



Heterotaxy

Damien Bonnet

Unité médico-chirurgicale de Cardiologie Congénitale et Pédiatrique
Hôpital Universitaire Necker Enfants malades – APHP, Université Paris Descartes, Sorbonne Paris Cité
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





ACCUEIL

QUI SOMMES-NOUS ?

ACTUALITÉS M3C-
NECKER +

PROCÉDURES
INNOVANTES 2019

BANQUE D'ADN CARREG

ESSAIS & REGISTRES

ÉVÉNEMENTS

PLUS +



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M3C

Centre de Référence

Malformations Cardiaques Congénitales Complexes

cept of laterality



Papuina pulcherrima, with a dextral shell



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





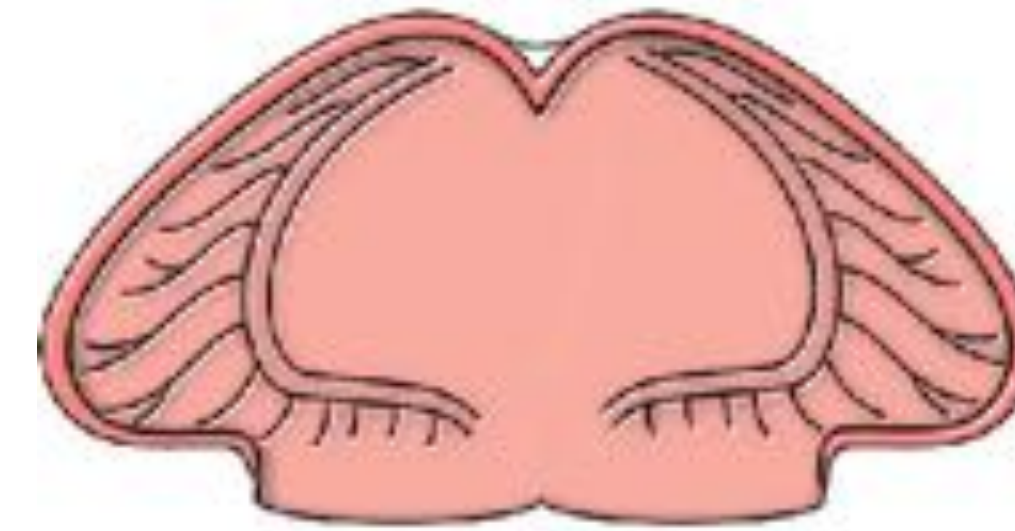
Hetero

Taxon
taxonomy

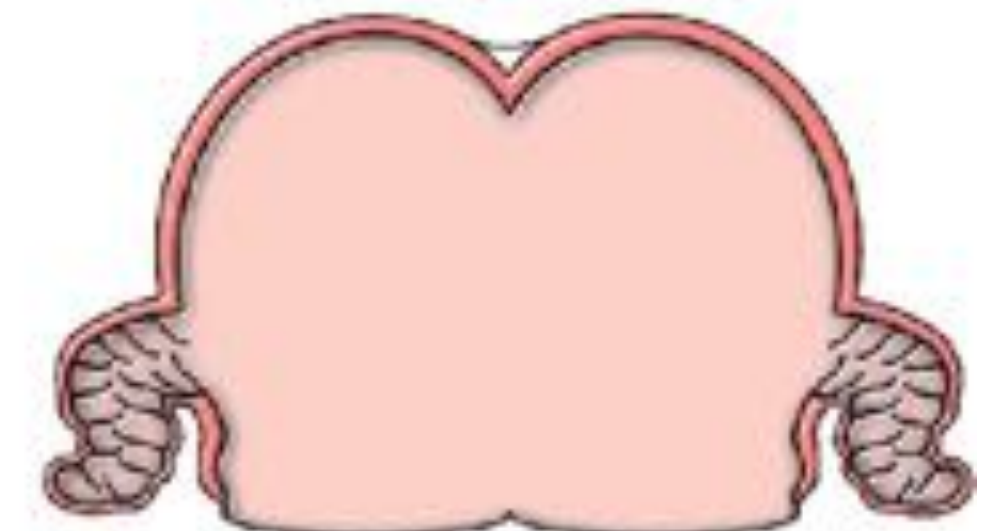
heterogeneity of arrangements

In heterotaxy syndrome, the pattern of arrangement of the viscera is other than situs solitus or its mirror image -situs inversus.

Heterotaxy is a laterality defect



Right isomerism

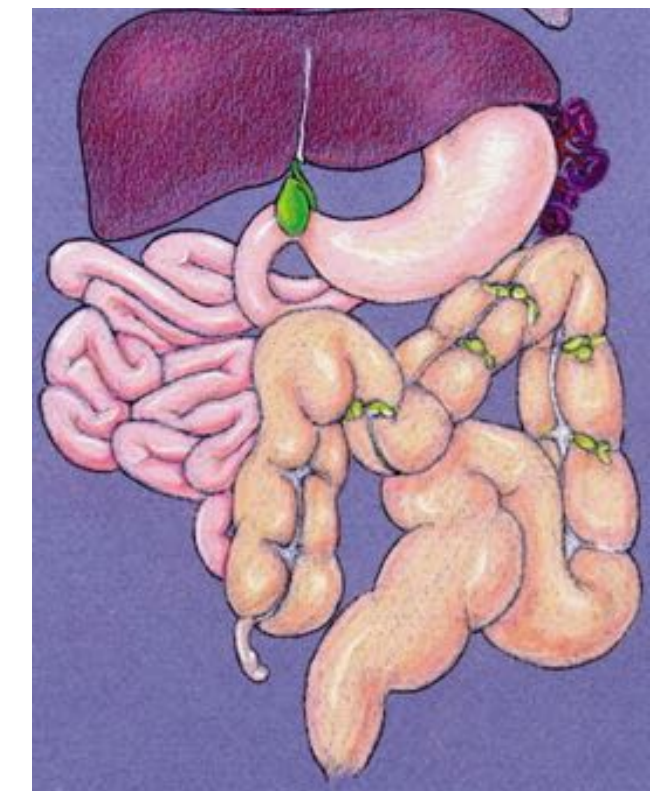
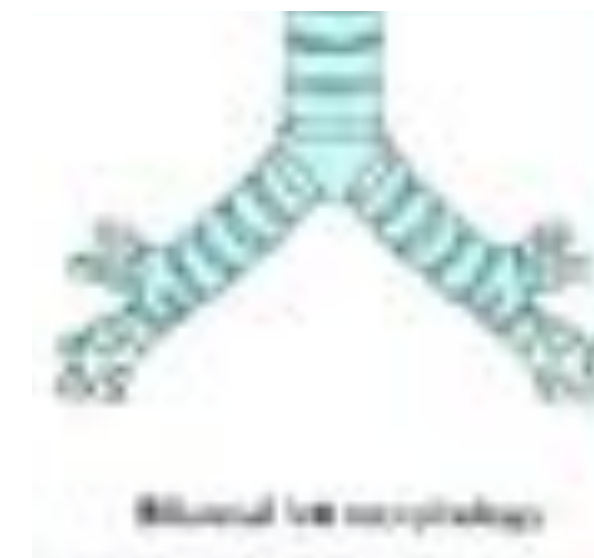
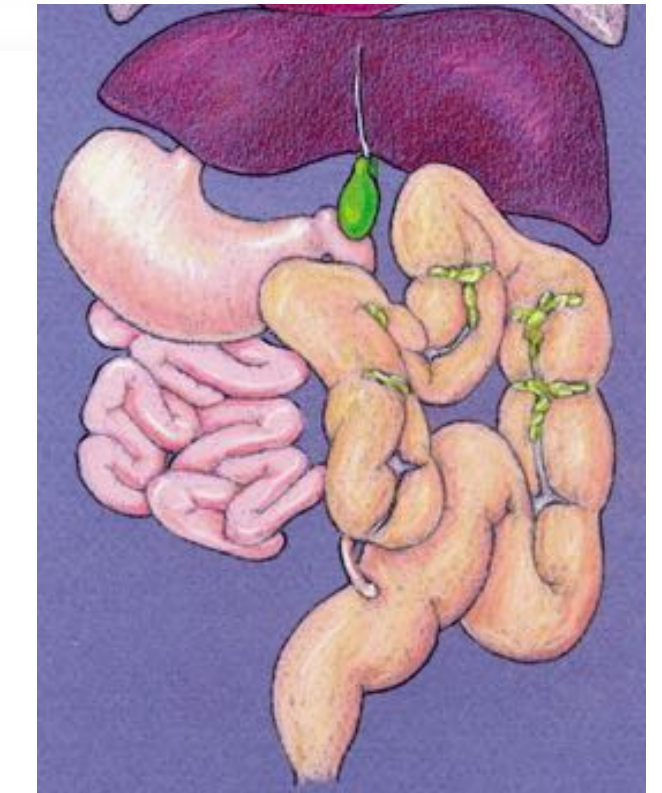
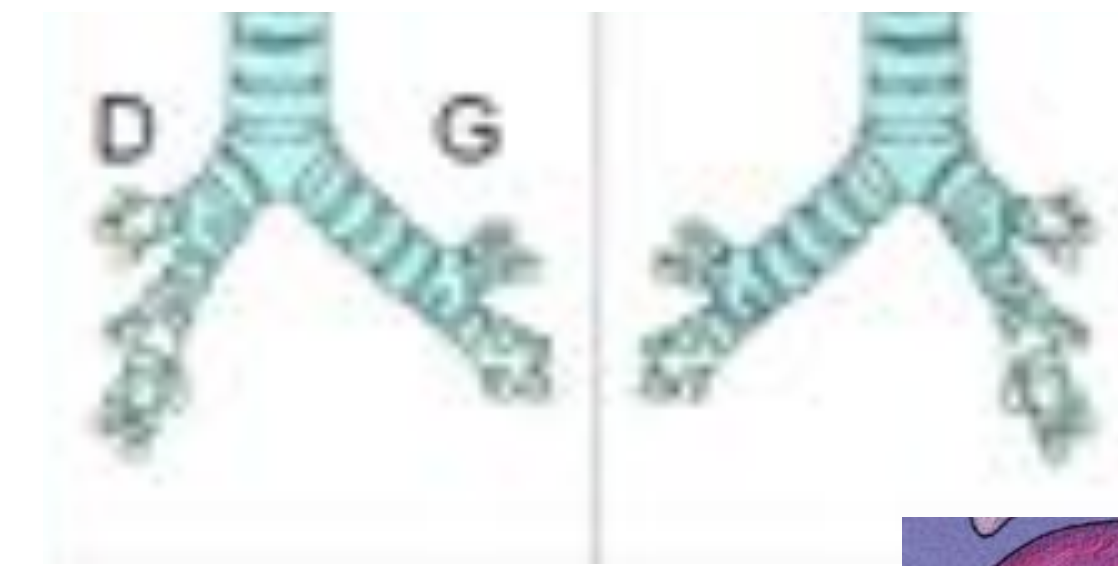


Left isomerism

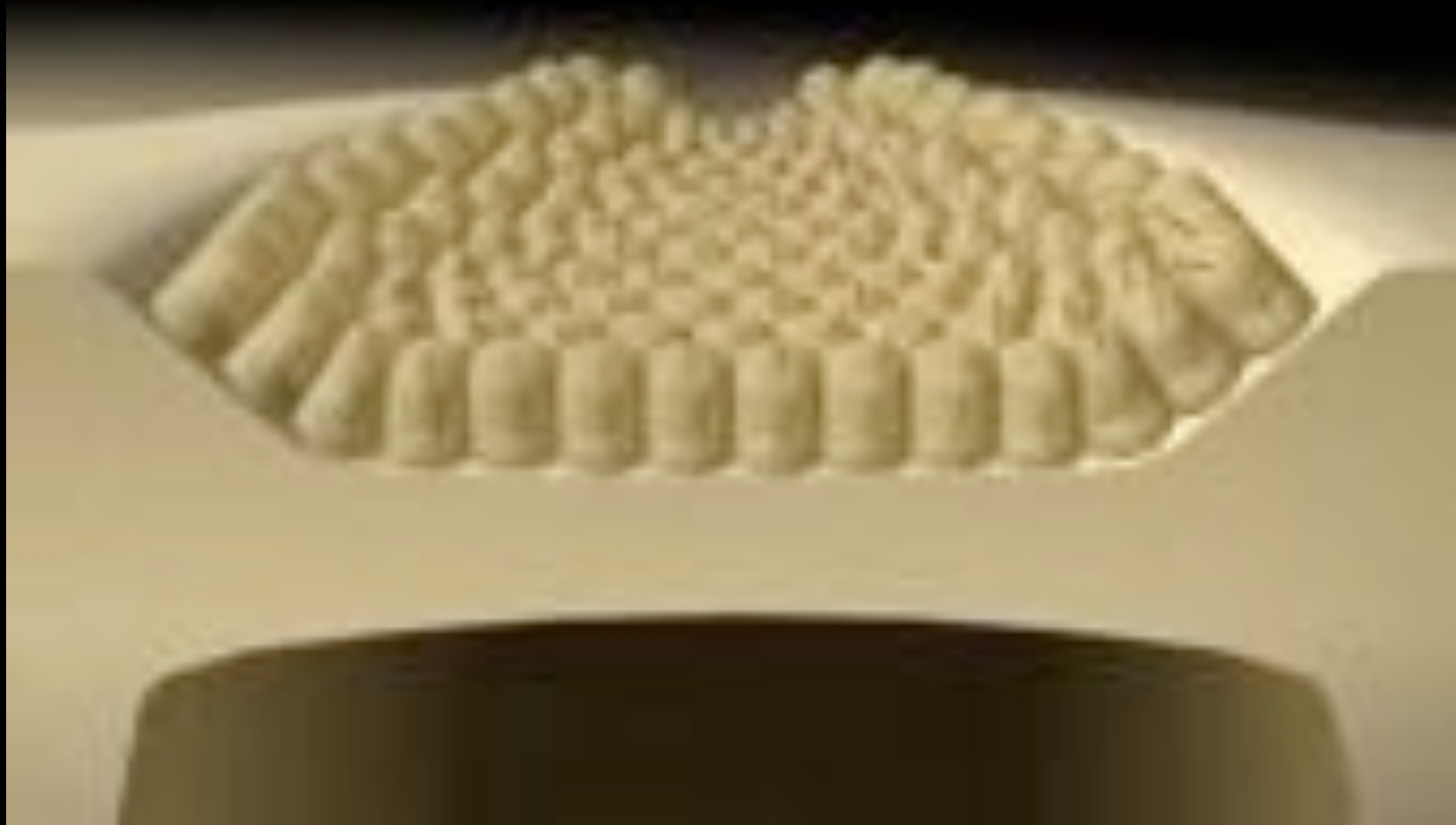
- ISNPCHD : “A congenital malformation in which the internal thoraco-abdominal organs demonstrate abnormal arrangement across the left-right axis of the body....Heterotaxy does not include normal and mirror-imaged arrangements of the internal organs (situs solitus or inversus)”.
- Usually stratified in right isomerism and left isomerism, on the basis of the extent of the pectinate muscles
- Tremblay C et al, 2017 : 188 human heart specimens, atrial appendages isomeric in all (131 right, 57 left)

The isomerism concept

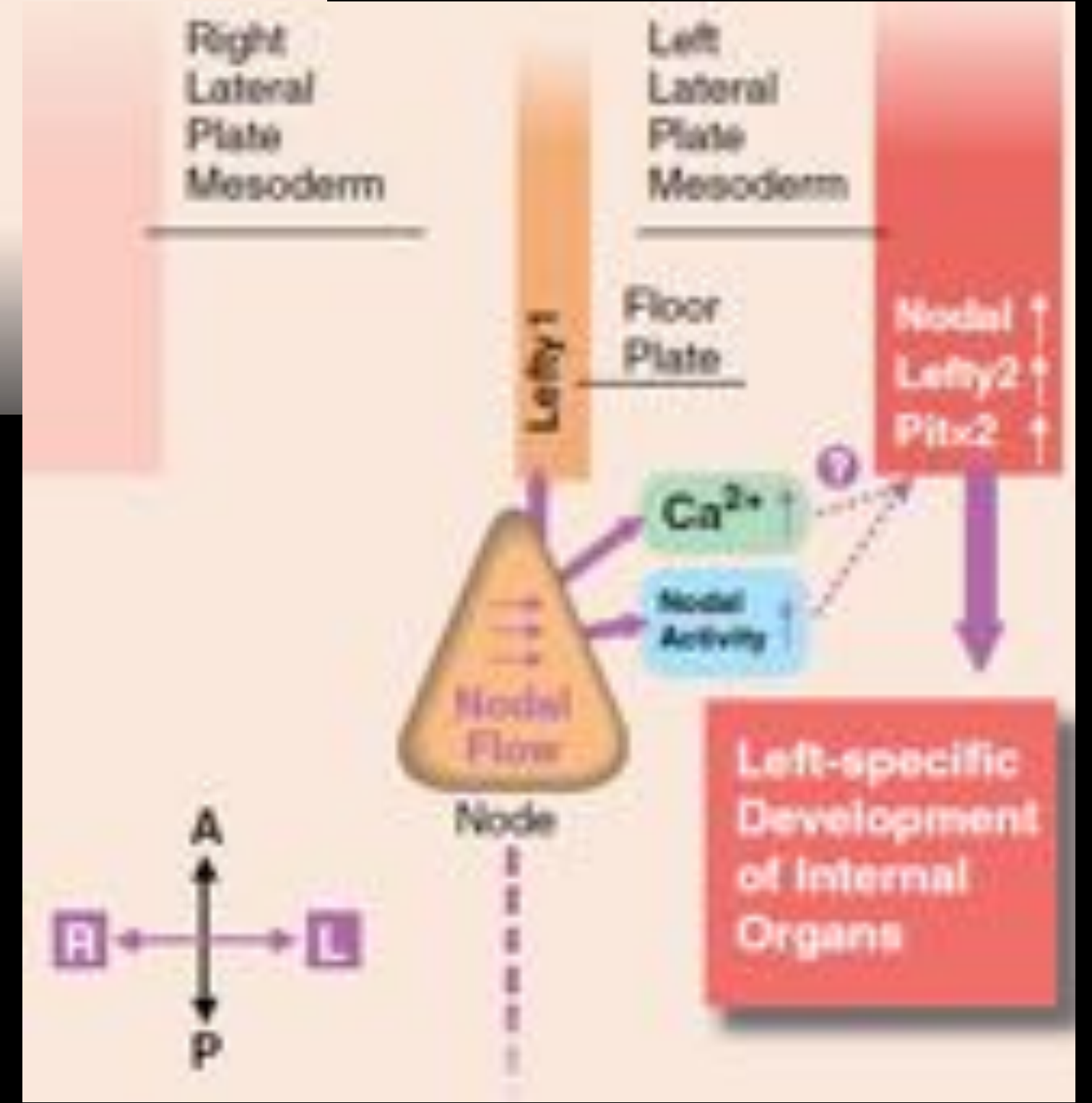
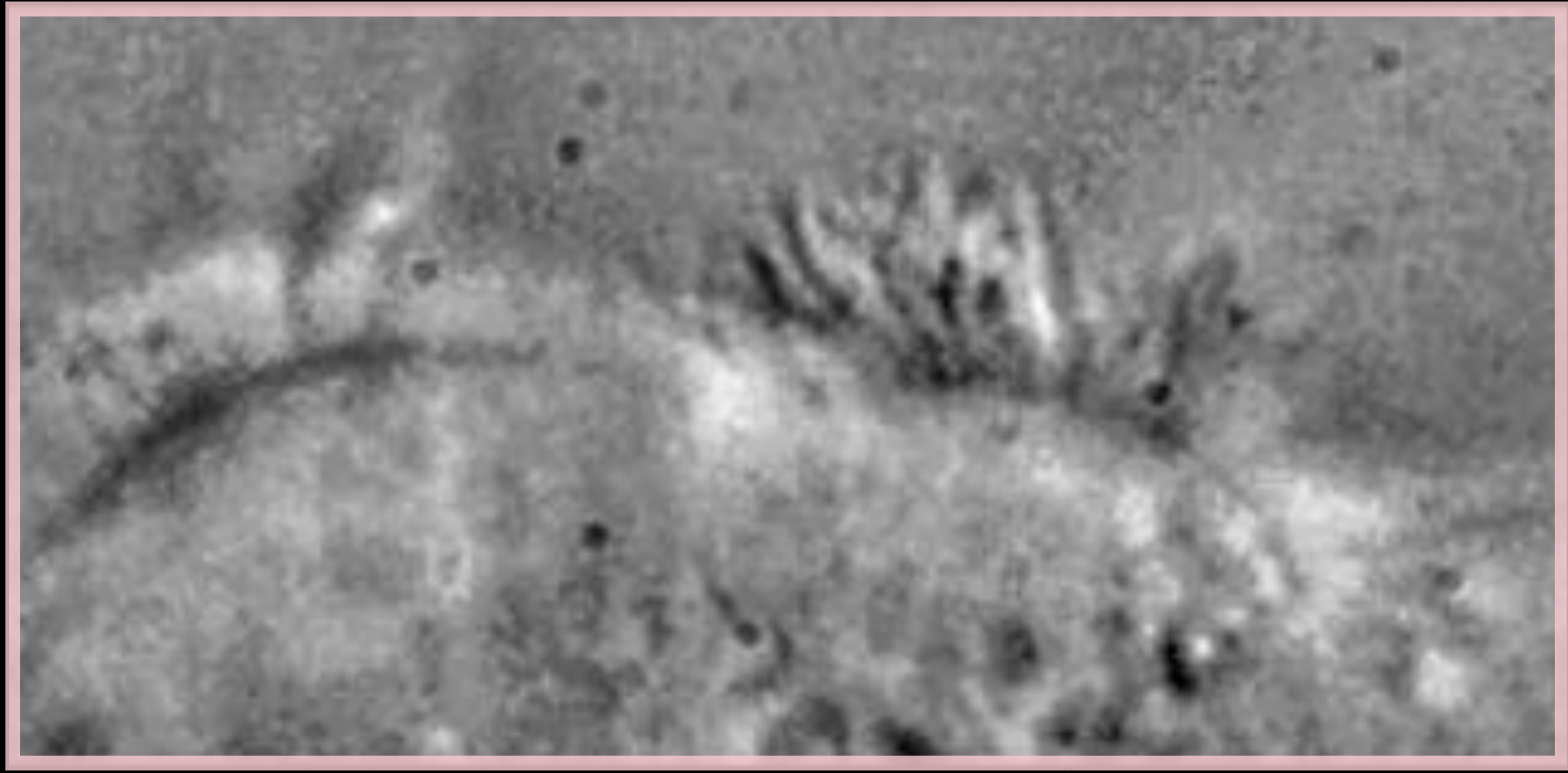
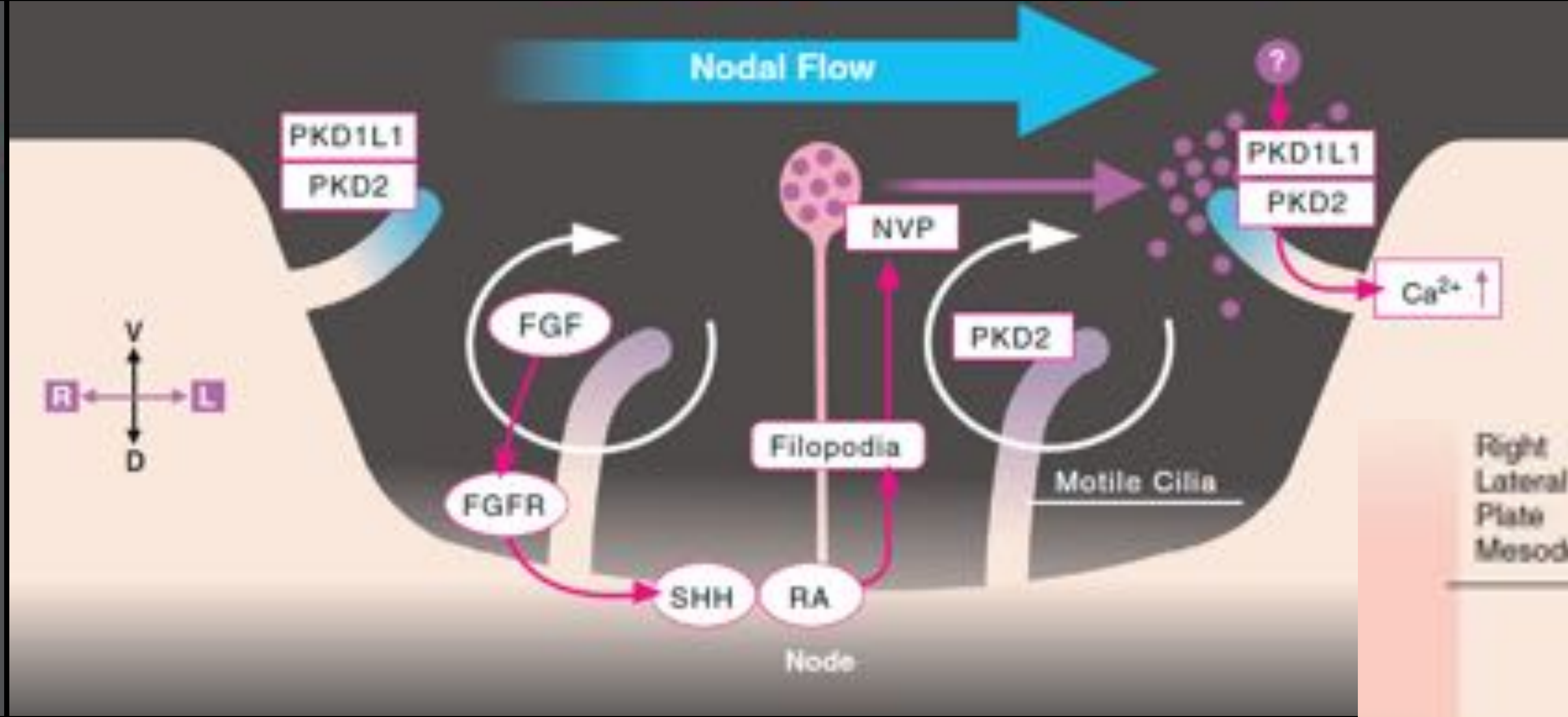
- Right isomerism
 - ▶ bilaterally right-sided atrial appendages
 - ▶ bilaterally right-sided bronchi and lungs
 - ▶ asplenia
- Left isomerism
 - ▶ bilaterally left-sided atrial appendages
 - ▶ bilaterally left-sided bronchi and lungs
 - ▶ polysplenia
- **BUT** : considerable overlap between these two groups

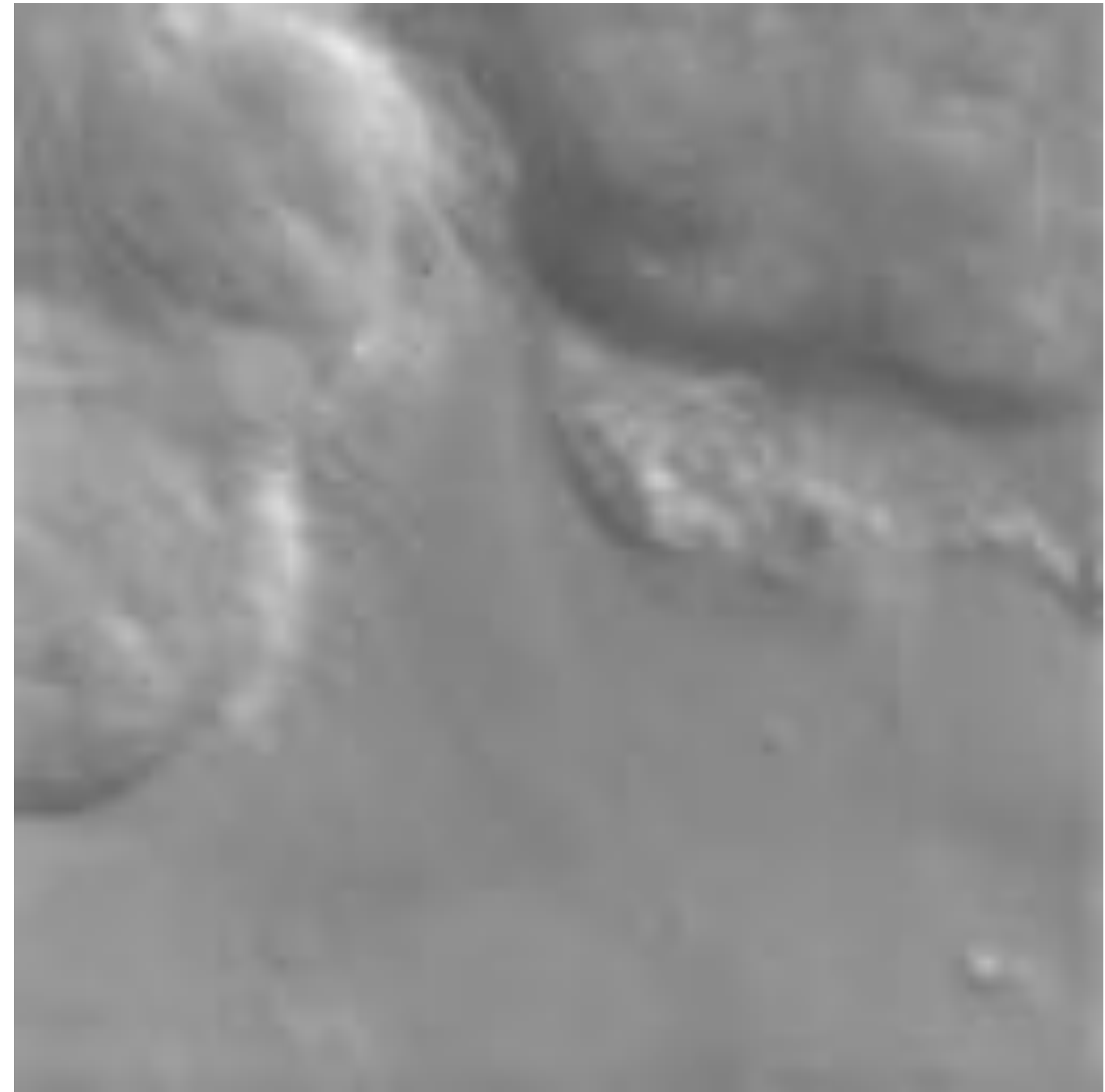
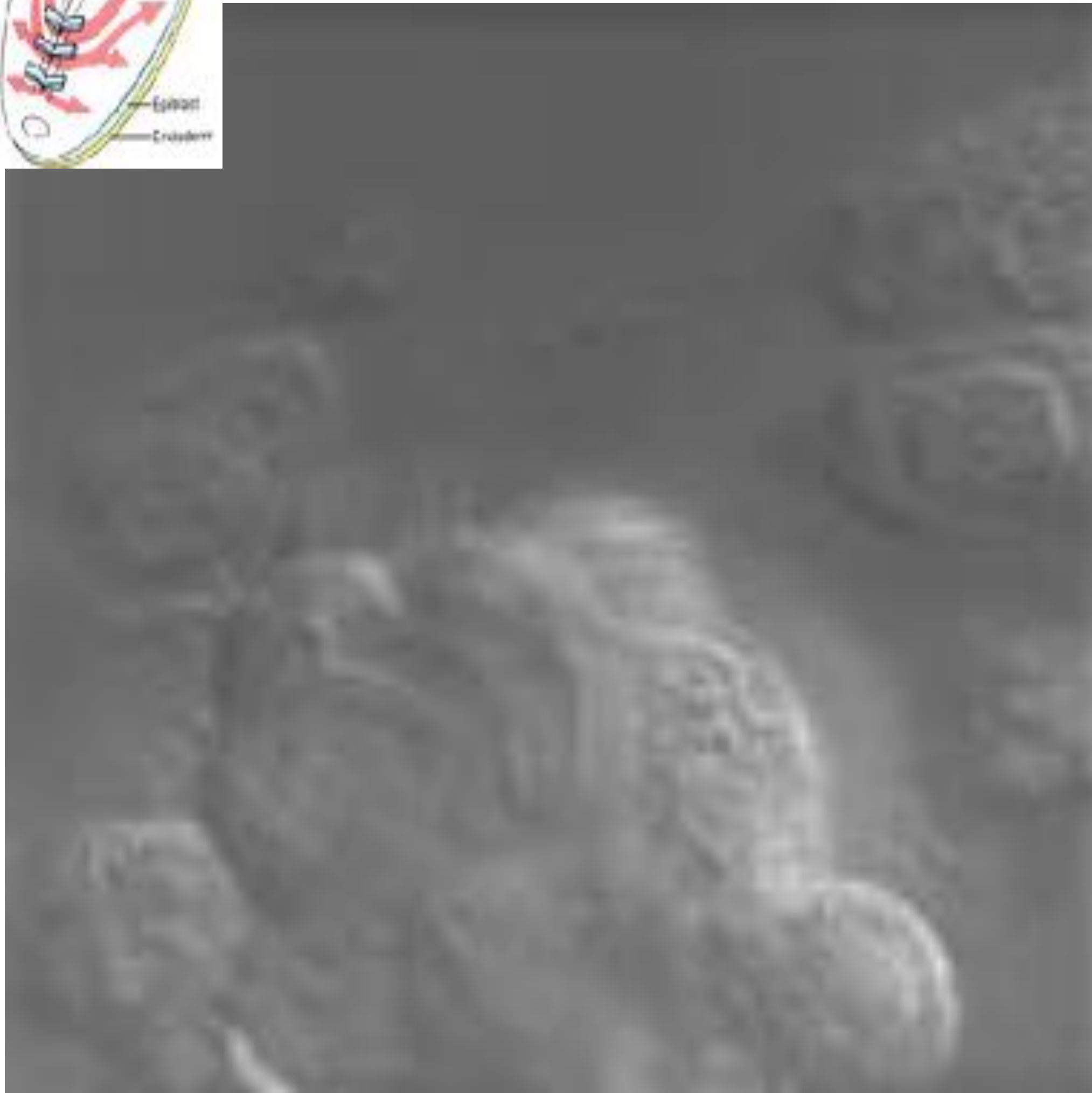
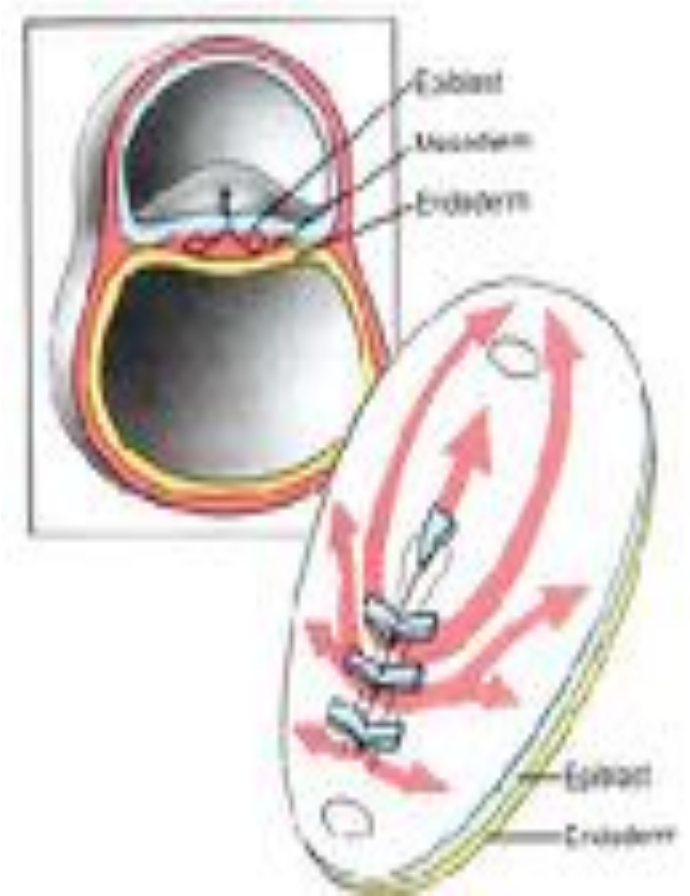


