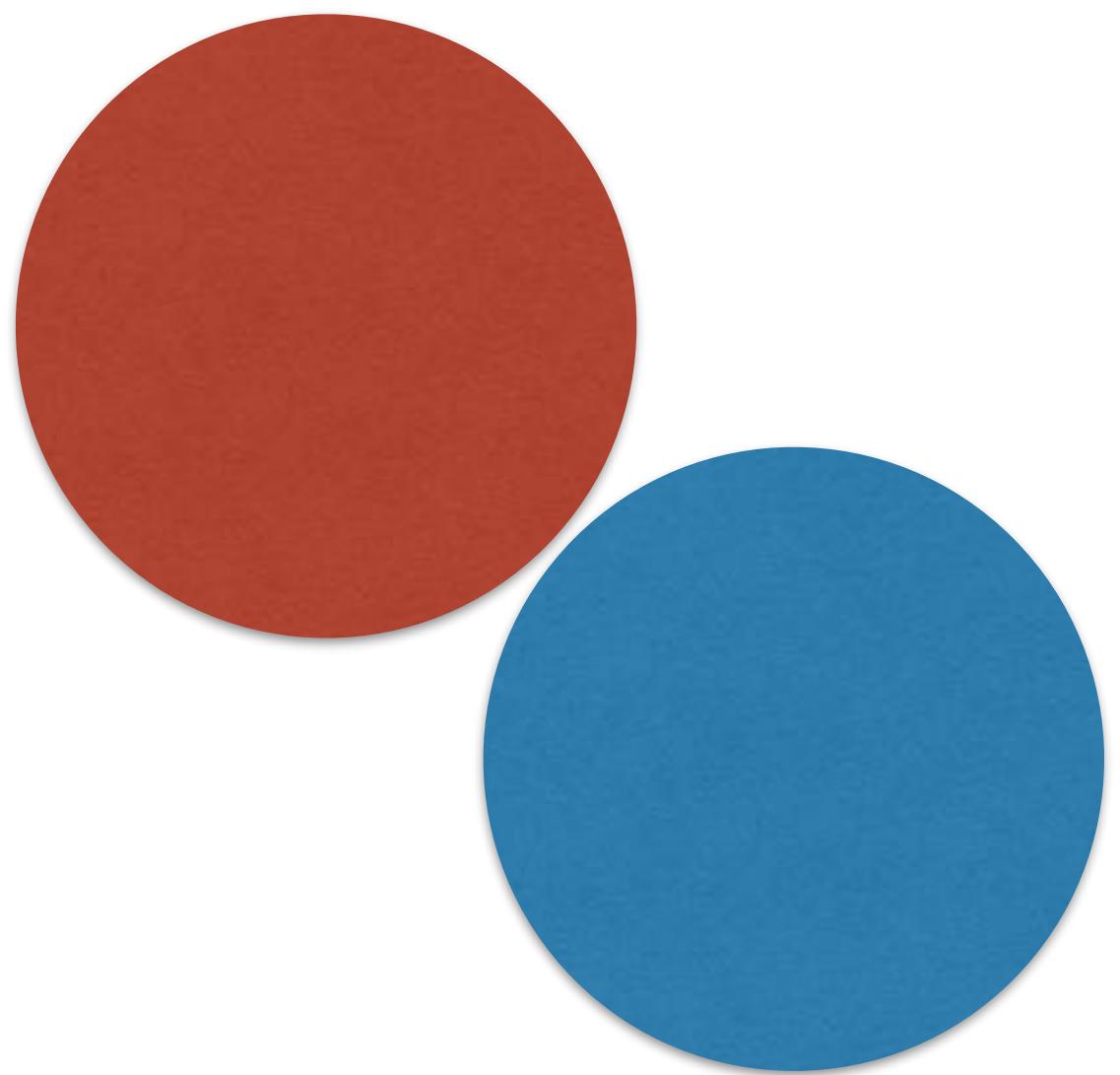


**Inversus (I)**

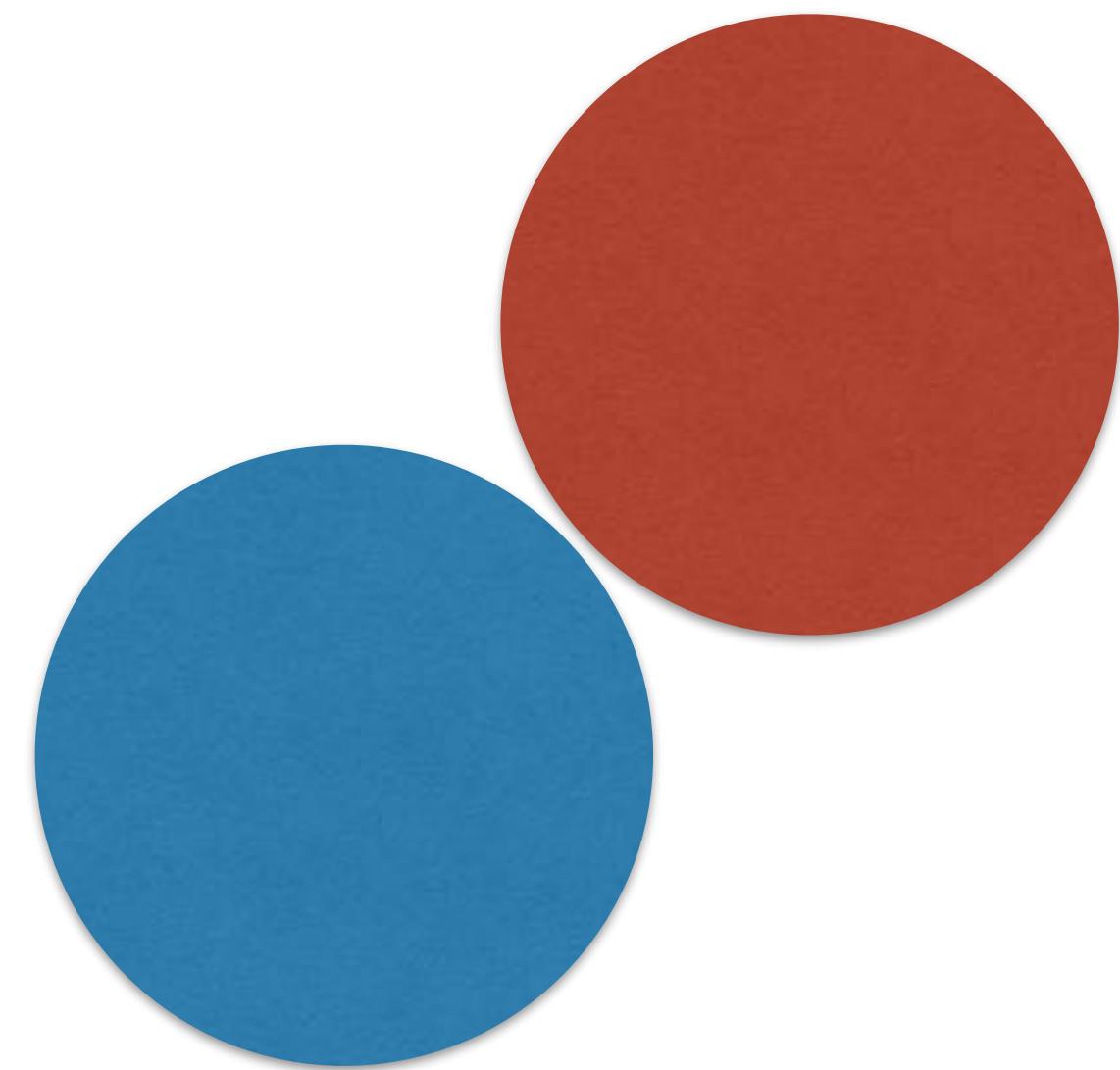
# Great Arteries



# **Malposed Great Arteries**

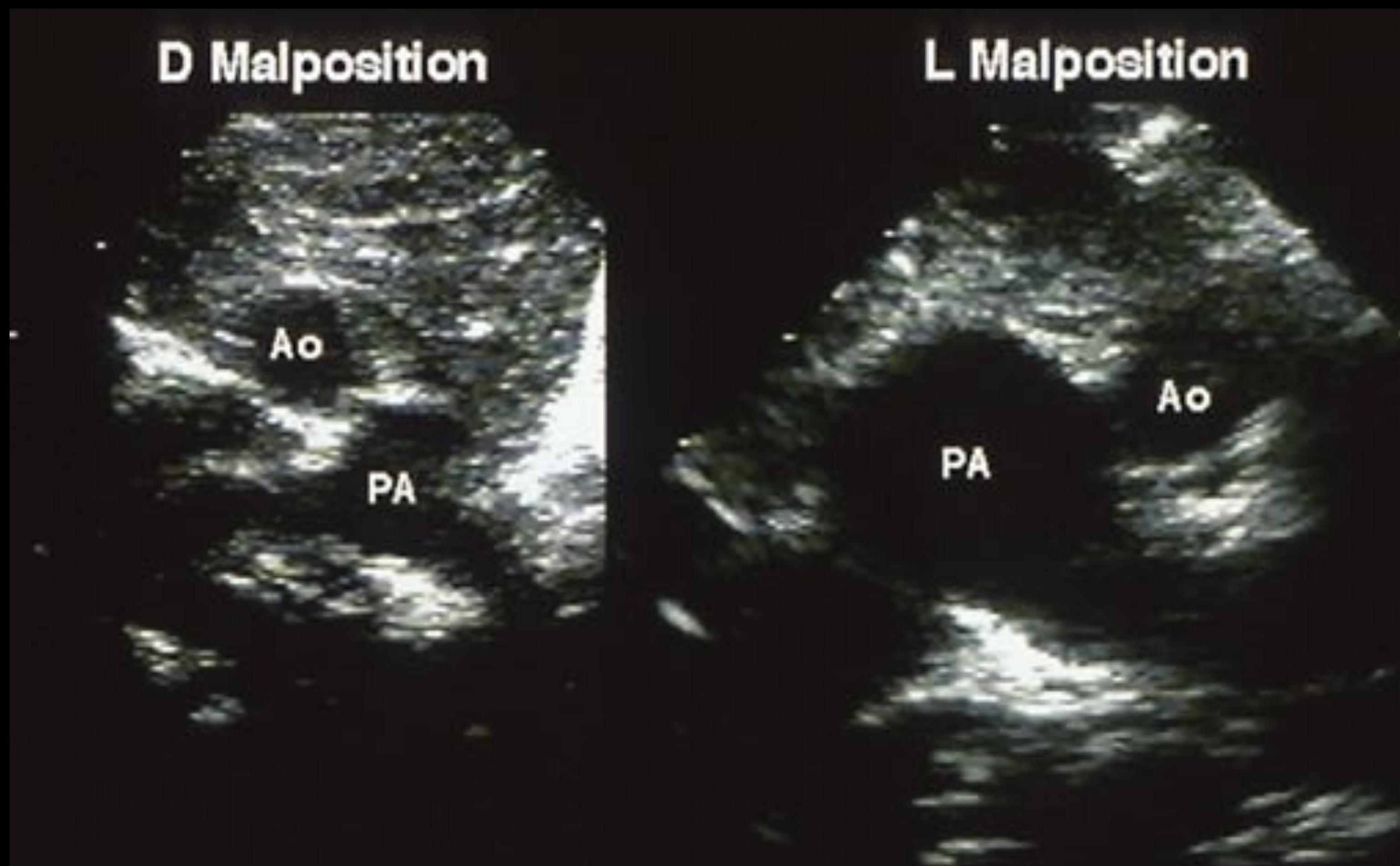


