Univentricular hearts

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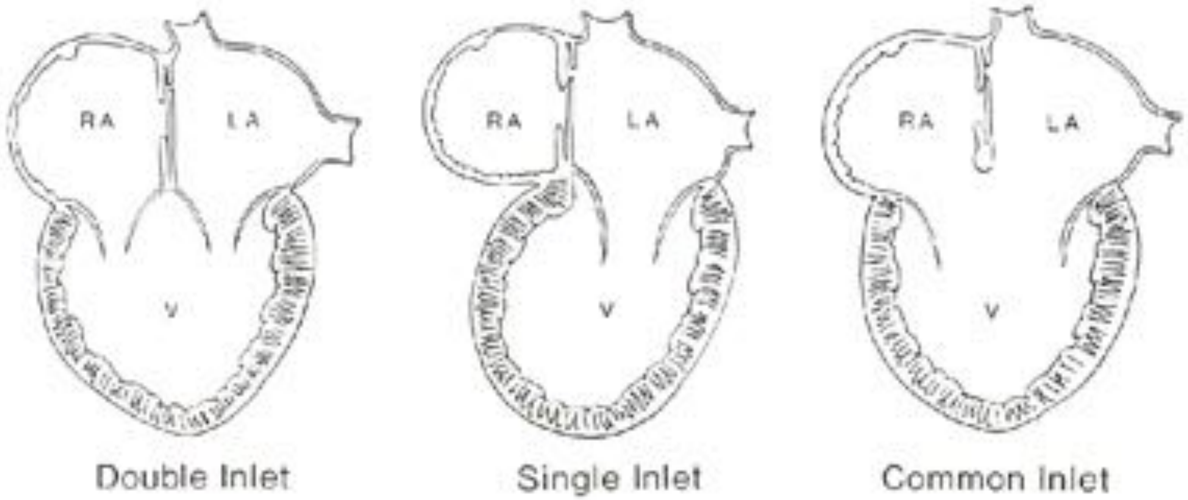
Malformations Cardiaques Congénitales Complexes-M3C

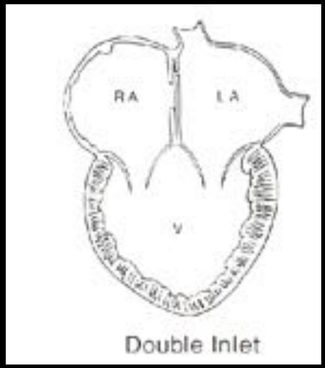
Centre de Référence Maladies Rares
Maladies Cardiaques Héréditaires- CARDIOGEN

Cardiopathies univentriculaires

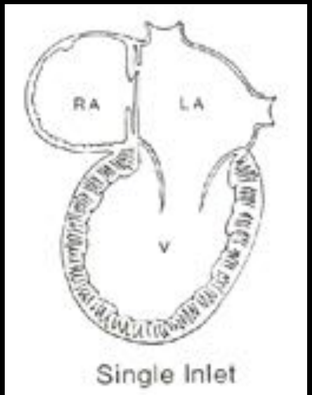
Définition anatomique

- Définition du « ventricule unique » :
  - Ventricule à double entrée
  - Les deux jonctions AV sont connectées à un seul ventricule
  - Connexion AV univentriculaire
- Valves AV
  - Toutes 2 perméables
  - 1 seule perméable, atrésie de l'autre
  - ou 1 VAV commune
- Ventricule accessoire
  - N'a pas d'inlet (ne reçoit pas de valve AV)
  - Essentiellement outlet
  - Apex très hypoplasique