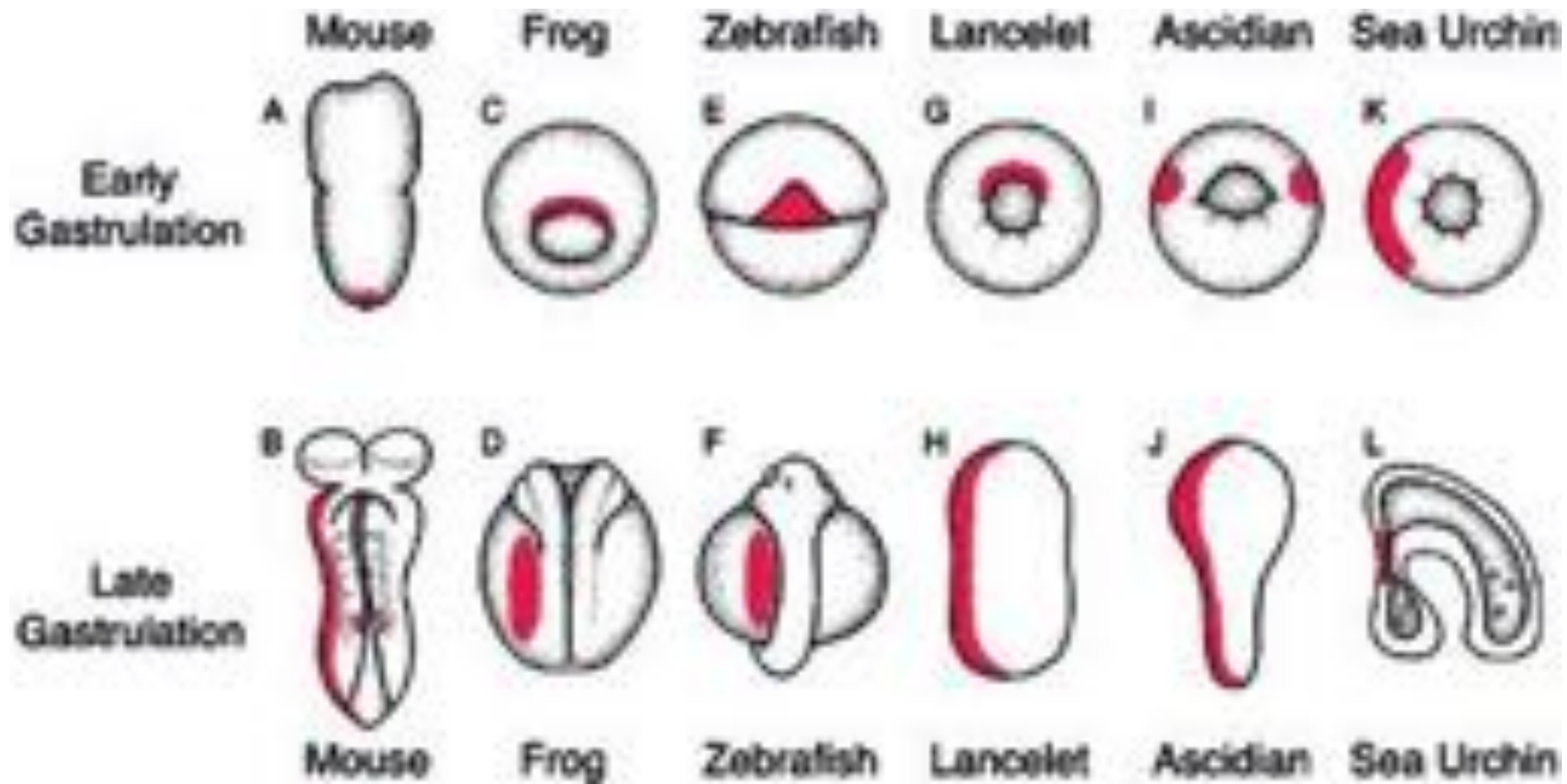
Everything starts with cilia movement



Left-right axis in the embryo





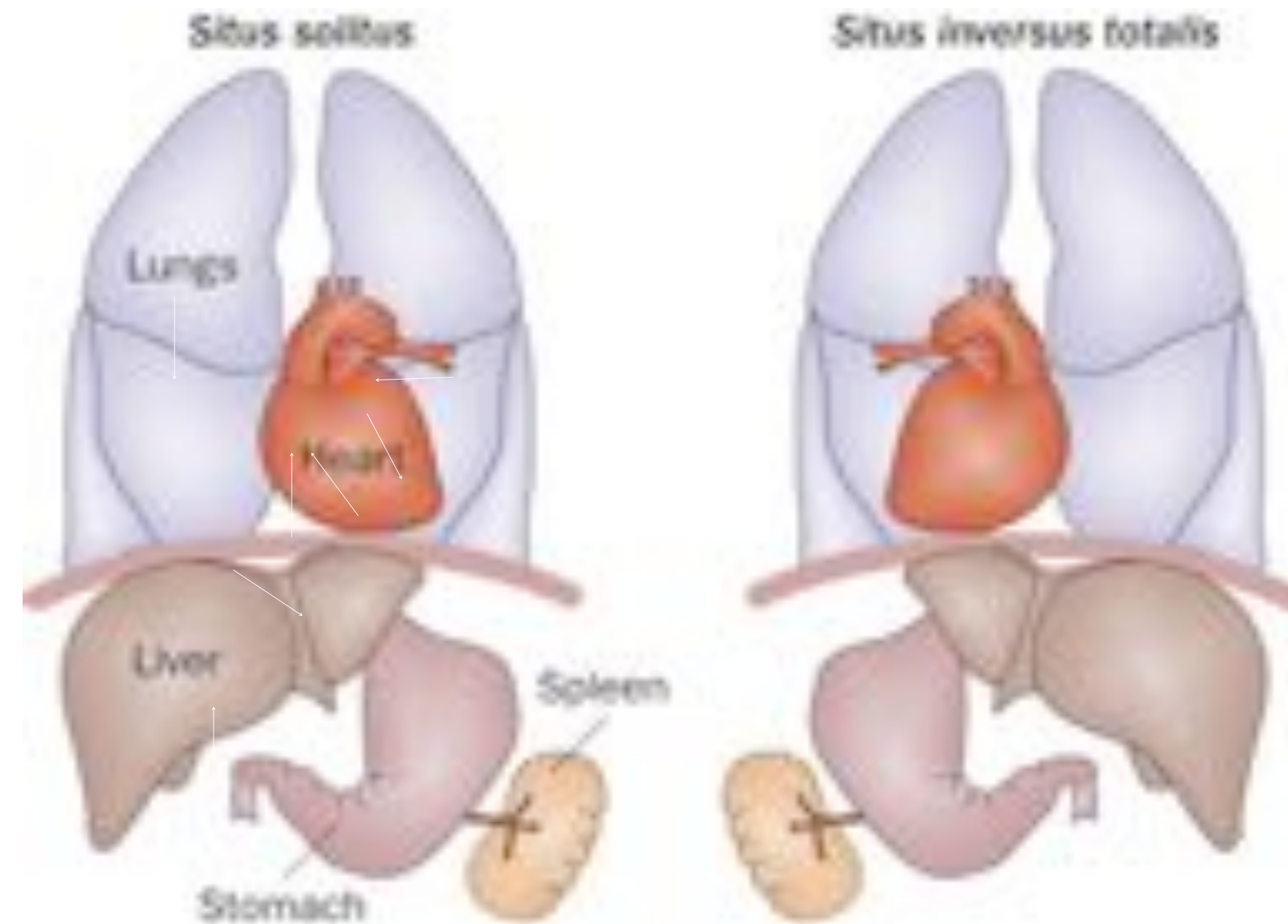


Expression of Nodal in different species is on the left side

What happens in the absence of left-right signaling ?

1.1/10,000 live births

3% of all Congenital Heart Diseases



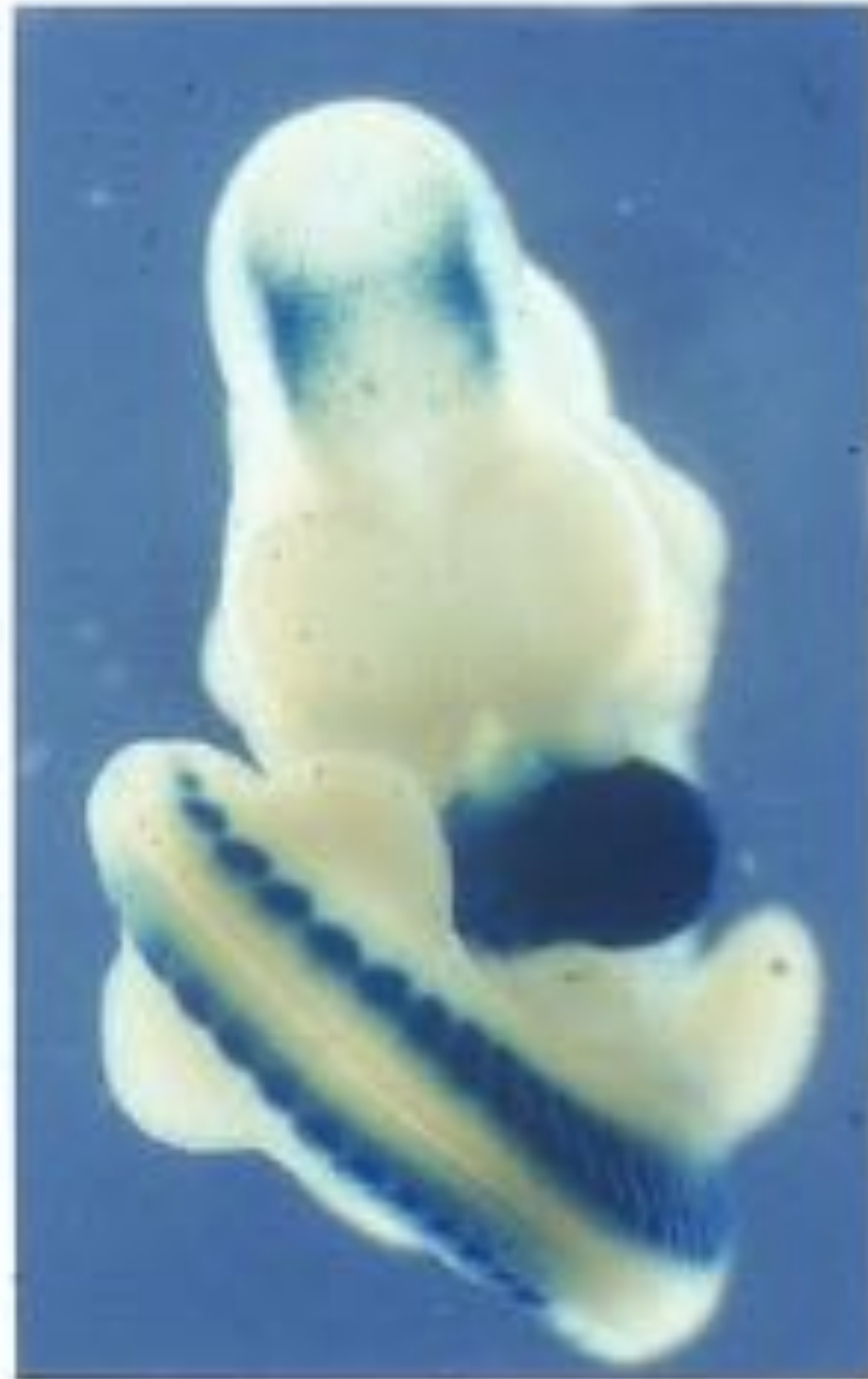
Impairment of Left/Right signaling

Formation of the node : *ZIC3*, *MMP21*

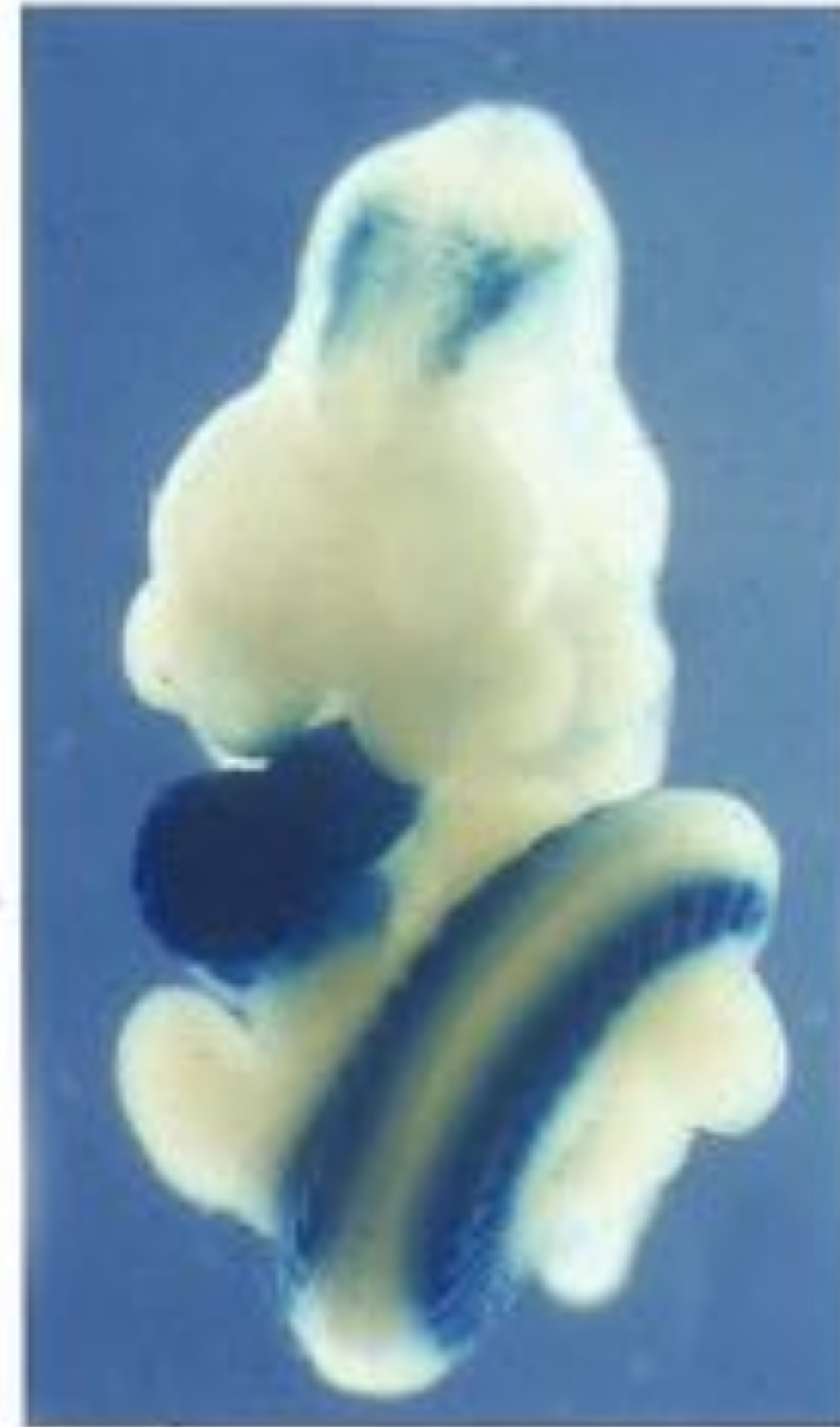
Ciliogenesis : *DNAH11*, *INVS*

Nodal signalling : *NODAL*, *LEFTY2*, *CFC1*, *ACVR2A*

Mouse mutant with absent left-right signaling



Situs solitus



Situs inversus

Mlc3f-2 X iv/iv



Lymnaea stagnalis

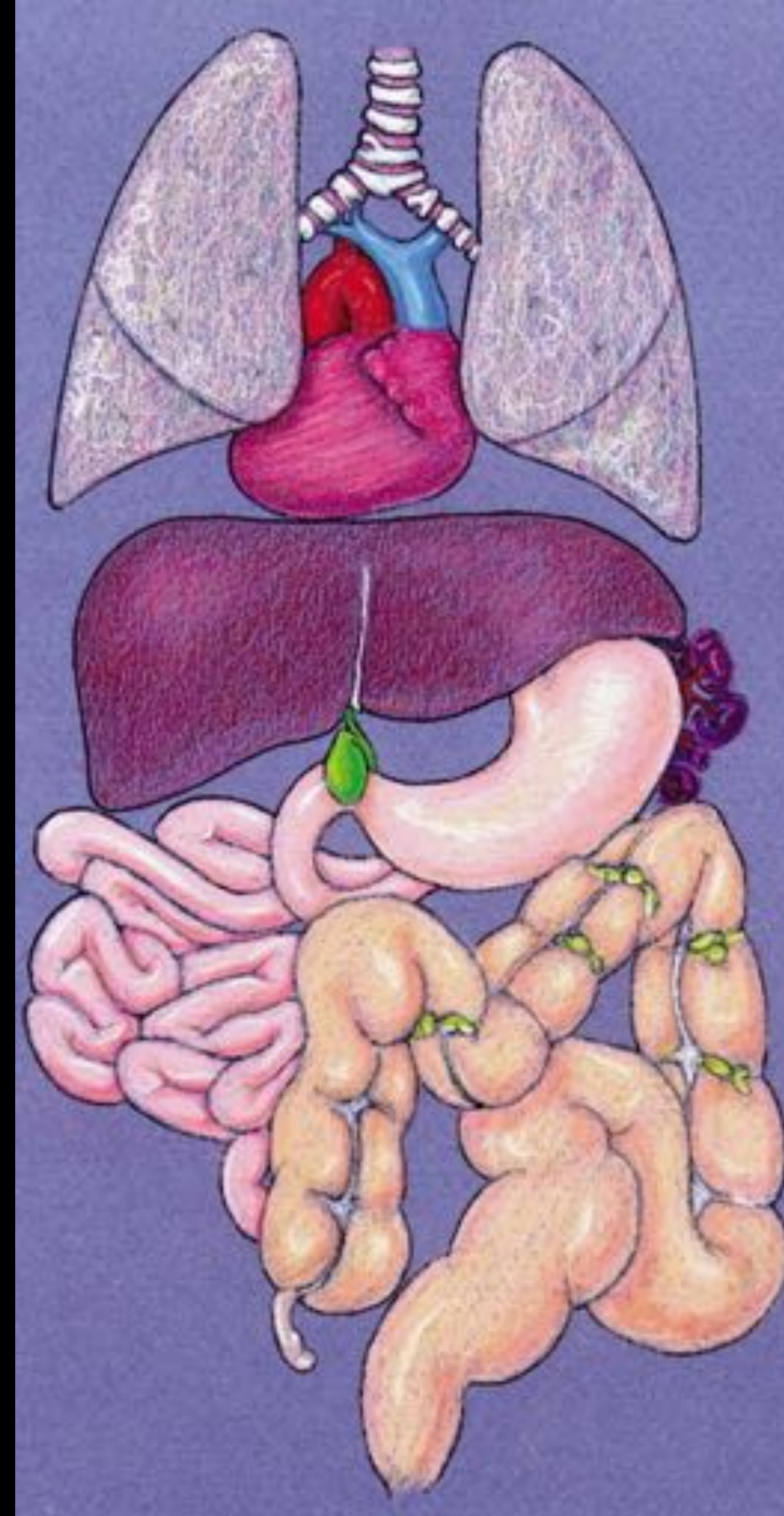
Absence of left-right signaling
Inversion-mirror image, Isomerism-Heterotaxy



Isomerism is easy to understand for pair organs
Heterotaxy is abnormality of visceral asymmetry



Right and left liver



Polysplenia



Situs Possibilities - Bronchial Arrangements

Right Isomerism



Bilateral Right
bronchi



Left Isomerism

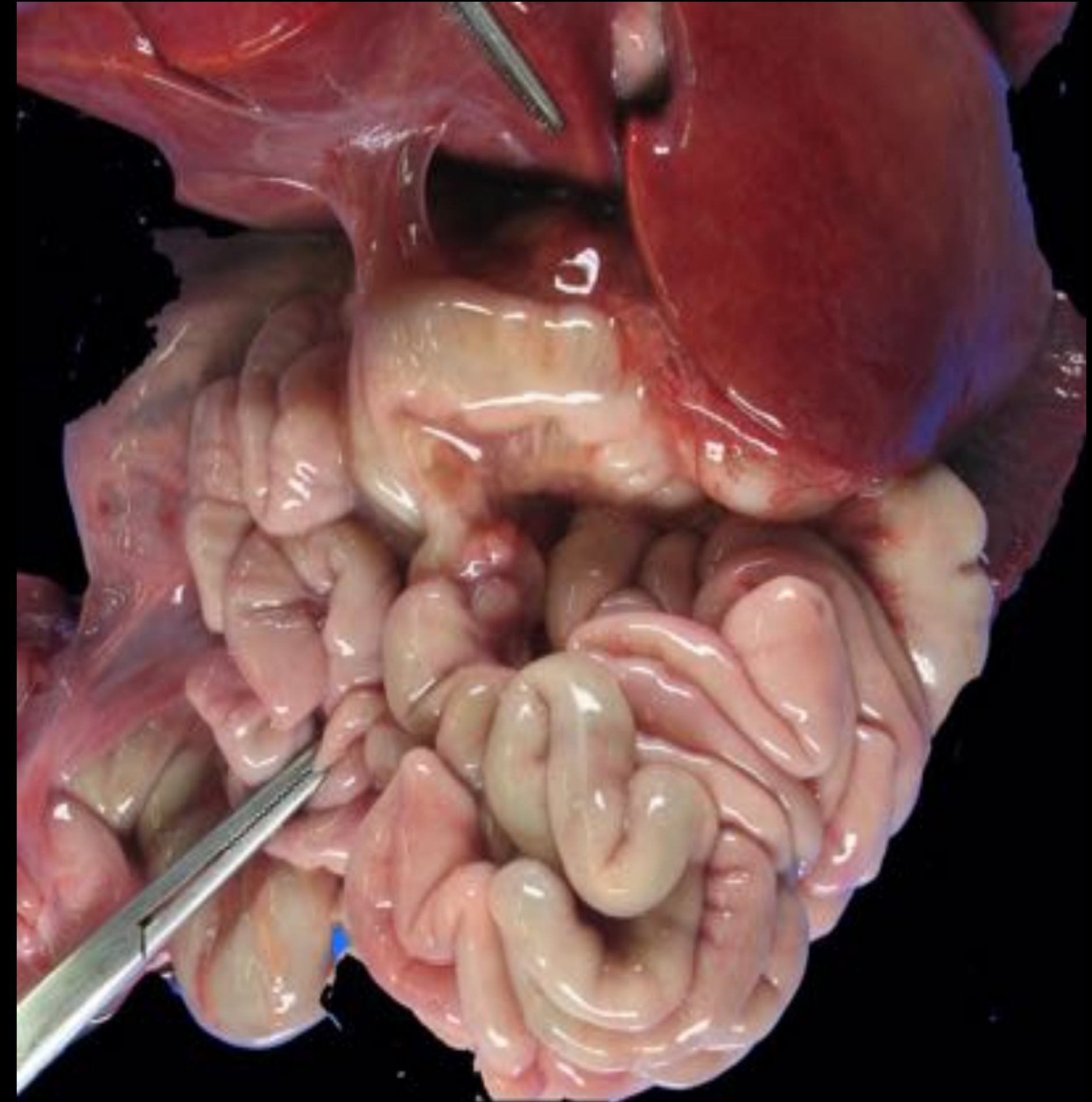
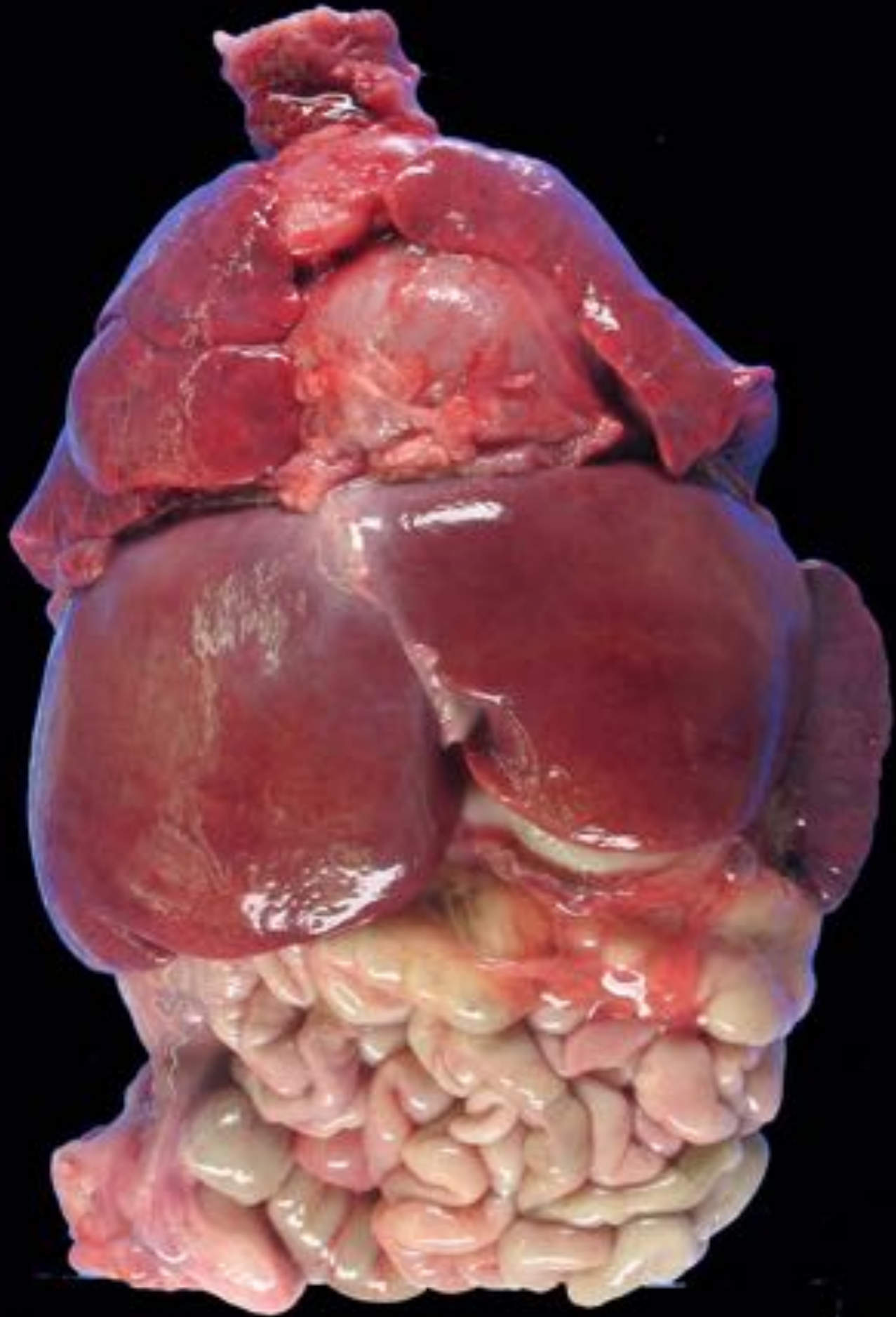