**D- Malposition**

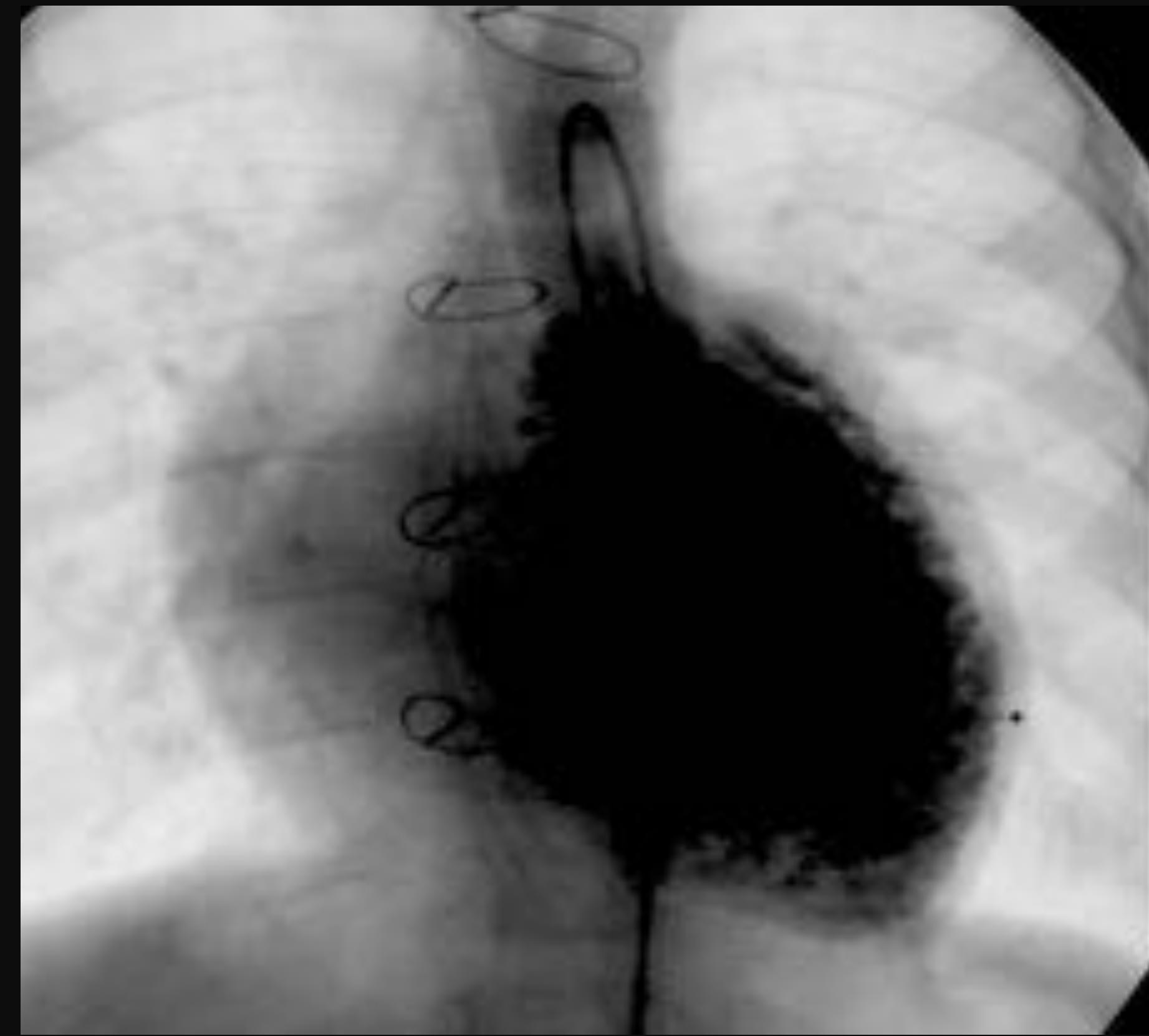


**L- Malposition**

# Great Arteries



# Corrected TGA {S,L,L}



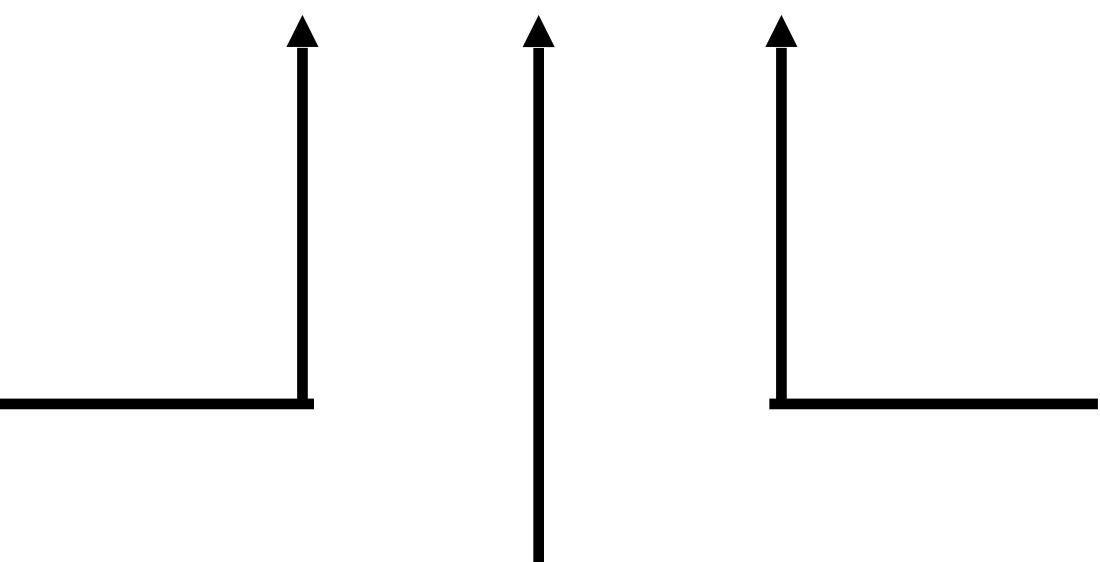
# Great Arteries

- Usage
  - S, I - normally related great arteries