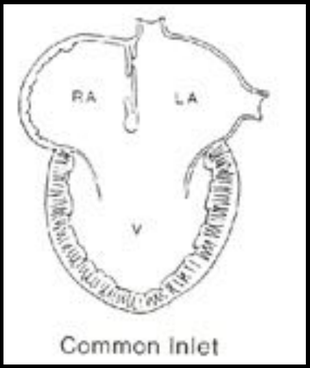




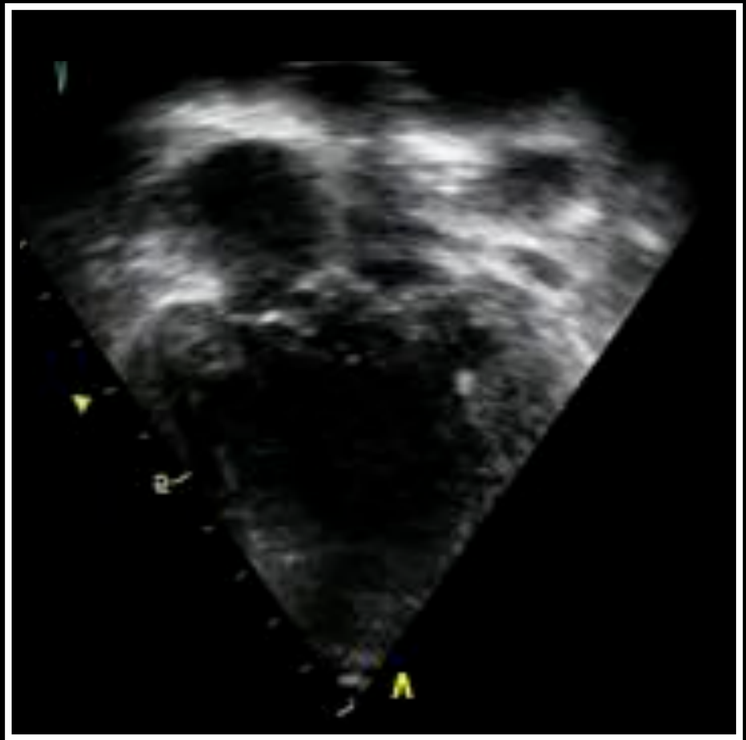
Double Inlet

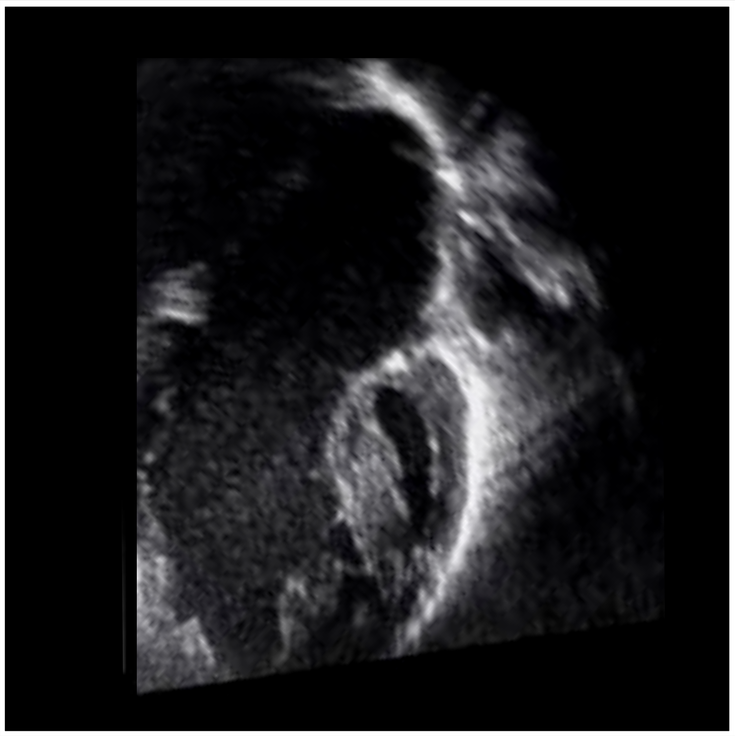


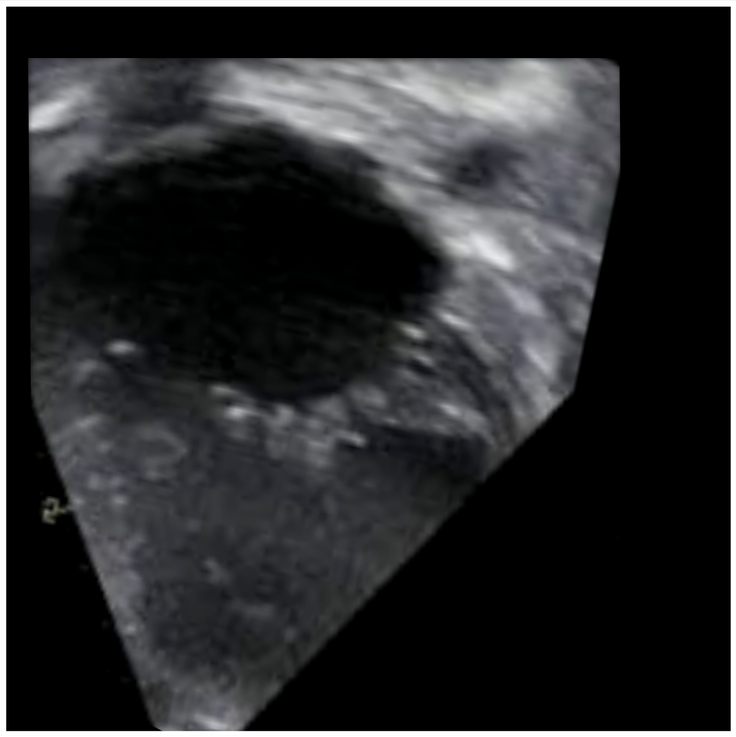
Single Inlet



Common Inlet

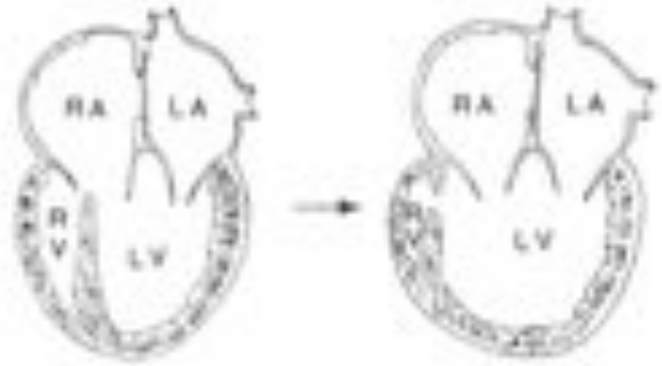






Ventricule unique
Définition physiologique

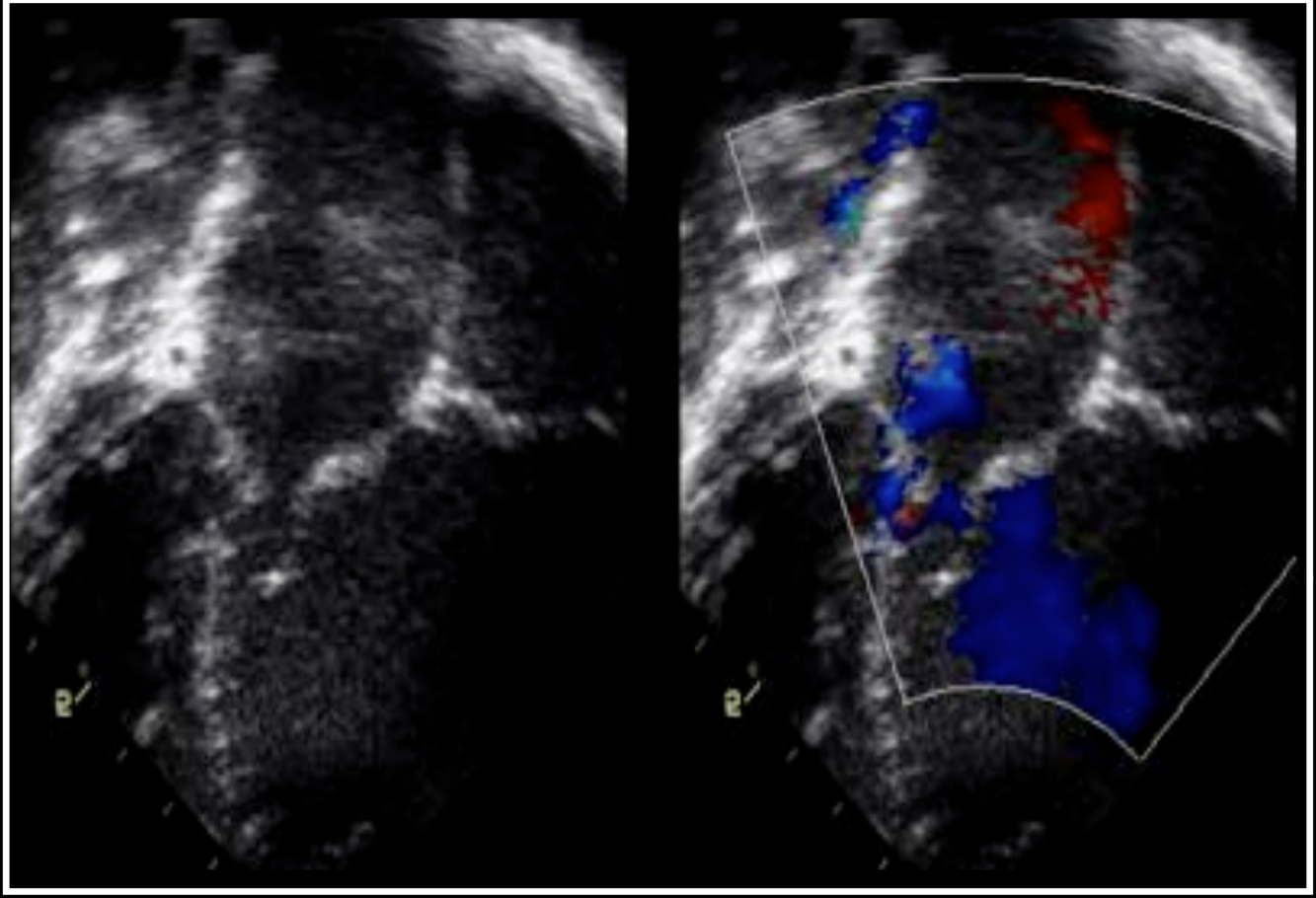
- Tous les cœurs non réparables sur 2 ventricules
- 2 grandes catégories
  - Connexion AV de type univentriculaire
    - Ventricule à double entrée
      - Gauche, droit, indéterminé
    - Absence d'une connexion AV
      - Atrésie tricuspide, atrésie mitrale, valve imperforée
  - Connexion AV de type biventriculaire
    - CIV extrêmement larges
    - Hypoplasies du cœur gauche
      - HLHS, coarctations, certains VDDI avec CIV non committed ou atrésie mitrale
    - Hypoplasies du cœur droit
      - APSI, hypoplasie congénitale du VD
    - CAV déséquilibré
    - Straddling avec hypoplasie sévère d'un des ventricules



Double Inlet LV with Overriding

Double Inlet LV without Overriding

RA
LA
RV
LV
Double Inlet LV
with
Overriding

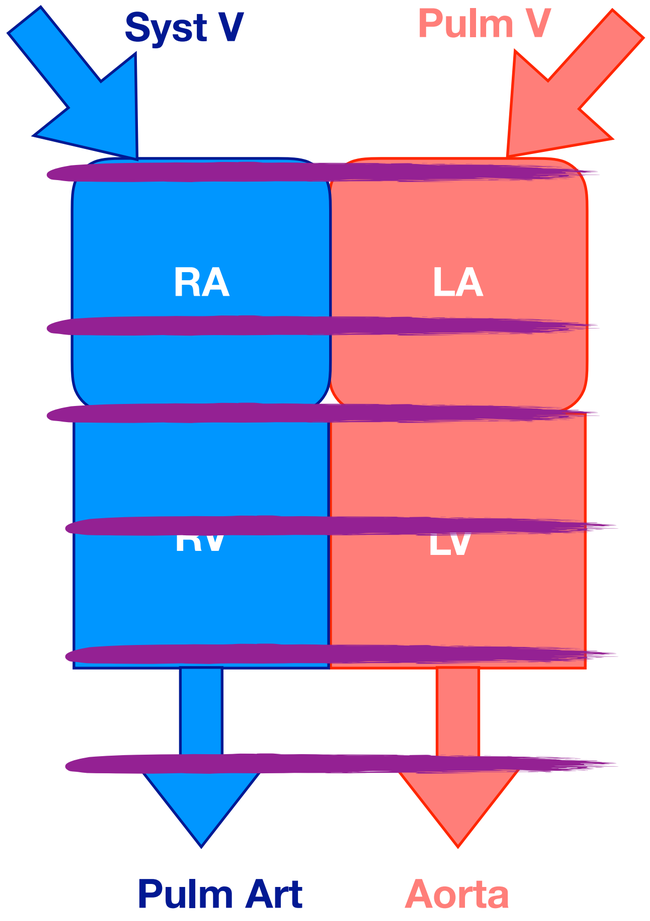


The EPICARD study

EPIdémiologie des enfants ou fœtus ayant une **CARD**iopathie congénitale

Anatomic and Clinical Classification of Congenital Heart Diseases ACC-CHD

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



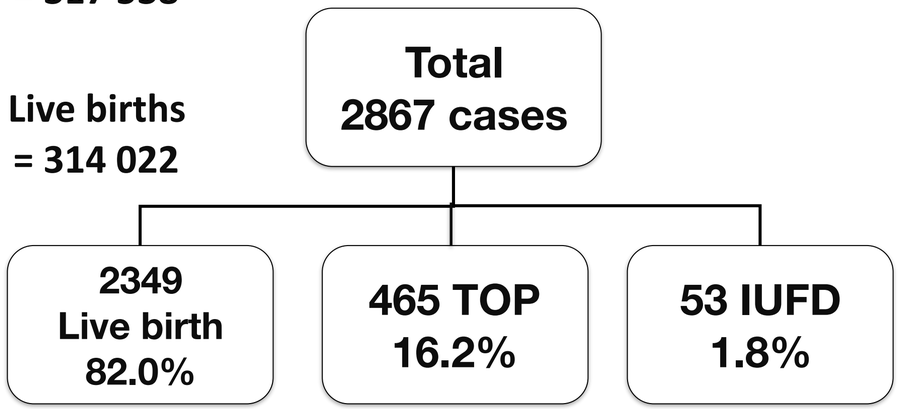
Houyel L, Bonnet D. Orphanet J 2011

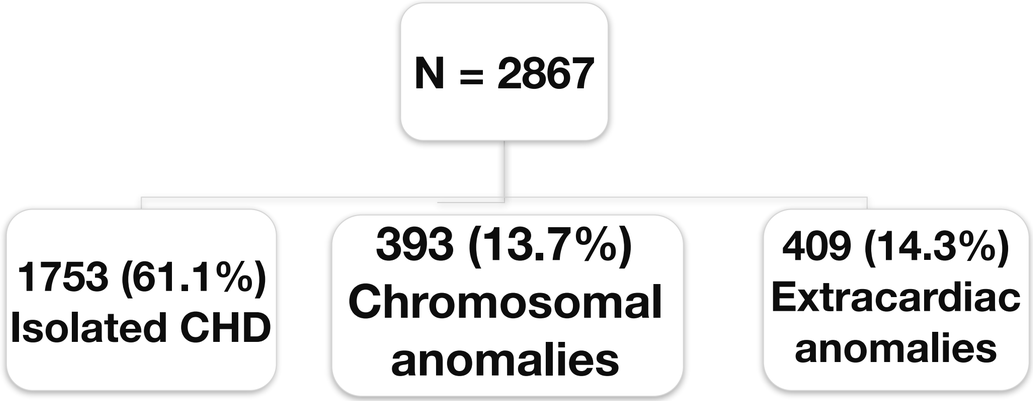
Prevalence, pre- and post-natal diagnosis, and infant mortality of newborns with congenital heart defects: A population-based study using the International Paediatric and Congenital Cardiac Code (IPCCC)

The EPICARD Study Group

Total number of birth
= 317 538

Live births
= 314 022





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

Khoshnood B et al. Heart 2012;98:1667-73

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

Proportion of prenatal diagnosis

All CHDs

ACC-CHD categories	% of prenatal diagnosis
All cases excluding chromosomal anomalies	25.6
All cases excluding chromosomal and other extra cardiac anomalies	23
All cases excluding chromosomal, other anomalies and simple VSD	40.2

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)

Specific CHDs

Type of CHD	% of prenatal diagnosis
Congenitally corrected transposition of the great	100
Functionally univentricular heart	92.5
TGA	74
DORV	98

Khoshnood B et al. Heart 2012;98:1667-73

Prevalence, pre- and post-natal diagnosis, and infant mortality of newborns with congenital heart defects:
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The EPICARD Study Group

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

Khosnood B et al. Heart 2012;98:1667-73

Pre- and postnatal diagnosis in CHD without chromosomal anomalies
The EPICARD Study Group

ACC-CHD categories	Prenatal diagnosis	Postnatal diagnosis			
	%	<7days	8-28 days	29 days-3 months	3 months -1 year
Heterotaxy	89.2	8.1	0.0	2.7	0.0
Anomalies of venous connections	16.0	32.0	16.0	28.0	4.0
Anomalies of atria	4.3	29.3	26.8	26.8	11.6
Anomalies of AV junction and AV valves	67.0	19.8	3.3	2.2	2.2
Complex anomalies of AV junction	100.0	0.0	0.0	0.0	0.0
Functionally univentricular heart	92.5	6.0	0.7	0.0	0.0
Ventricular septal defects	9.6	67.4	9.0	9.8	3.8
Anomalies of ventriculo-arterial connections	39.2	29.6	7.1	14.5	5.4
Anomalies of extra pericardial trunks	44.7	28.7	9.8	10.5	2.1
Congenital anomalies of coronary arteries	0	0	0	44.4	55.6
All except chromosomal anomalies and /or anomalies of other systems	**40.2**	**28.7**	**10.4**	**14.4**	**5.6**

Infant mortality in newborns with congenital heart defects
The EPICARD Study Group

ACC-CHD categories	Prenatal diagnosis	Postnatal diagnosis			Infant mortality	
	N	<7days %	8-28 days %	29 days-1 year %	%	95%CI
Heterotaxy	8	25.0	0.0	12.5	**37.5**	8.5-75.5
Anomalies of venous	26	3.9	11.5	11.5	**26.9**	11.6-47.8
Anomalies of atria	174	0.6	0.6	2.3	**3.5**	1.3-7.3
Anomalies of AV junction and AV valves	109	8.3	7.3	12.8	**28.4**	20.2-37.0
Complex anomalies of AV	7	0.0	0.0	14.3	**14.3**	0.4-57.9
Functionally univentricular	48	41.7	12.5	4.1	**58.3**	43.2-72.4
Ventricular septal defects	1396	0.2	0.5	0.9	**1.6**	1.0-2.4
Anomalies of ventriculo-arterial connections	447	2.3	2.0	4.0	**8.3**	5.9-11.2
Anomalies of extra pericardial trunks	124	3.2	6.5	2.4	**12.1**	6.9-19.2
Congenital anomalies of coronary arteries	9	0	0	11.1	**11.1**	0.3-48.2
All	2348	2.1	1.8	2.5	**6.4**	5.5-7.5
All except chromosomal anomalies and /or anomalies of other systems and IVSD	**784**	**2.9**	**2.2**	**3.6**	**8.7**	**6.8-10.9**