Bilateral Left
Bronchi

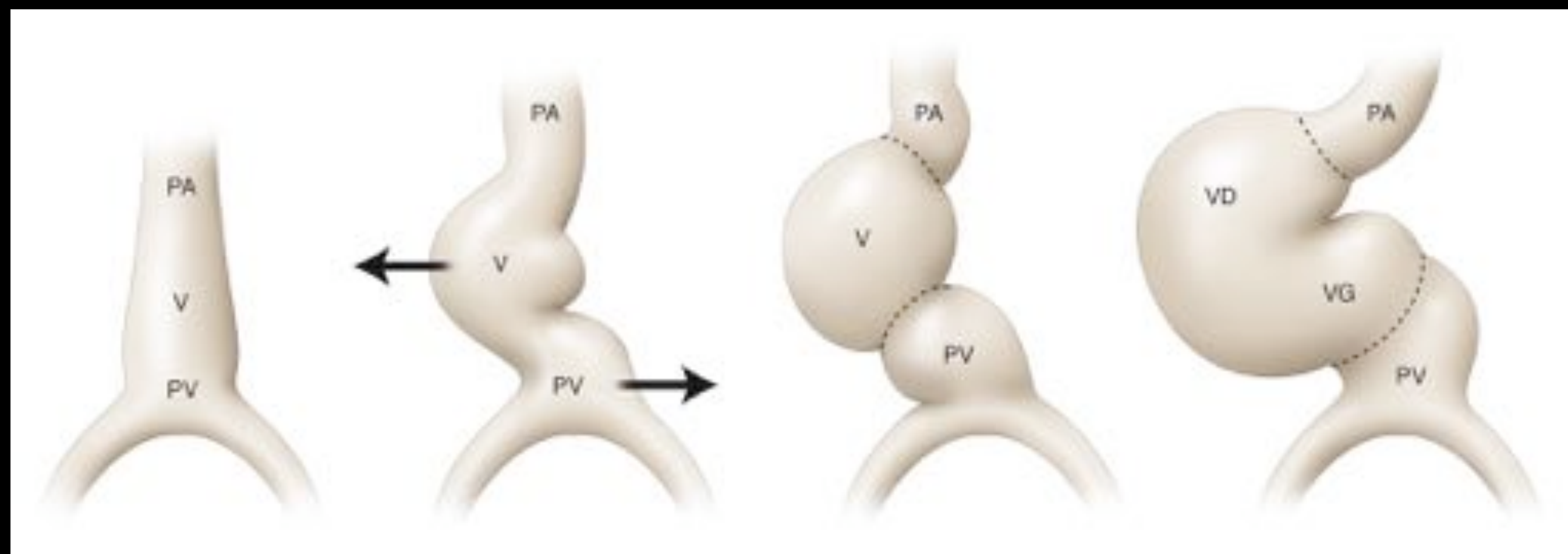


Specimens courtesy of
Dr. Bob Anderson

Gut Malrotation



Almost all heterotaxy patients have some malrotation

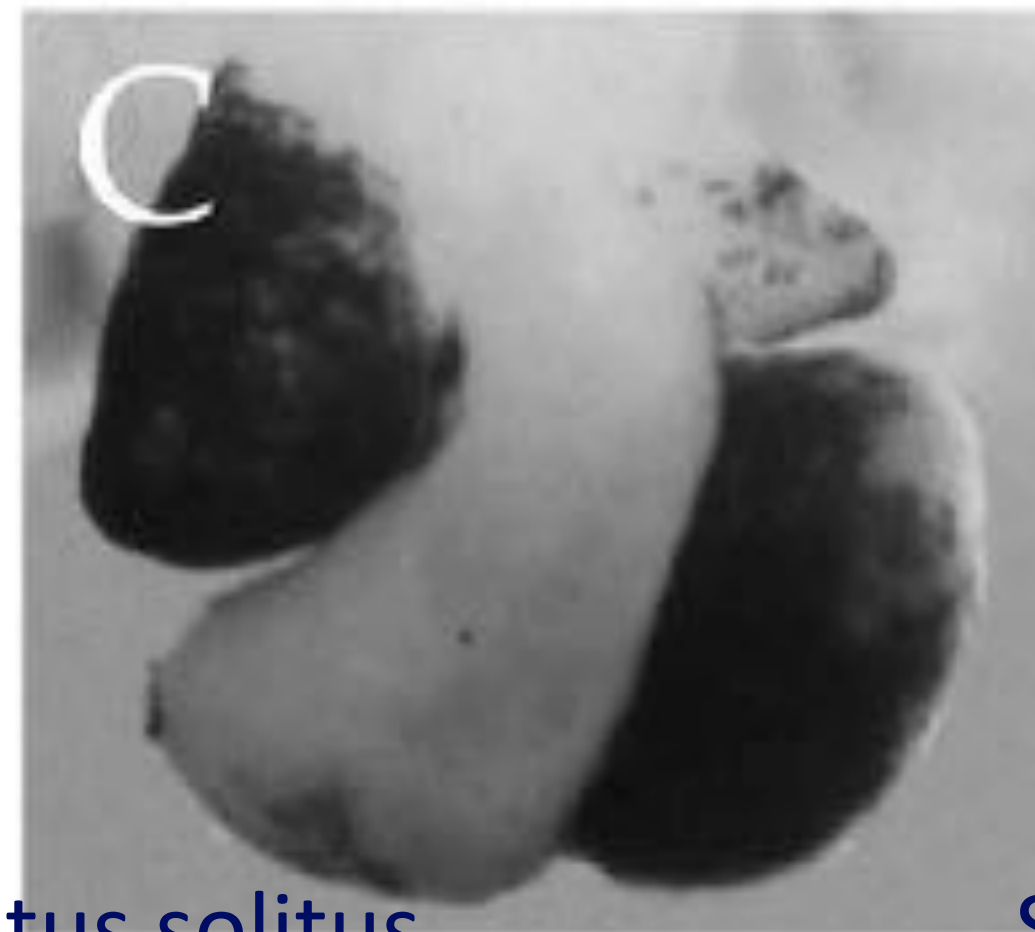
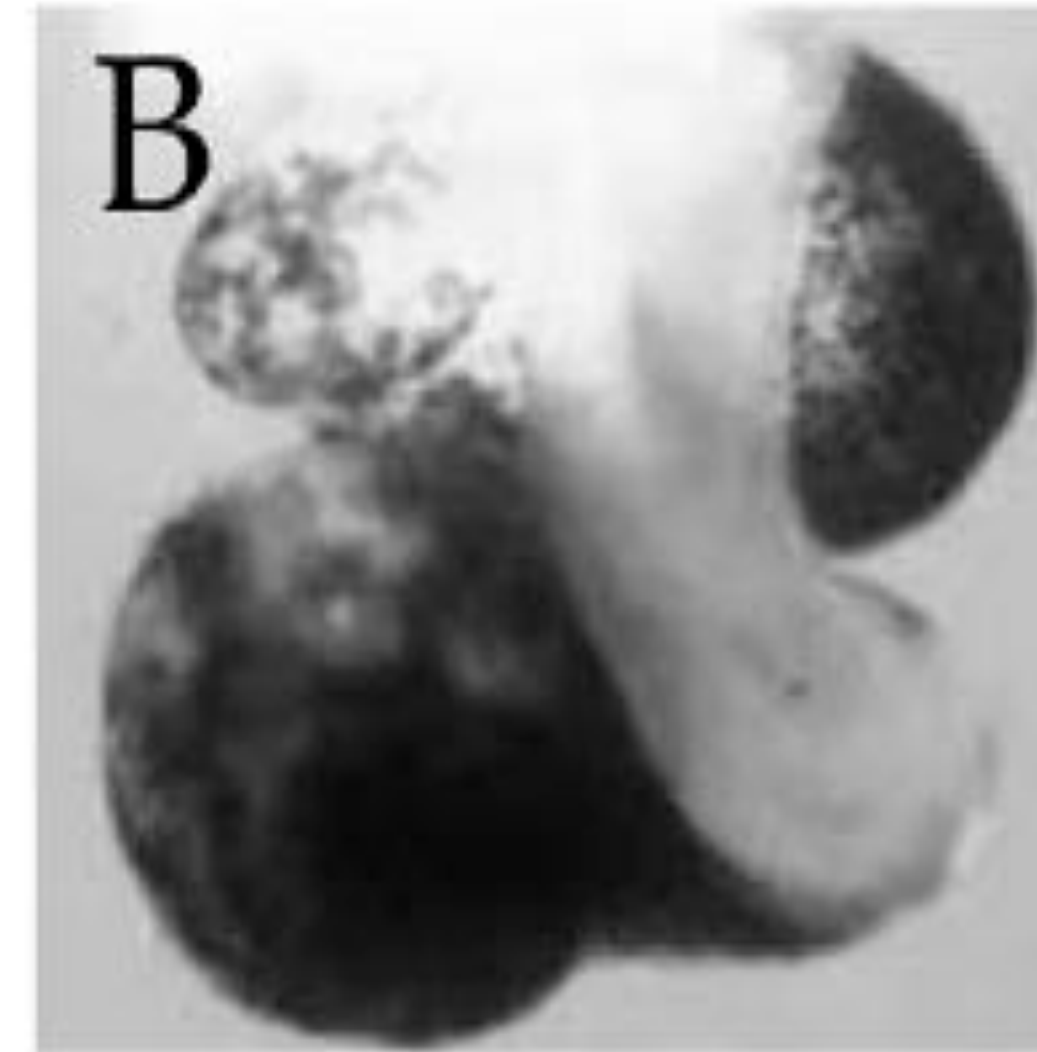
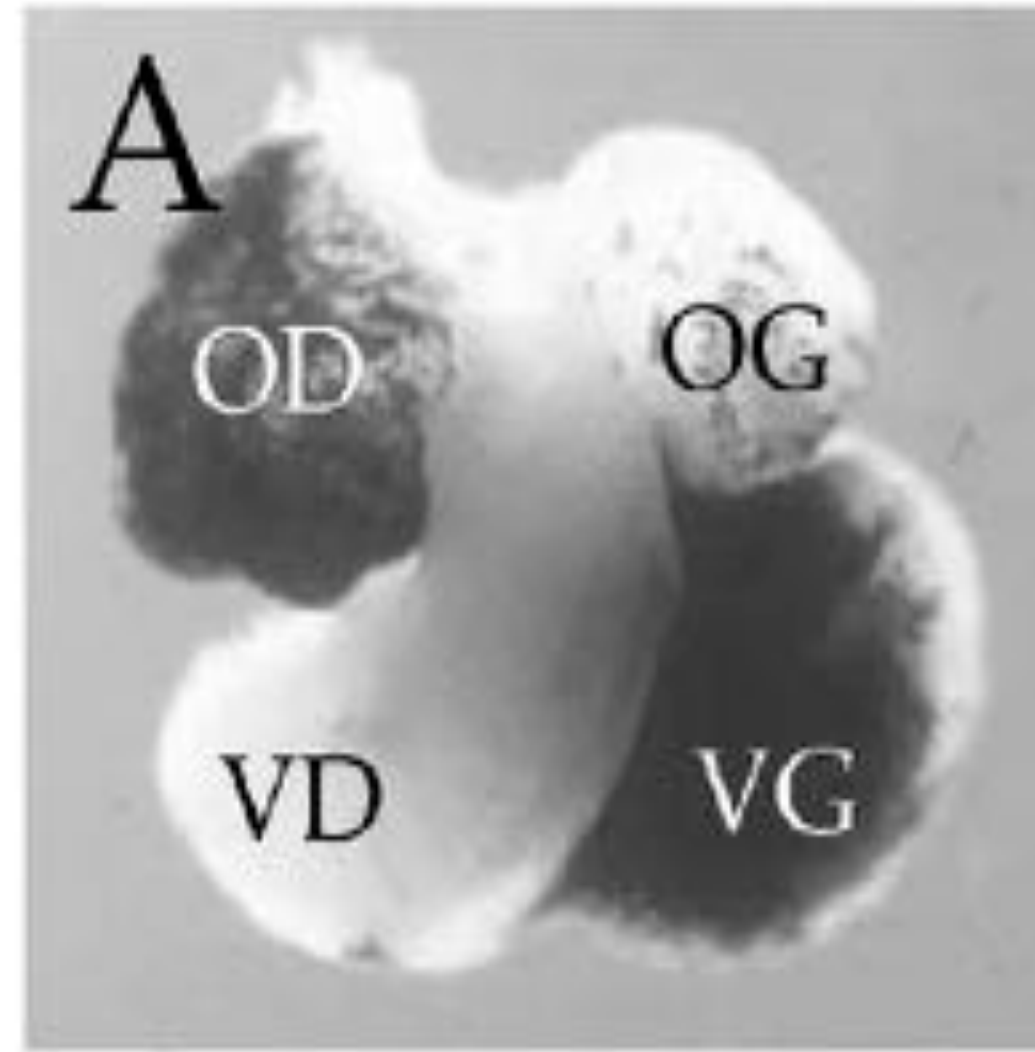


Right-sidedness and left-sidedness of cardiac structures are acquired during development, not present *de novo*

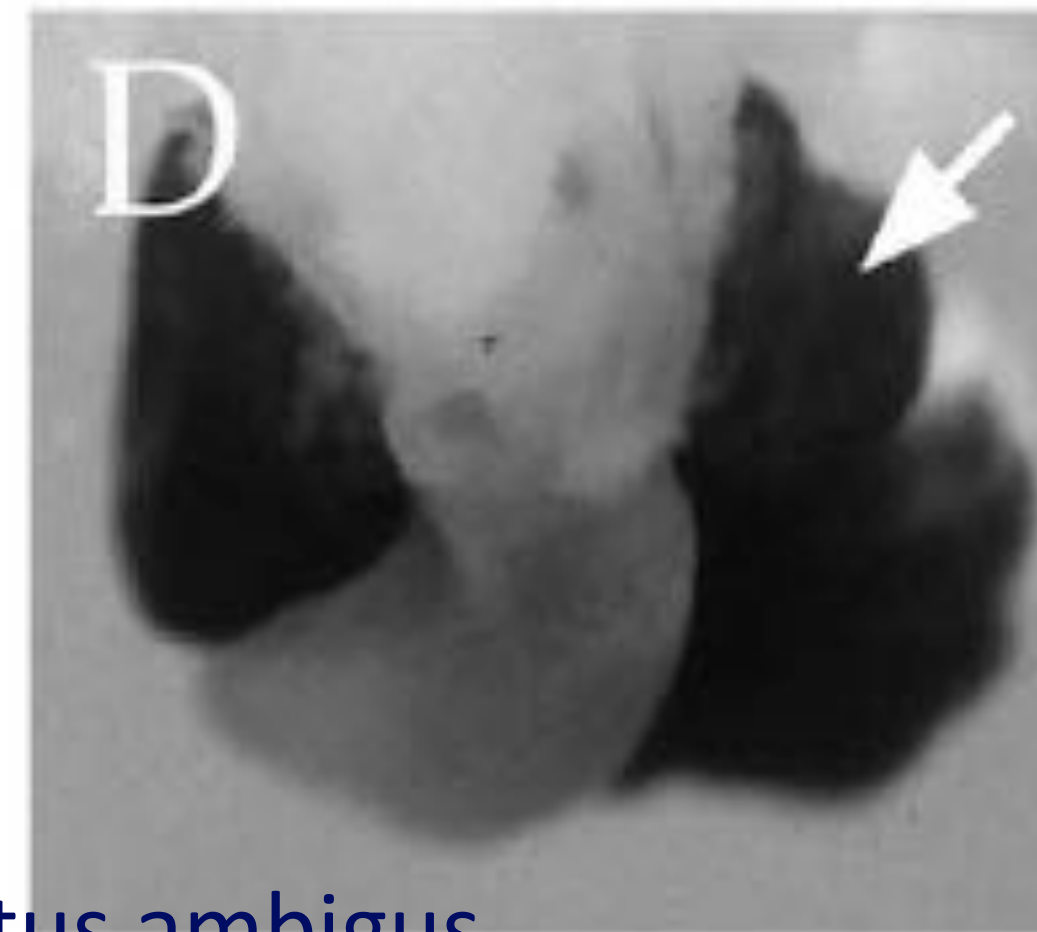
Transgenic mouse model for heterotaxy

Situs inversus

E10.5

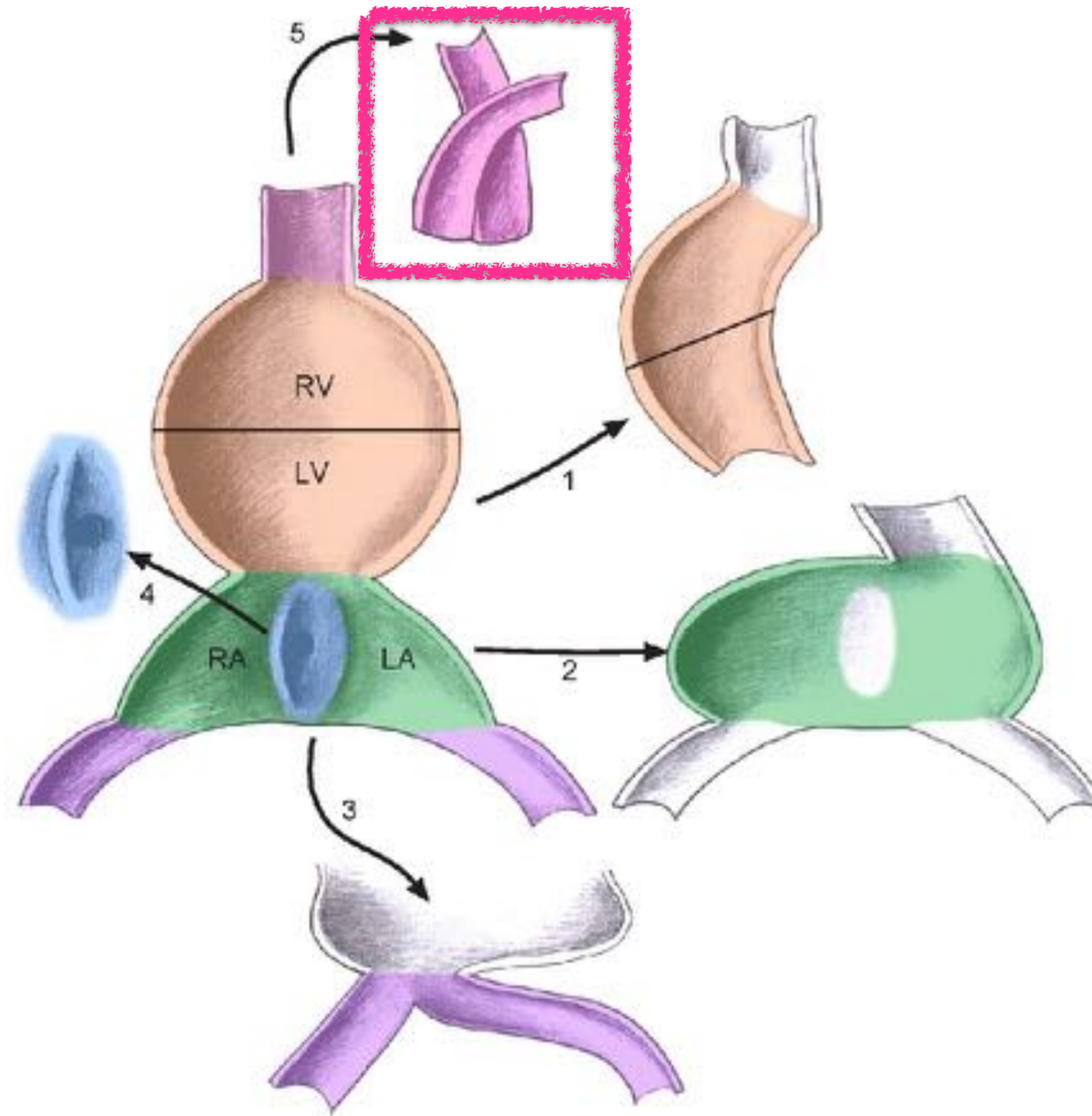


Situs solitus



Situs ambiguus

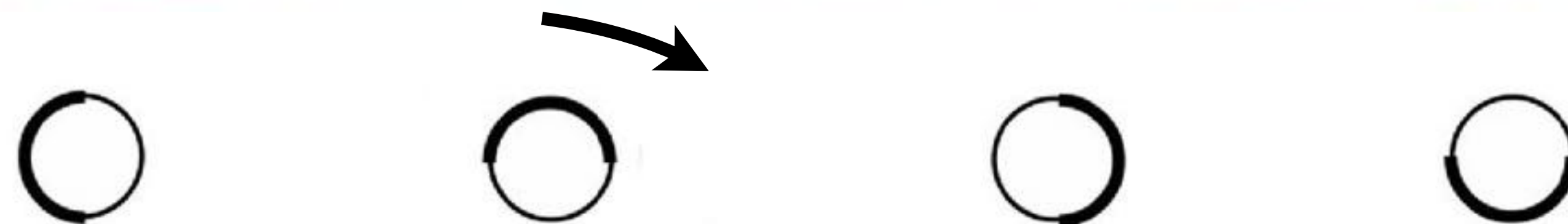
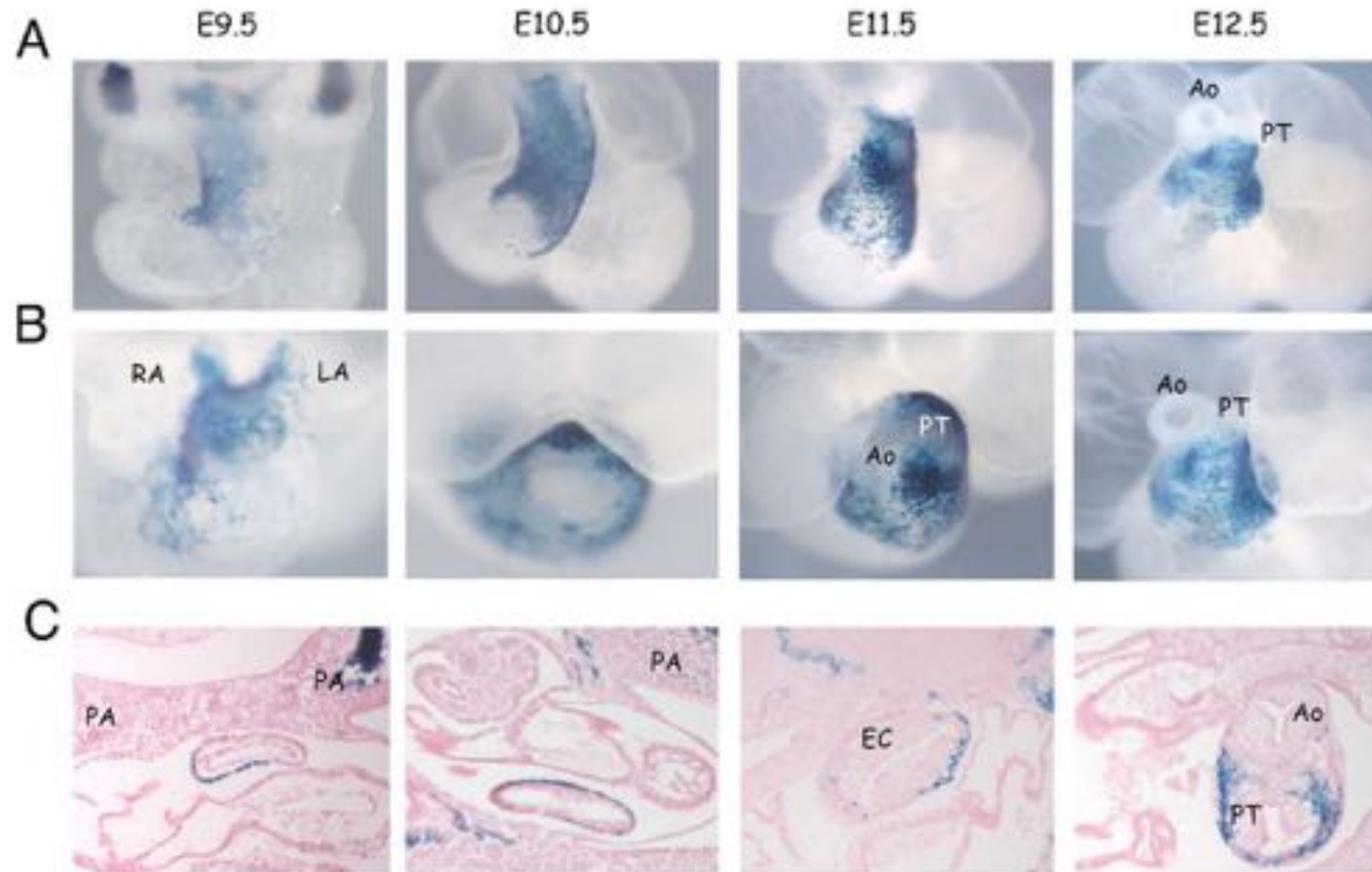
Mlc3f-2 X iv/iv



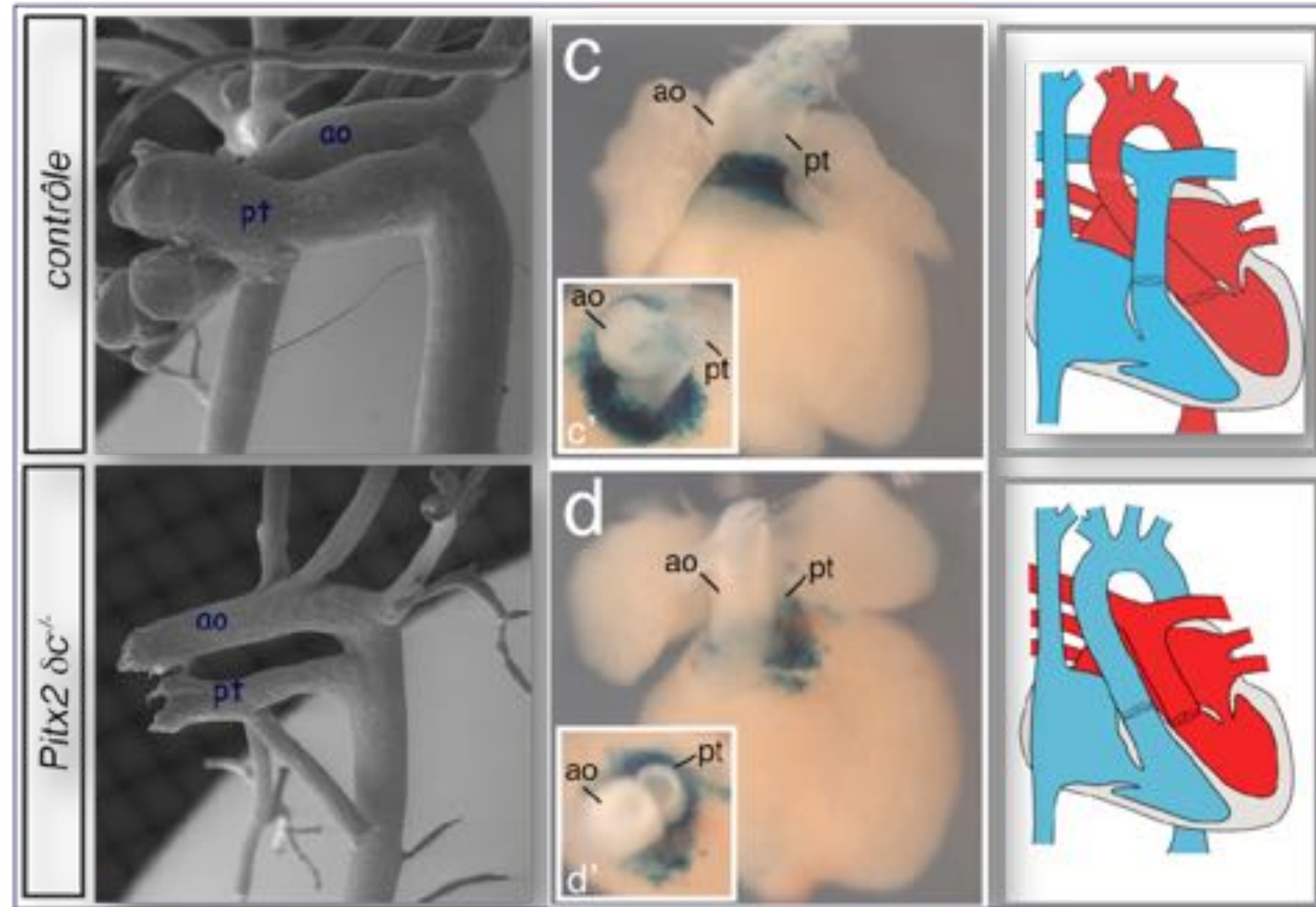
5 levels of asymmetry in the developing heart

Nigel Brown

Rotation of the myocardium in cardio sensor mouse



96-16 expression in *Pitx2 δ 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 signaling

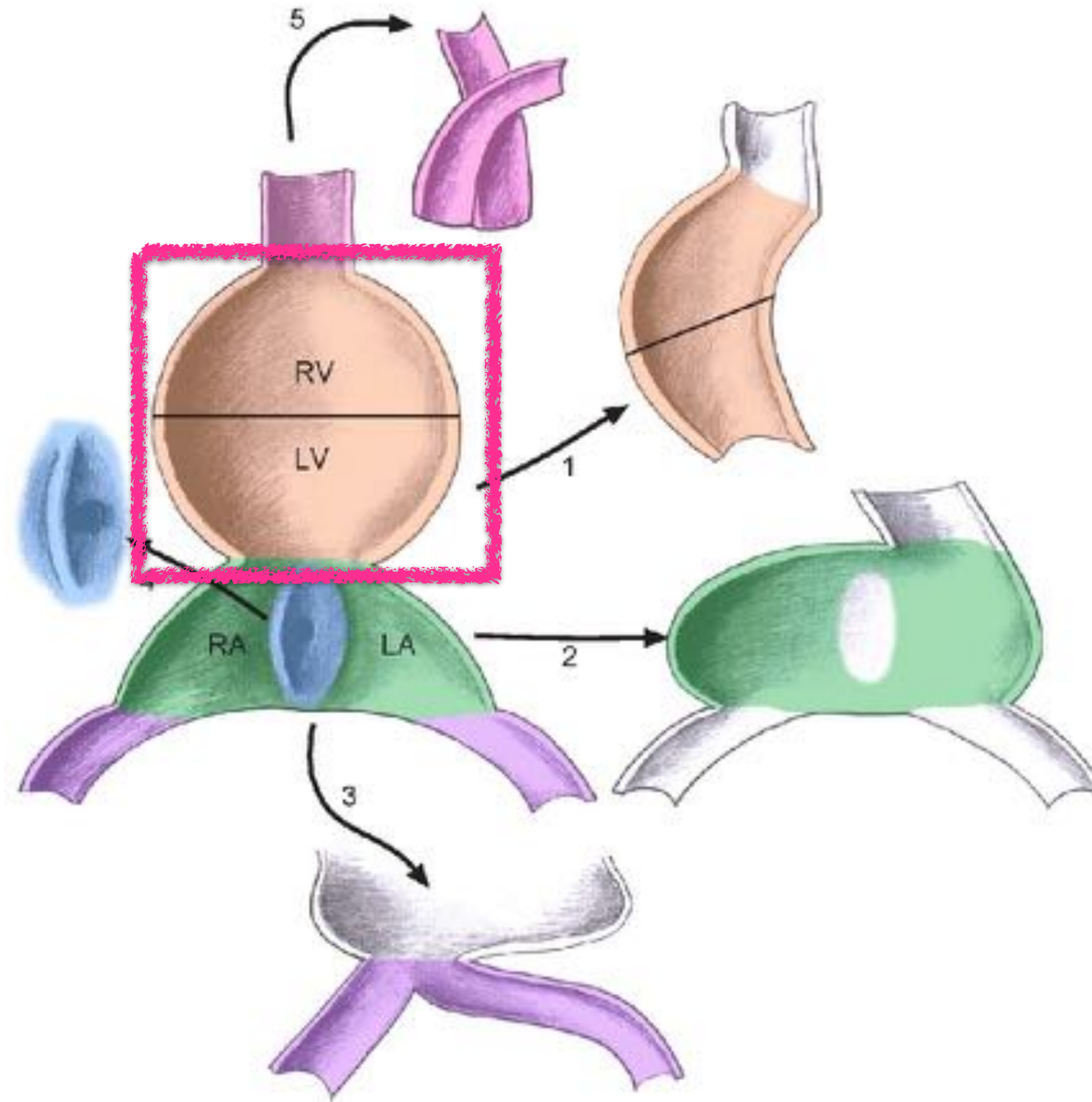
Familial transposition of the great arteries caused by multiple mutations in laterality genes

Alessandro De Luca,¹ Anna Sarkozy,^{1,6} Federica Consoli,¹ Rosangela Ferese,¹
Valentina Guida,¹ Maria Lisa Dentici,¹ Rita Mingarelli,¹ Emanuele Bellacchio,¹
Giulia Tuo,² Giuseppe Limongelli,³ Maria Cristina Digilio,⁴ Bruno Marino,⁵
Bruno Dallapiccola¹

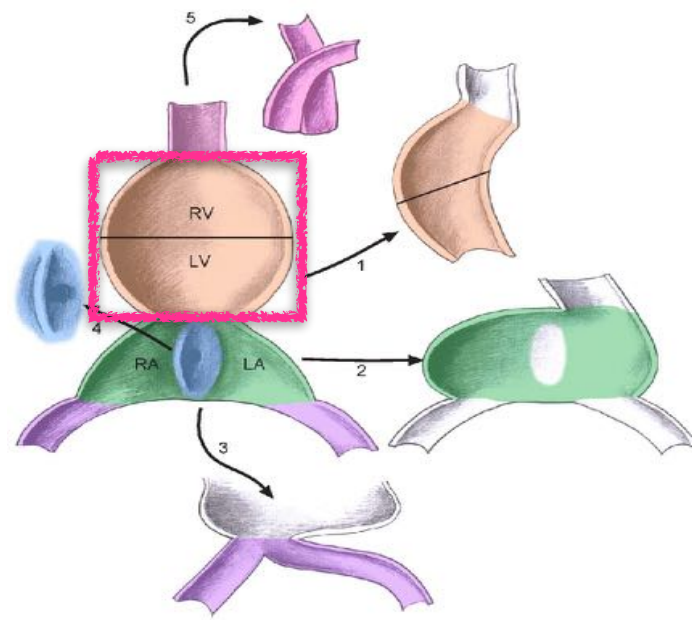
Heart 2010;**96**:673–677.