  - D, L, A - malposed great arteries

# **Segmental situs**

{ X, X, X }

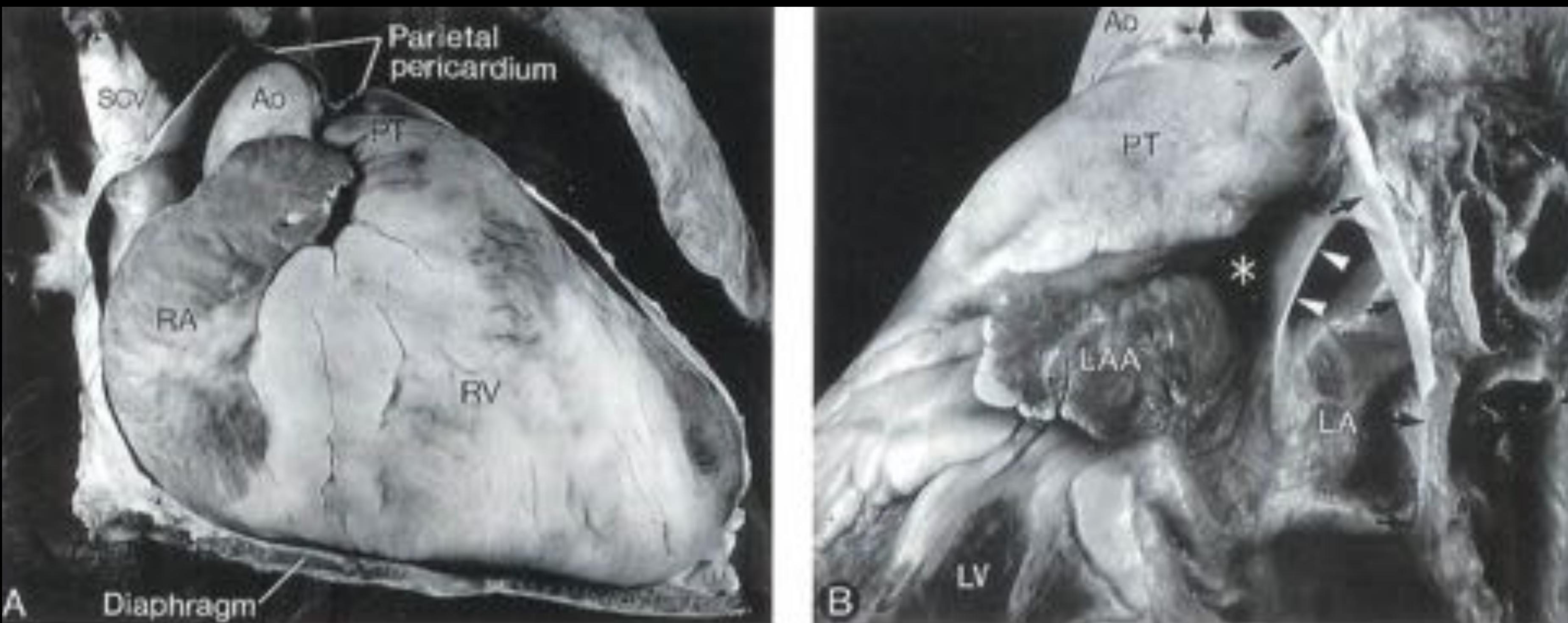
Atrial Situs  
(S,I,A)



Ventricular  
Loop  
(D,L)

Great Arteries  
(S,I  
D,L,A)