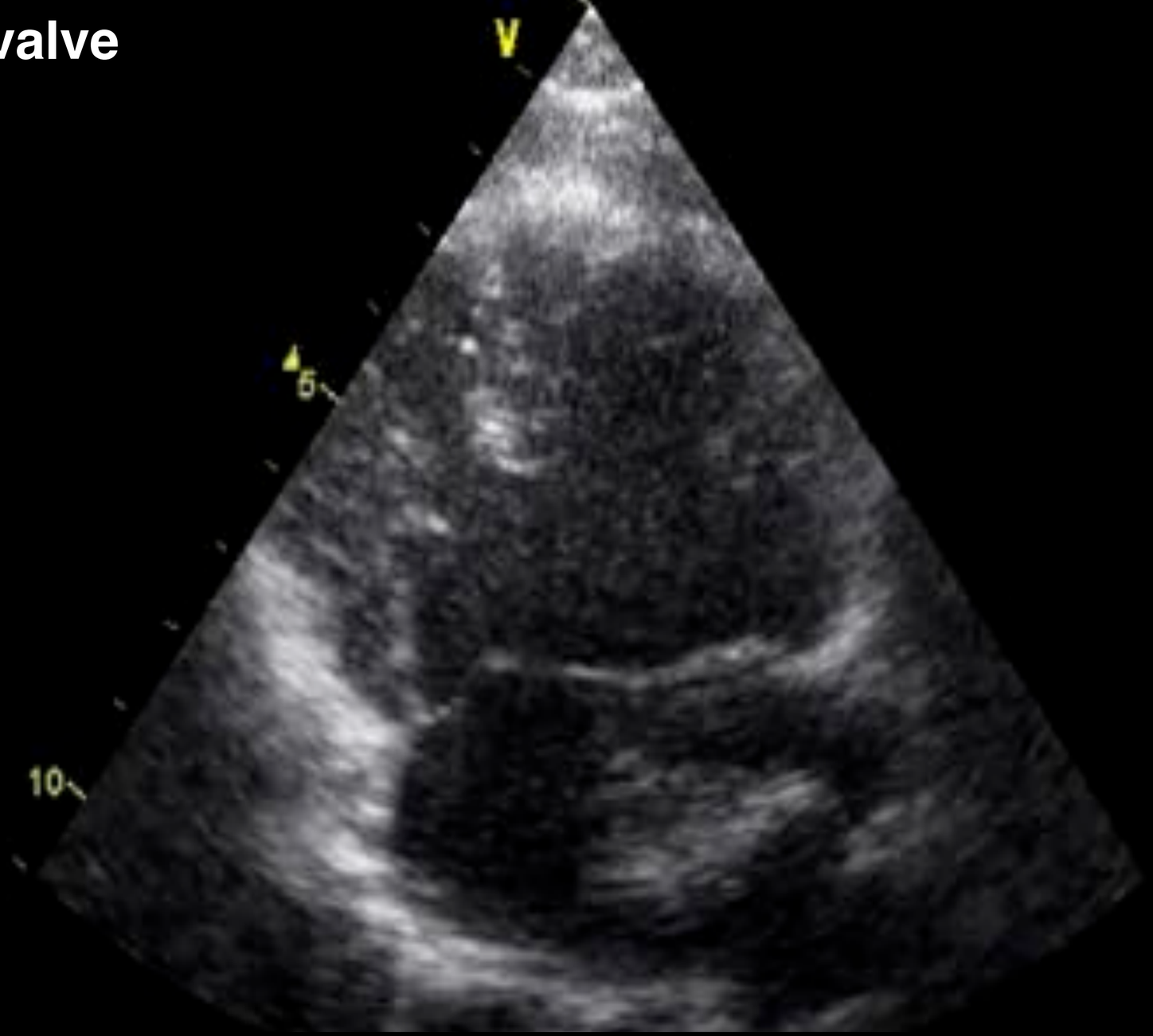
Résumé épidémiologie des cardiopathies univentriculaires

- Les cardiopathies univentriculaires représentent 5 à 7% de toutes les cardiopathies congénitales.
- *Le diagnostic est fait avant la naissance dans plus de 90% des cas depuis 20 ans.*
- Elle sont associées à des anomalies chromosomiques une fois sur 6 et à des anomalies extracardiaques une fois sur 5.
- *Elles représentent environ 20% des cardiopathies motivant un transfert in utero vers un centre tertiaire.*
- Dans 2/3 des cas ce transfert est justifié par la nécessité d'une intervention précoce.
- *Elle représentent avec le diagnostic précoce (<22 SA) et les anomalies extracardiaques, le principal facteur de décision d'interruption de grossesse.*
- Elle sont avec les atteintes extracardiaques majeures la principale cause de mortalité de la première année.
- *La survie à un an des nouveau-nés vivants est de 50% (4% pour les hypoplasies du coeur gauche).*