It is not a conotruncal defect

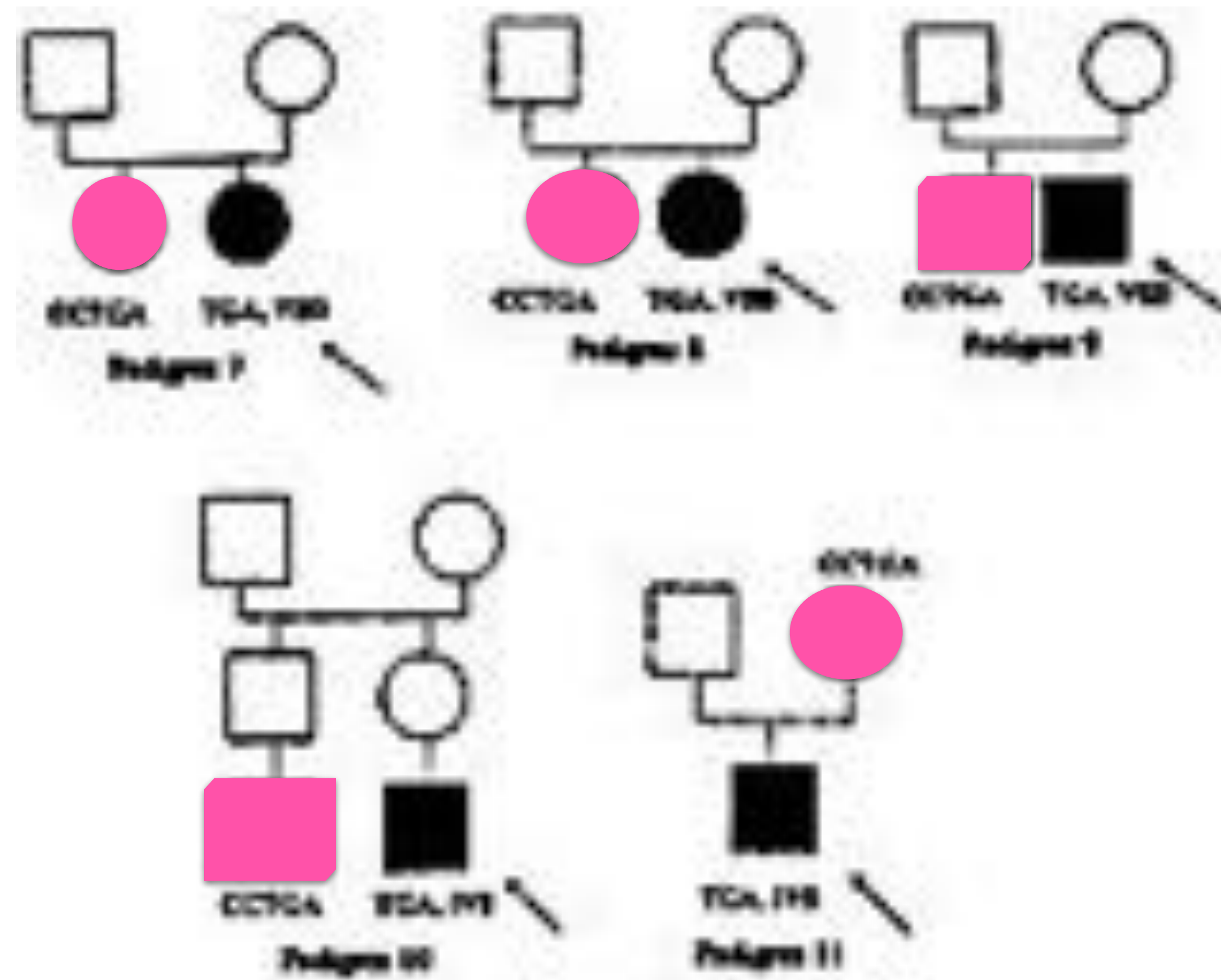
It is a laterality (rotation) restricted to a single segment of the developing heart

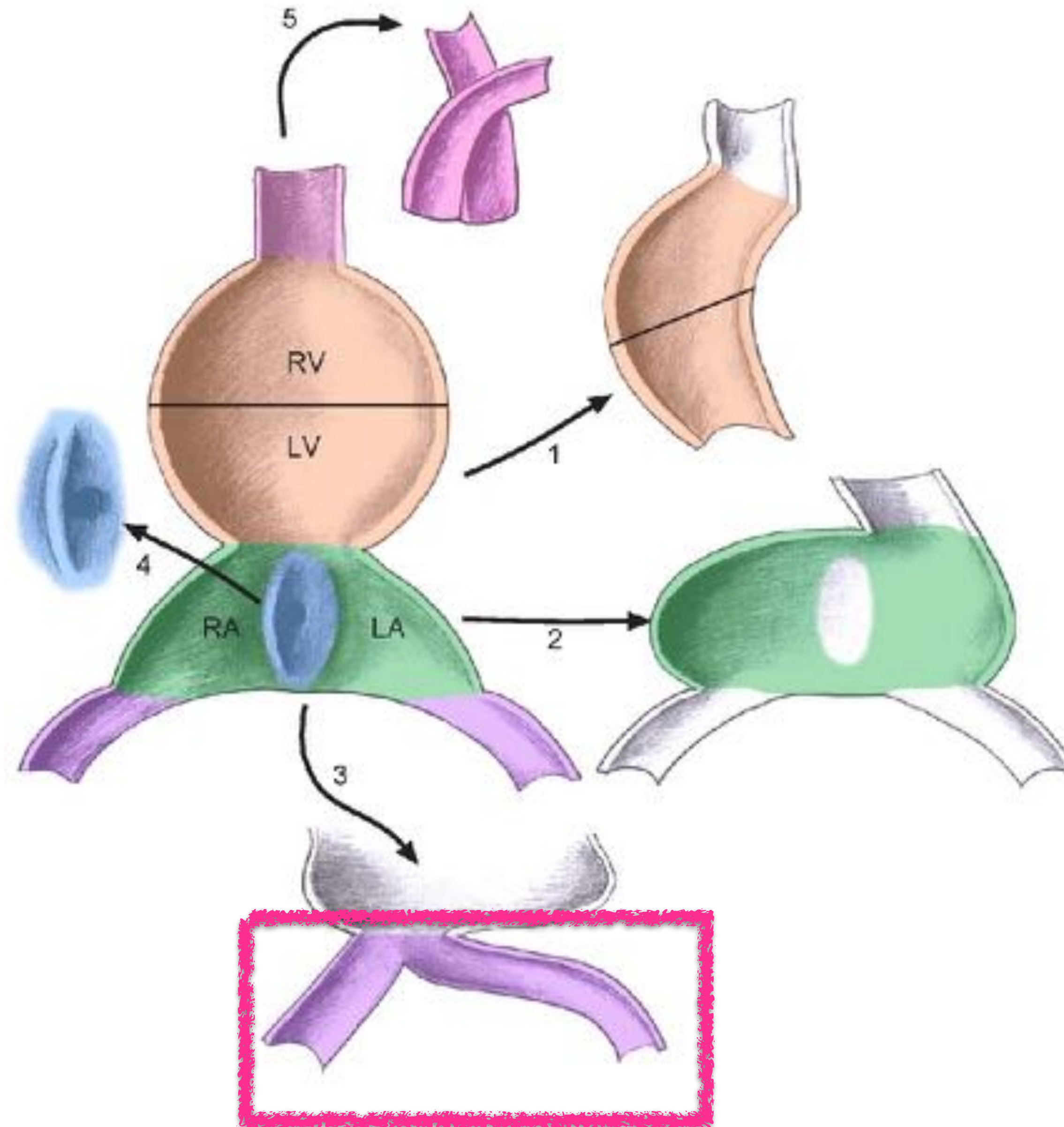


5 levels of asymmetry in the developing heart

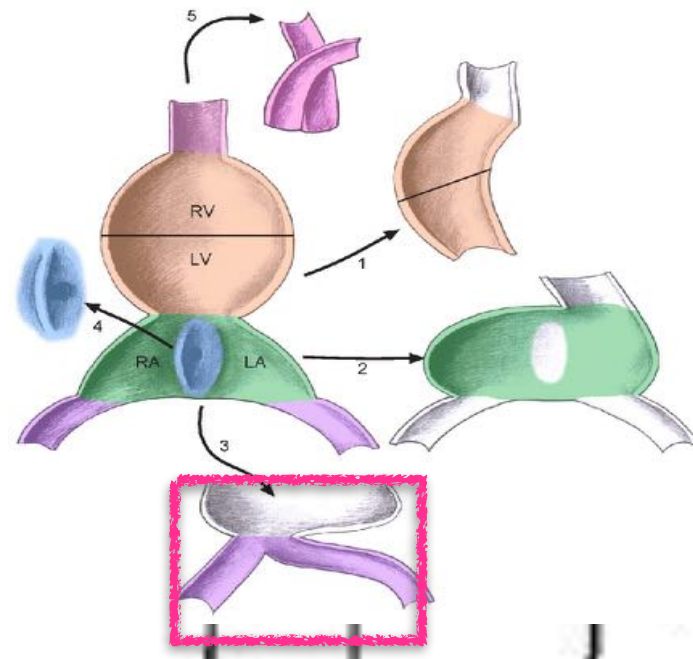


Families TGA & CC-TGA

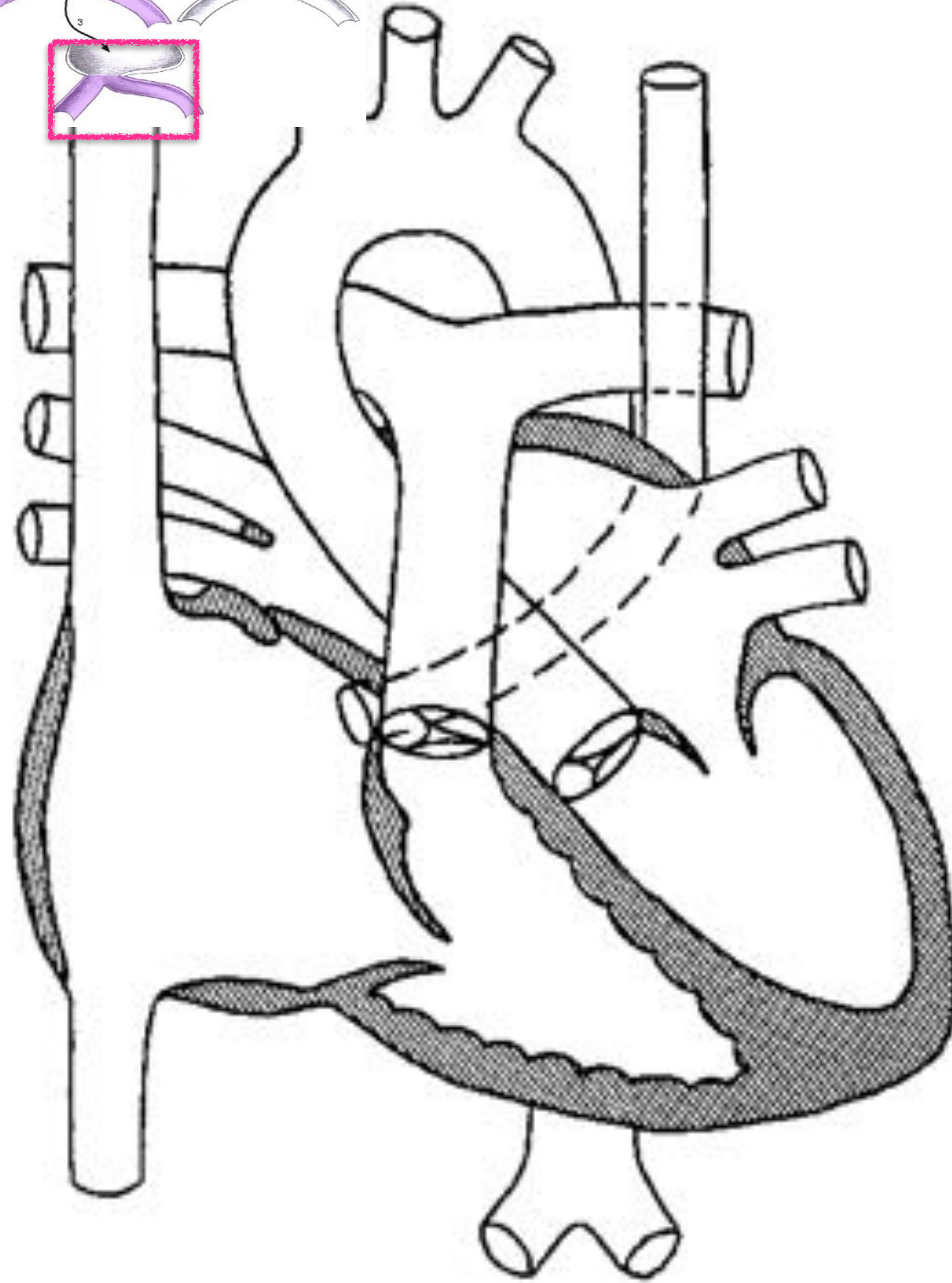




5 levels of asymmetry in the developing heart



Think out of the box



Left superior caval vein

What you see is not what it is ?

LSCV is a common finding

...that may be associated with aortic coarctation

The clinical diagnosis is COARCTATION, the
« embryological » diagnosis is systemic vein maldevelopment

7 families in our data base with:

Index case: let heart obstructive defect + LSCV

Recurrence in siblings : laterality defects

Segmental Anatomy

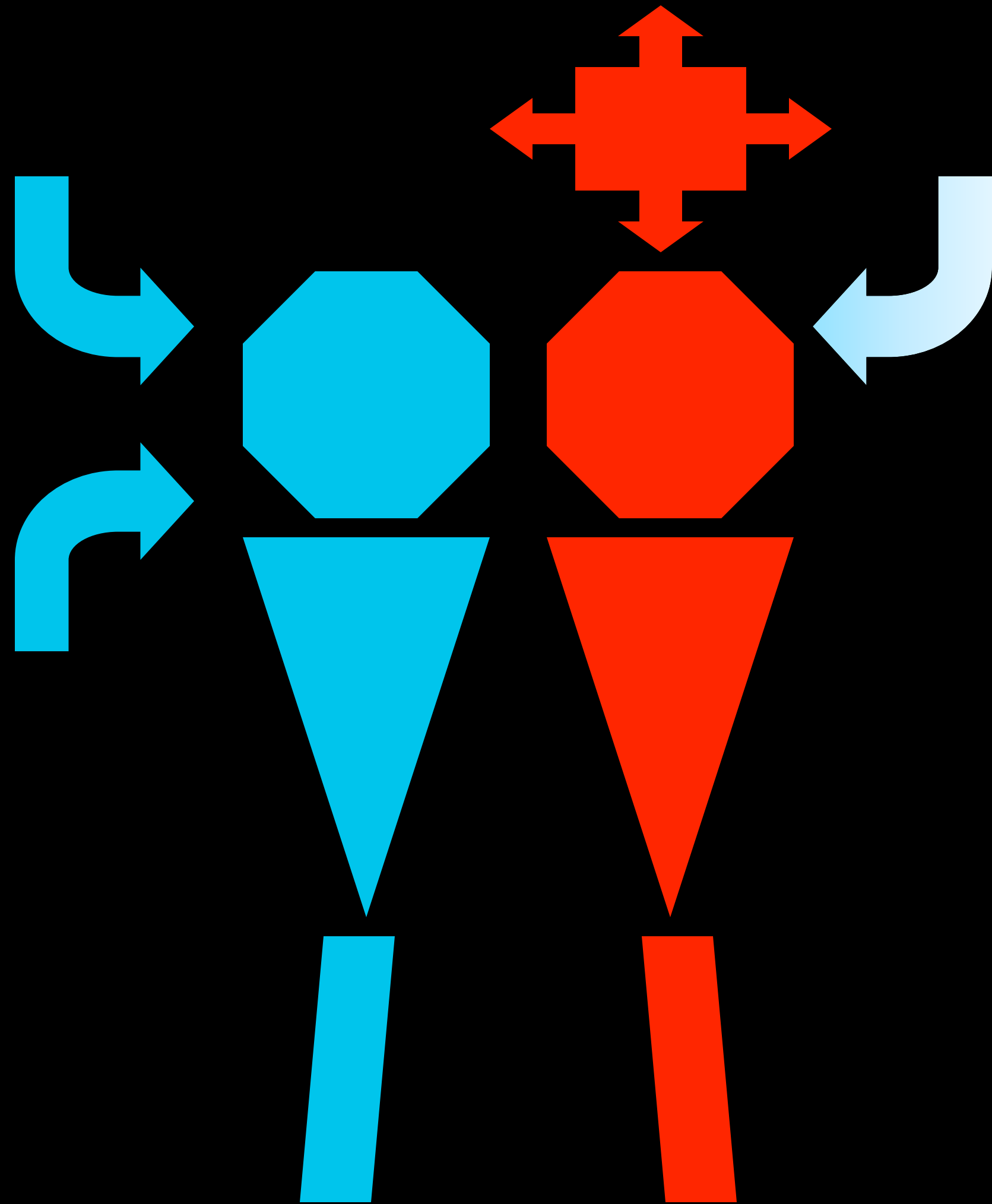
1. Alignment	Anterior	1 Concordant AV Alignment	2 Discordant AV Alignment	3 Concordant AV Alignment	4 Discordant AV Alignment
1. Normal					
2. Isolated Atrial Discordance					
3. Isolated Ventricular Discordance					
4. Isolated Infundibular Atrial Discordance					
5. Transposition of the Great Arteries					
6. Anatomically Corrected Malposition of the Great Arteries					
7. Double Outlet Right Ventricle					
8. Double Outlet Left Ventricle					

Segmental Vessels, Alignments, and Connections: This table summarizes the possible situs relationships and alignment relationships according to the Van Praagh nomenclature system. Note that some abnormal AV alignments (e.g. DILV) are not depicted. Modified from Van Praagh, E. Segmental Approach to Diagnosis. In Kame JE, Lock JE, Roper DC, editors. *Nuclear Pediatric Cardiology* 2nd ed. Philadelphia: Elsevier; 2006.

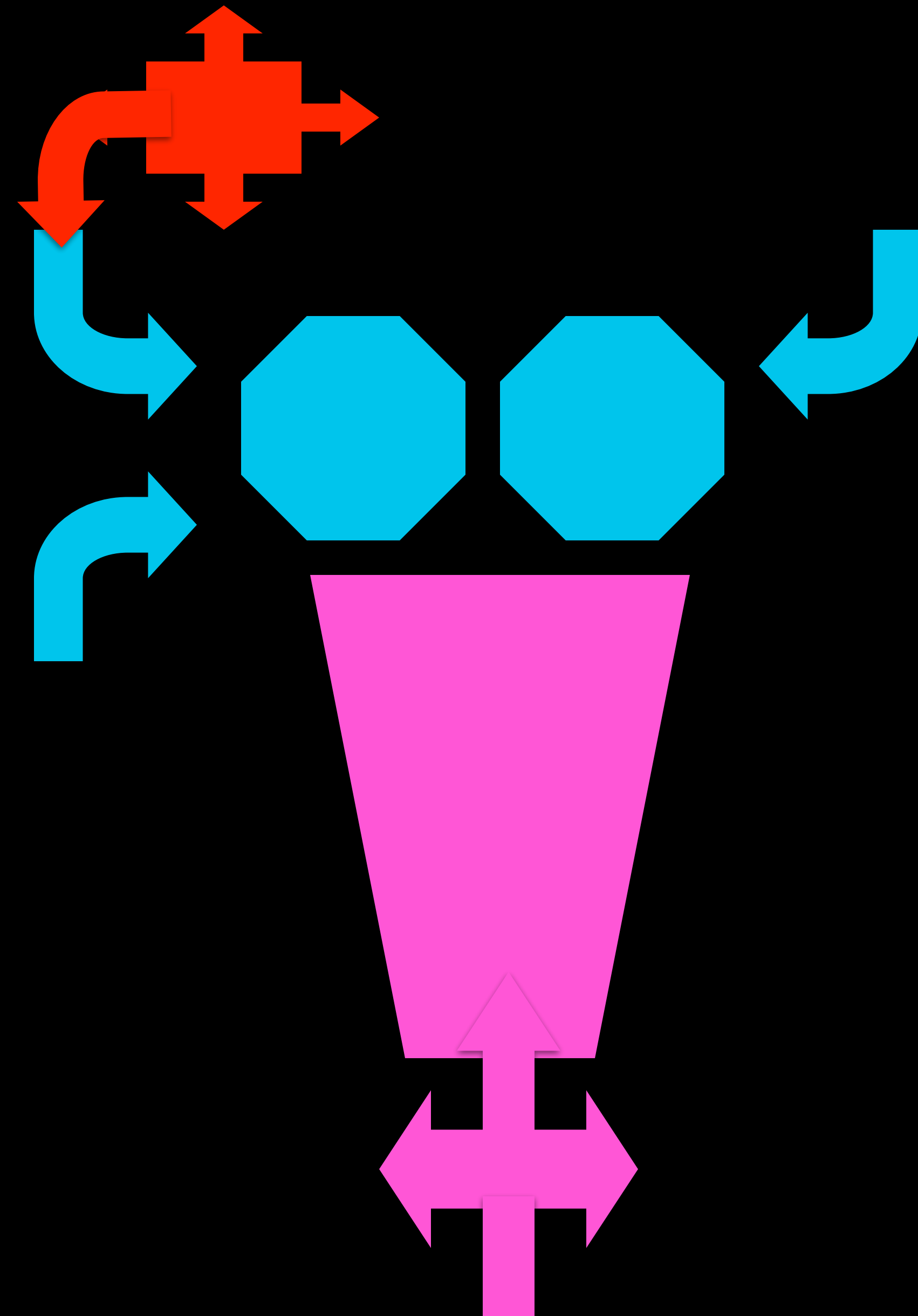
Sequential Segmental Anatomy

1	Atrial Arrangement	Usual Right Isomerism	Mirror-Imaged Left Isomerism
2	Venoatrial Connections (e.g. anomalous pulmonary venous return)		
3	Atrioventricular Connections	1 Atrium to its Own Ventricle Concordant Discordant Mixed Usual atrial arrangement Mirrored atrial arrangement RT isomerism LT isomerism	
		1 Atrium to 2 Ventricles Absent R AV Valve & Straddling L AV Valve Absent L AV Valve & Straddling R AV Valve	
		2 Atria to 1 Ventricle Absent Right Connection Absent Left Connection Double Inlet Ventricle Dominant LV Dominant RV Indeterminate Ventricle 2 AV Valves Common AV Valve	
4	Atrioventricular Valve Morphology	2 patent valves 1 patent & 1 atretic valve Common Valve Straddling Valve Overriding Valve Right Left Common Both	
5	Ventricular Topology	Right handed Left handed	
6	Ventriculoarterial Connections	Concordant Discordant Double Outlet Single Outlet Right Ventricle Left Ventricle Indeterminate Ventricle Common Trunk Pulmonary Atresia Aortic Atresia	
7	Arterial Valve Morphology (e.g. bicuspid valve)		
8	Infundibular Morphology	Subaortic Subpulmonary Bilaterally Present Bilaterally Absent	
9	Great Artery Anatomy	Aorta directly anterior to the PT Aorta anterior & to the right of PT Aorta side by side to PT, to the right Aorta posterior & to the right of PT Aorta directly posterior to the PT Aorta anterior & to the left of PT Aorta side by side to PT, to the left Aorta posterior & to the left of PT Spiraling - Normal Spiraling - Mirror-Imaged Parallel	
10	Septal Anatomy (e.g. atrial septal defect, ventricular septal defect)		
11	Abdominal & Bronchial Anatomy (e.g. right isomerism)		