# Pericardium

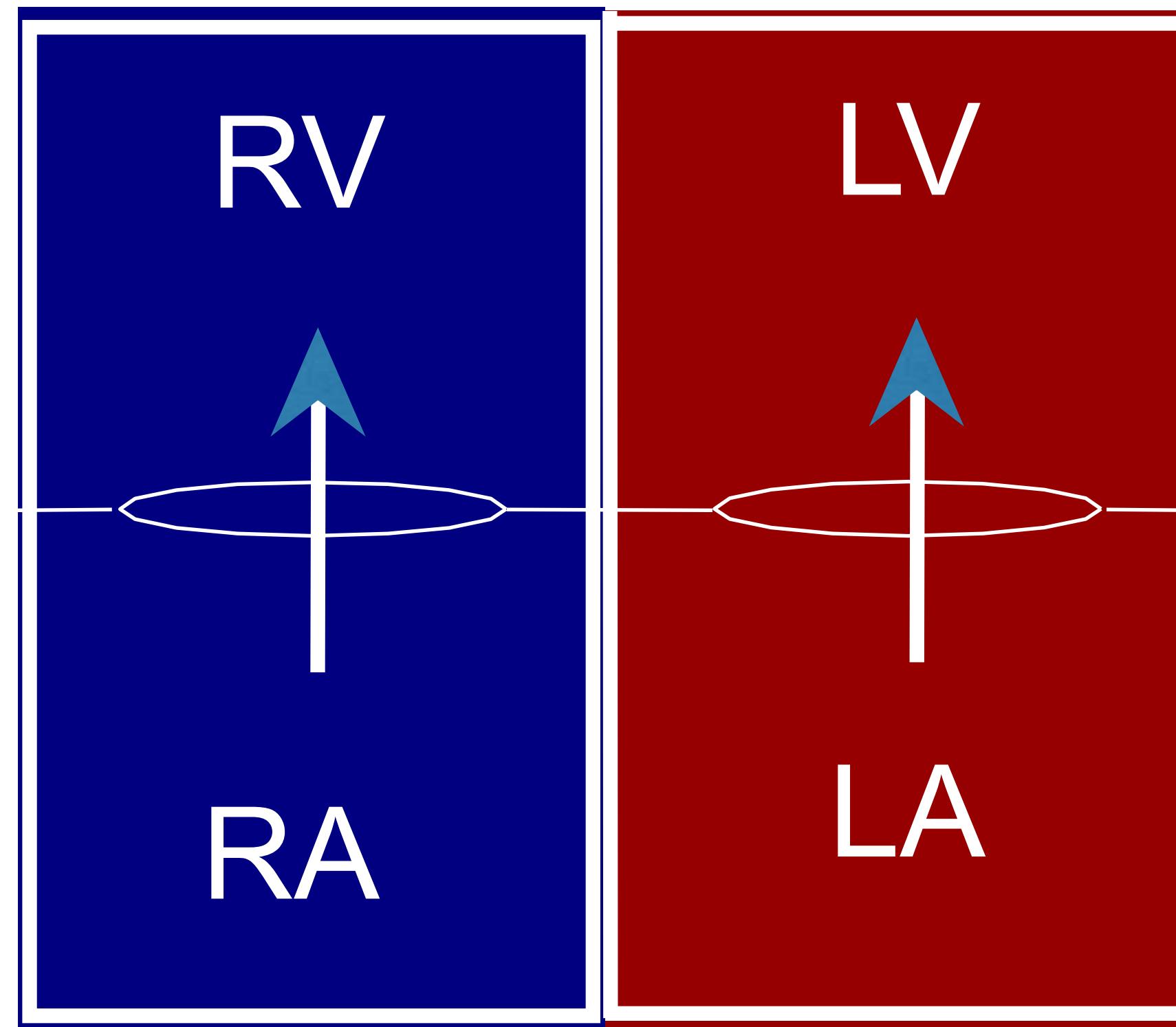


## Common Segmental Sets

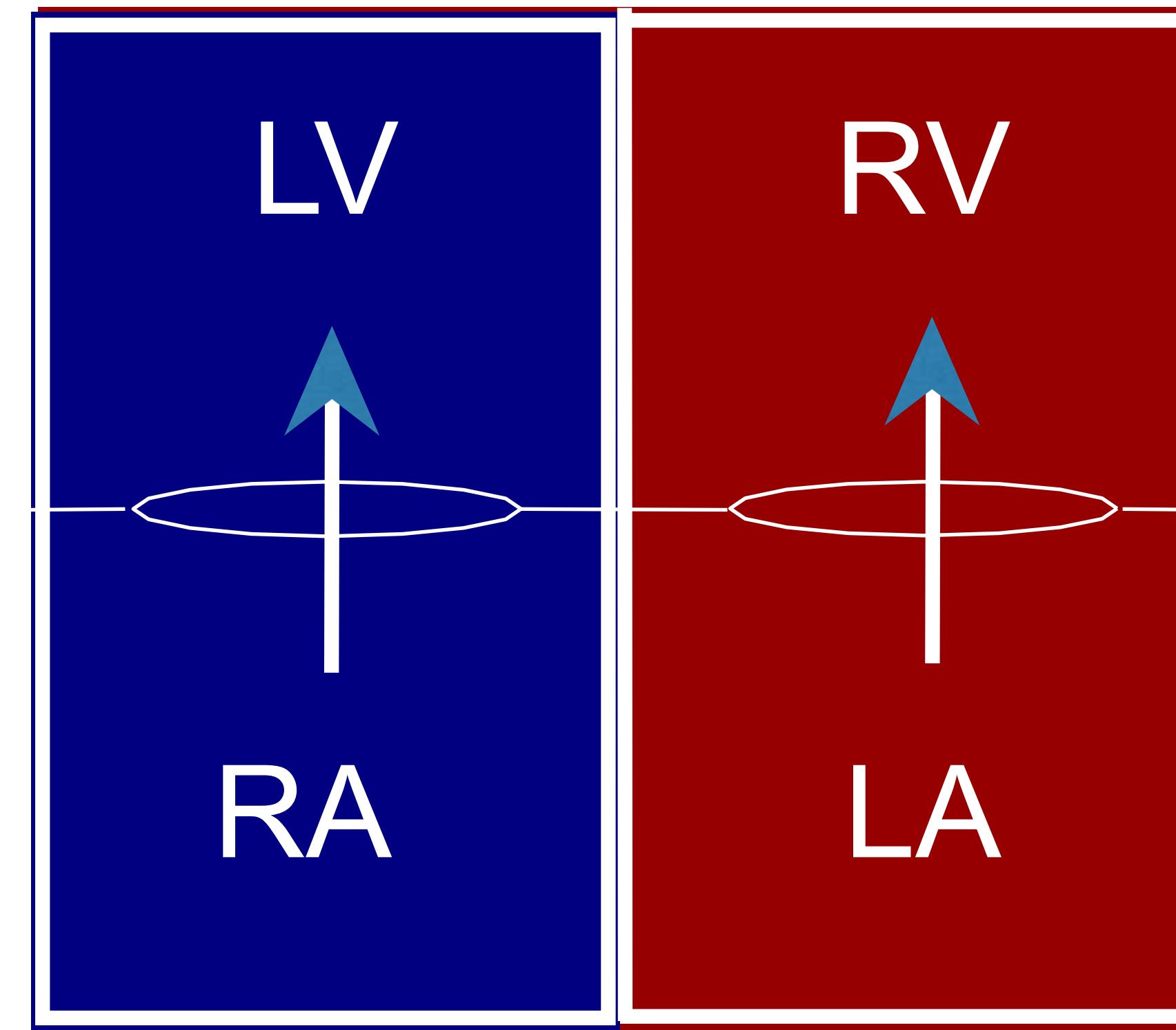
- Normally related great arteries {S,D,S}
- Situs Inversus Totalis {I,L,I}
- Transposition of the great arteries {S,D,D}
- Corrected Transposition-Transposition-Double discordance {S,L,L}
- Heterotaxy syndrome with asplenia {A,D,D}

# A-V Alignments

## Concordant



## Discordant



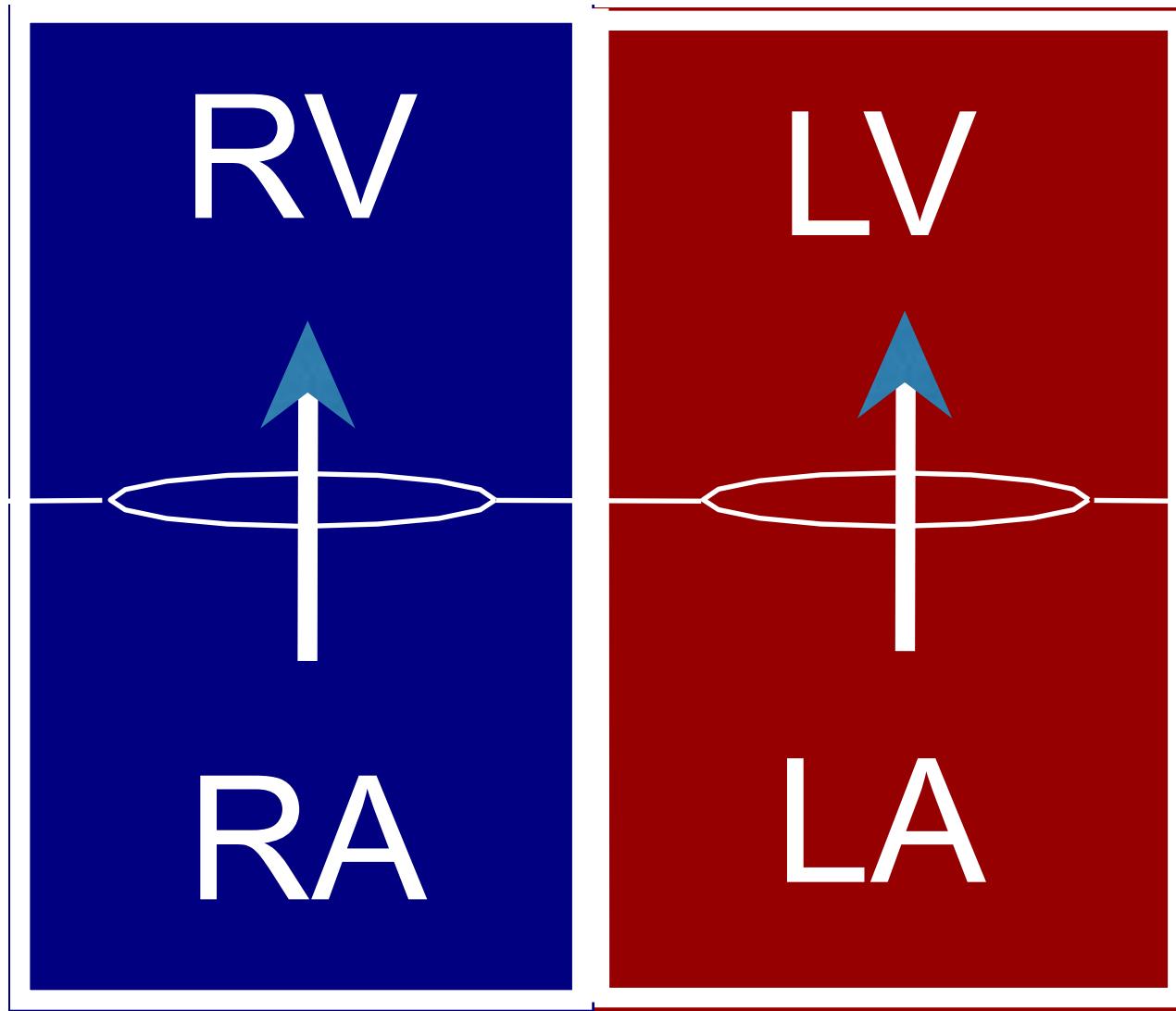
# A-V Alignments

- Two separate AV valves
  - separate ventricles
  - straddling
  - double inlet
- Common AV valve
  - two ventricles
  - common inlet
- AV valve atresia
  - one ventricle
  - straddling