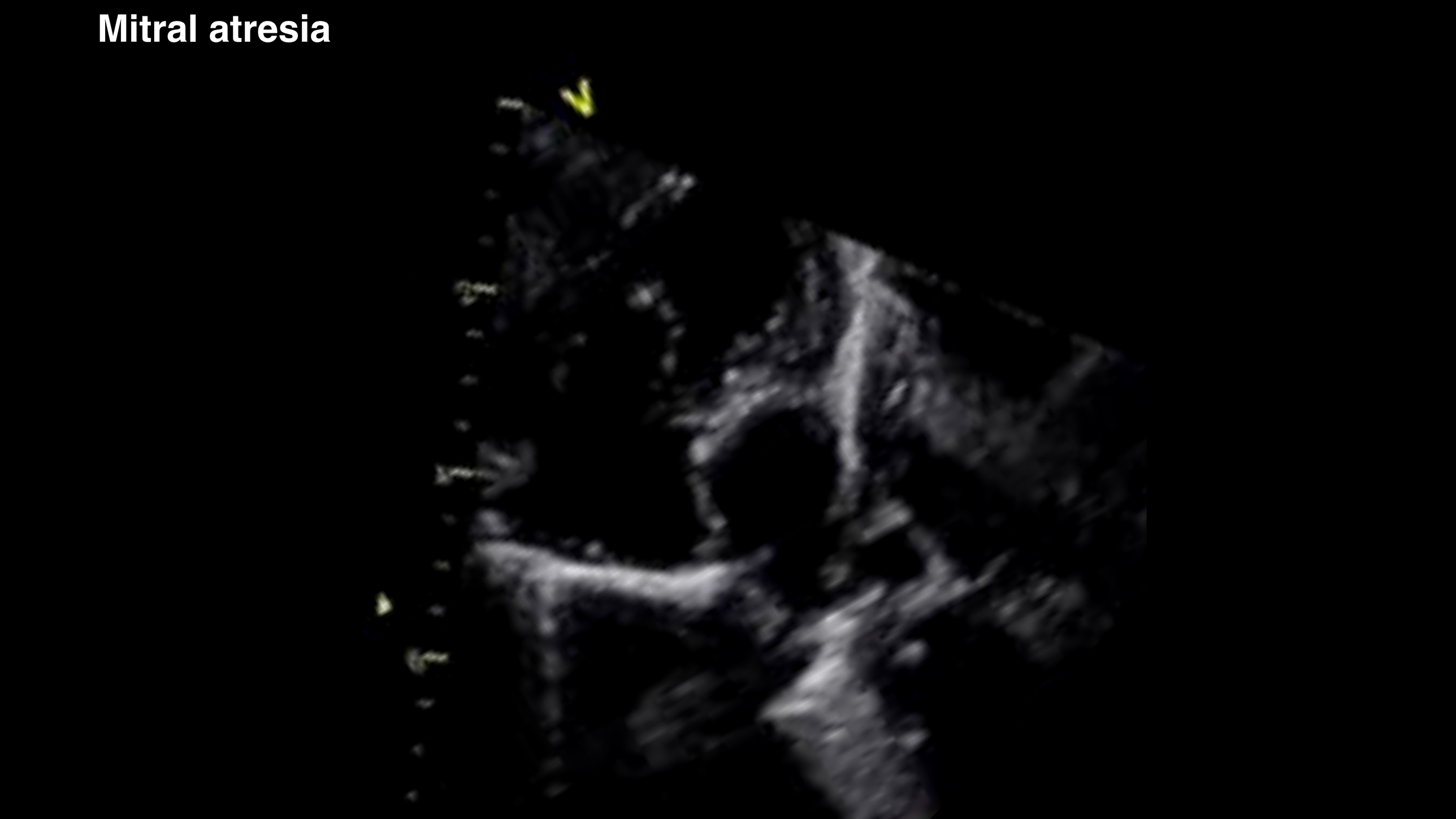
UVH 2 AV Valves
Discordance AV

UVH 2 AV Valves

UVH with AVSD valve

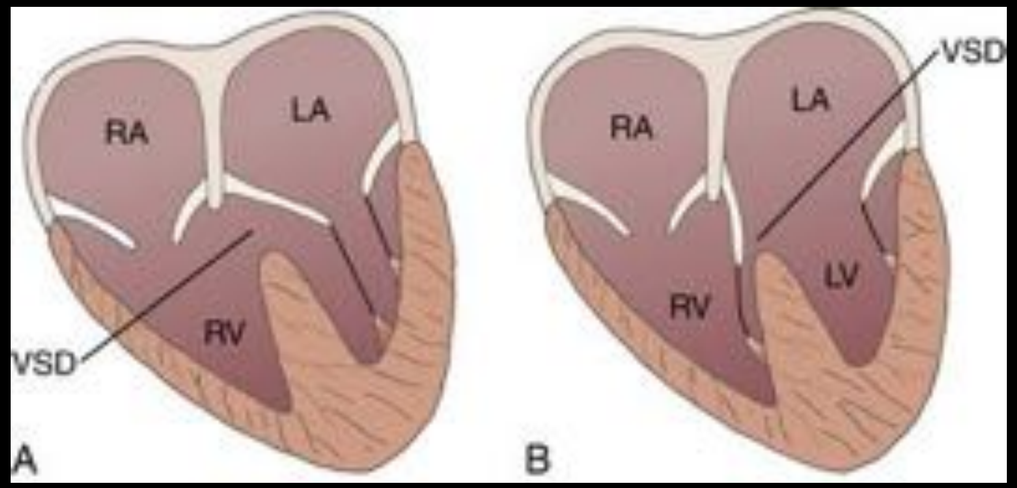


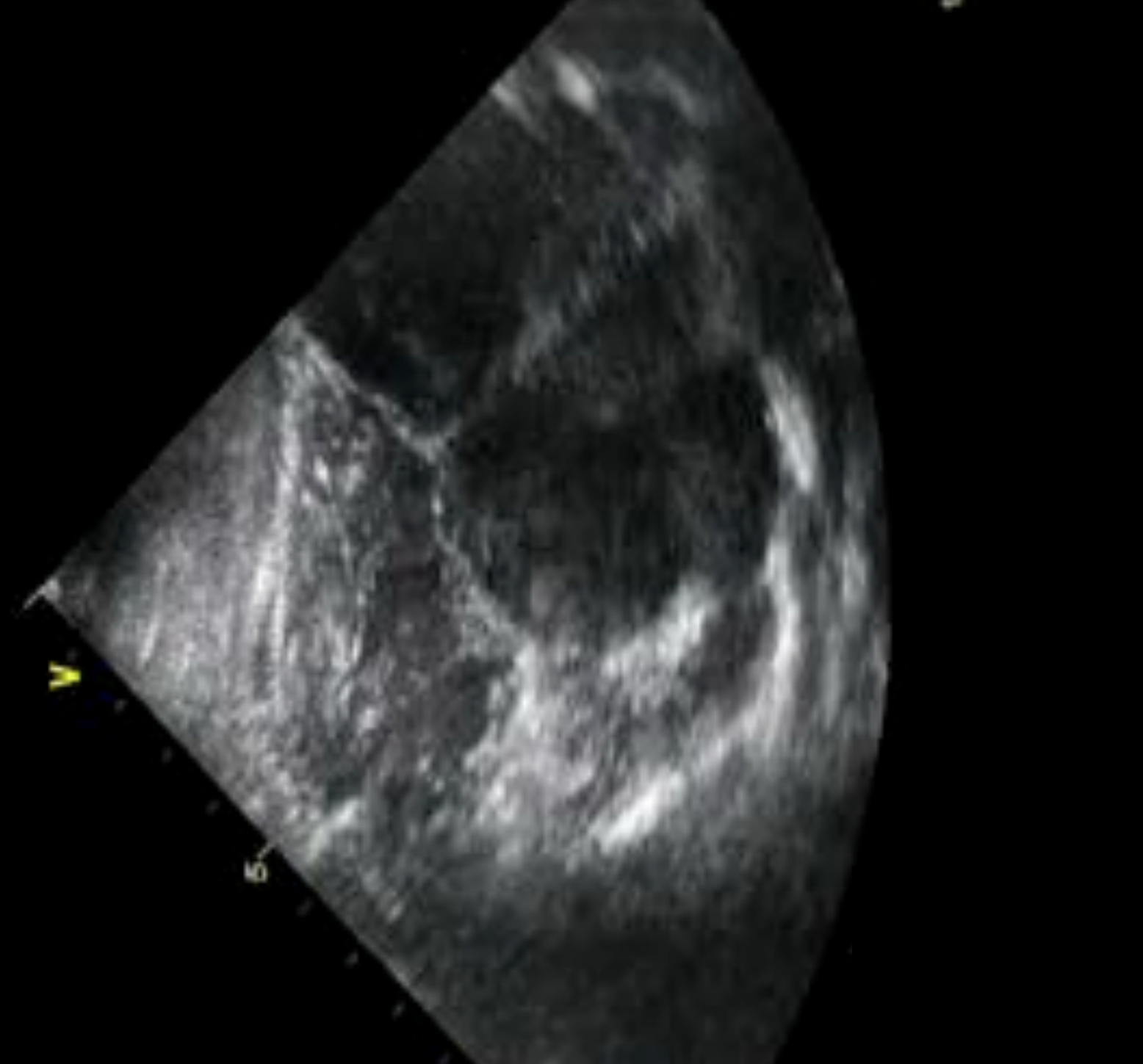
Mitral atresia



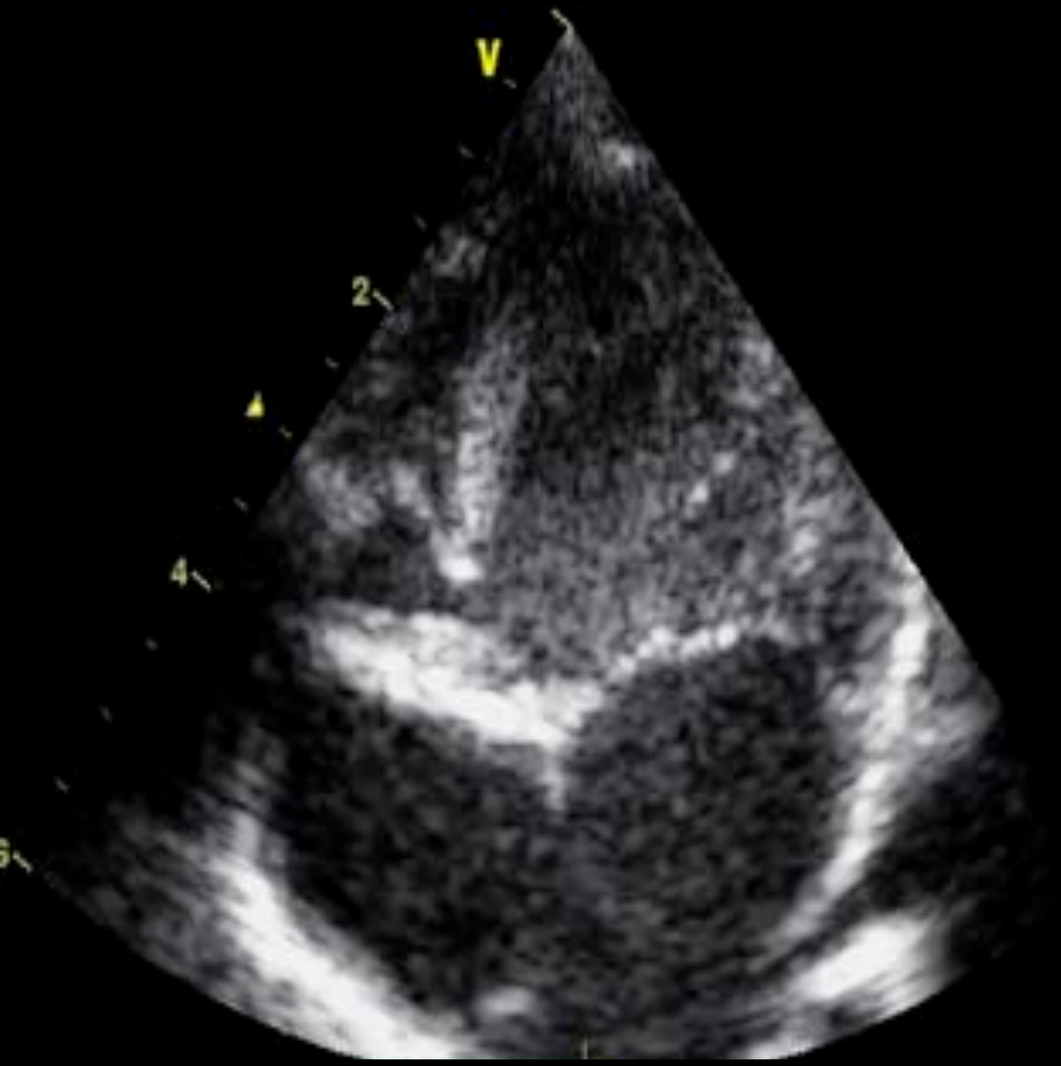
Mitral valve hypoplasia

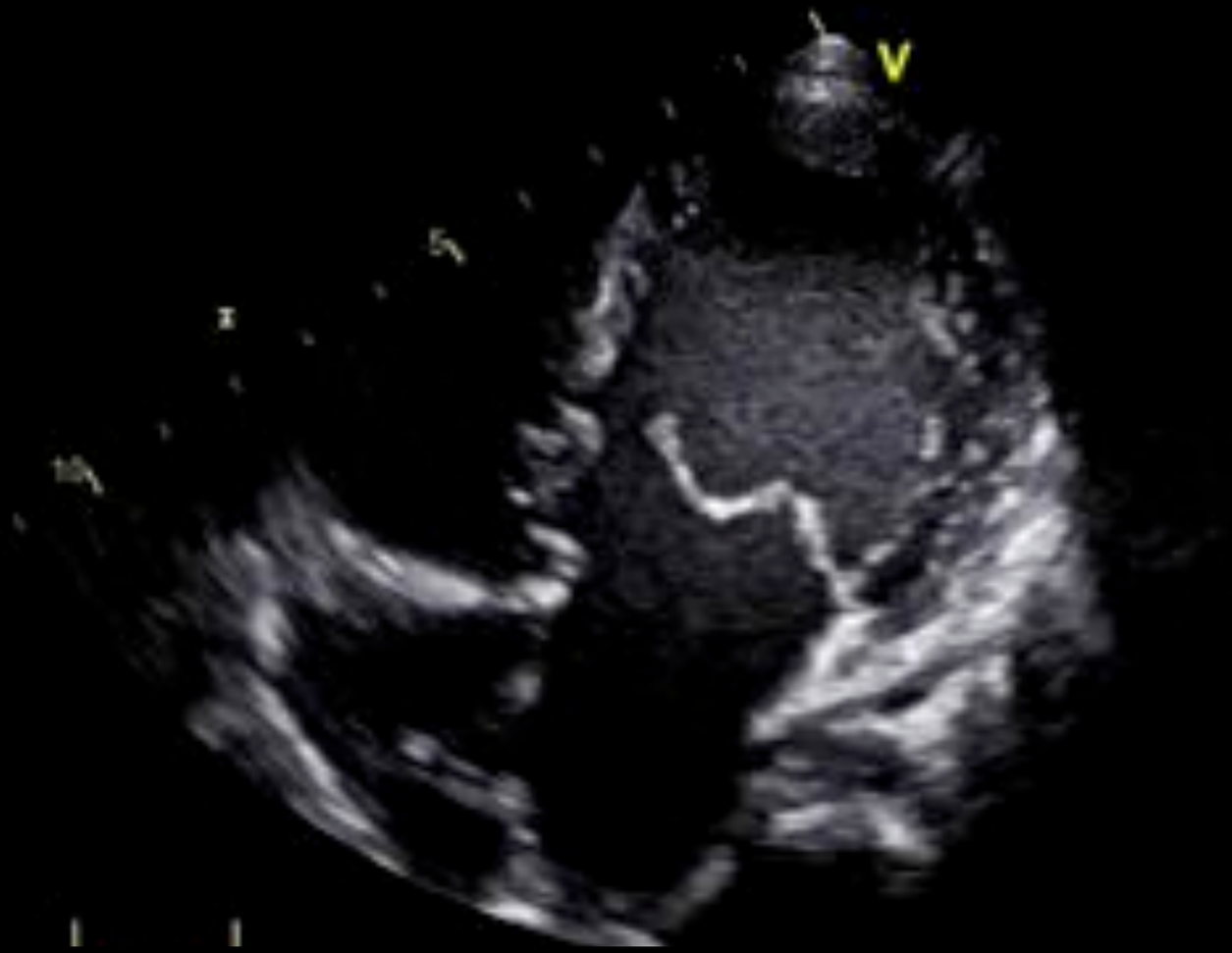
Straddling of the mitral valve



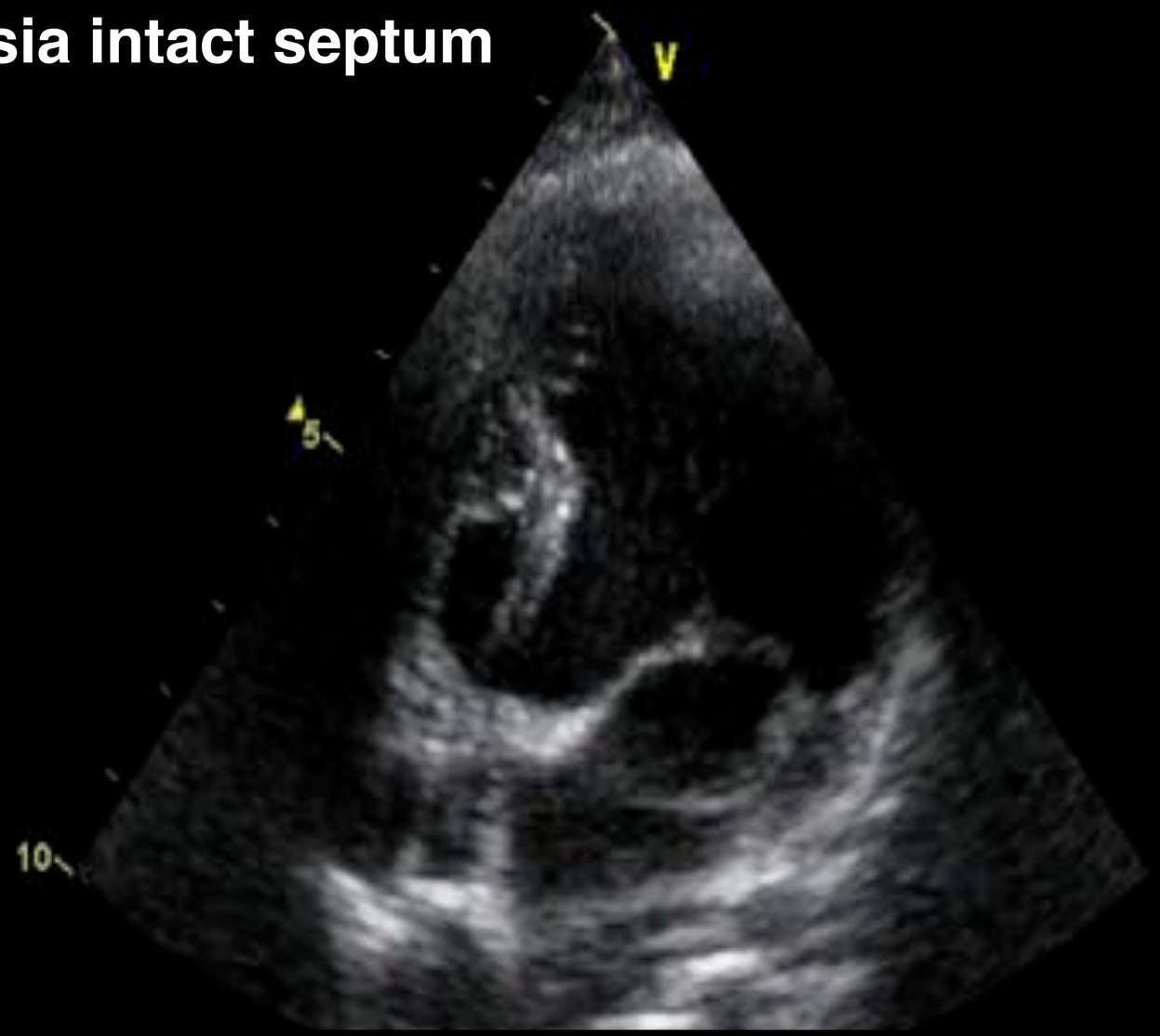