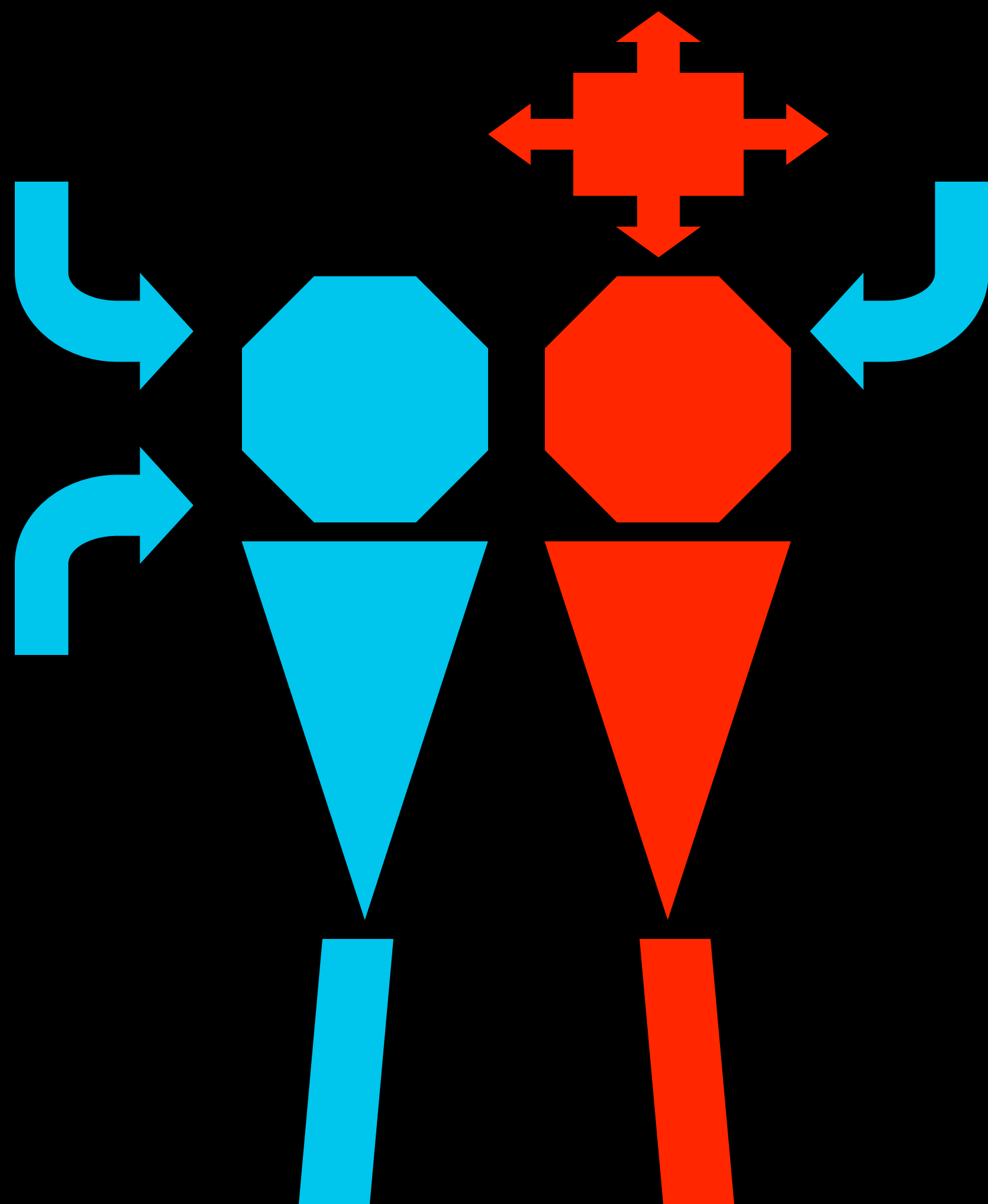
Complex but algorithmic



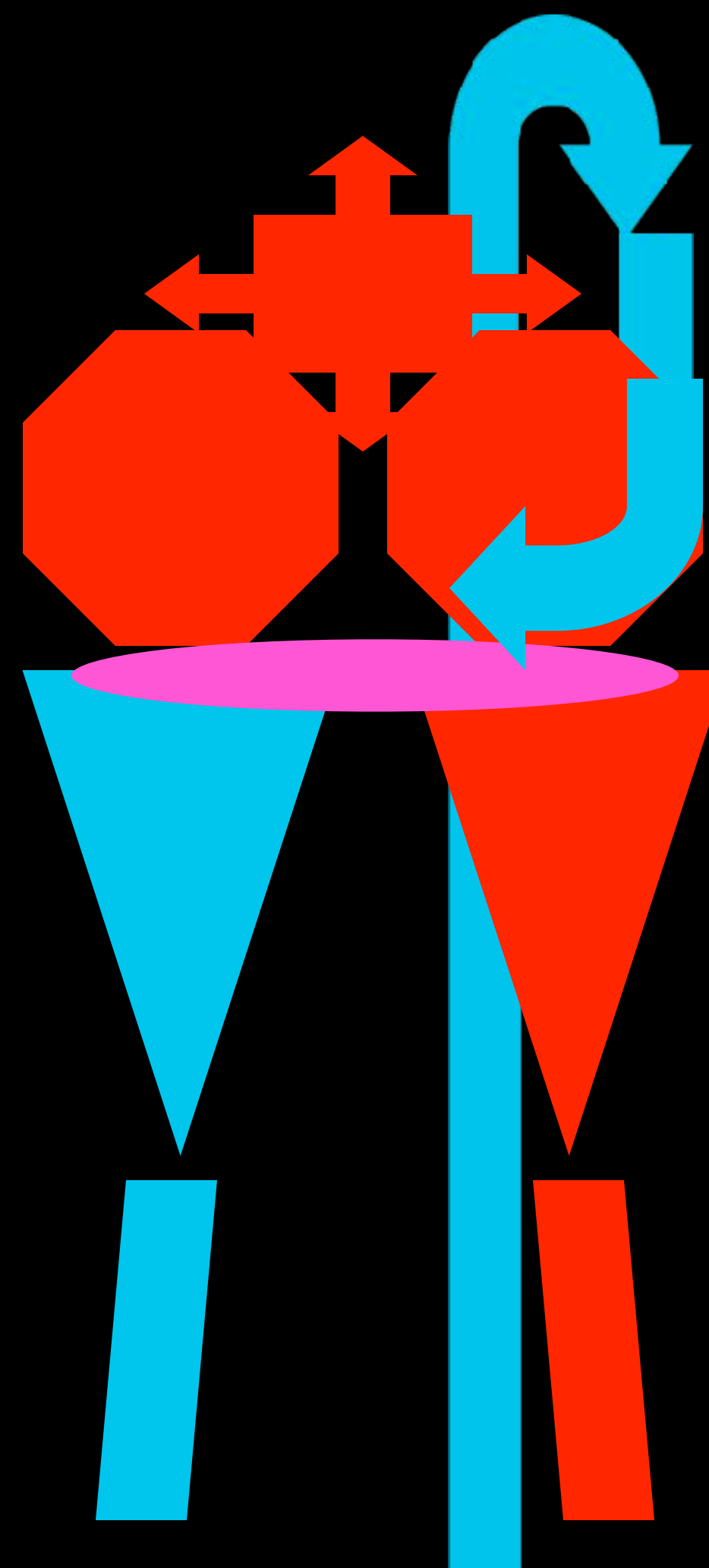
Right-isomerism



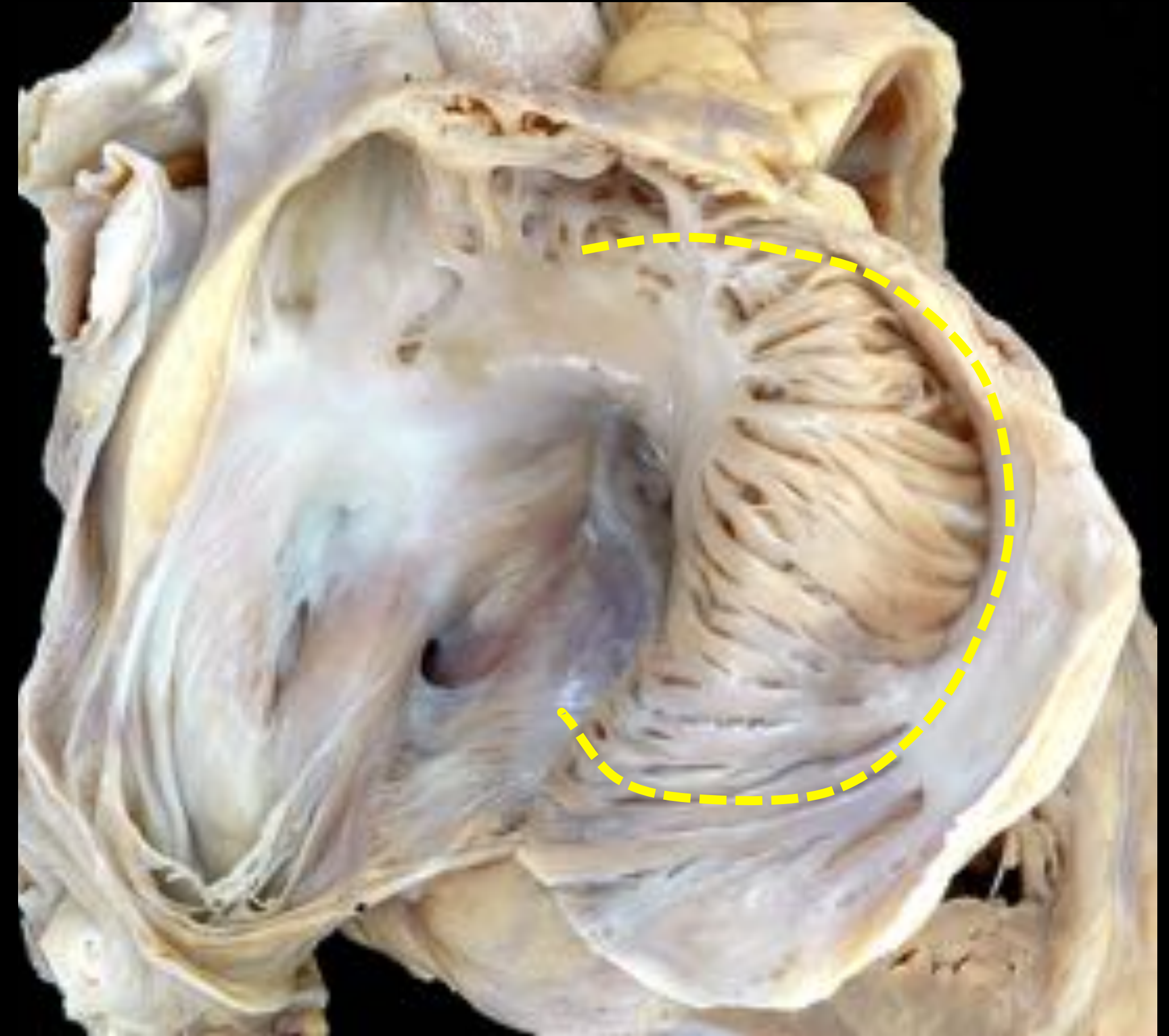
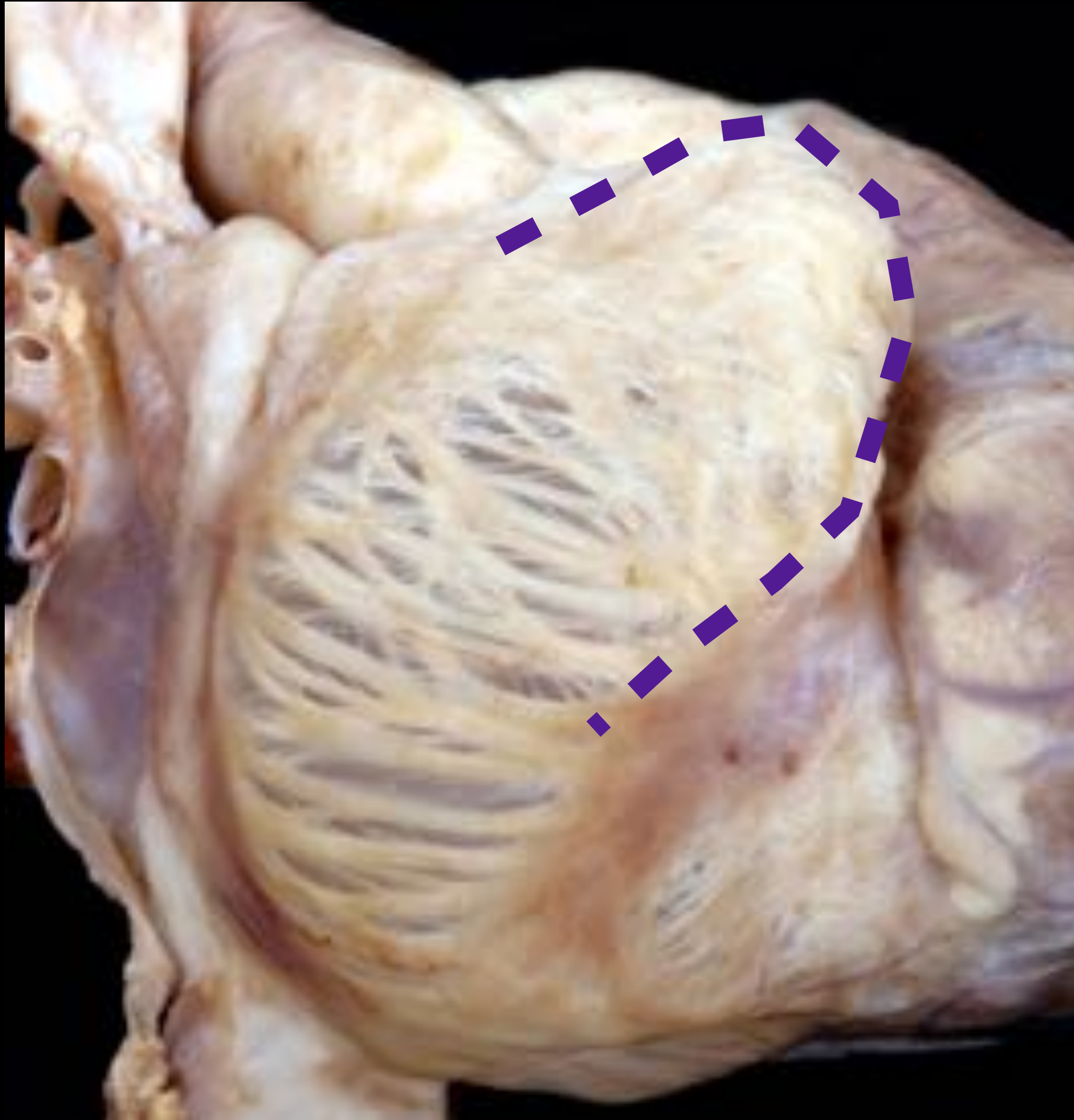
Complex but algorithmic

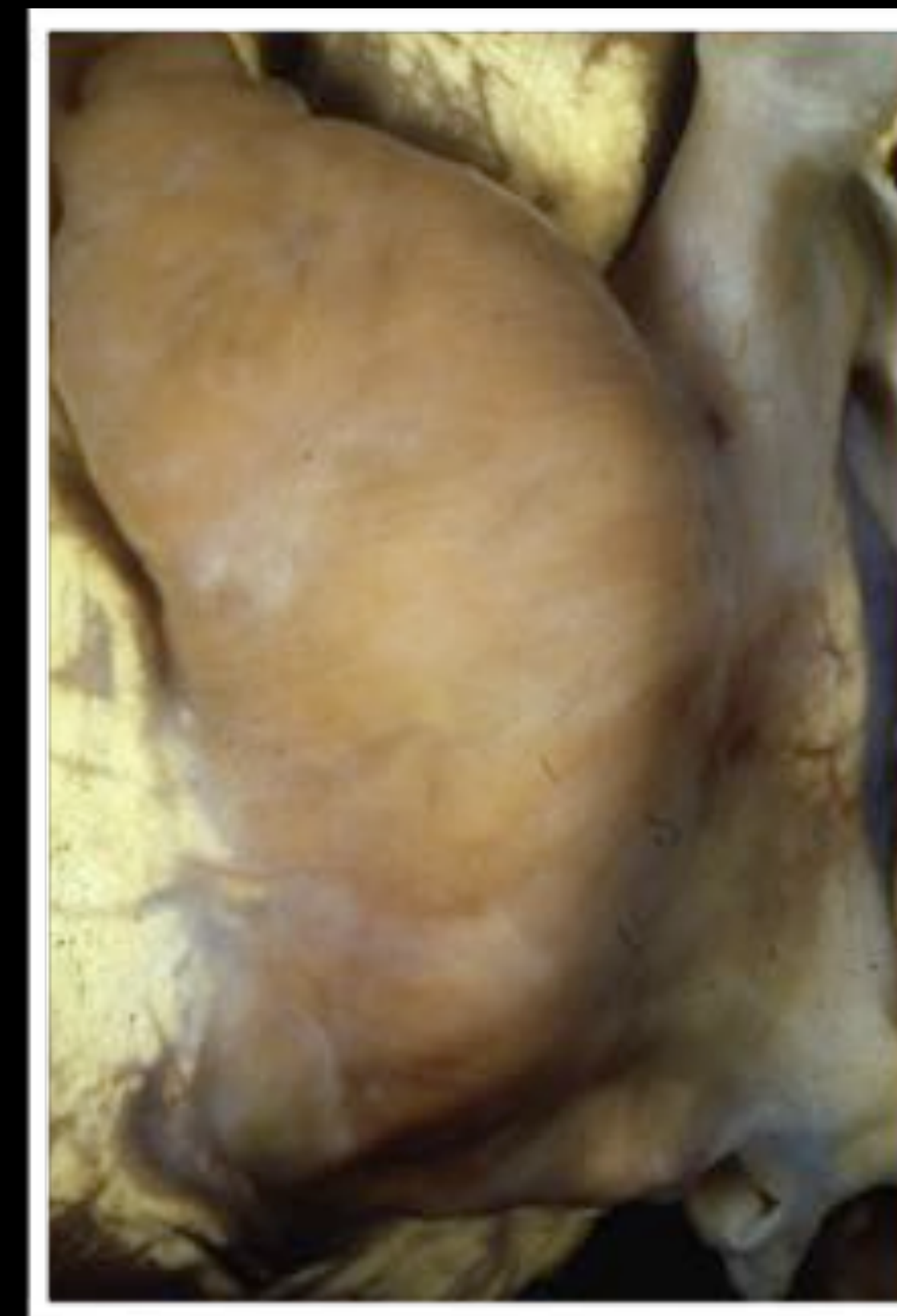
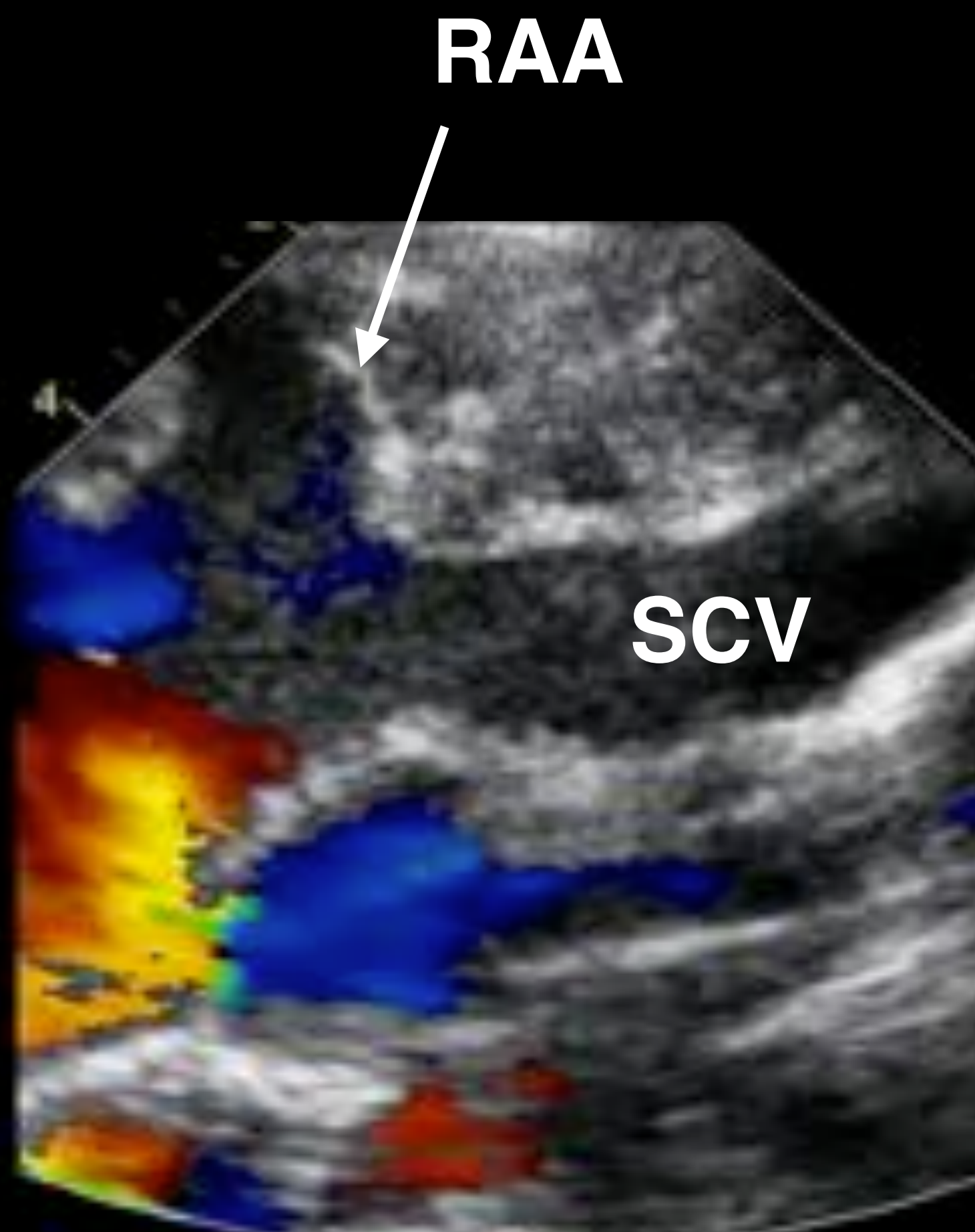


Left-isomerism

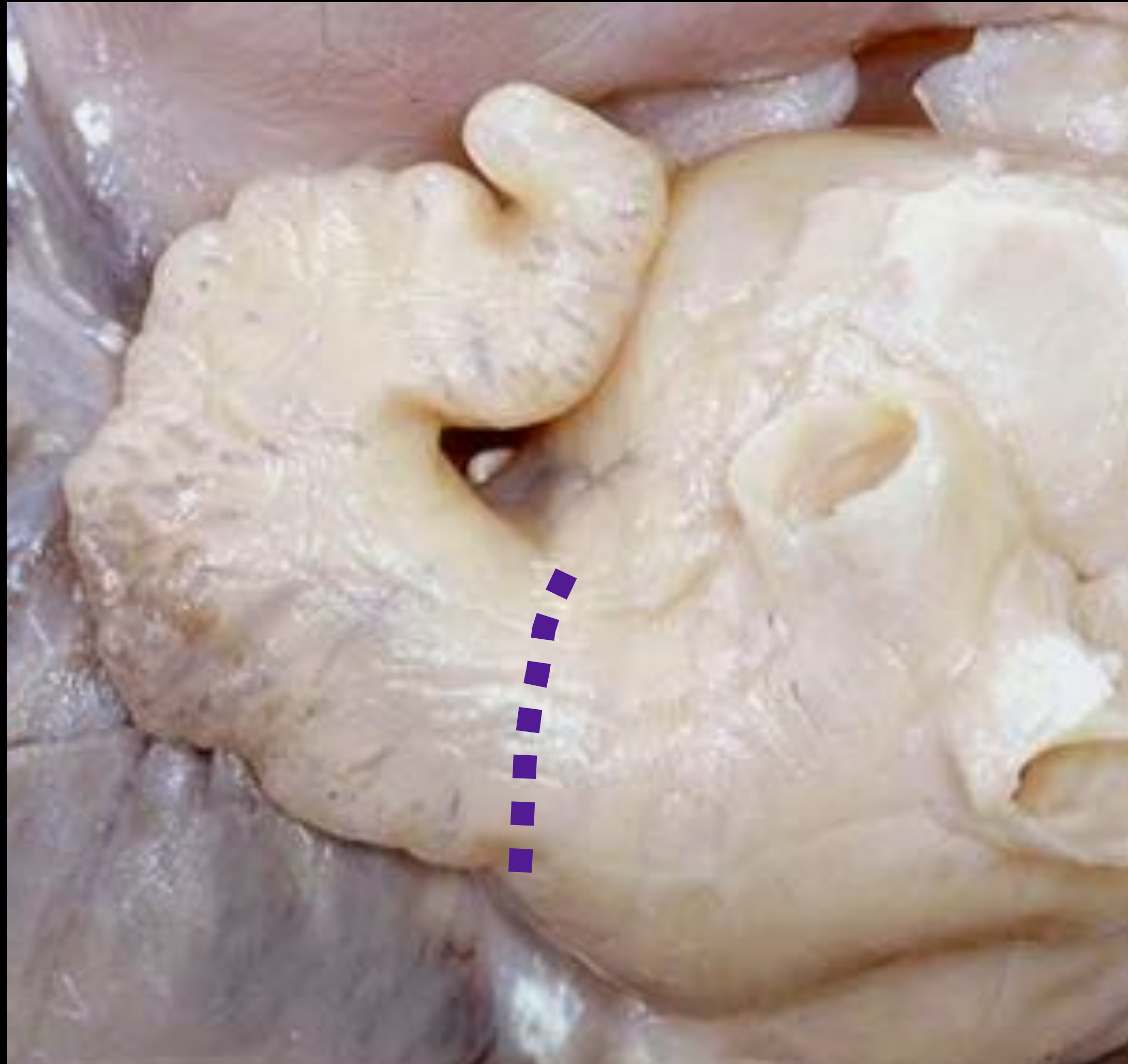


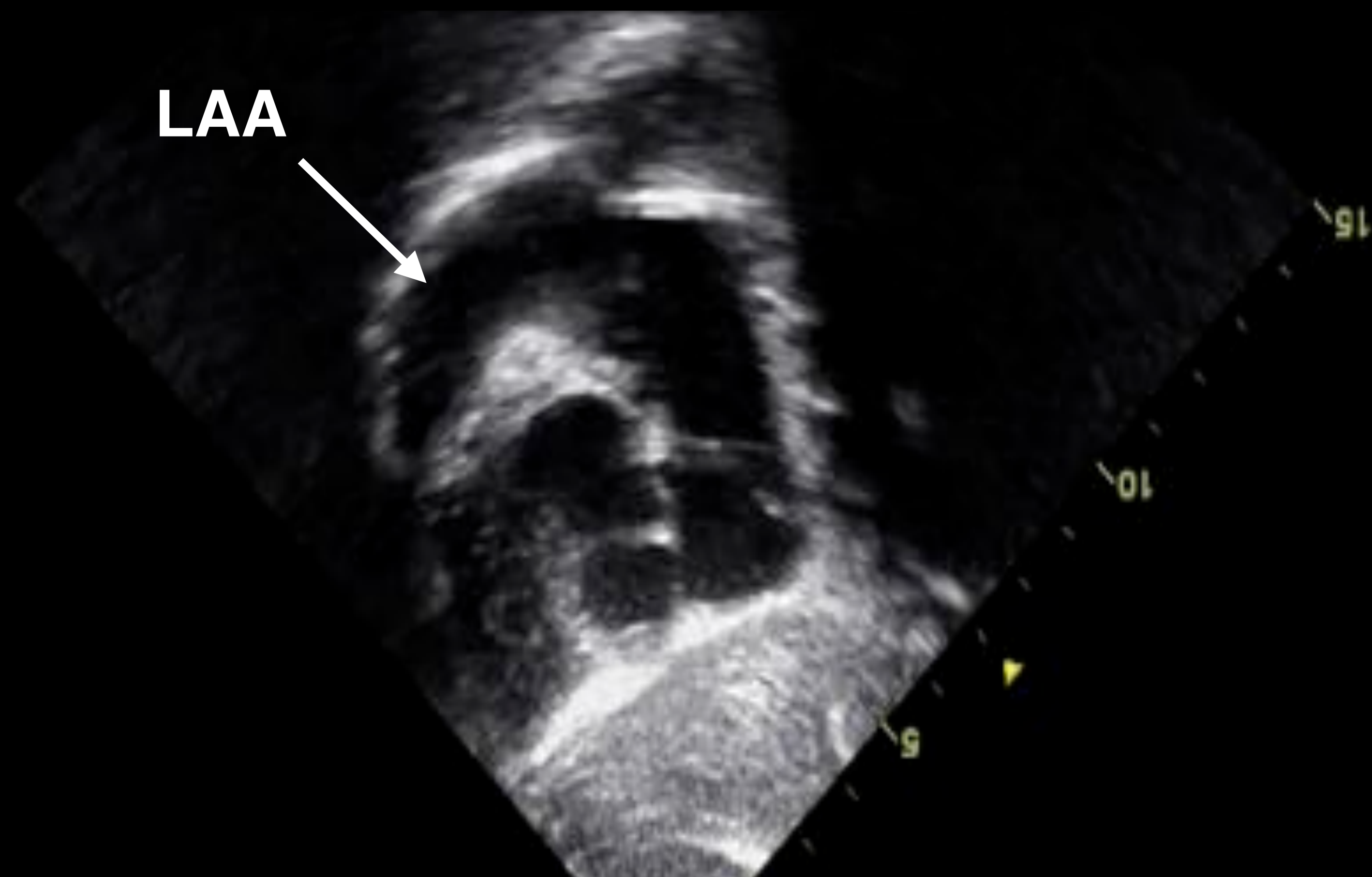
Morphologically Right Atrial Appendages



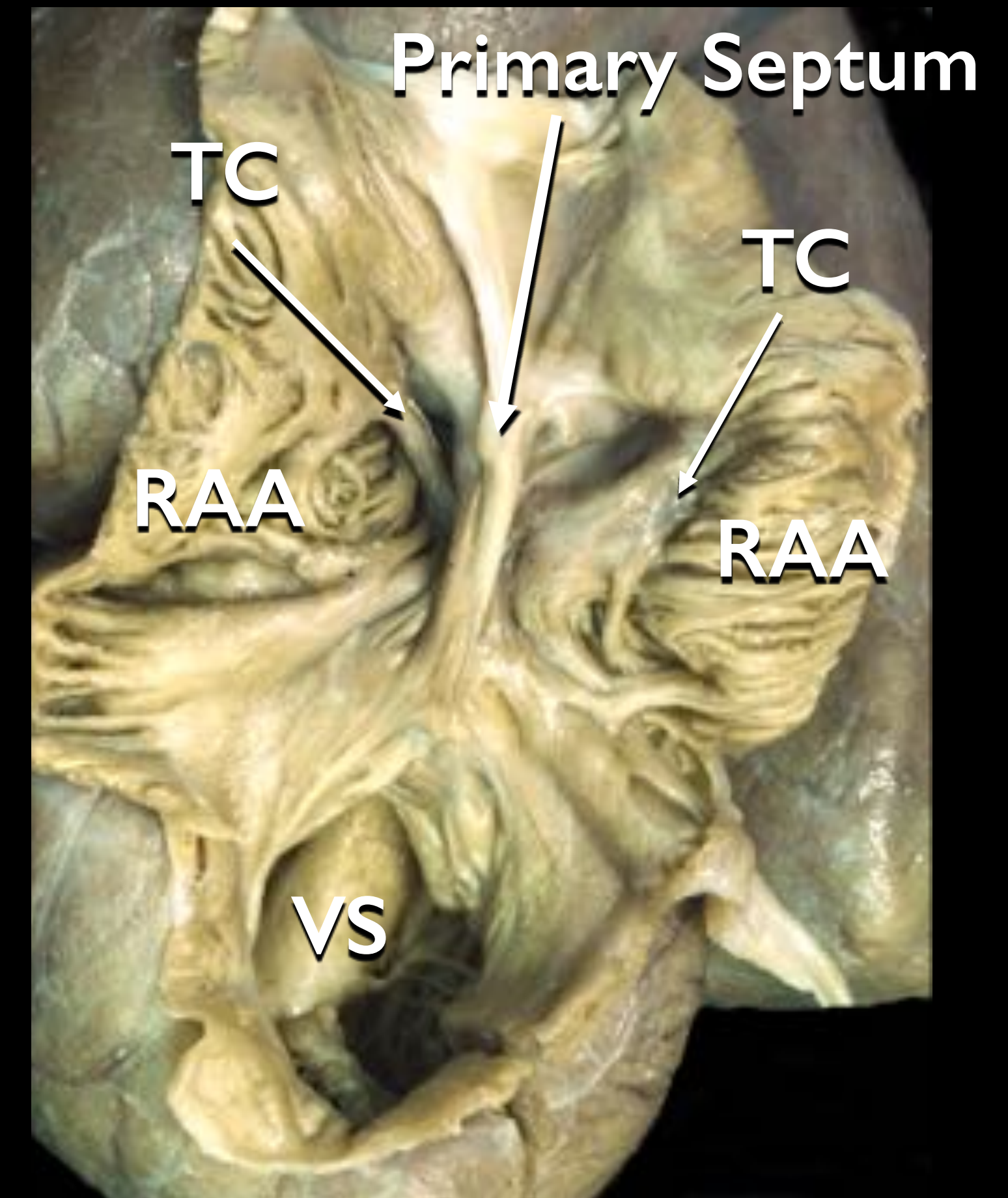
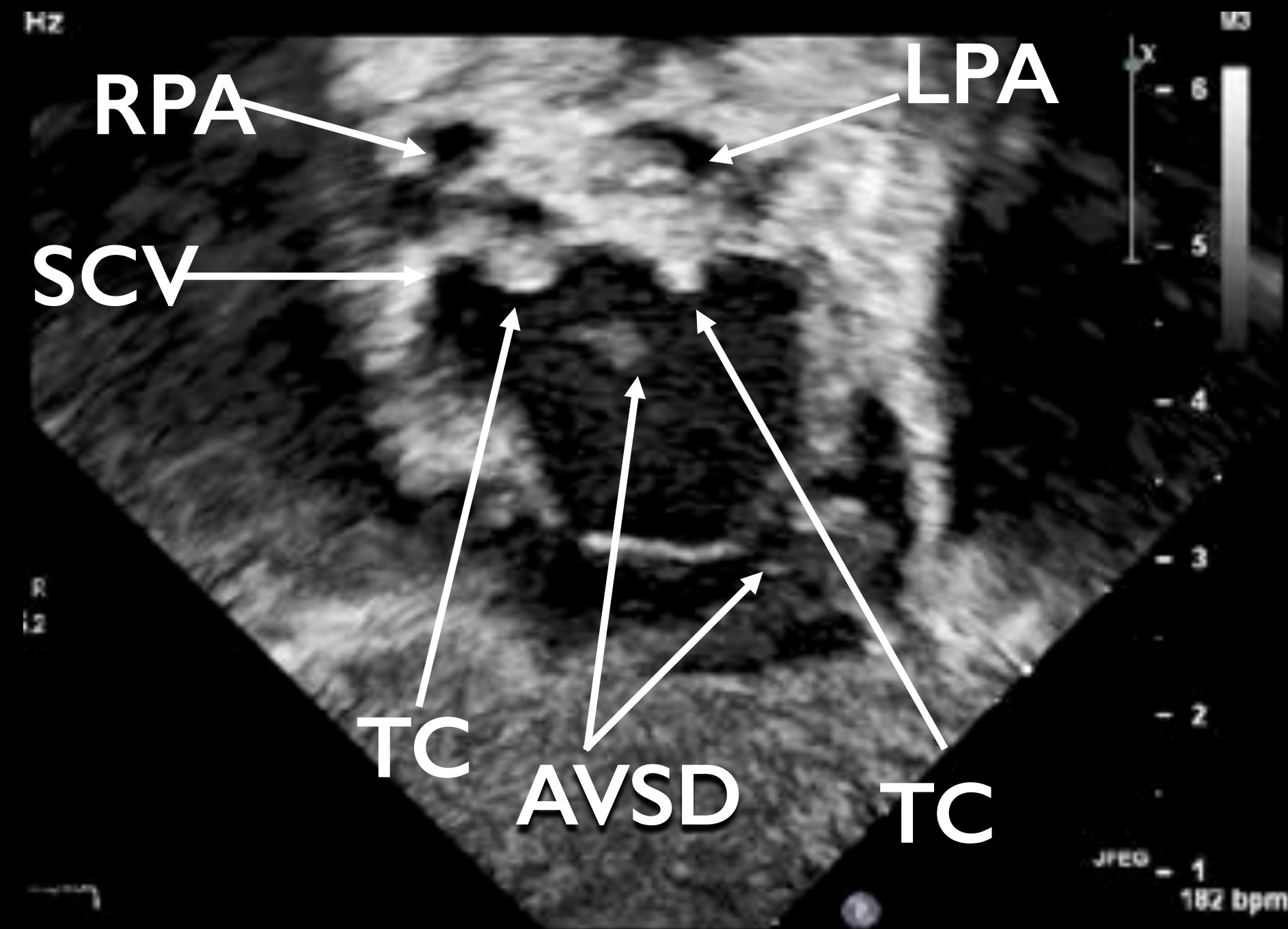