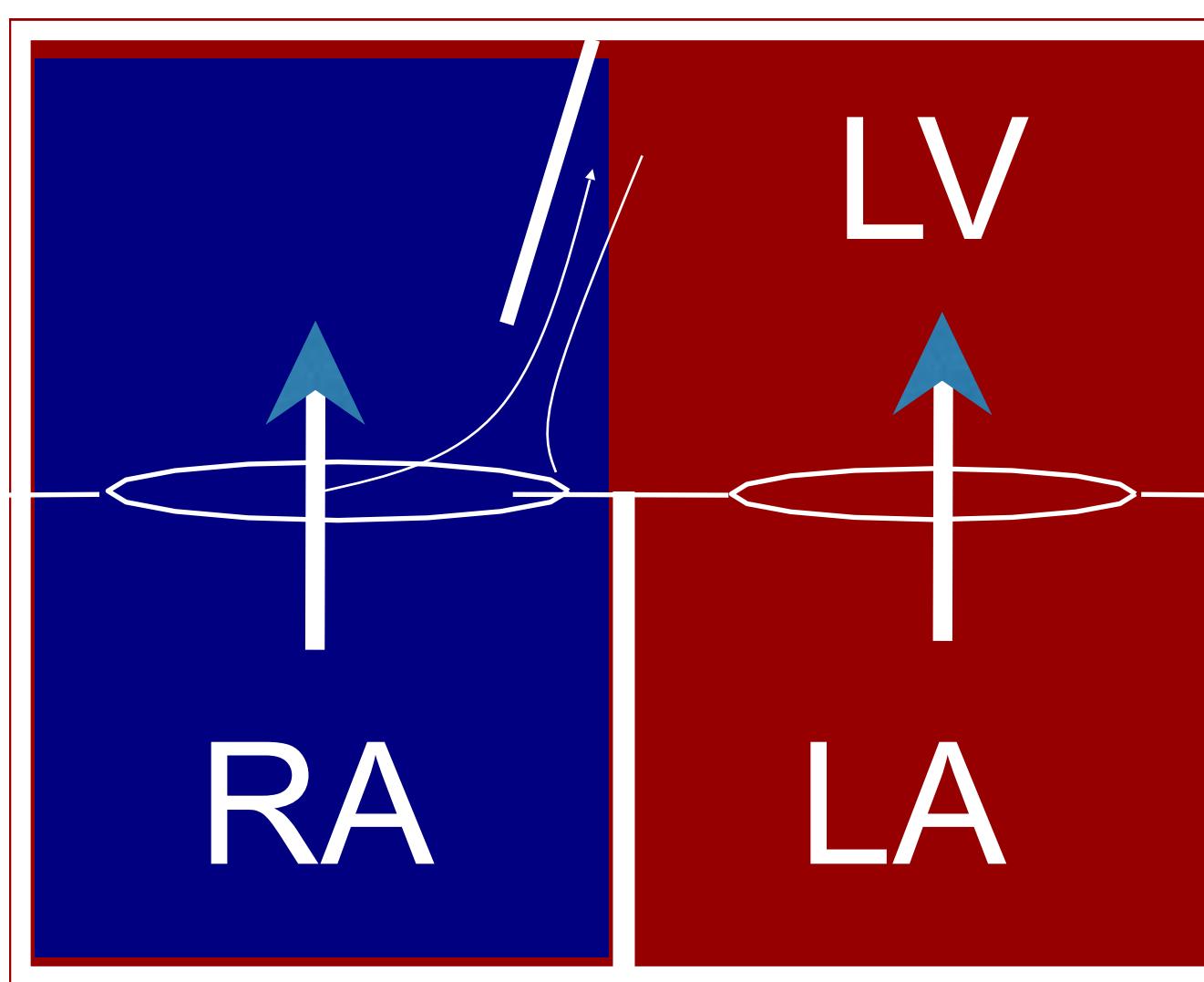
# A-V Alignments

## 2 Valves

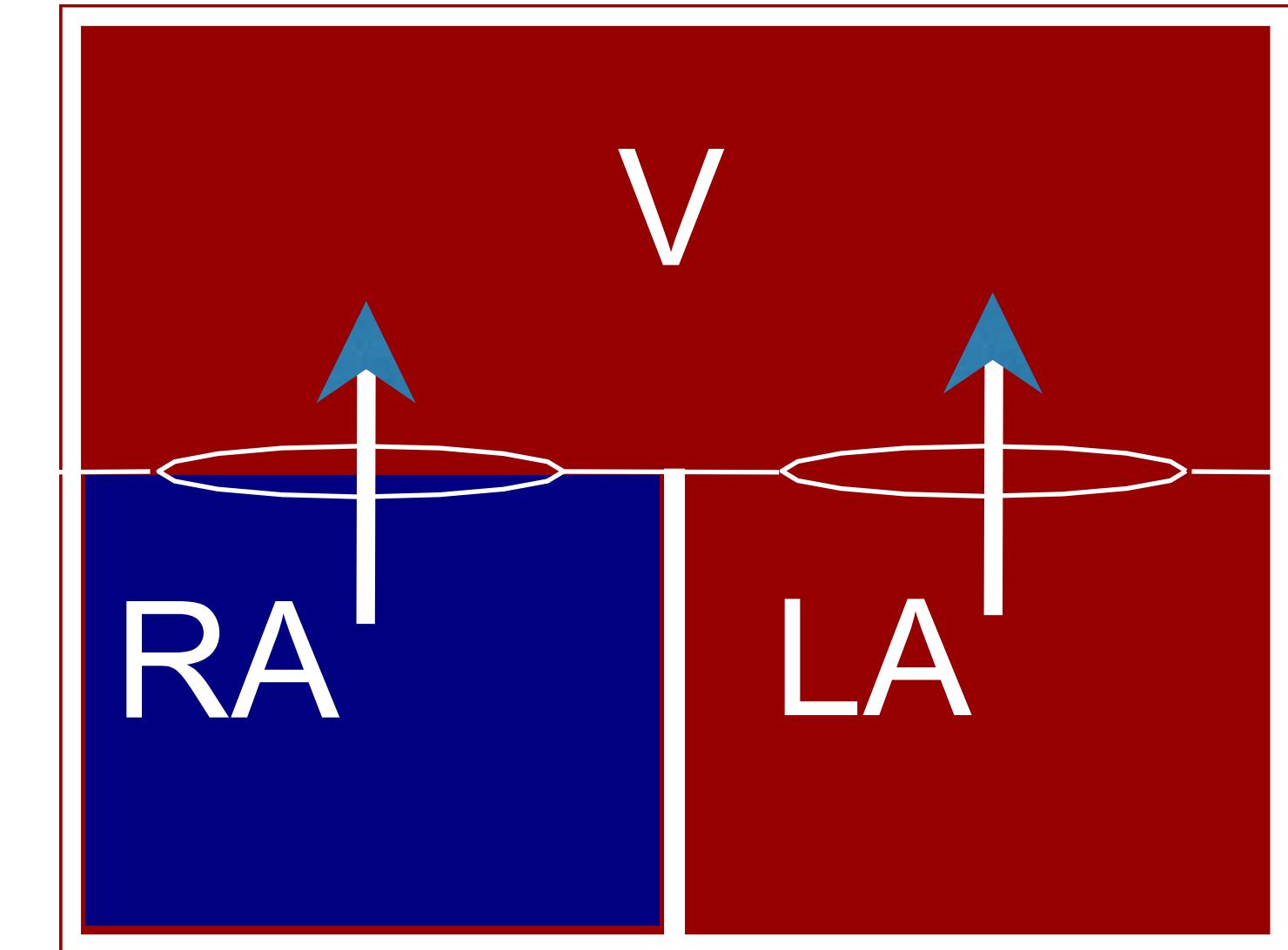
Separate



Straddling



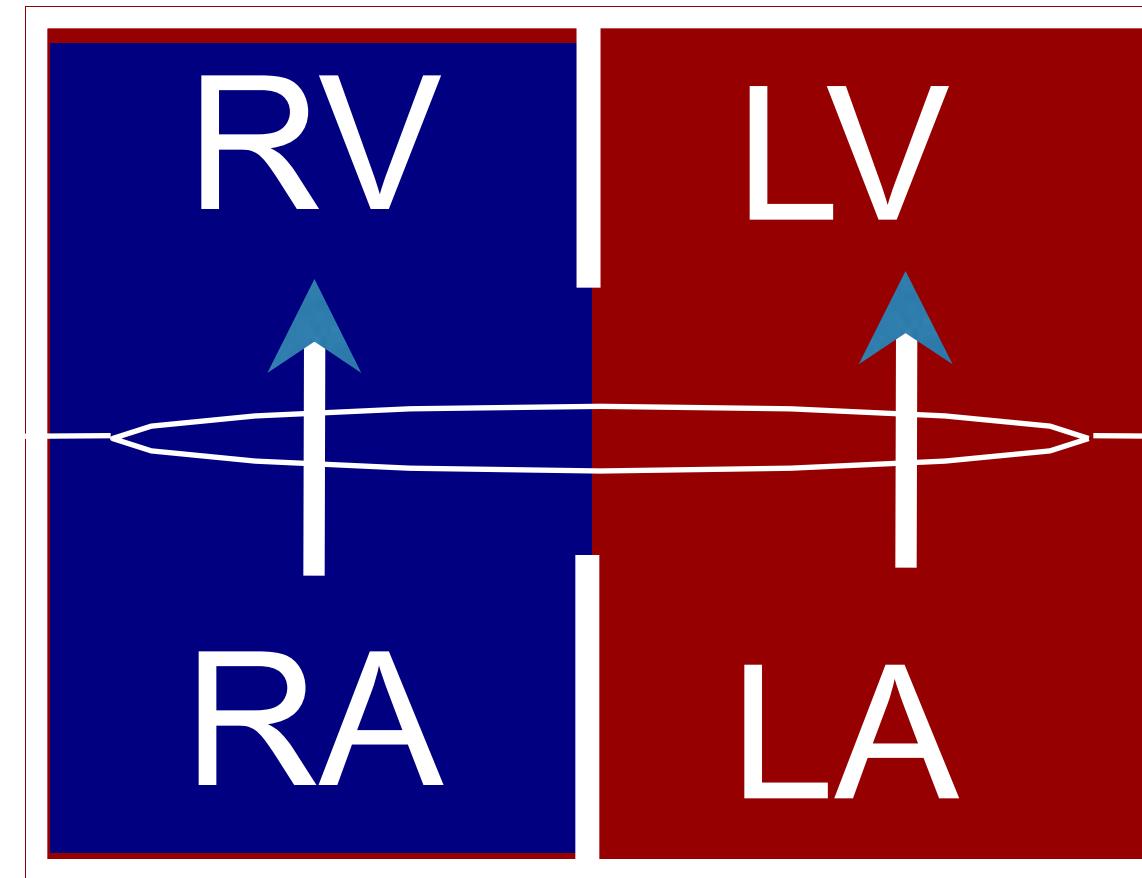
Double inlet



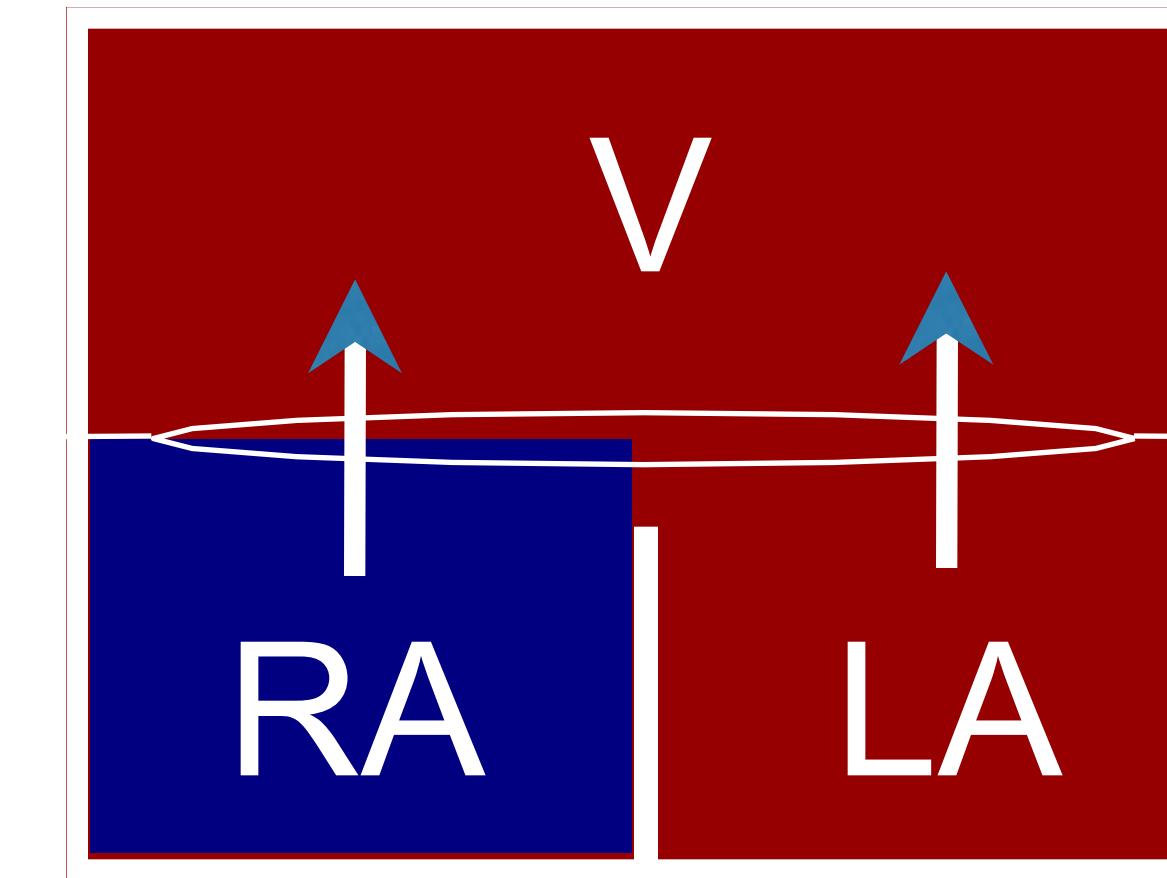
# A-V Alignments

## Common Valve

2 ventricles



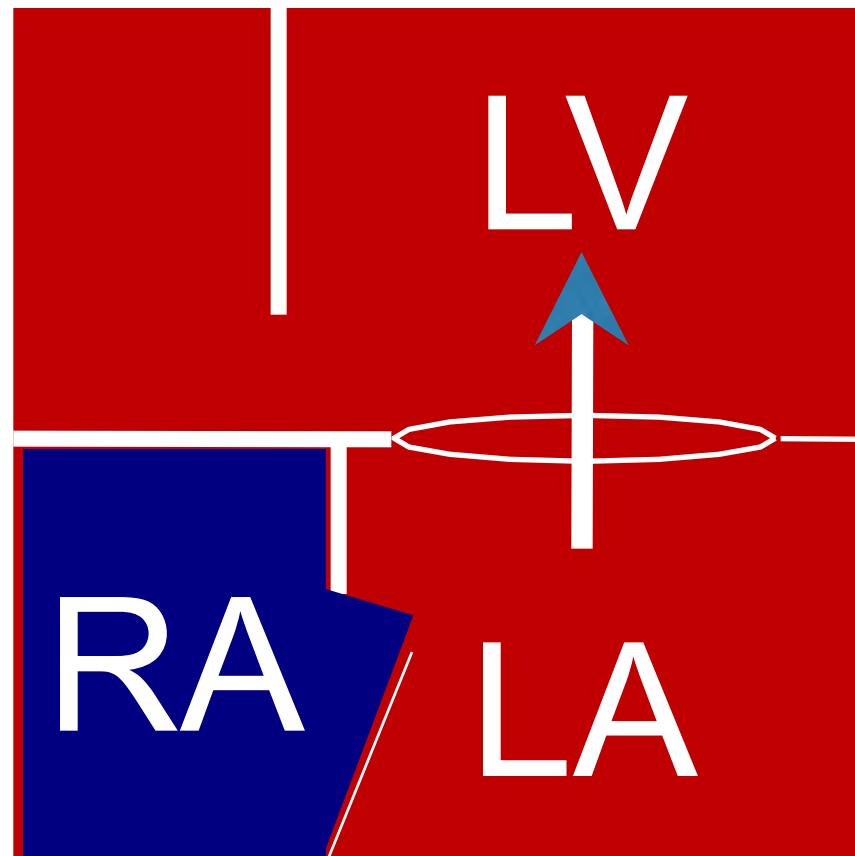
Common inlet



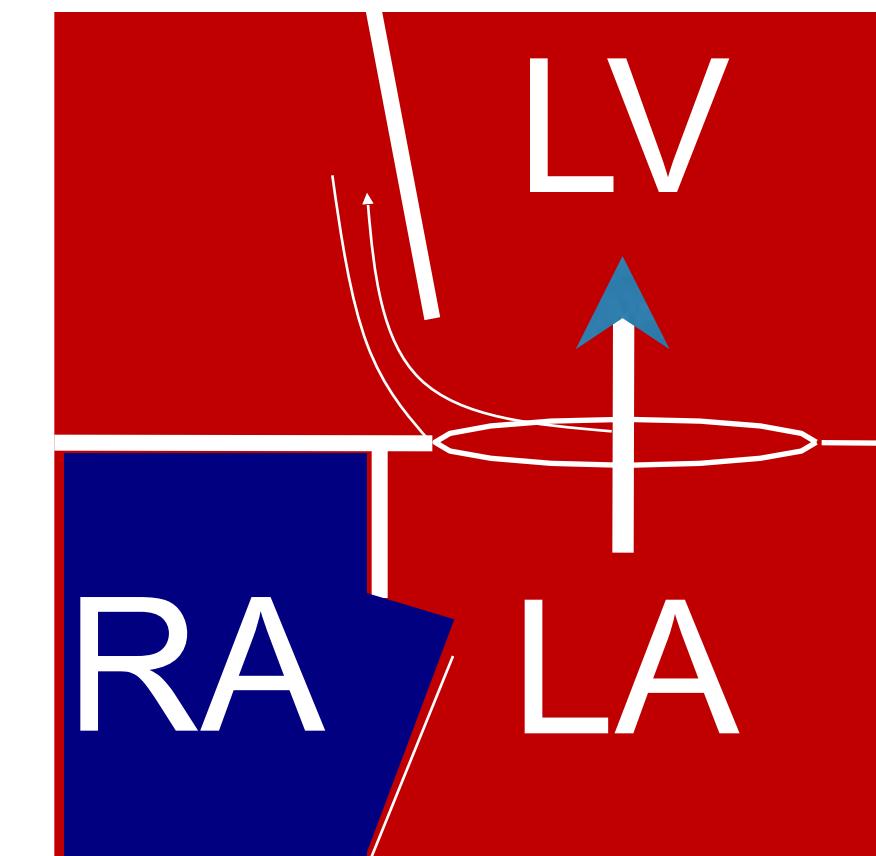