Tricuspid atresia

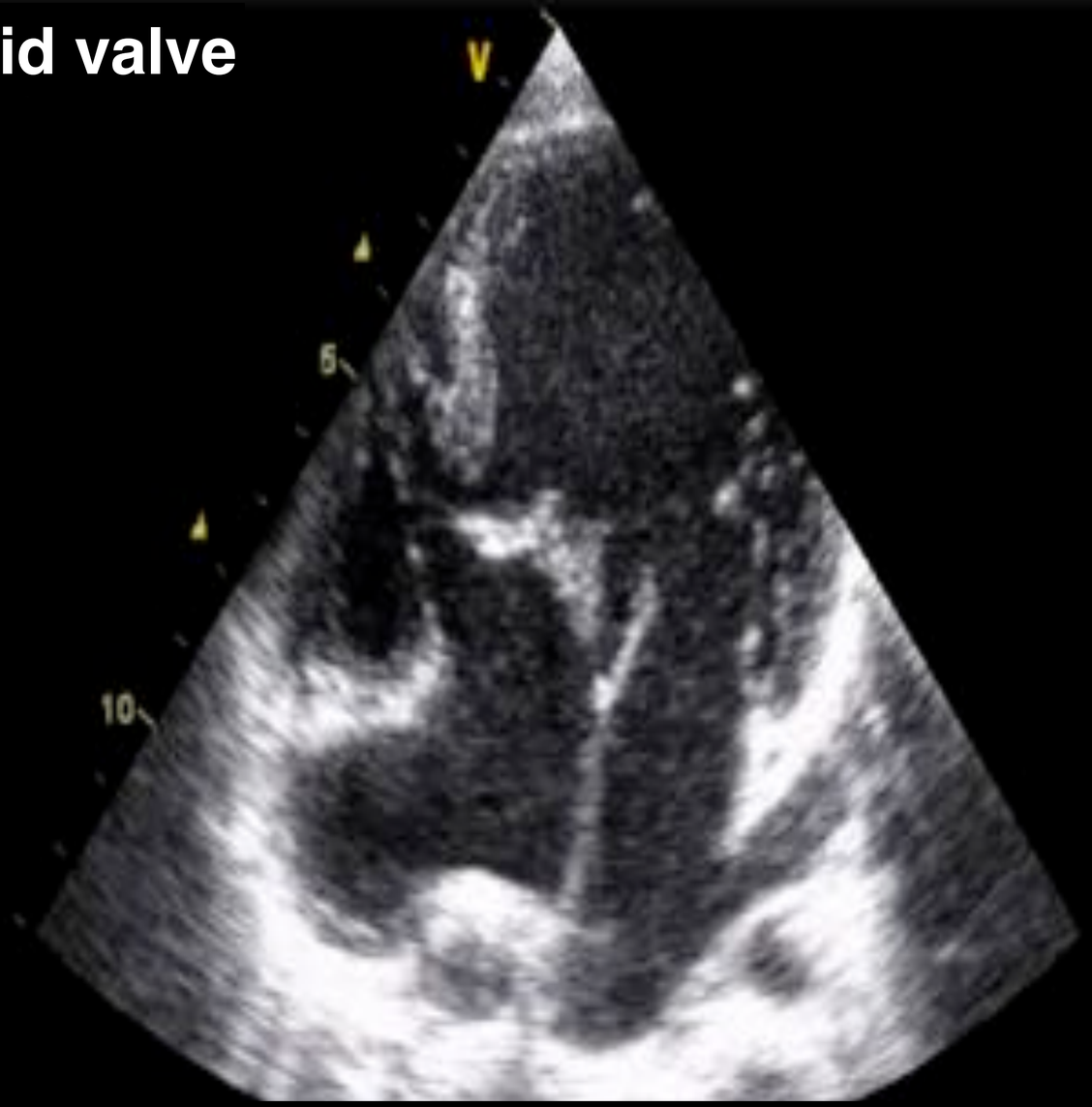




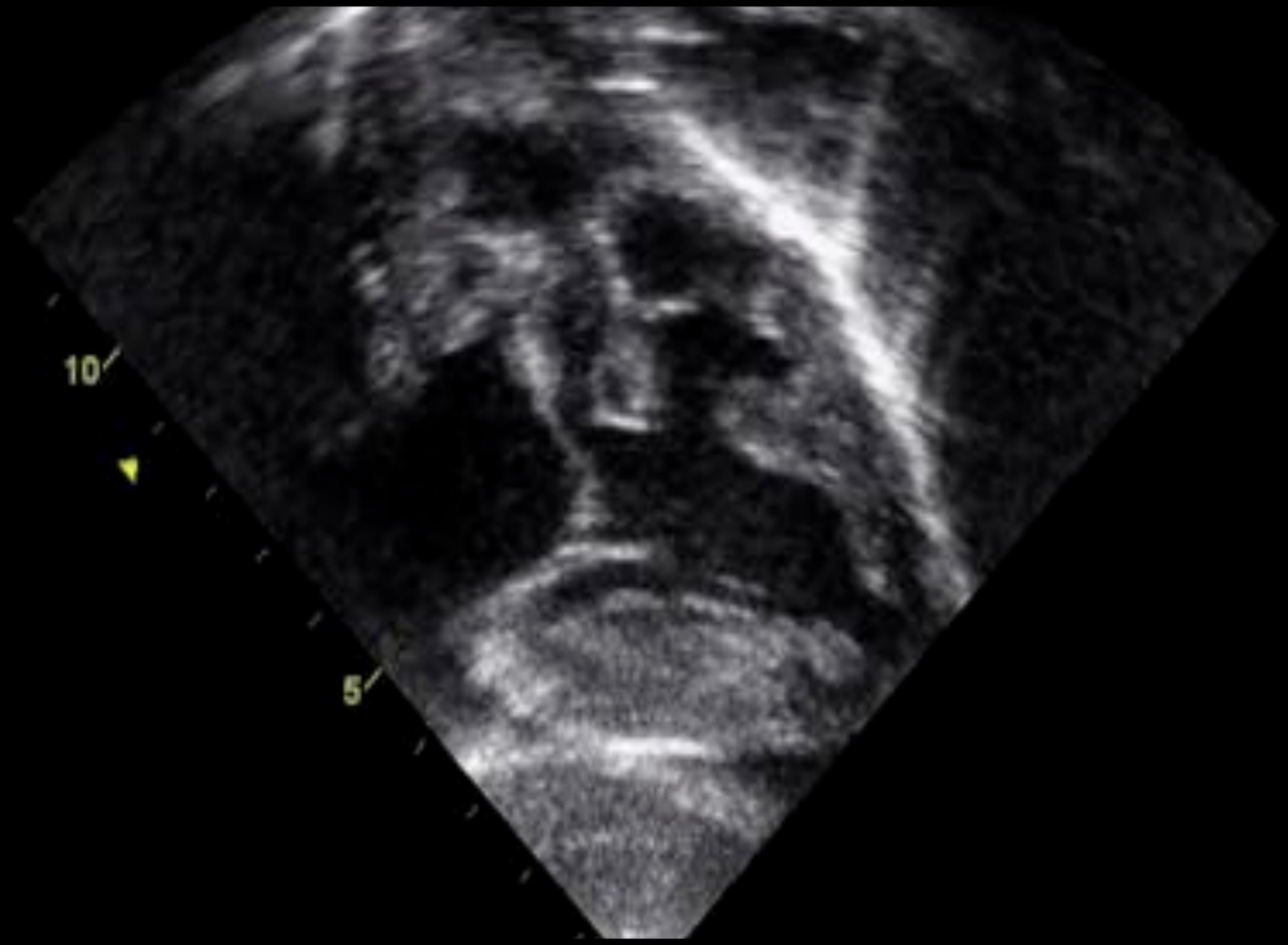
Pulmonary atresia intact septum



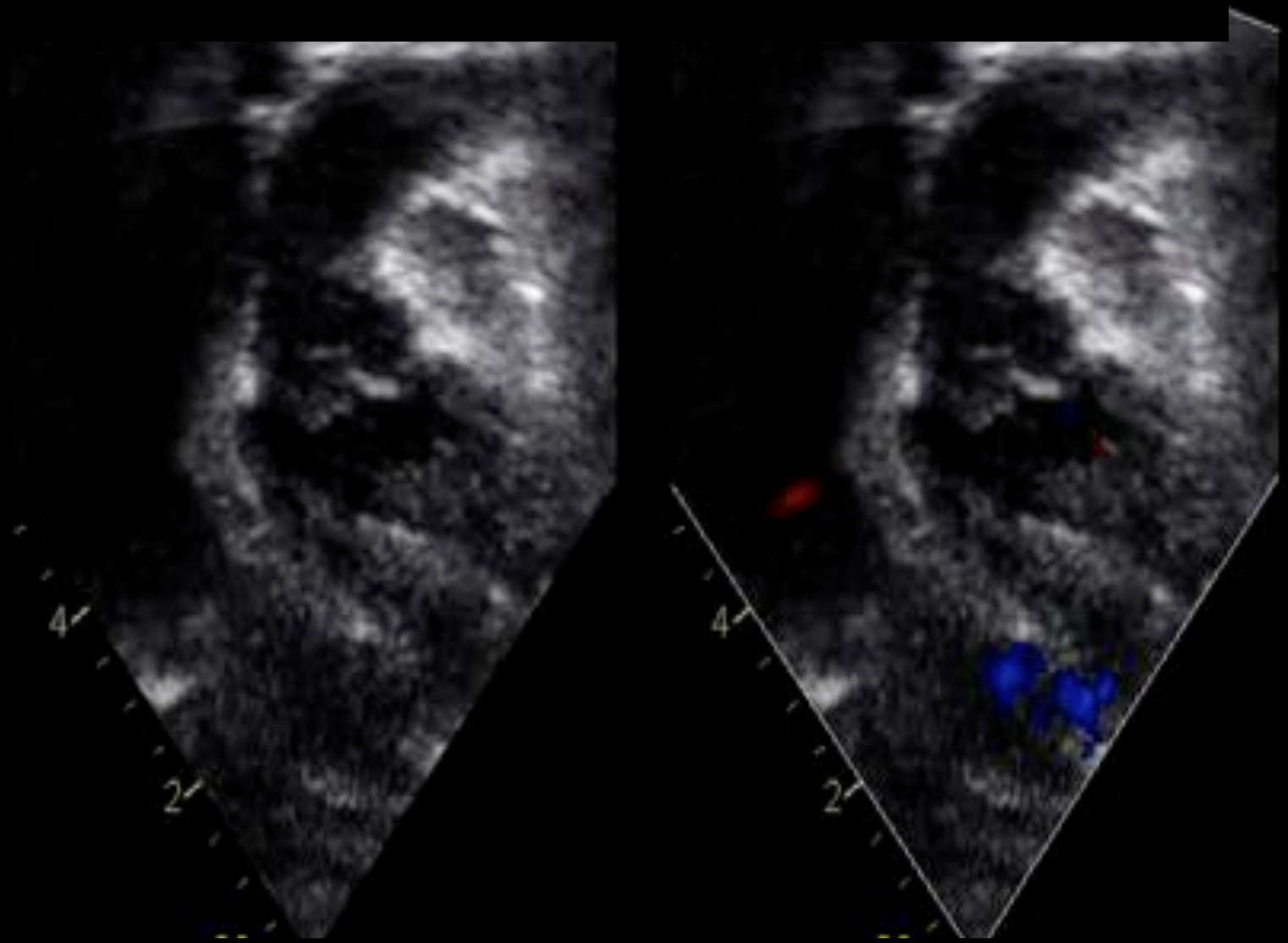
Straddling of tricuspid valve



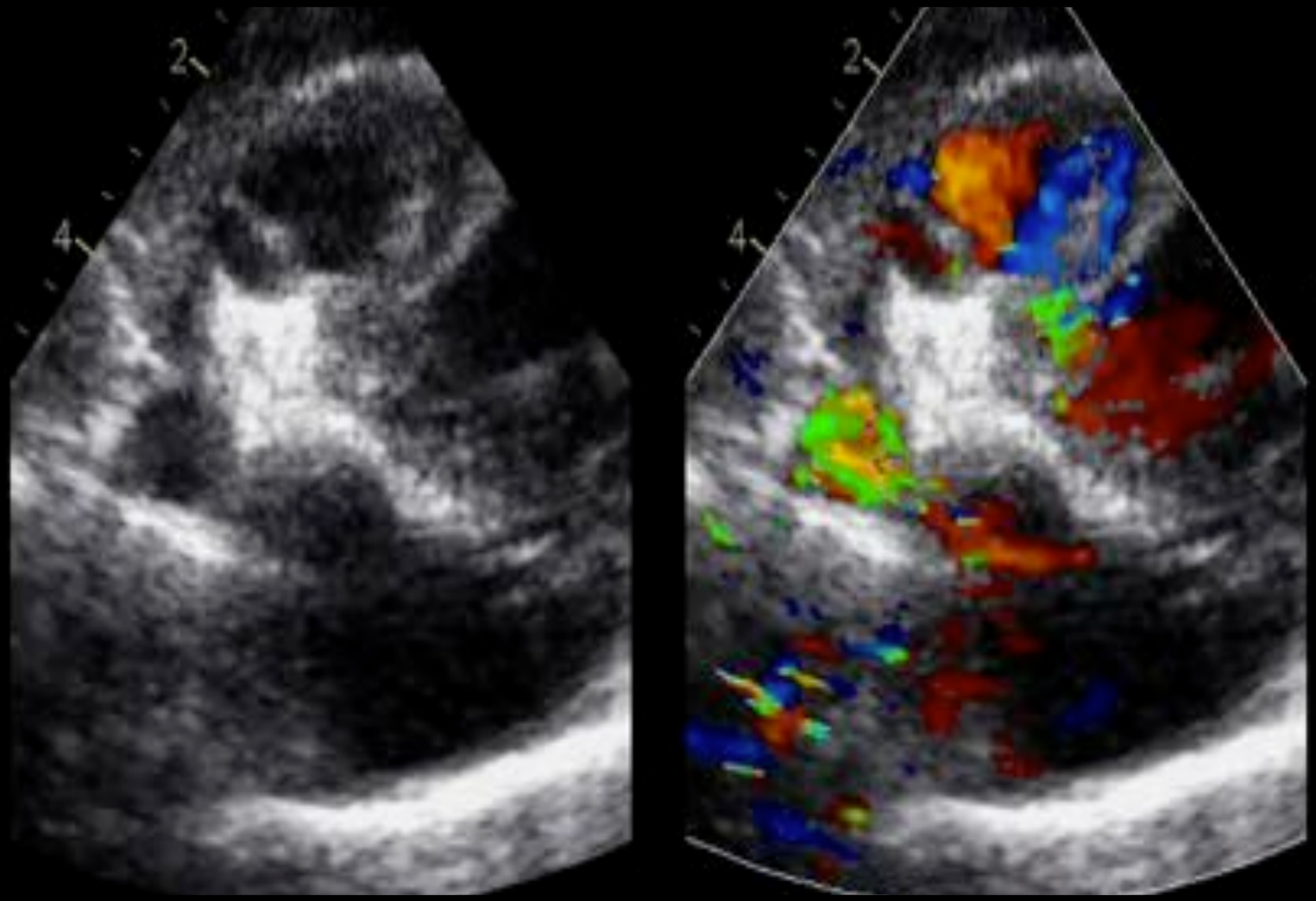
Outflow tracts in univentricular heart: accessory ventricle



Outflow tracts in univentricular heart: accessory ventricle