Morphologically Left Atrial Appendages

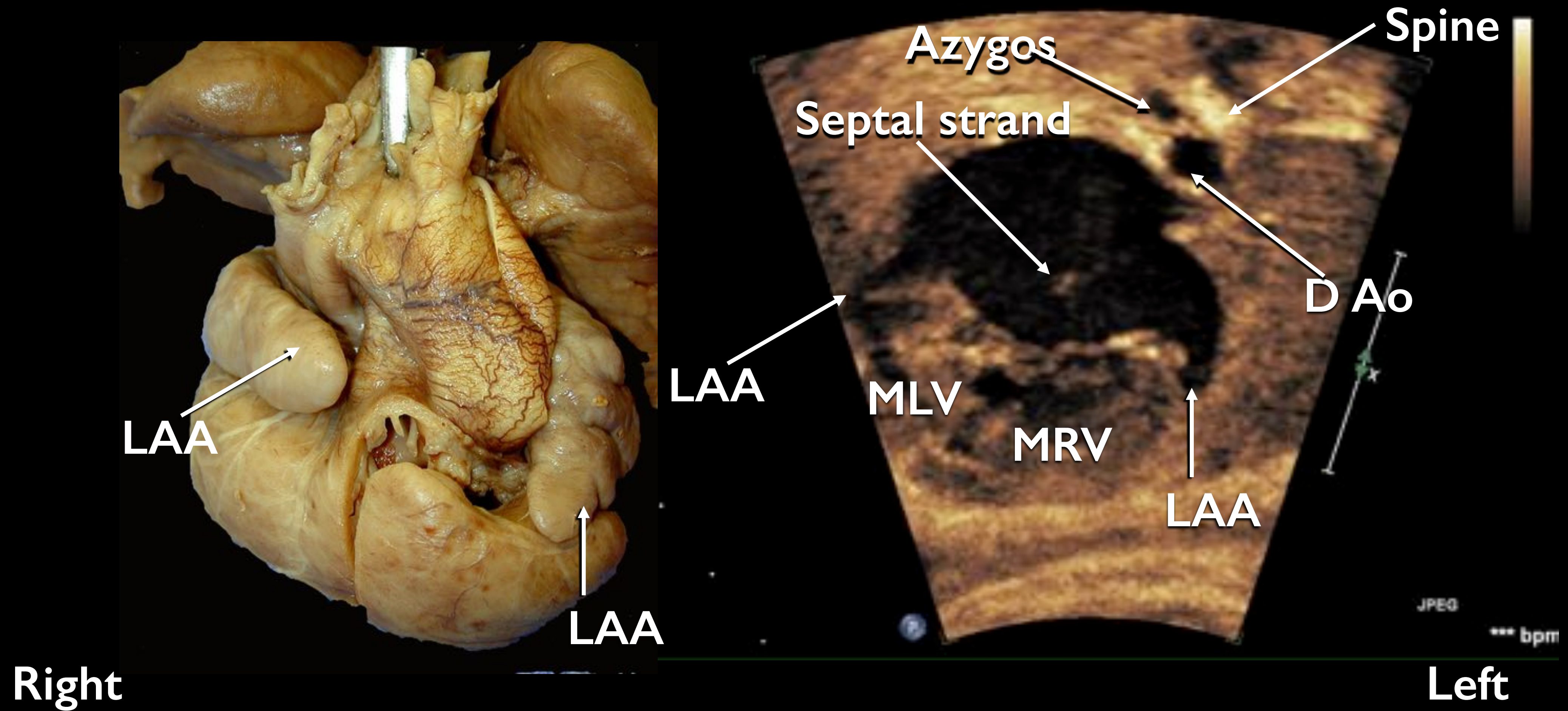




Right Isomerism: Bilateral Terminal Crests

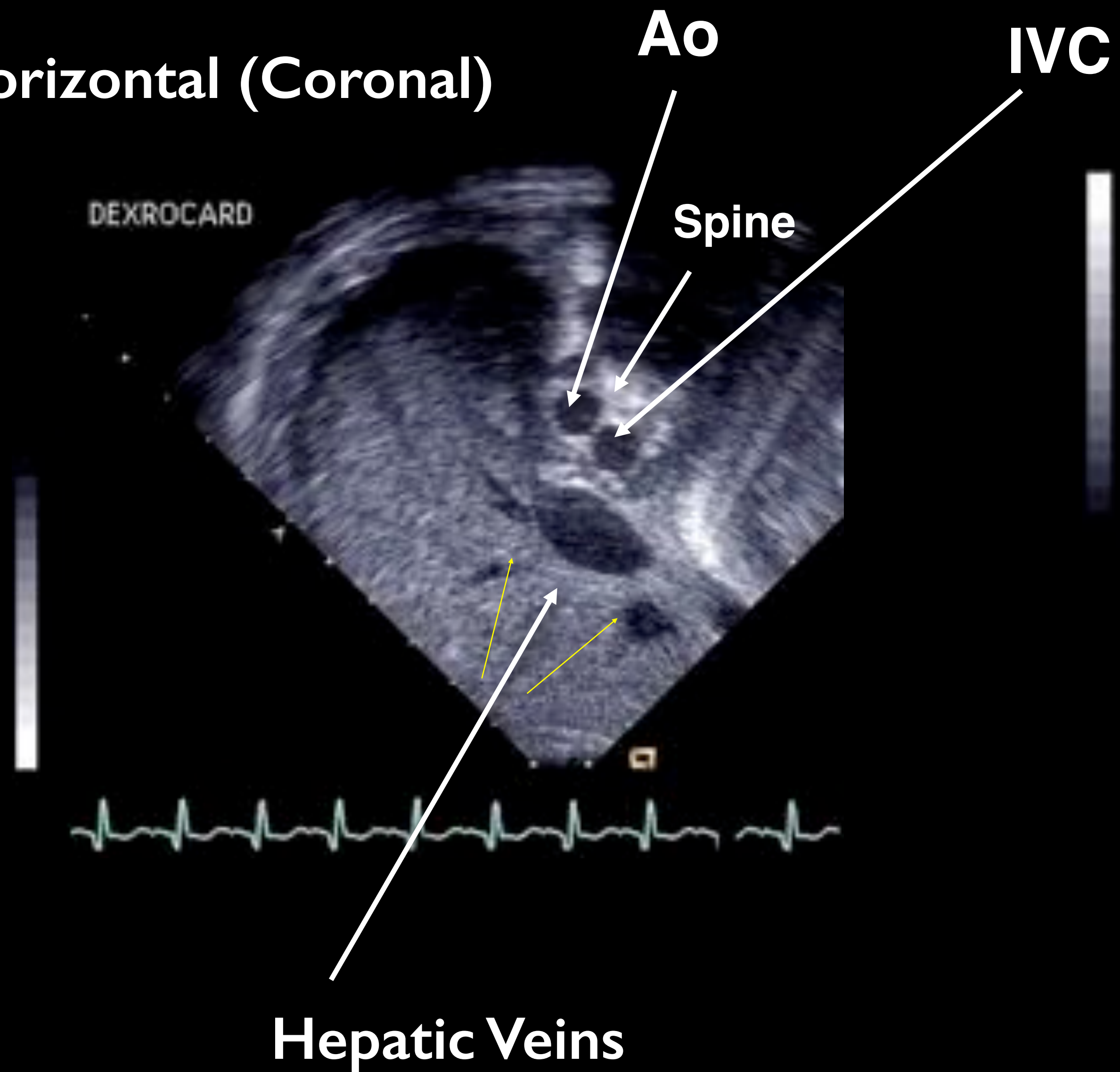


How many left atrial appendages are there?



More frequent in RIGHT isomerism

Horizontal (Coronal)

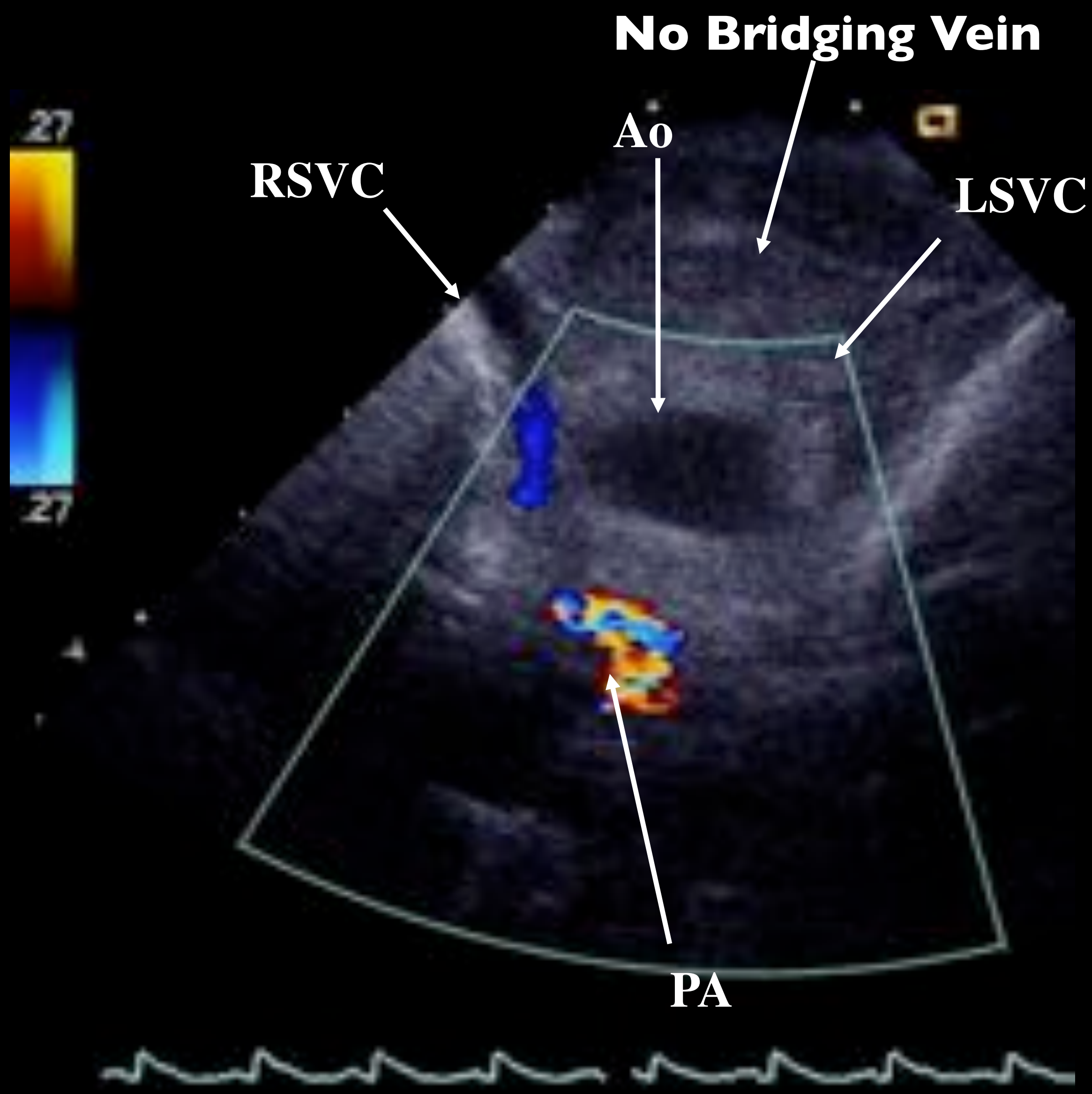


Longitudinal

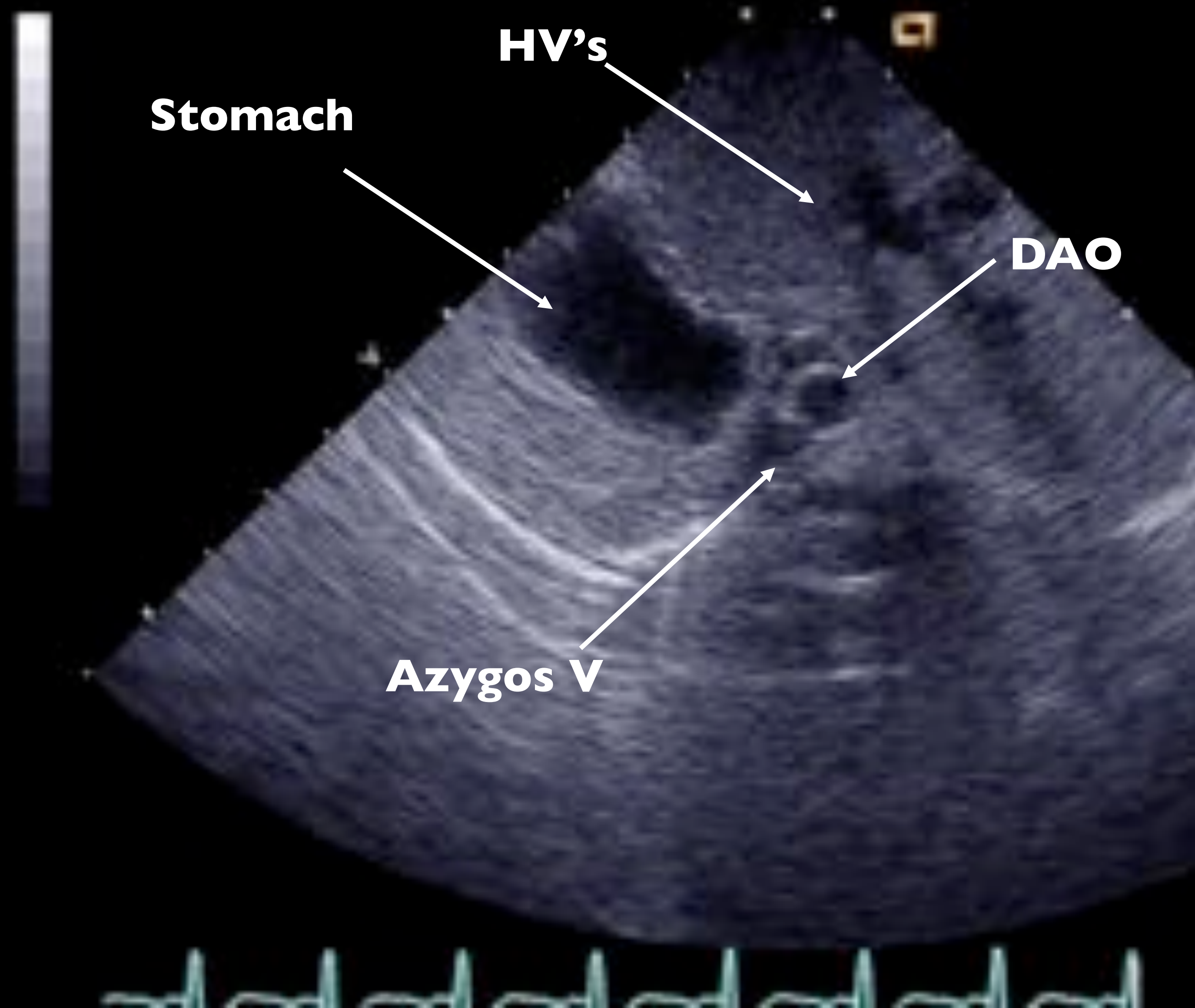


More frequent in RIGHT isomerism

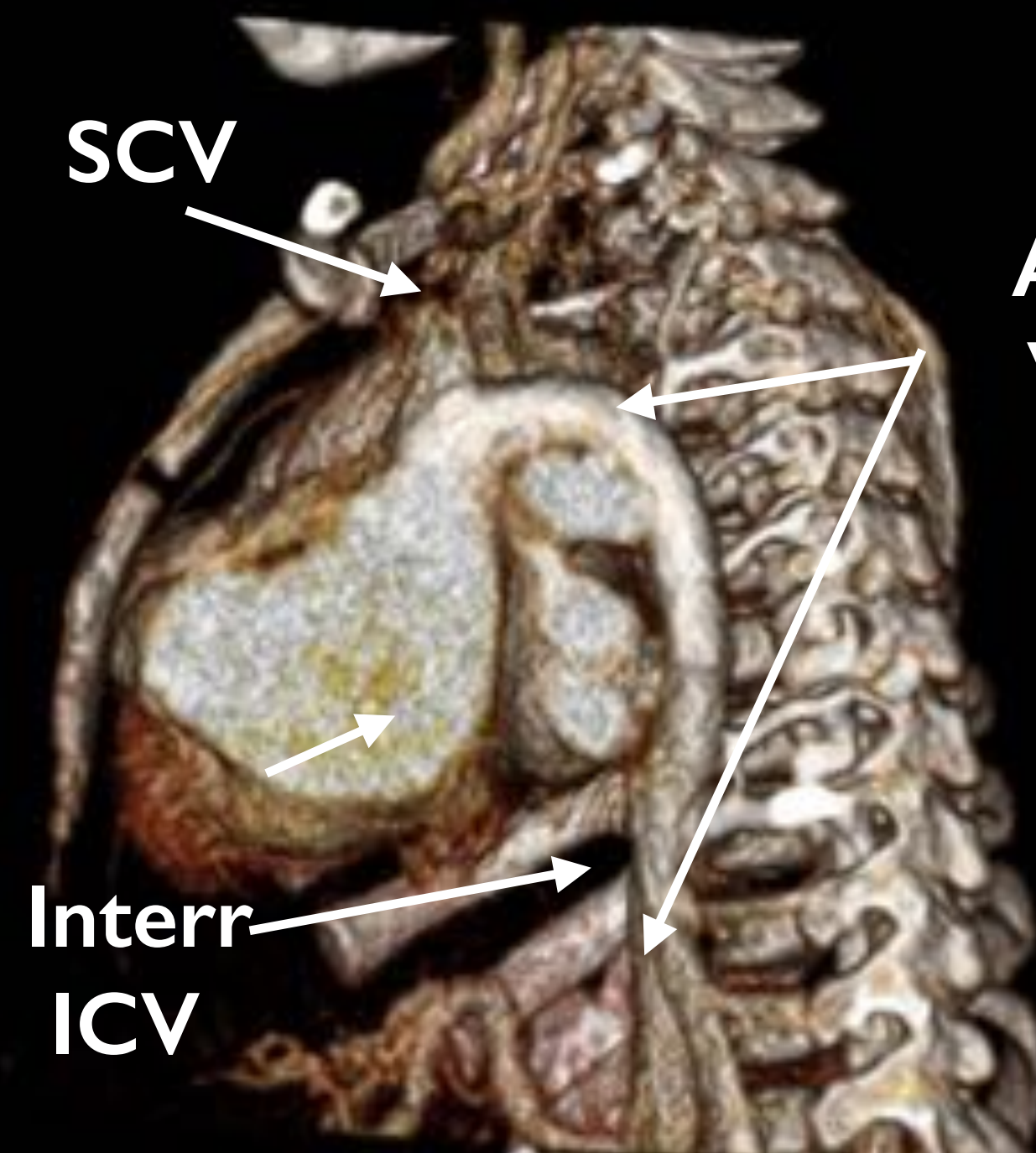
Suprasternal Coronal



More frequent in LEFT isomerism

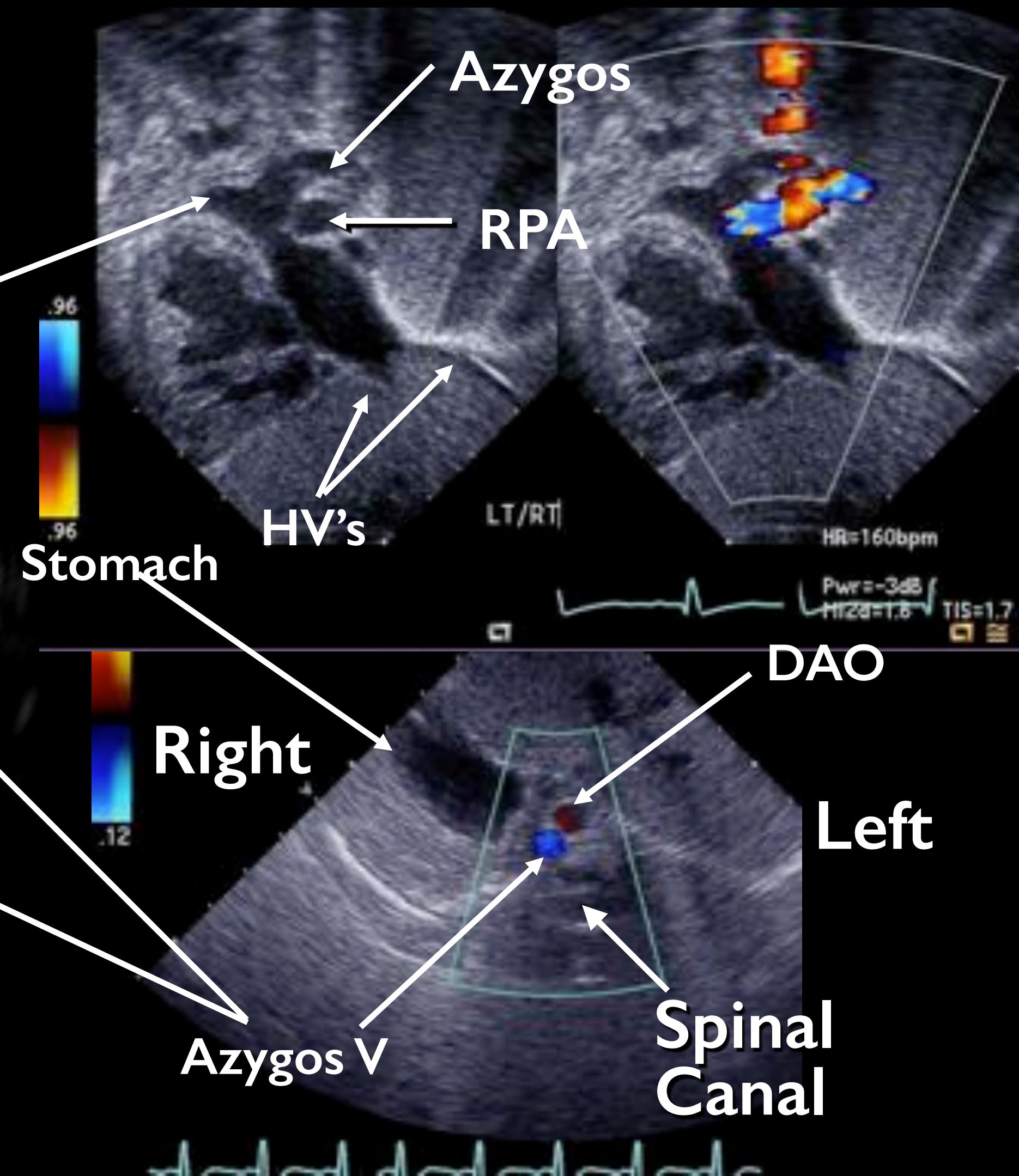


Azygos Arrangement: Left Isomerism

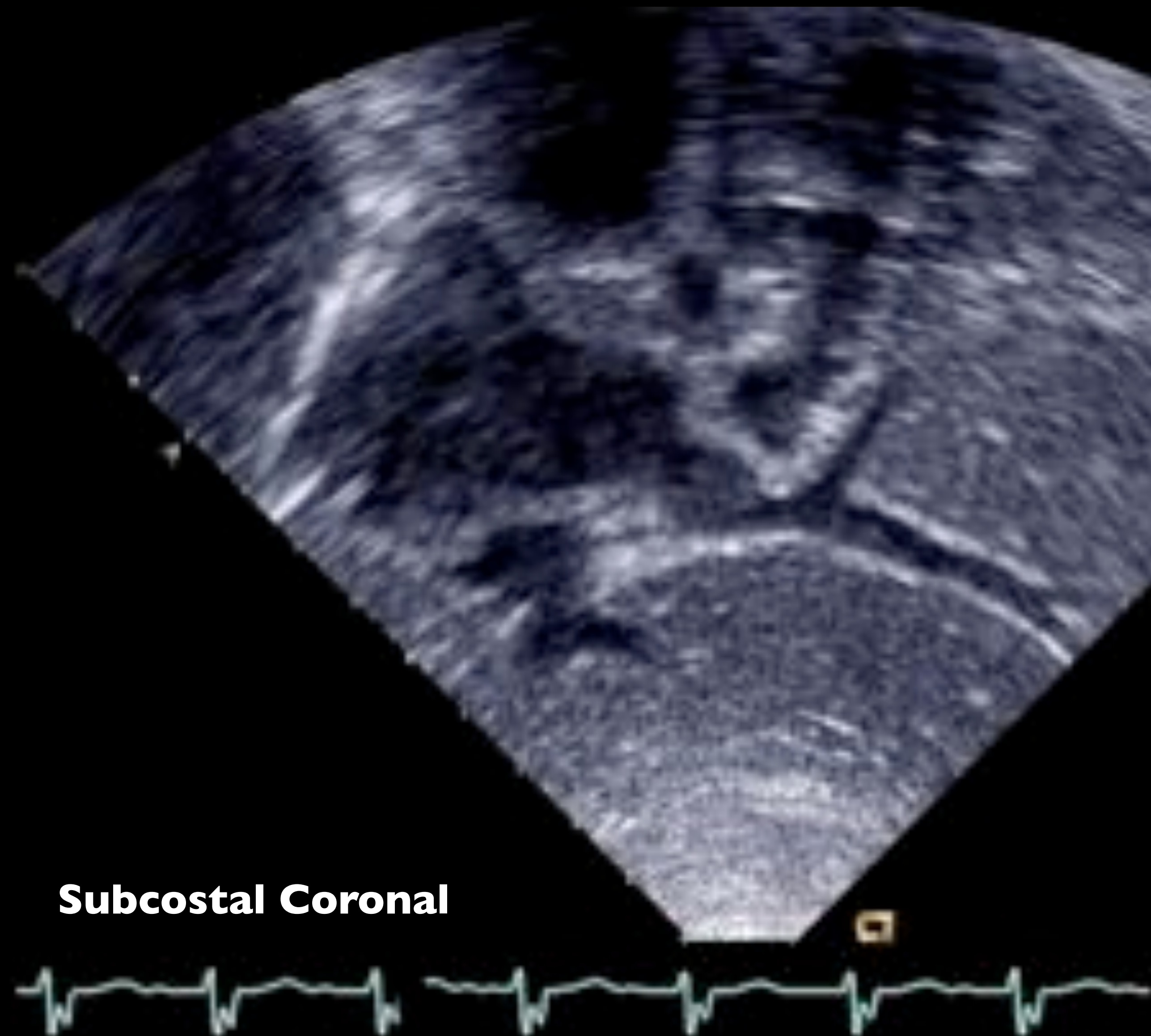


Azygos Vein

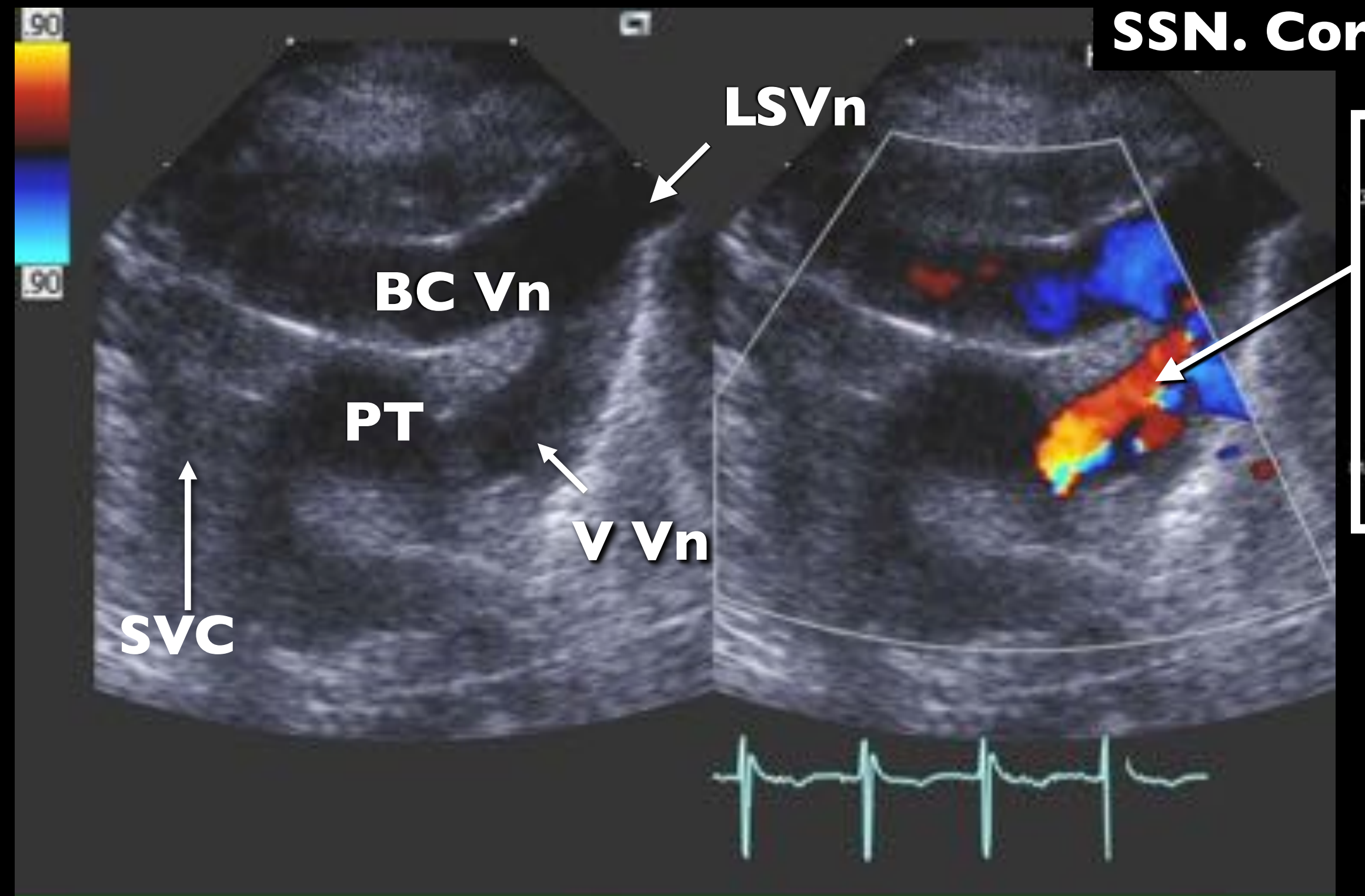
SCV



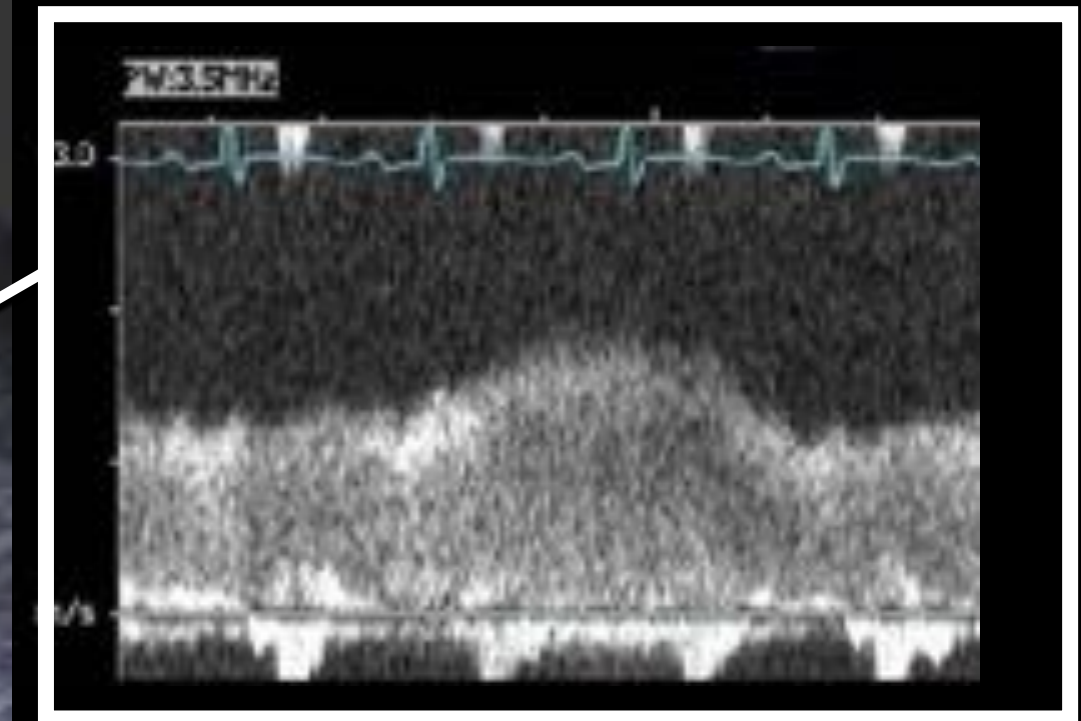
More frequent in LEFT isomerism



Supracardiac TAPVR with Obstruction.