# A-V Alignments

## AV Valve Atresia

1 Ventricle



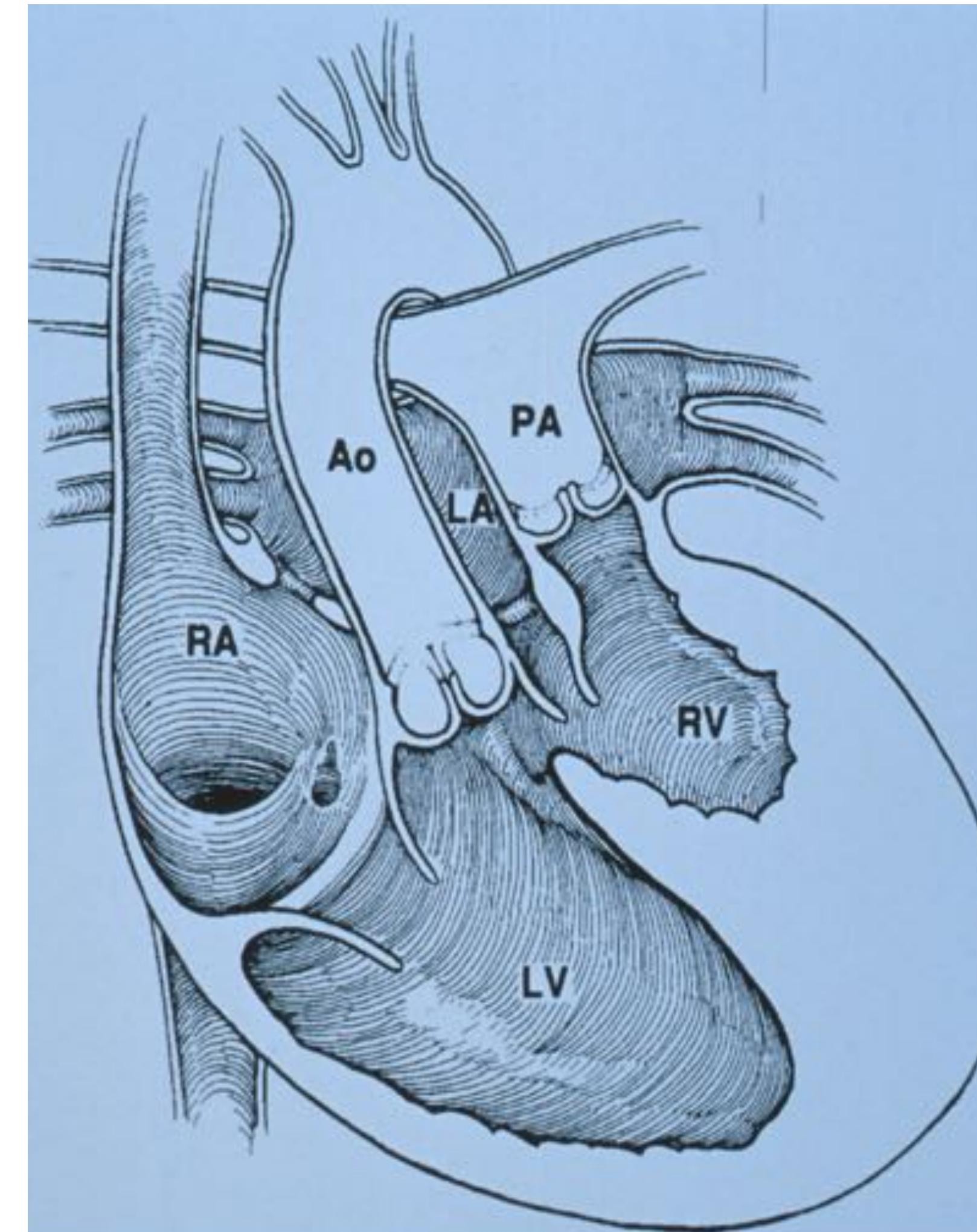
Straddling



# **AV Connections**

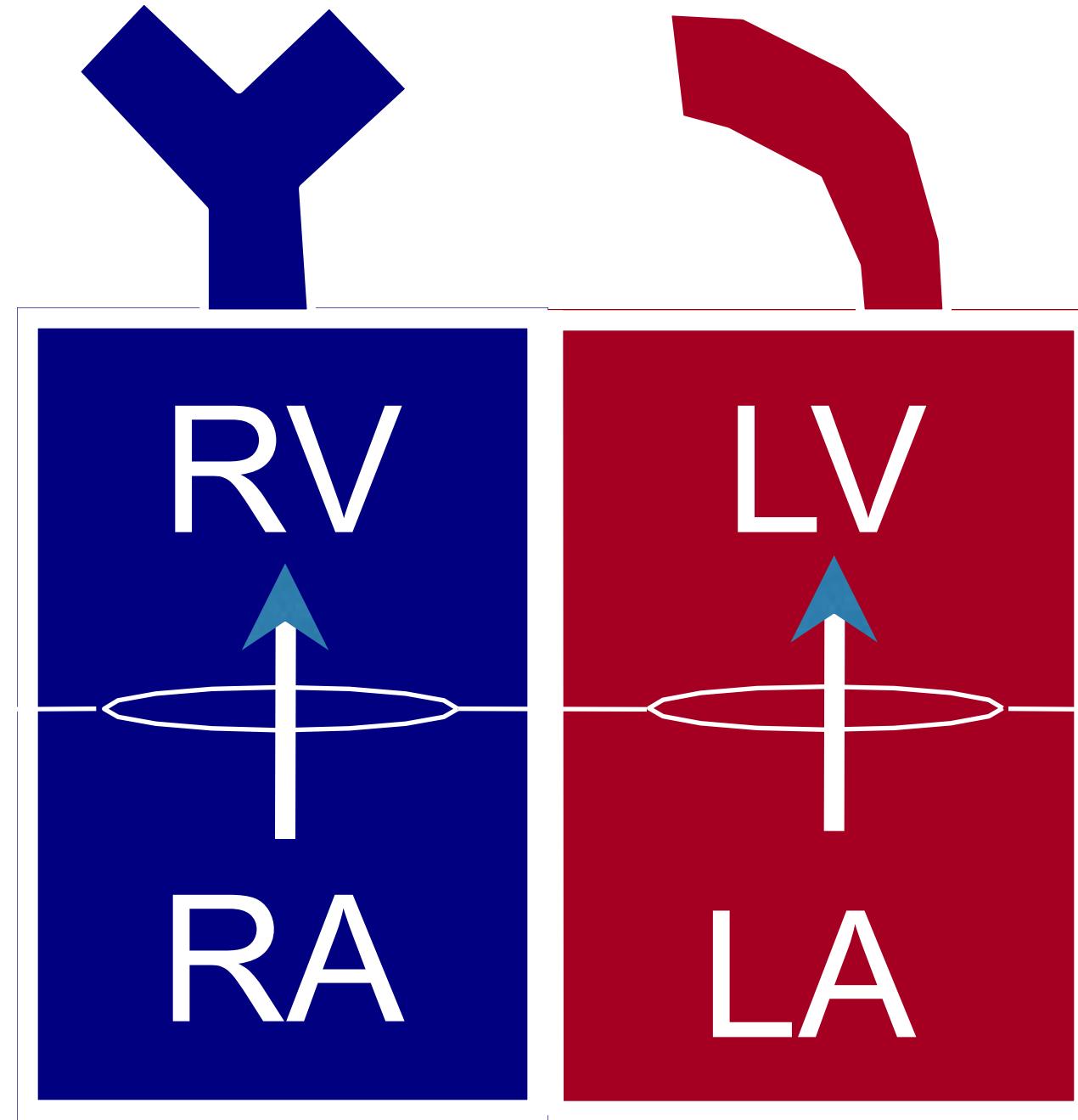
- Same as alignments
- Uniquely determined by AV canal

# A-V Situs–Alignment Discordance

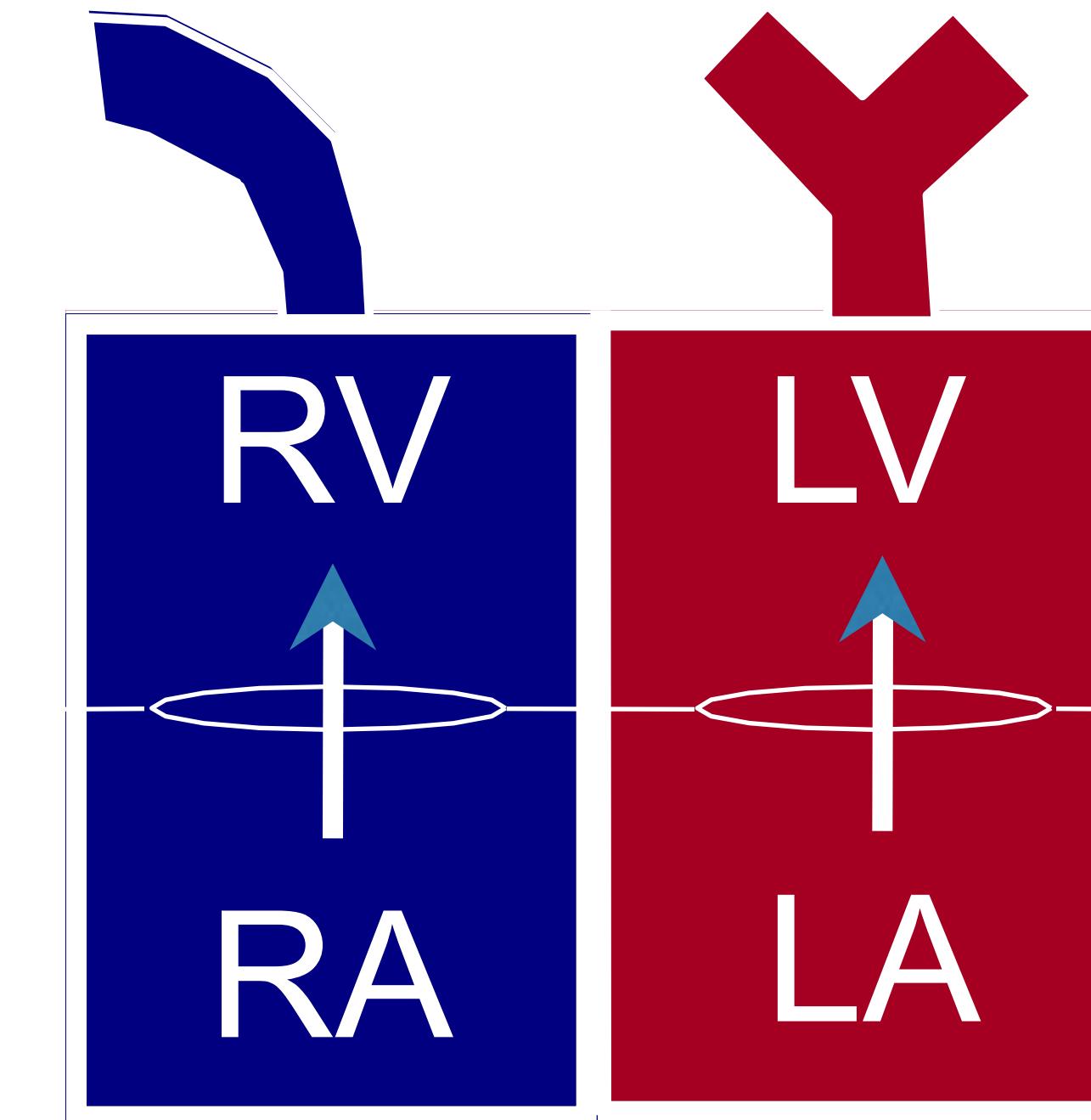


Geva et al Am Heart J 1993;125:459-64

# V-A Alignments



Concordant



Discordant

# The EPICARD study

EPIdémiologie des enfants ou fœtus ayant une CARDiopathie congénitale

## Anatomic and Clinical Classification of Congenital Heart Diseases ACC-CHD

ACC-CHD categories	Examples
Heterotaxy	<b>Heterotaxy syndromes</b>
Anomalies of venous connections	<b>Total anomalous pulmonary venous return</b>
Anomalies of atria	<b>Atrial septal defect</b>
Anomalies of AV junction and AV valves	<b>Atrioventricular septal defect</b>
Complex anomalies of AV junction	<b>Double discordance</b>
Functionally univentricular heart	<b>Hypoplastic left heart syndrome</b>
Ventricular septal defects	<b>Perimembranous VSD</b>
Anomalies of ventriculo-arterial connections	<b>Transposition of the great arteries, DORV</b>
Anomalies of extra pericardial trunks	<b>Coarctation of the aorta</b>
Congenital anomalies of coronary arteries	<b>ALCAPA</b>