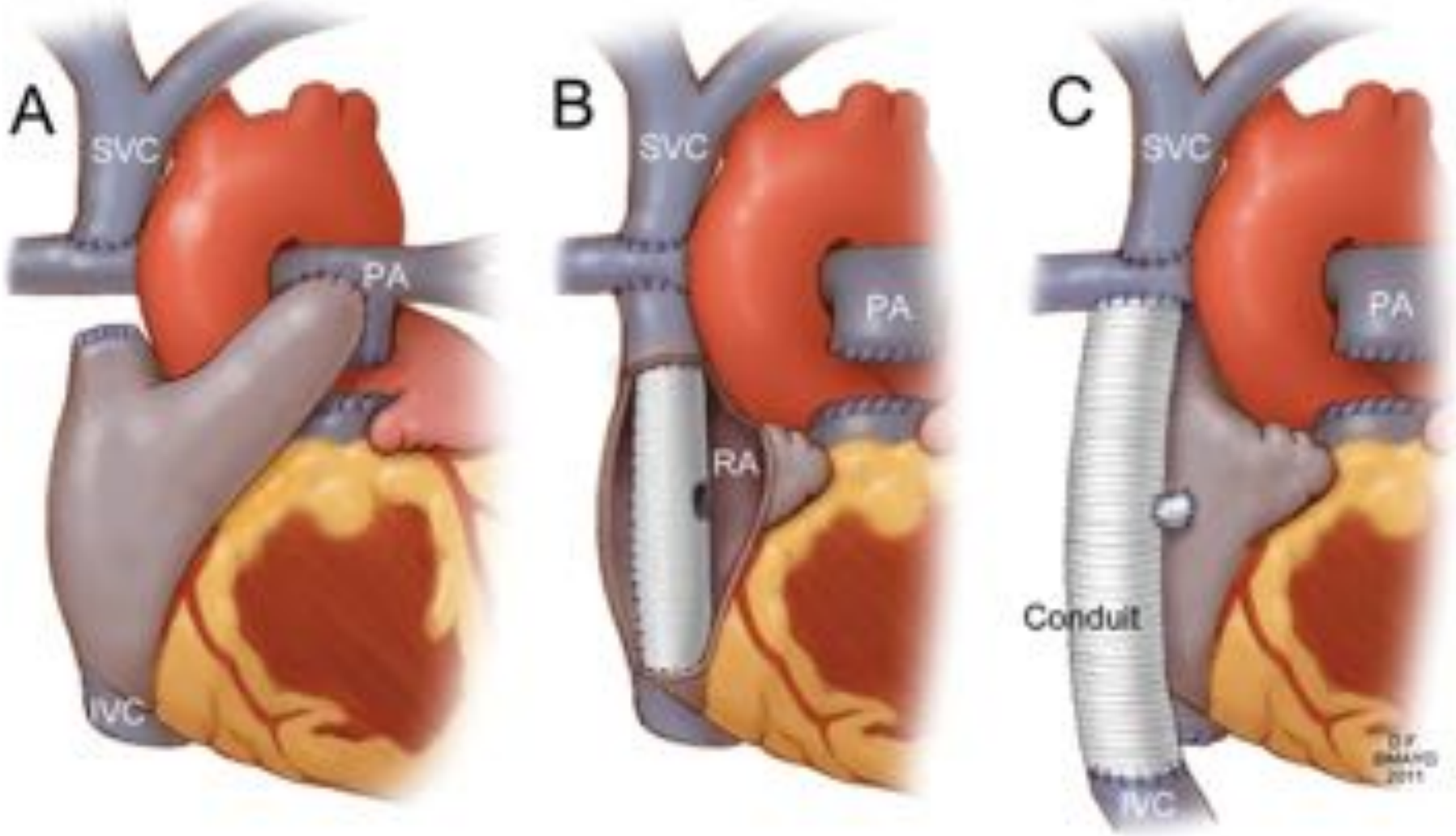
Outflow tracts in univentricular heart: accessory ventricle



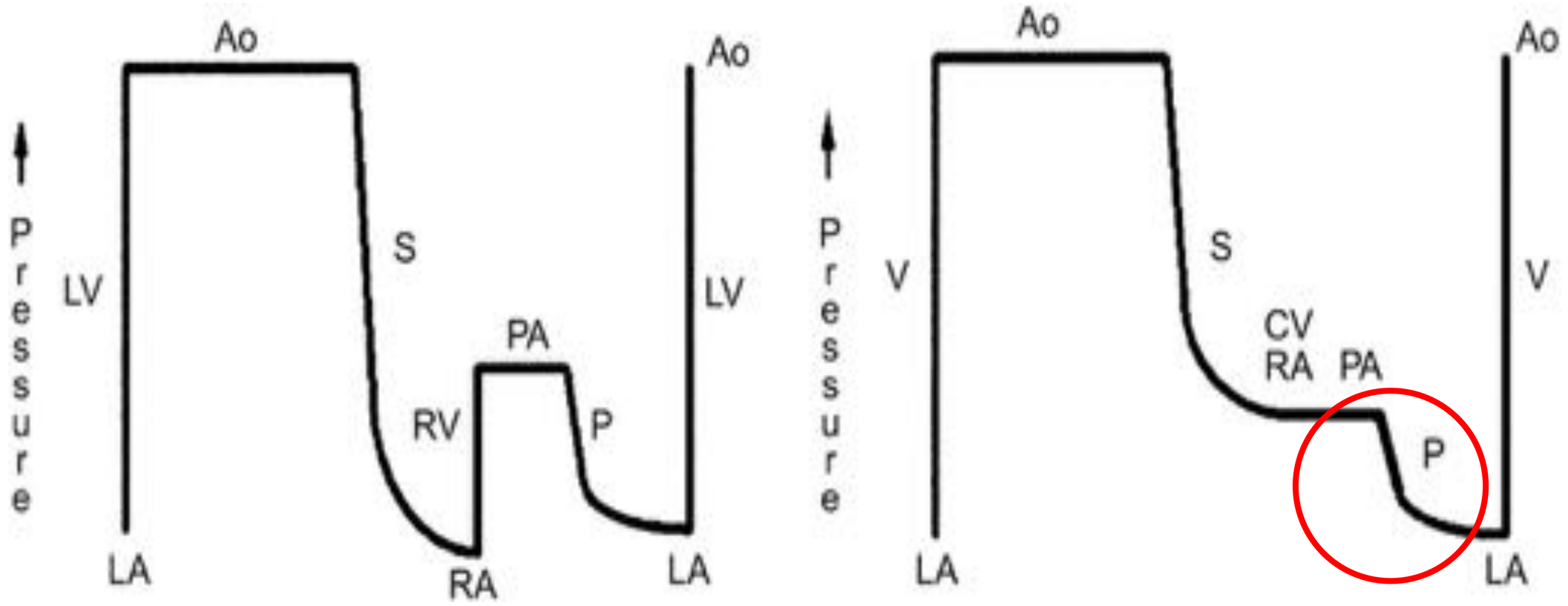
Criss-cross

Criss-cross

TCPC program



Représentation schématique des circulations normale et de type "Fontan"



Gewillig M. et al. Interact CardioVasc Thorac Surg 2010;10:428-433

Quels sont les objectifs du traitement des VU ?