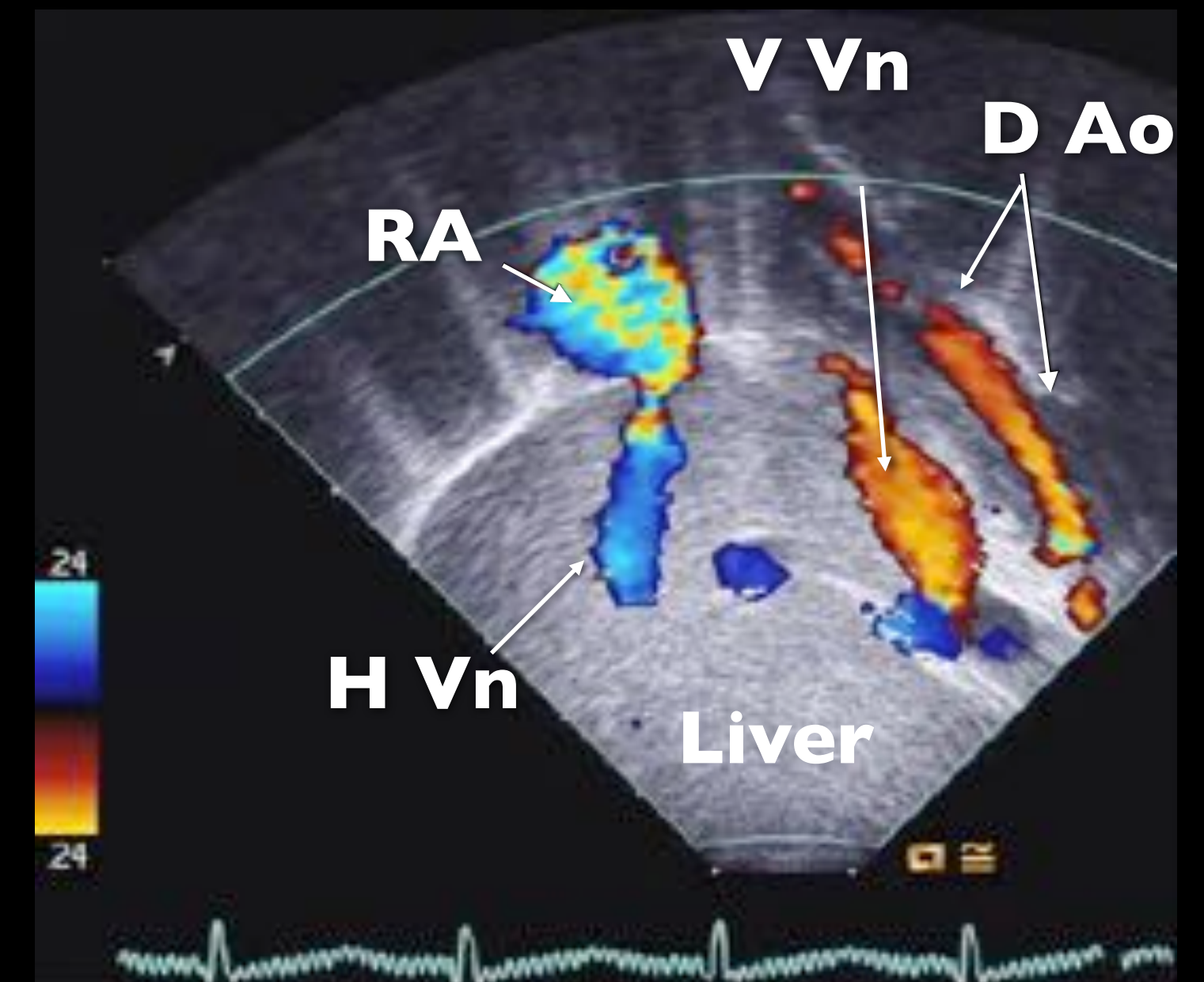
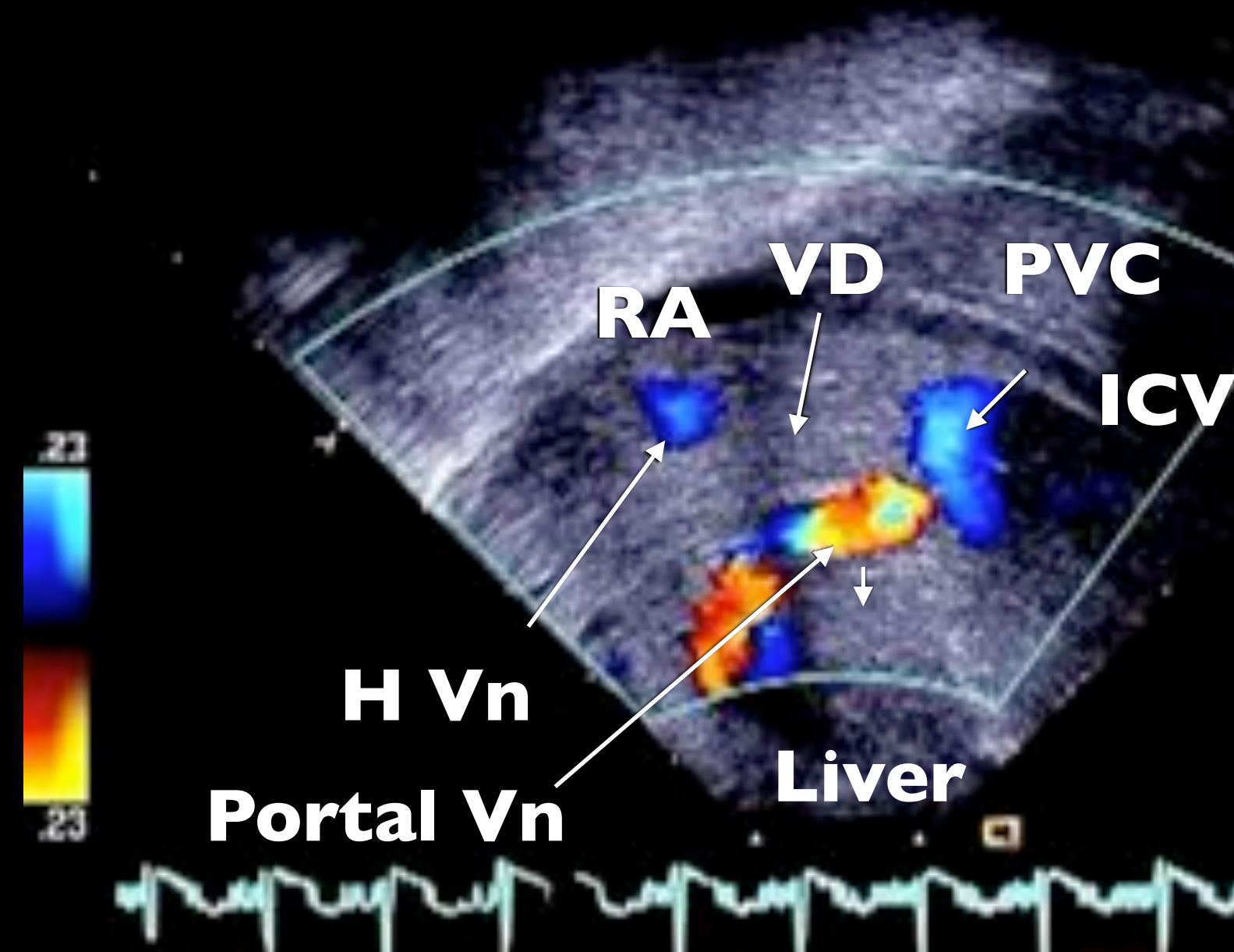
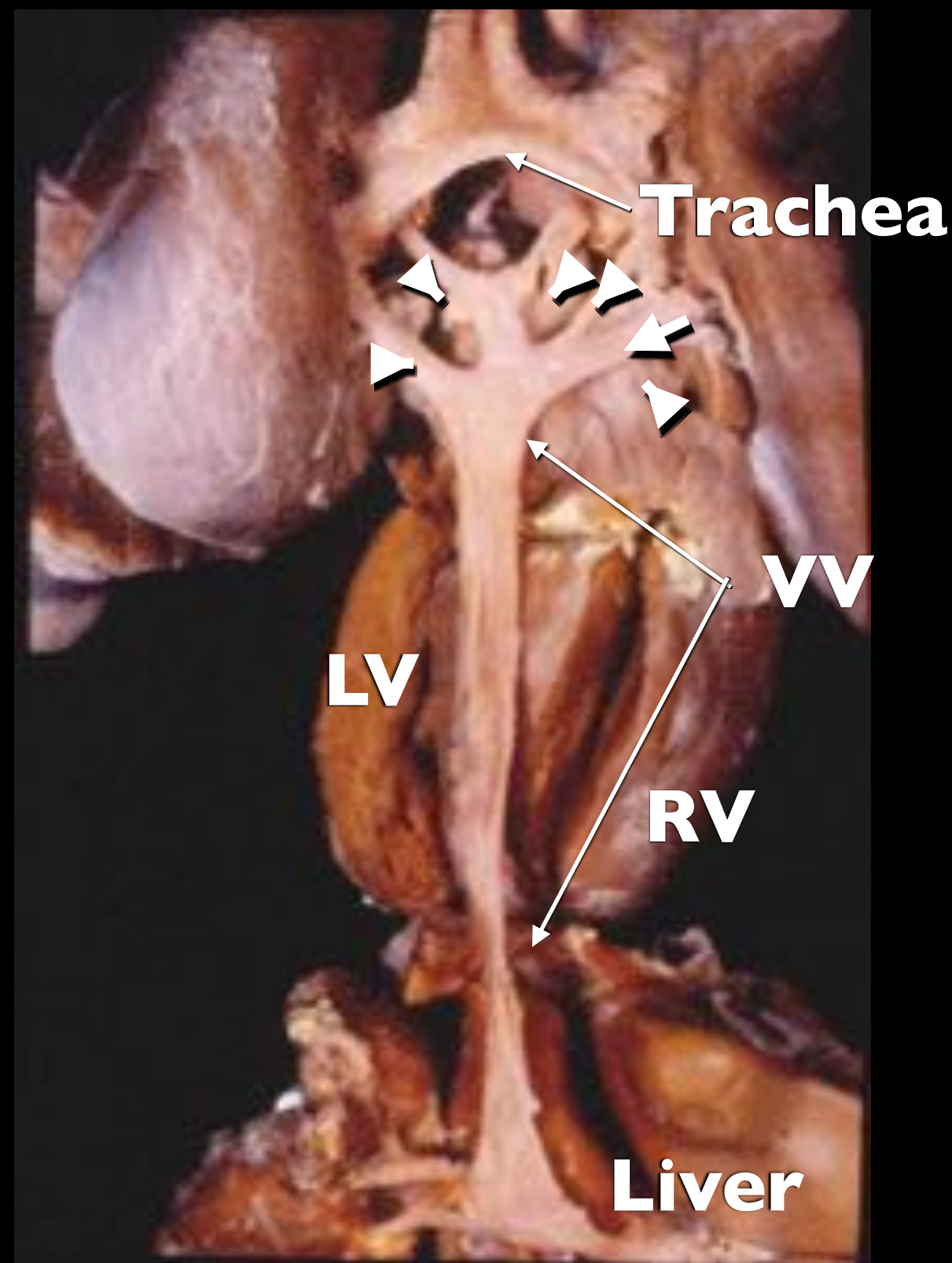


SSN. Cor



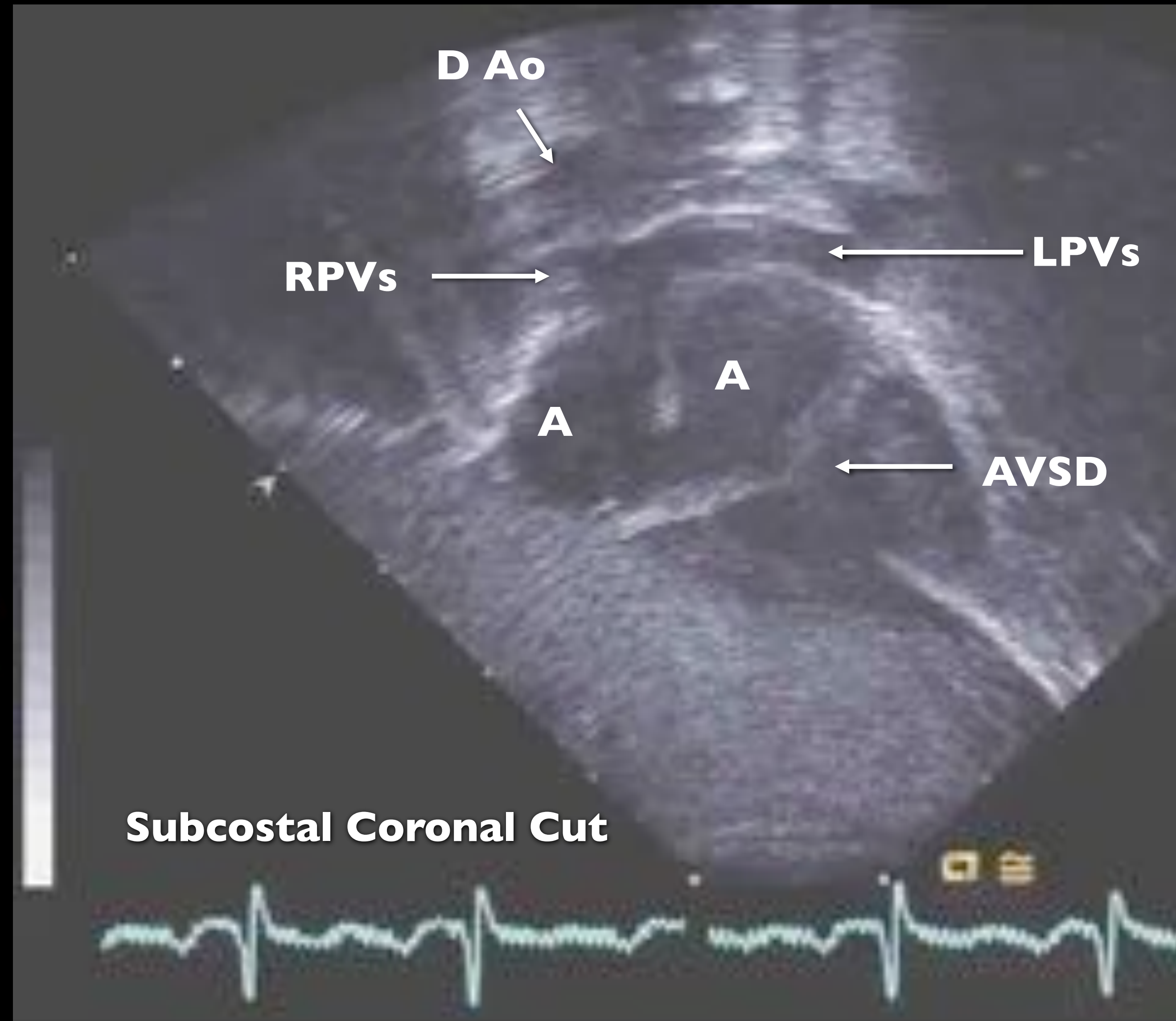
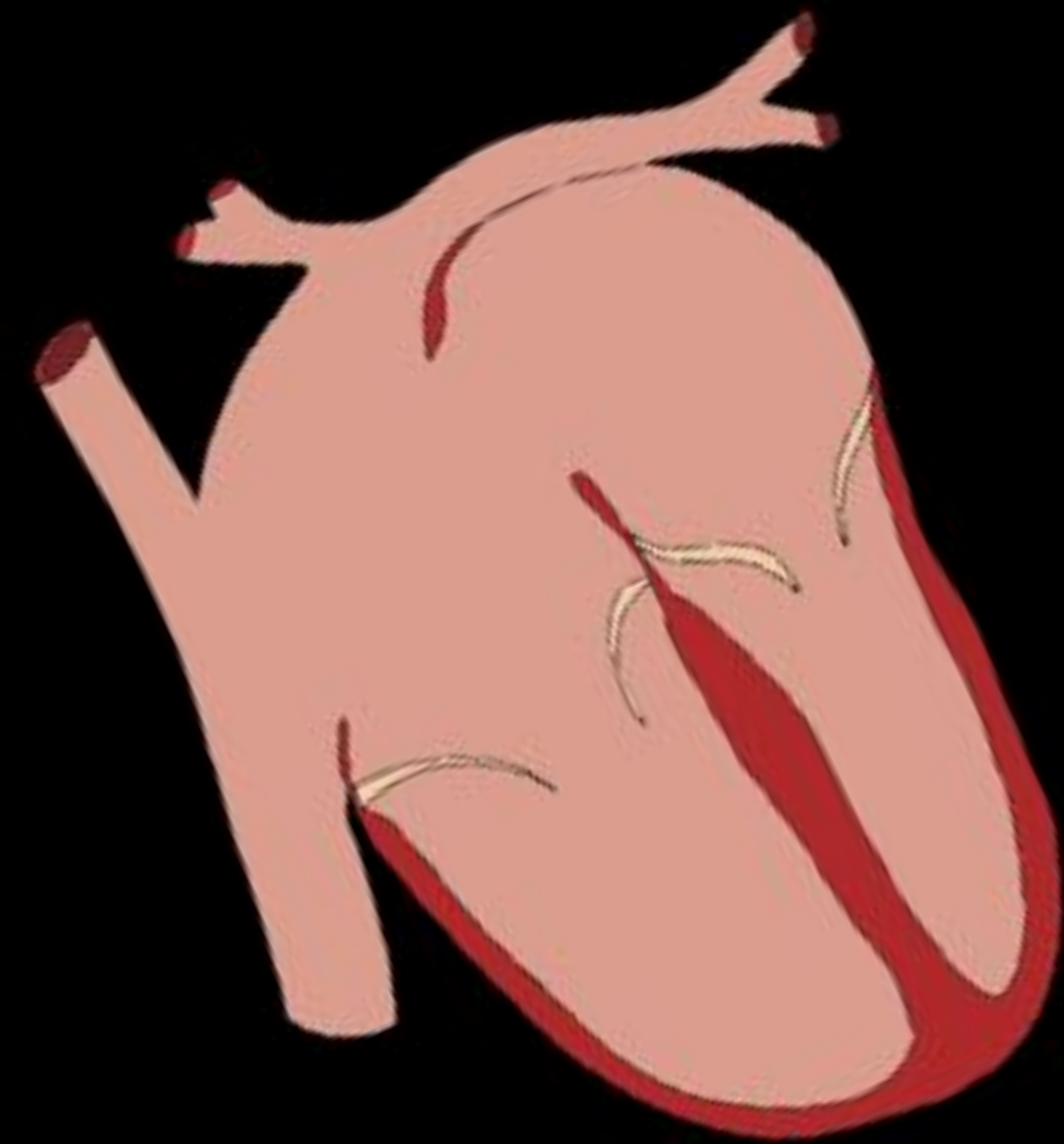
CW Doppler

Right Isomerism: TAPVR Below Diaphragm



S Cost. Sag.

Right Isomerism: Anomalous Pulmonary Venous Drainage to the Right Sided Atrium

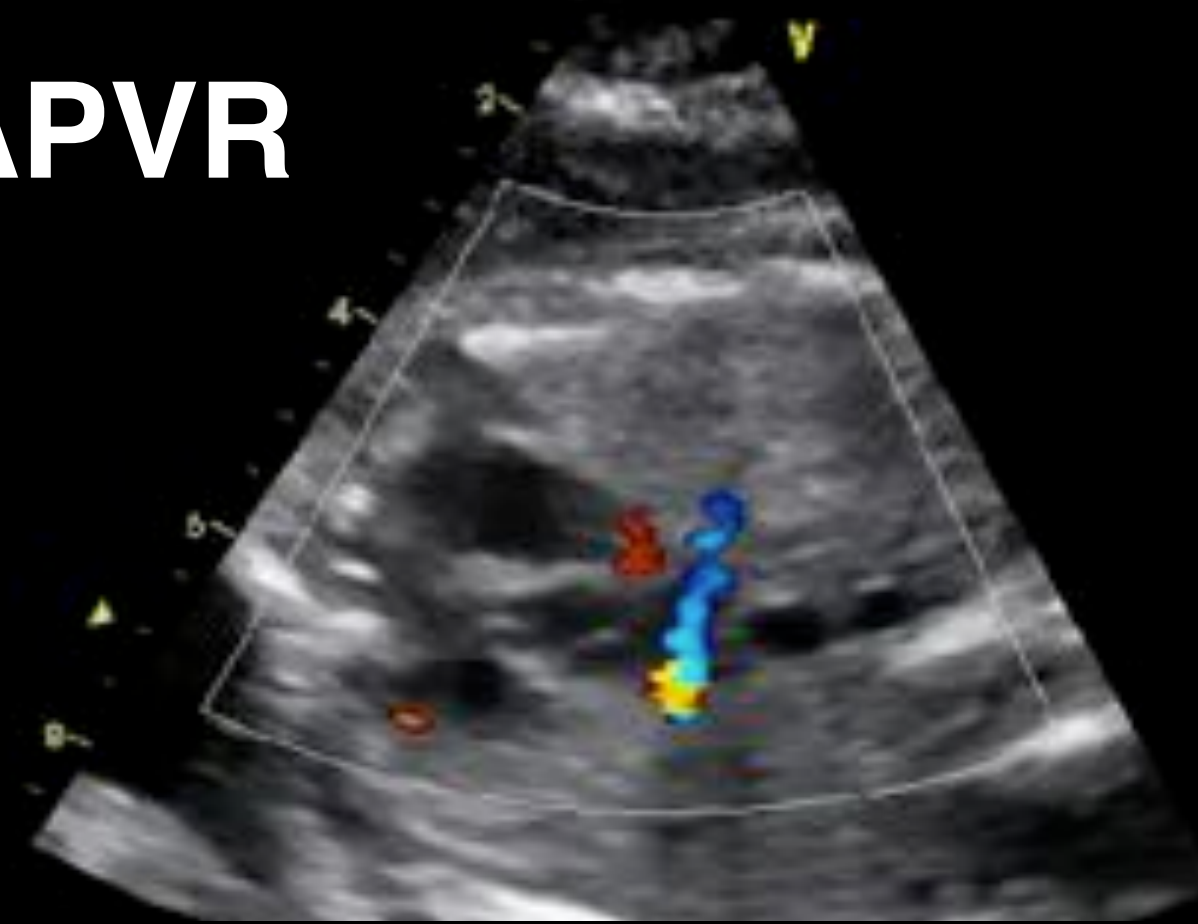


Right isomerism

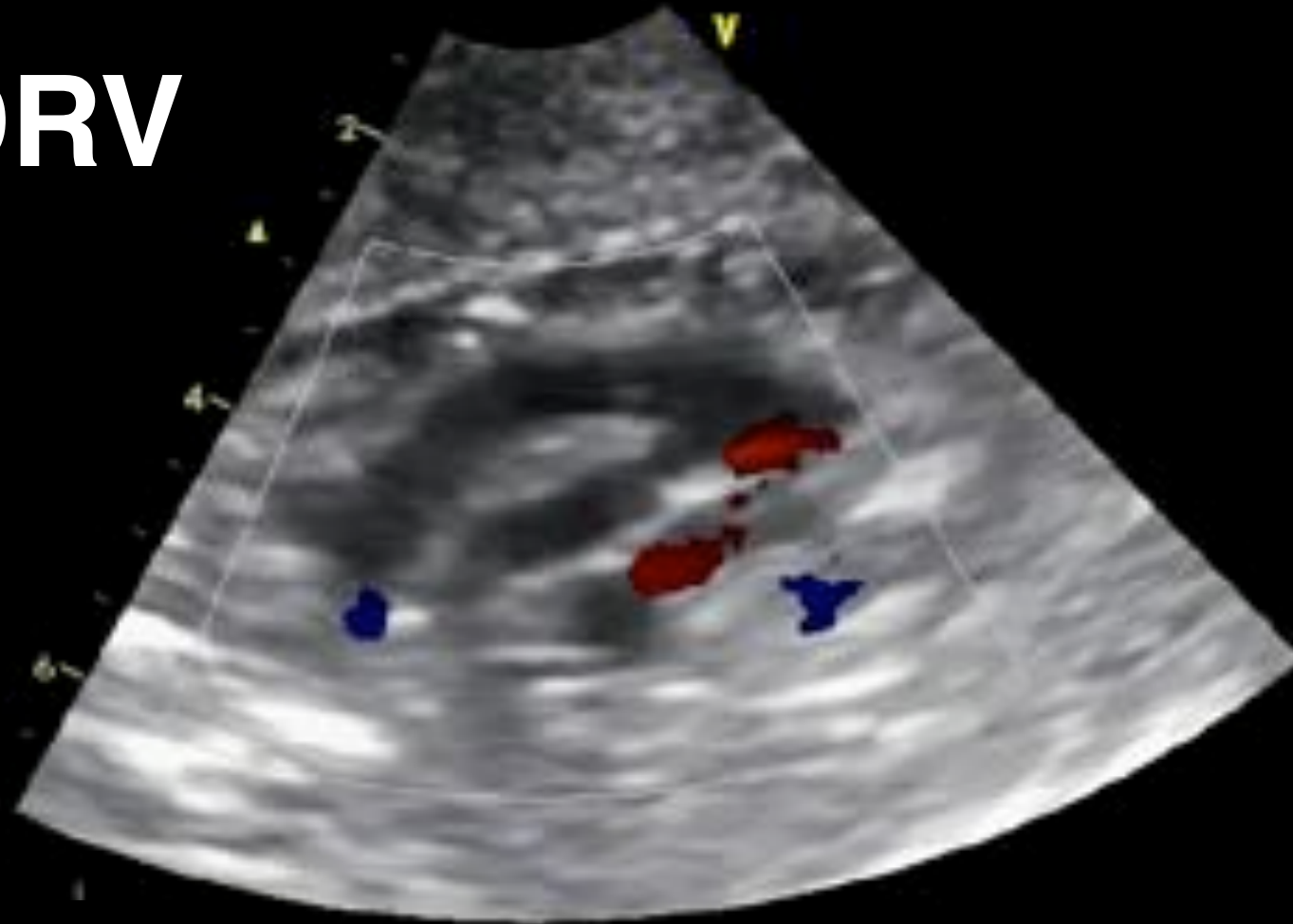
AVSD



TAPVR



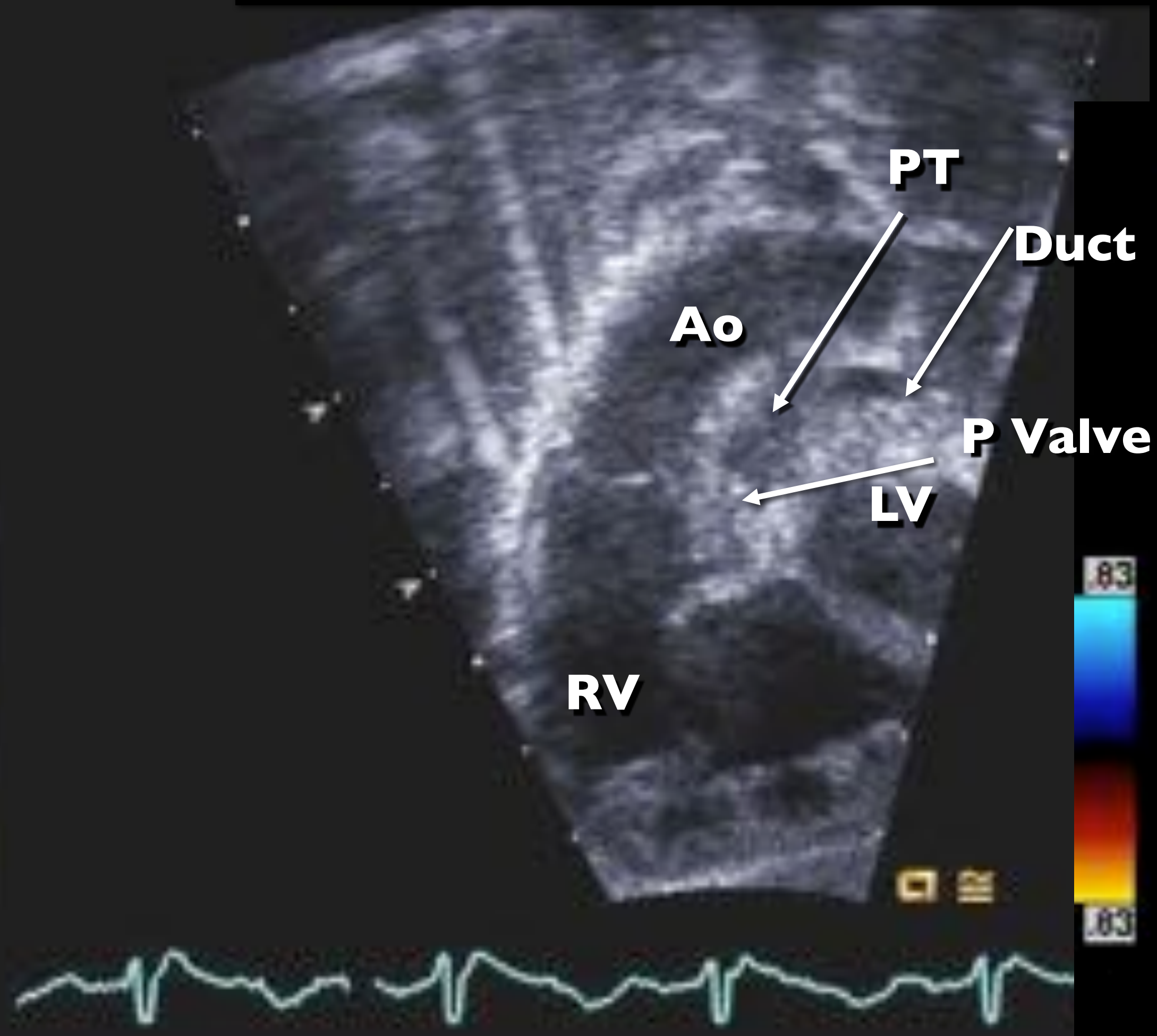
DORV



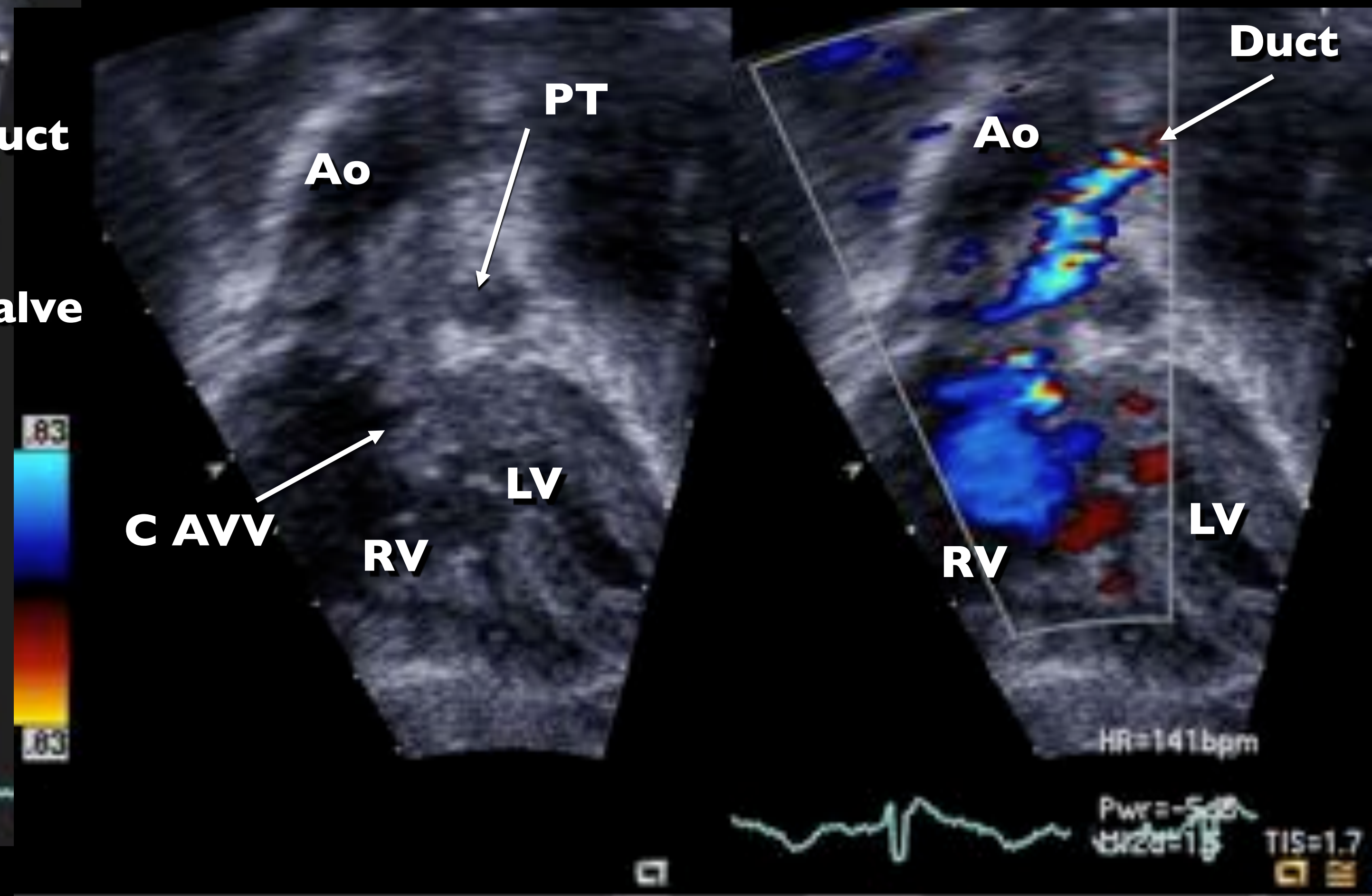
PS



Right Isomerism: Pulmonary Stenosis/ Atresia with TGA/DORV

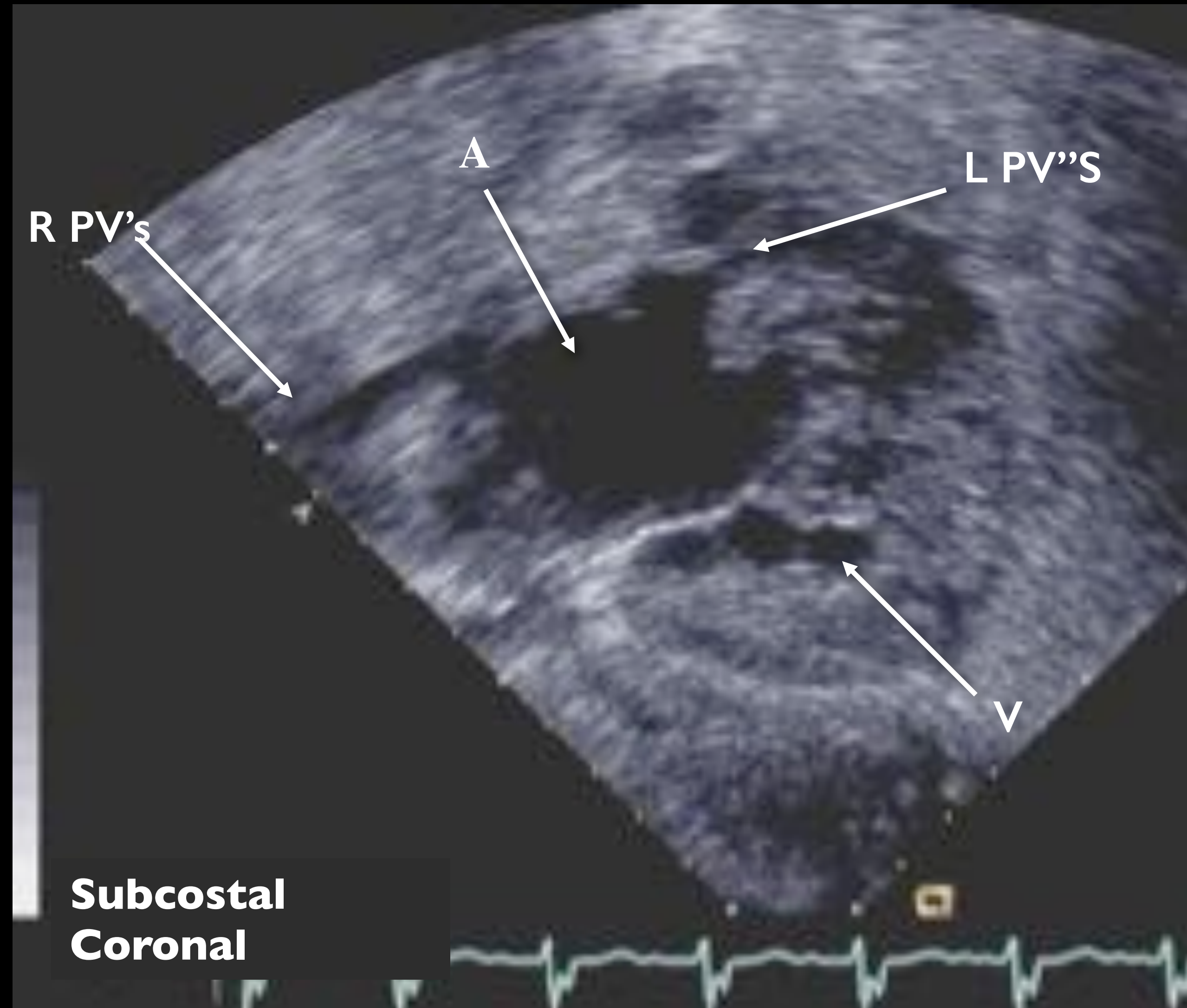


Subcostal Sagittal

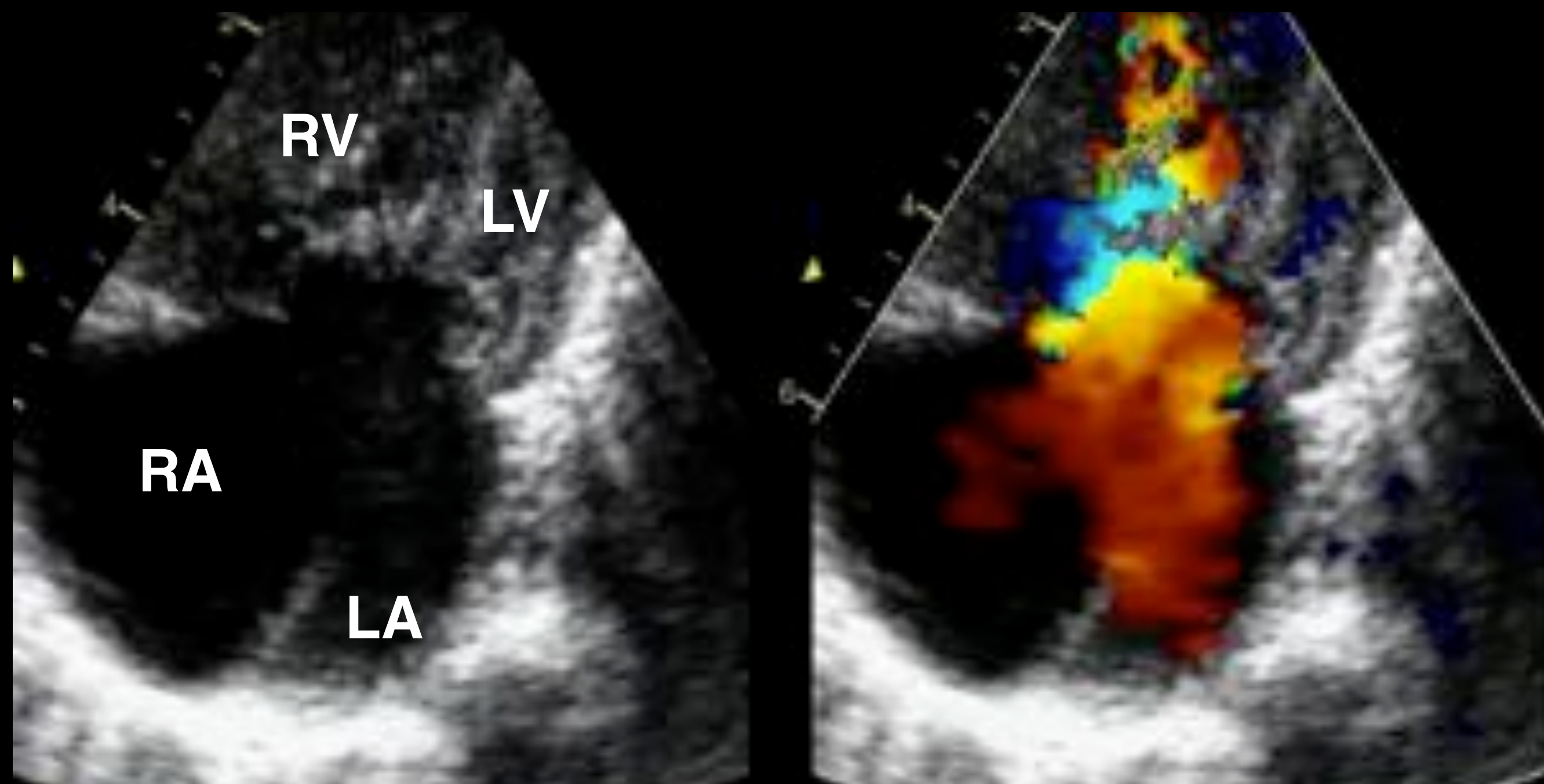


Subcostal Coronal

Left isomerism: AVSD with single atrium



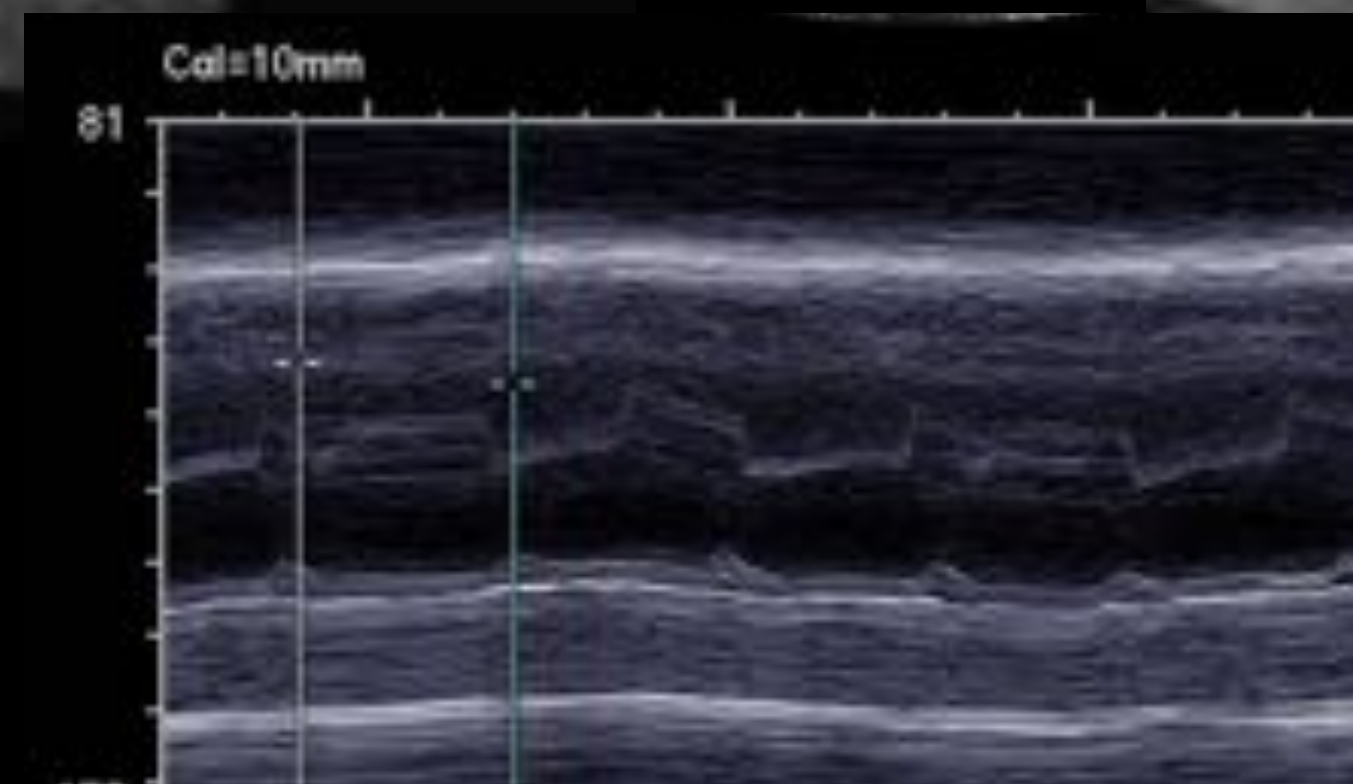
Left isomerism - AVSD with small LV



AV Block



Left isomerism - “Single Ventricle” with Atrioventricular Valve

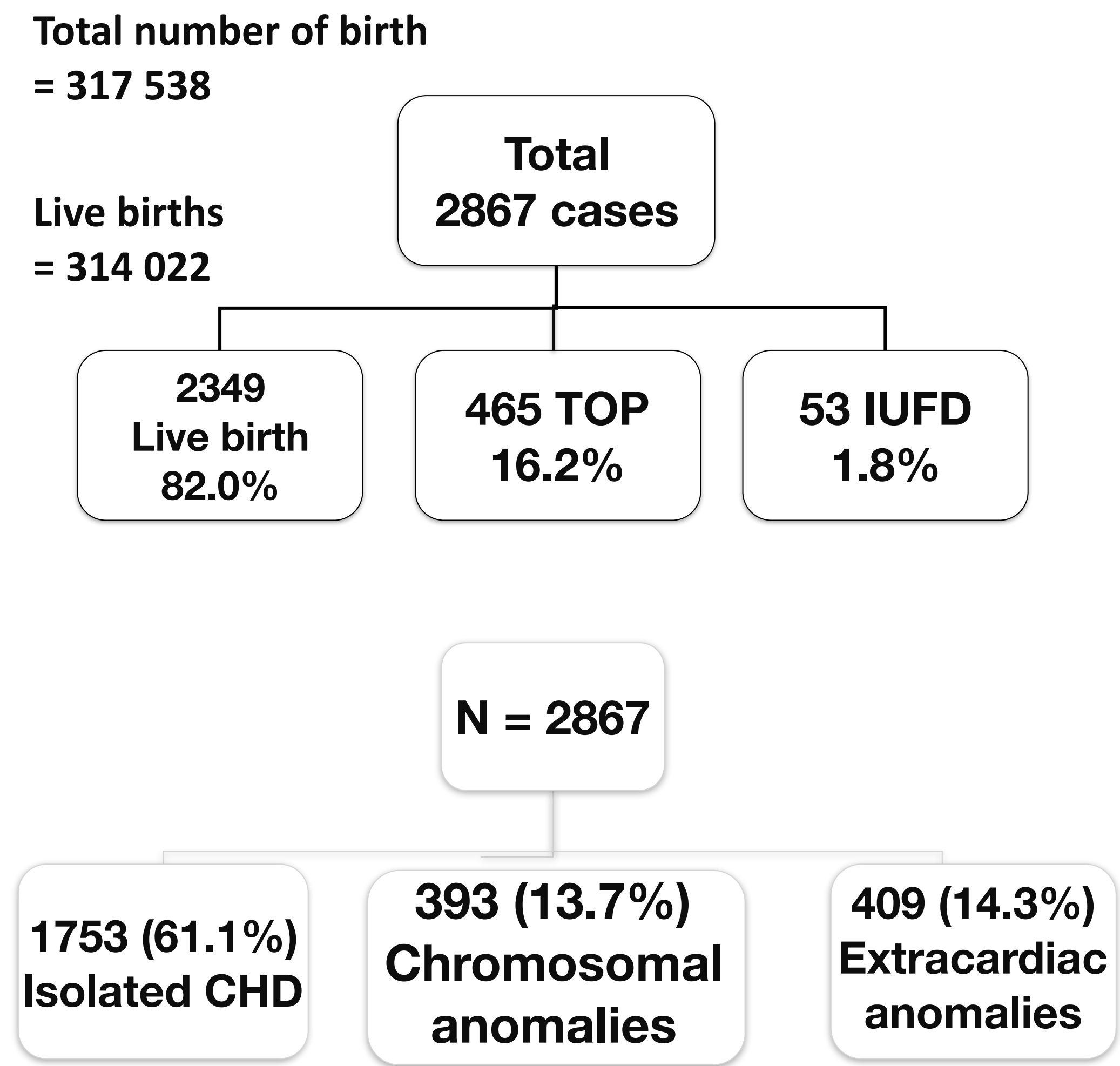


Heterotaxy is currently recognised prenatally

- Quite frequent
 - Incidence varies between 3-10% of major CHD in infants
 - Constitutes
 - 6% of one fetal echo series of CHD (Huggon JACC 2000)
 - 11% of a fetal pathology series (Cook CitY 2001)
- Easily recognizable in fetus because of the complexity or type of CHD
- Associated with a very poor prognosis
 - Including intra uterine fetal death

Prevalence, pre- and post-natal diagnosis, and infant mortality of newborns with congenital heart defects: A population-based study using the International Paediatric and Congenital Cardiac Code (IPCCC)

The EPICARD Study Group



Distribution of categories of CHD and associated anomalies

ACC-CHD categories	Total		Live births	
	% of chromosomal anomalies	% of extra cardiac anomalies	% of chromosomal anomalies	% of extra cardiac anomalies
Heterotaxy	0	24.3	0	25.0
Anomalies of venous connections	19.4	16.1	7.7	15.4
Anomalies of atria	9.9	19.8	7.5	19.0
Anomalies of AV junction and AV valves	57.3	12.7	43.1	13.8
Complex anomalies of AV junction	0	7.7	0	0
Functionally univentricular heart	15.8	19.6	8.3	20.8
Ventricular septal defects	9.3	11.1	3.9	11.0
Anomalies of ventriculo-arterial connections	10.7	18.8	4.5	14.1
Anomalies of extra pericardial trunks	15.9	31.2	3.2	26.4
Congenital anomalies of coronary arteries	0	0	0	0

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Proportion of prenatal diagnosis

In categories of CHDs

ACC-CHD categories	% of prenatal diagnosis (n)
Heterotaxy	89.2 (37)
Anomalies of venous connections	16.0 (25)
Anomalies of atria	4.3 (164)
Anomalies of AV junction and AV valves	67.0 (91)
Complex anomalies of AV junction	100.0 (13)
Functionally univentricular heart	92.5 (133)
Ventricular septal defects	9.6 (1353)
Anomalies of ventriculo-arterial connections	39.2 (503)
Anomalies of extra pericardial trunks	44.7 (143)
Congenital anomalies of coronary arteries	0 (9)

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Live birth - Termination of pregnancy

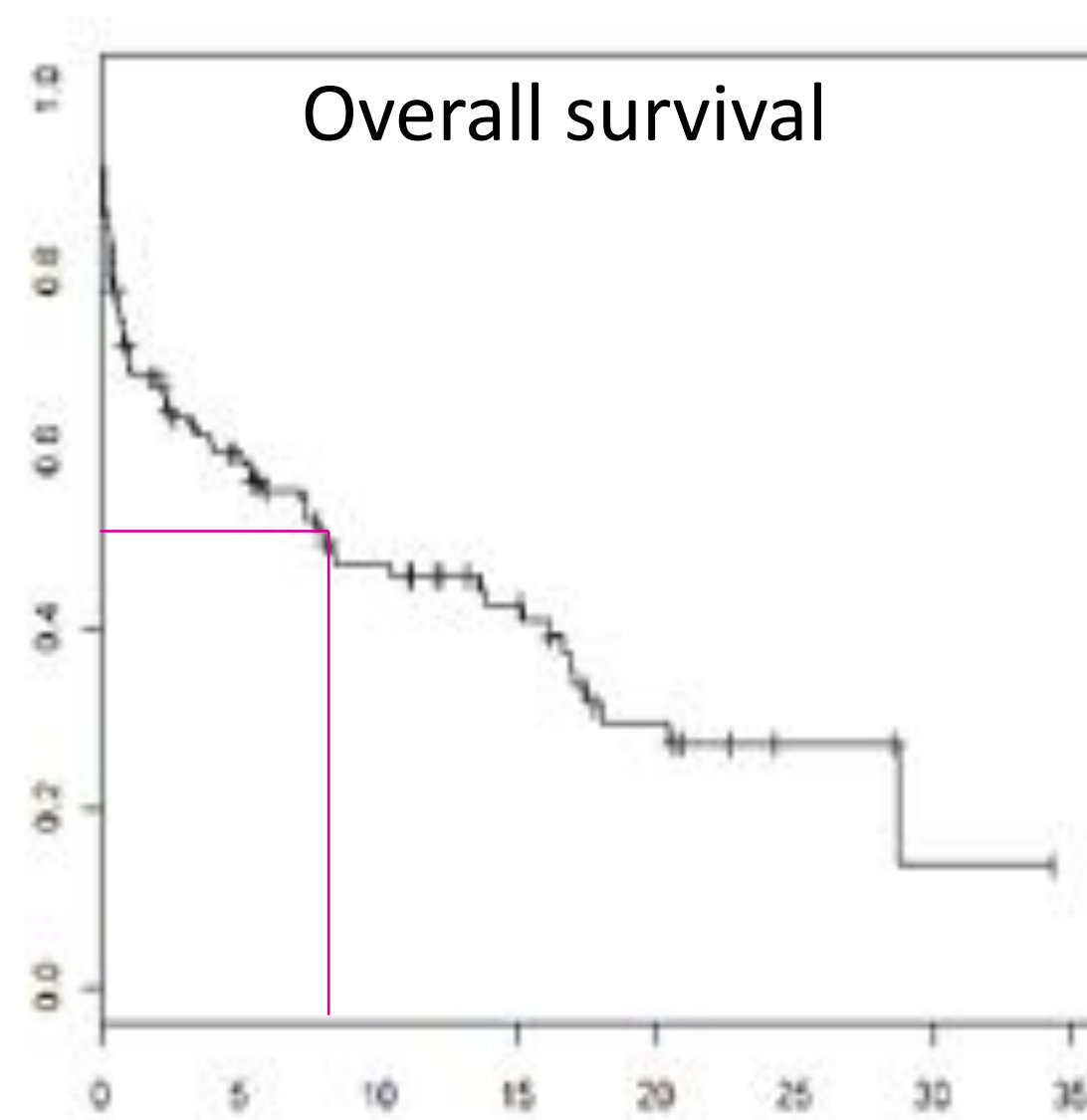
All CHDs

ACC-CHD categories	% TOP
All cases excluding chromosomal anomalies	9.8
All cases excluding chromosomal and other extra cardiac anomalies	6.4
All cases excluding chromosomal, other anomalies and simple VSD	14.0

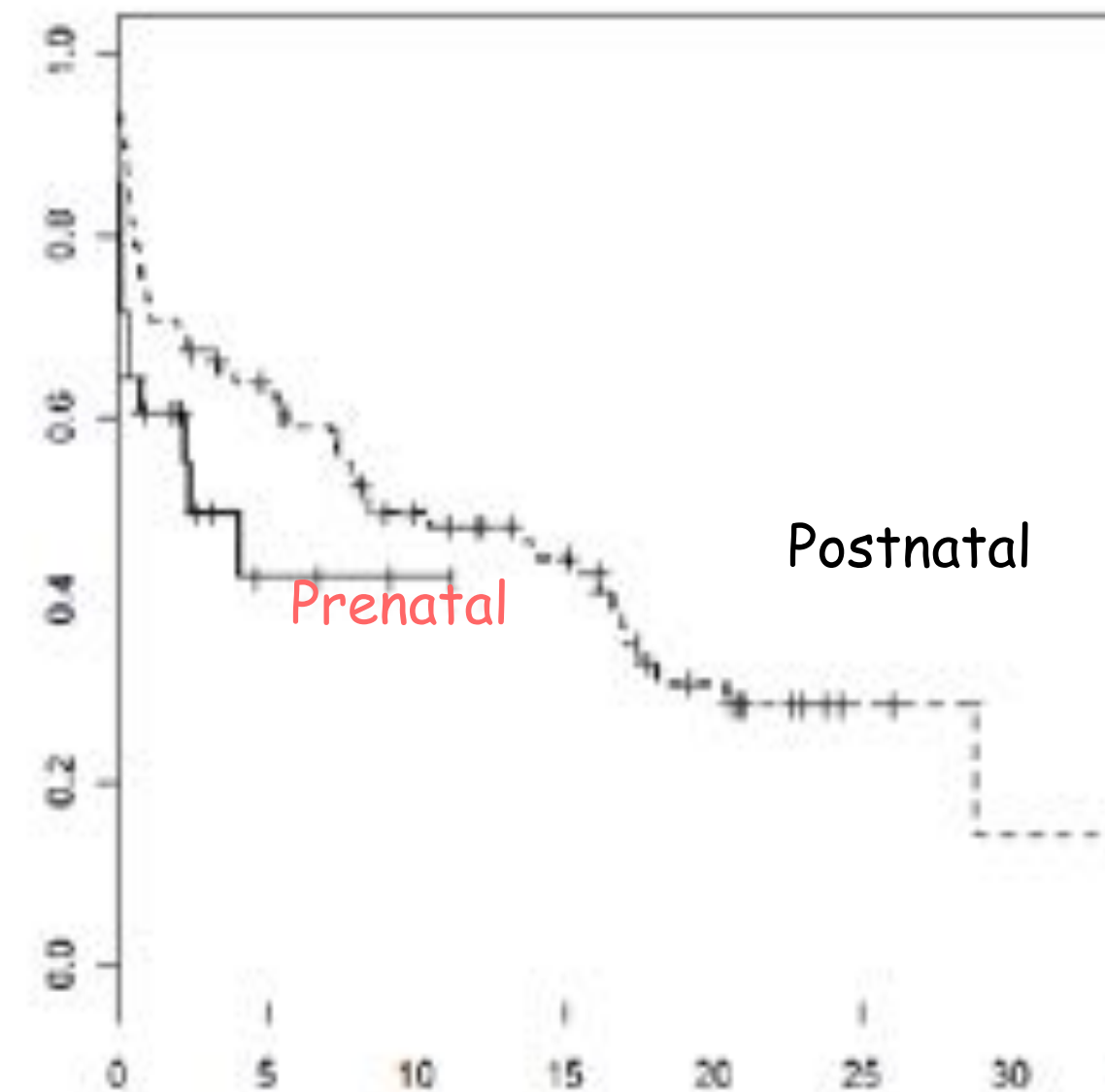
In categories of CHDs

ACC-CHD categories	% TOP
Heterotaxy	75.7
Anomalies of venous connections	16.1
Anomalies of atria	4.4
Anomalies of AV junction and AV valves	42.7
Complex anomalies of AV junction	46.2
Functionally univentricular heart	62.7
Ventricular septal defects	5.7
Anomalies of ventriculo-arterial connections	18.5
Anomalies of extra pericardial trunks	23.5
Congenital anomalies of coronary arteries	0

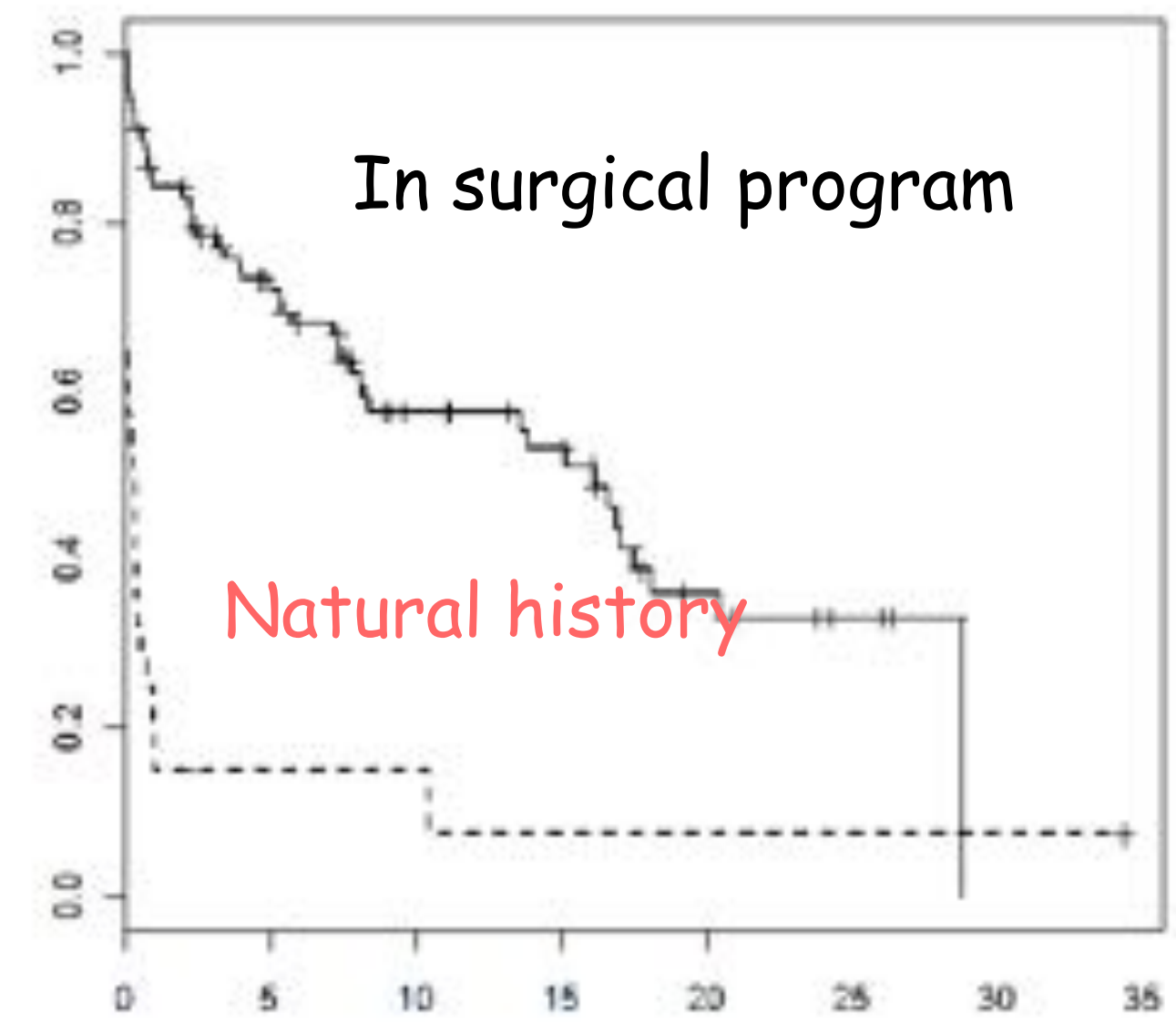
Heterotaxy in UVH program



Long term survival



Pre- vs. Postnatal



Natural history

Risk factors of mortality

Right isomerism

- Absence of pulmonary blood flow obstruction (RR 2.23)
- Major AV valve anomaly (RR 5.23)
- Obstructed pulmonary veins (RR 5.43)
- Need for neonatal surgery

Hashmi A et al. JACC 1998

Left isomerism

- UVH program (RR 2.79)
- Congenital AV block (RR 4.57)
- Coarctation of the aorta (RR 3.38)
- Biliary atresia (RR 2.76)
- Gastrointestinal malformations (RR 2.19)

Gilljam T et al. JACC 2000



Thank you