- Protéger la circulation pulmonaire
  - Cerclage
  - Lever les obstacles au retour veineux: CIA – RVPA bloqués
- Calibrer le débit pulmonaire
  - Blalock, conduit VU-AP
- Préserver la fonction du ventricule et des VAV
  - Réduire la post-charge
    - Coarctation, sténose sous aortique
  - Limiter la surcharge diastolique
    - Calibrer le débit pulmonaire
  - Essayer de limiter la durée de clampage aortique pendant la chirurgie
- Préserver les artéres pulmonaires et les veines systémiques
- Limiter les cicatrices atriales et ventriculaires

Le décalogue : 10 commandements (Choussat-Fontan)

. situs solitus
. connection veineuse, systémique et pulmonaire, normale
. hypertrophie oreillette droite
. fonction ventriculaire normale
. fonction normale des valves auriculo-ventriculaires
. rythme sinusal
. artères pulmonaires de taille normale
. pression pulmonaire basse (< 15 mmHg)
. résistances vasculaires pulmonaires basses
. âge > 4 ans

Critères actuels

- "bon" lit vasculaire pulmonaire
    . absence d'hypoplasie diffuse
    . absence de sténose localisée (native ou iatrogène)
    . résistances vasculaires pulmonaires basses
    . gradient transpulmonaire bas

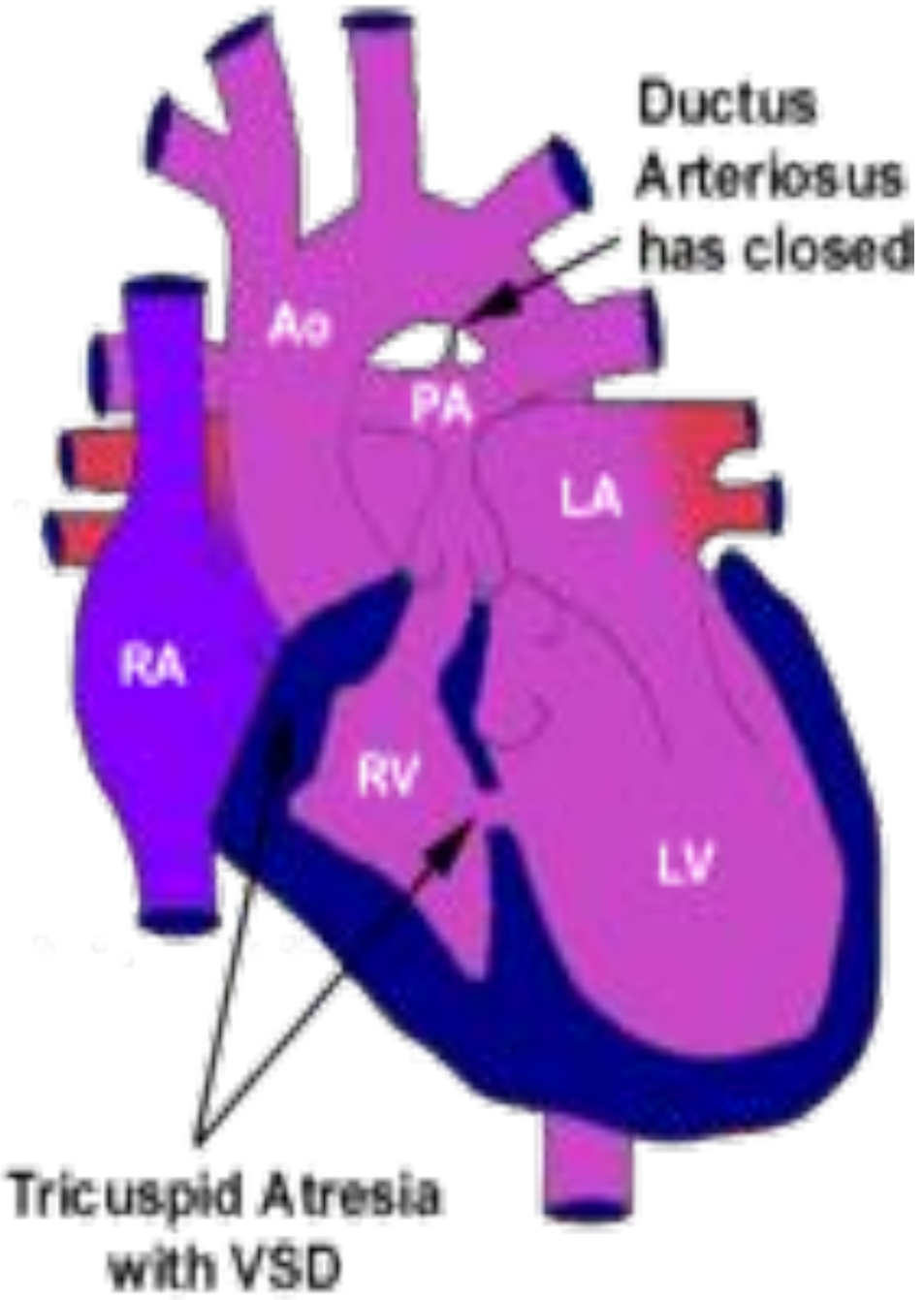
- "bon" ventricule
    . fonction normale (systolique and diastolique)
    . valve AV normale (au moins une)
        . voie de sortie sans obstacle
        . rythme sinusal stable
    . pression auriculaire gauche basse

Good and evil

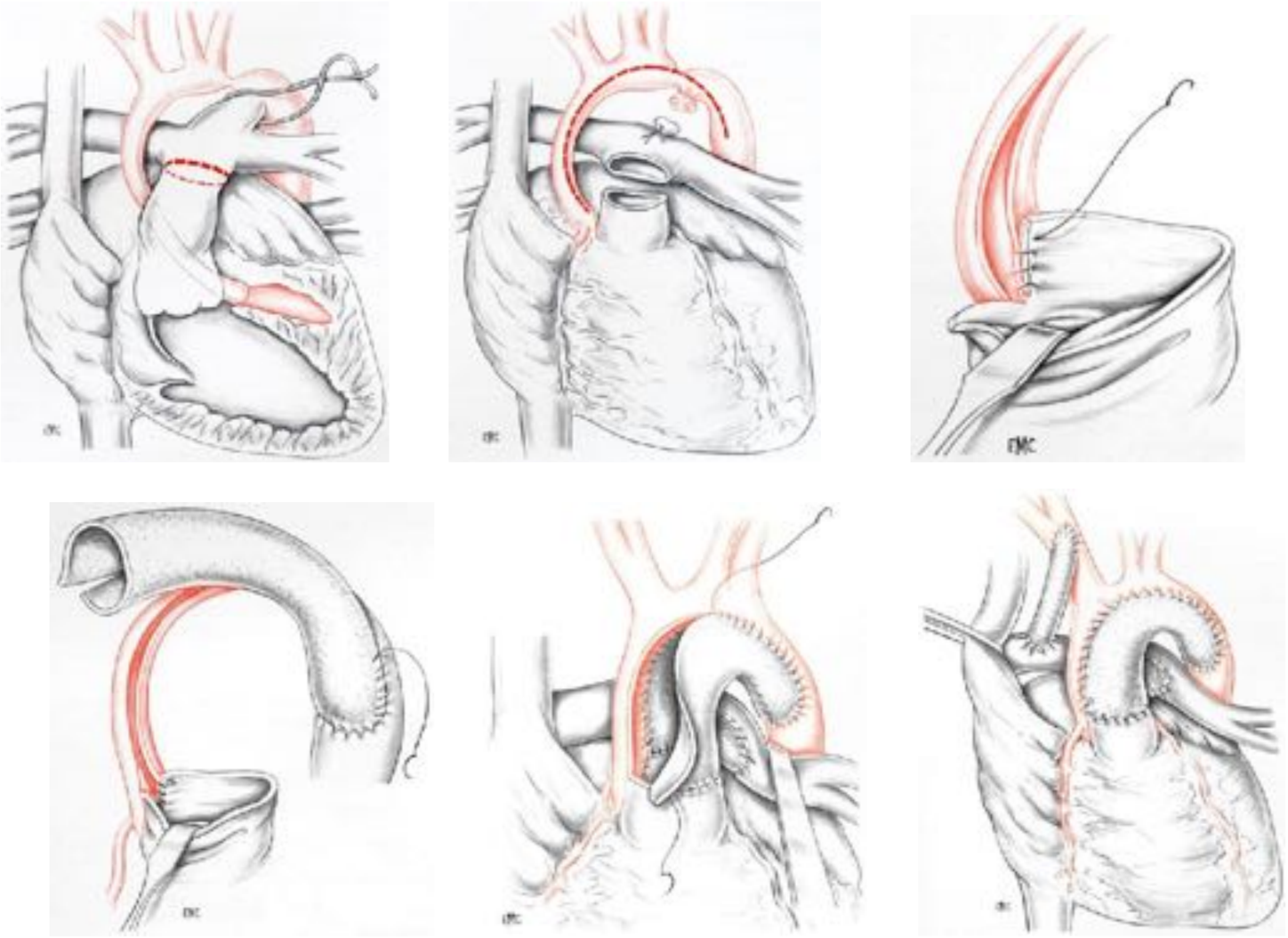
- VG versus VD versus Vx
- Mitrale vs tricuspide vs CAV
- Obstacle aortique
- Absence de protection pulmonaire
- Anatomie artérielle pulmonaire
- RVPAT ou PFO restrictif (atrésie mitrale)

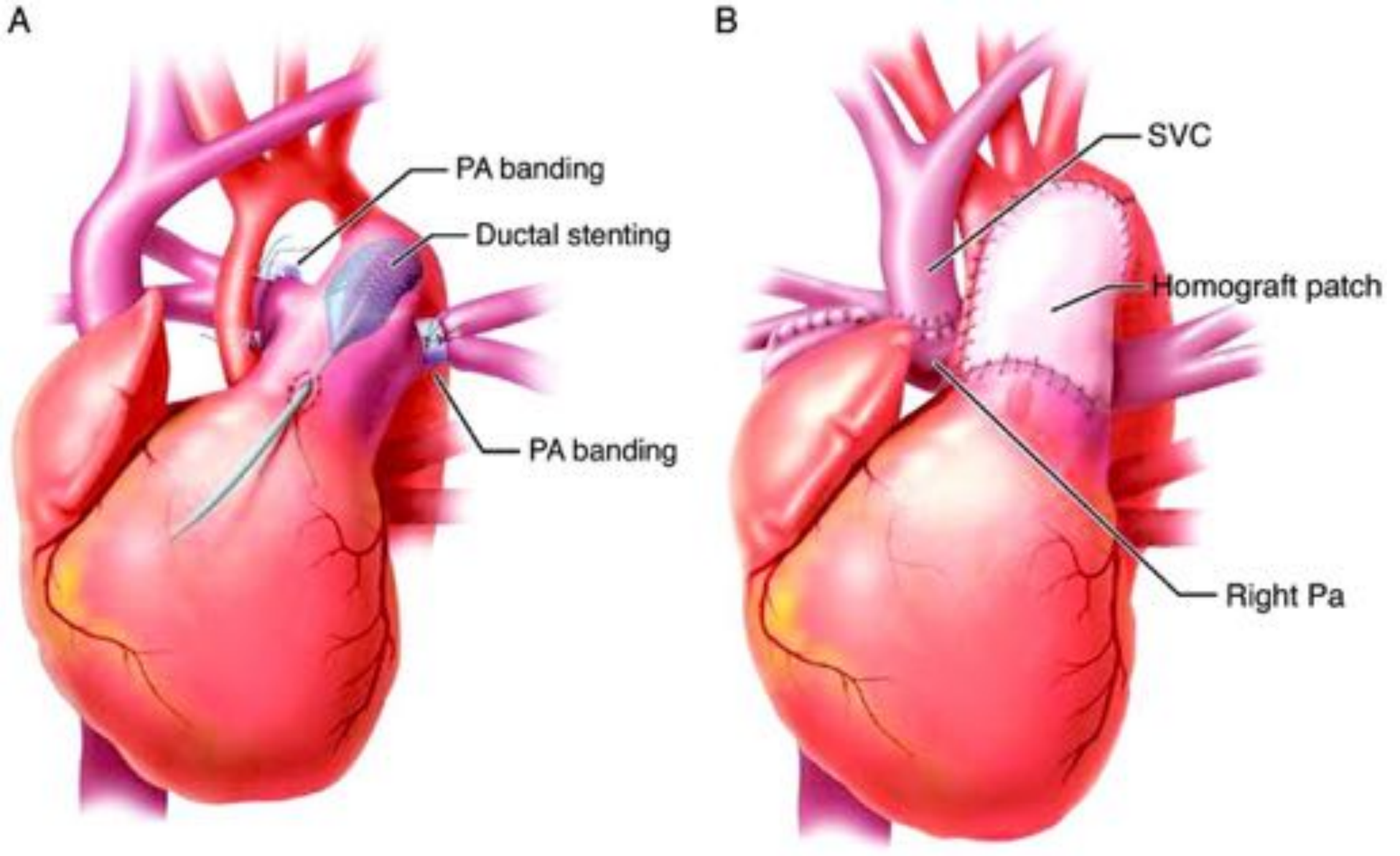
Situations néonatales

- Ducto-dépendance pour la circulation pulmonaire
  - PGE1 puis Blalock
- Ducto-dépendance pour la circulation systémique
  - Norwood
- Hypertension pulmonaire
  - Cerclage

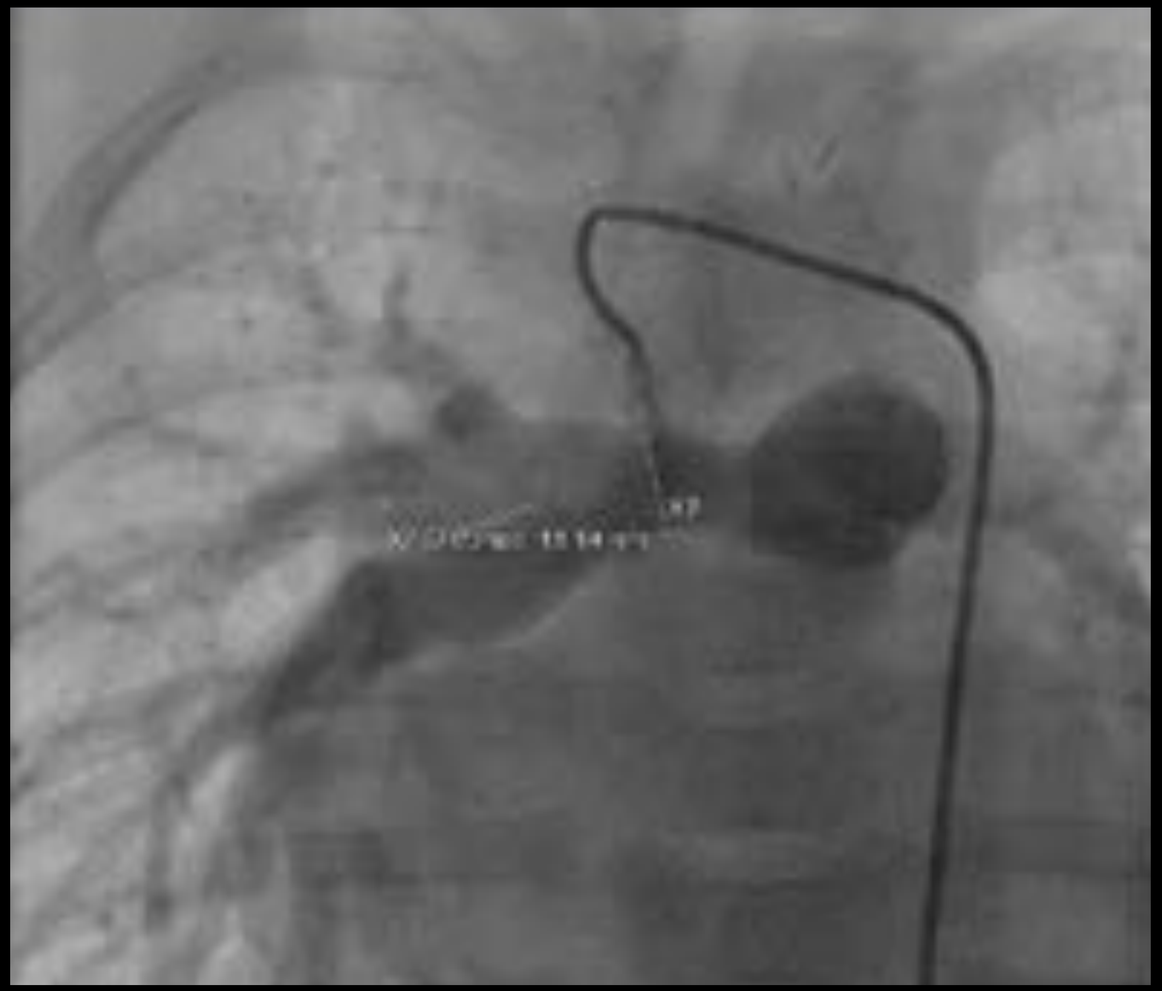

Ductus
Arteriosus
has closed
Ao
PA
LA
RA
RV
LV
Tricuspid Atresia
with VSD

Norwood procedure

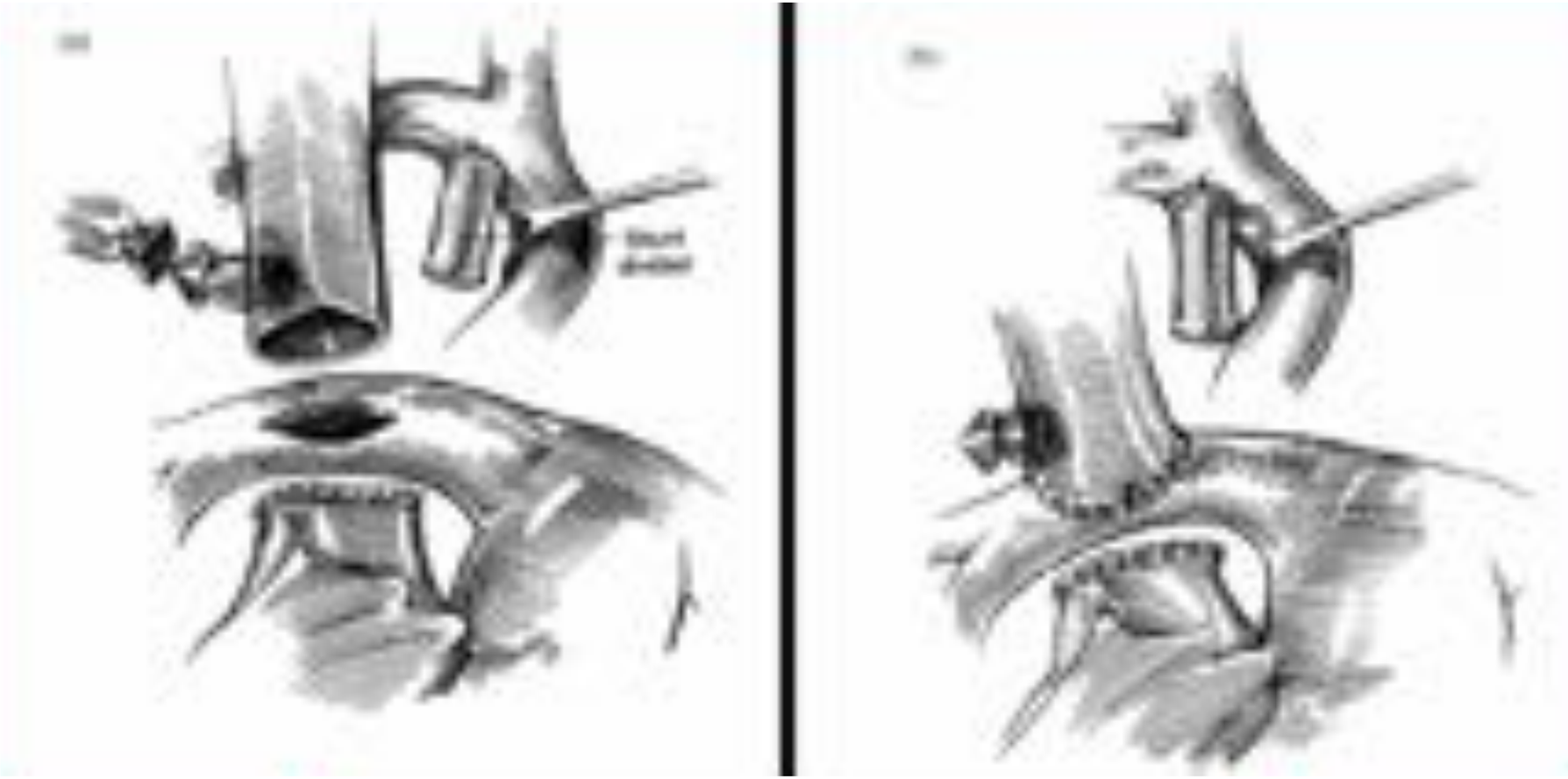



A
PA banding
Ductal stenting
PA banding
B
SVC
Homograft patch
Right Pa

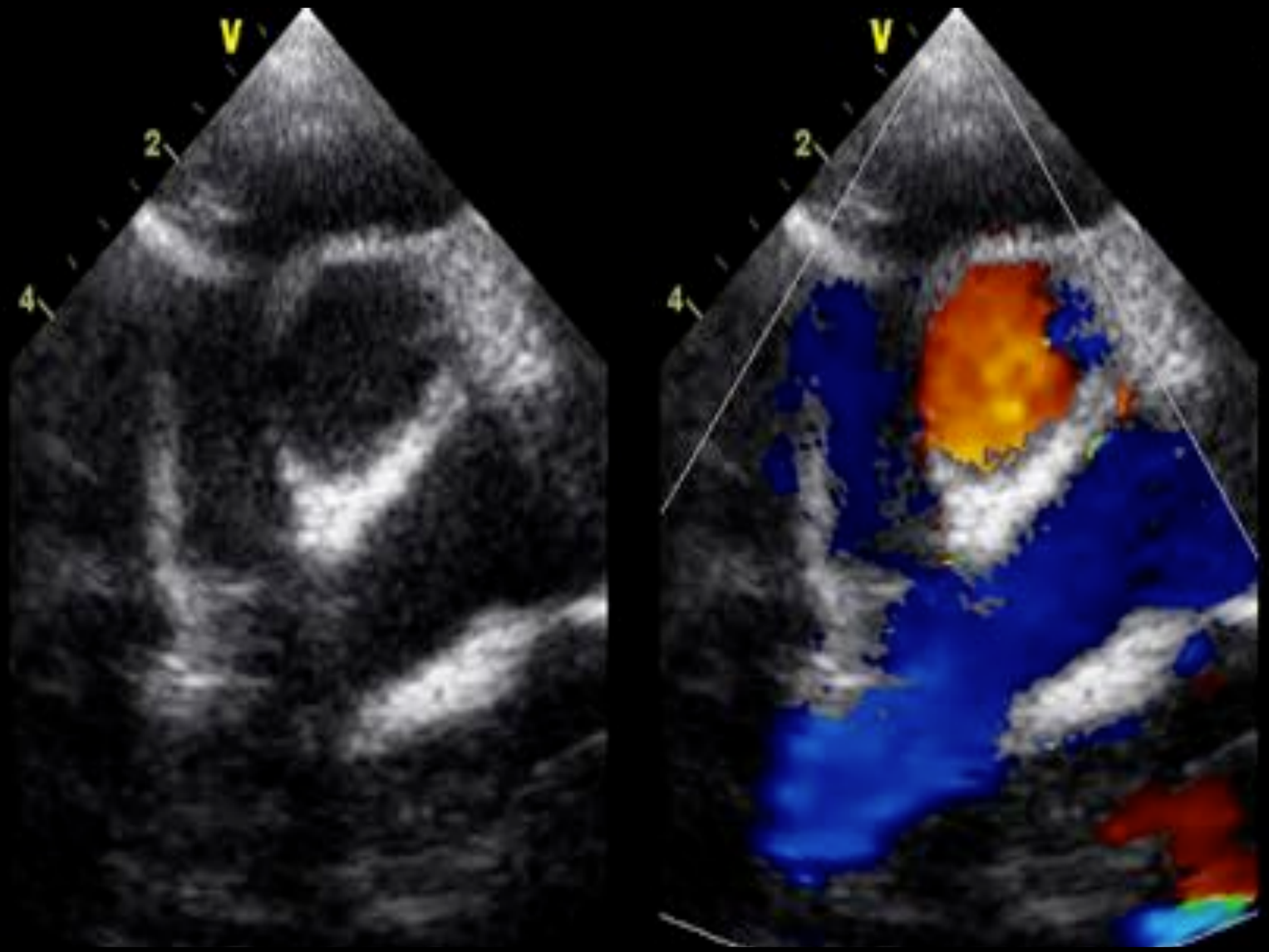
Evaluation pré DCPP



Glenn



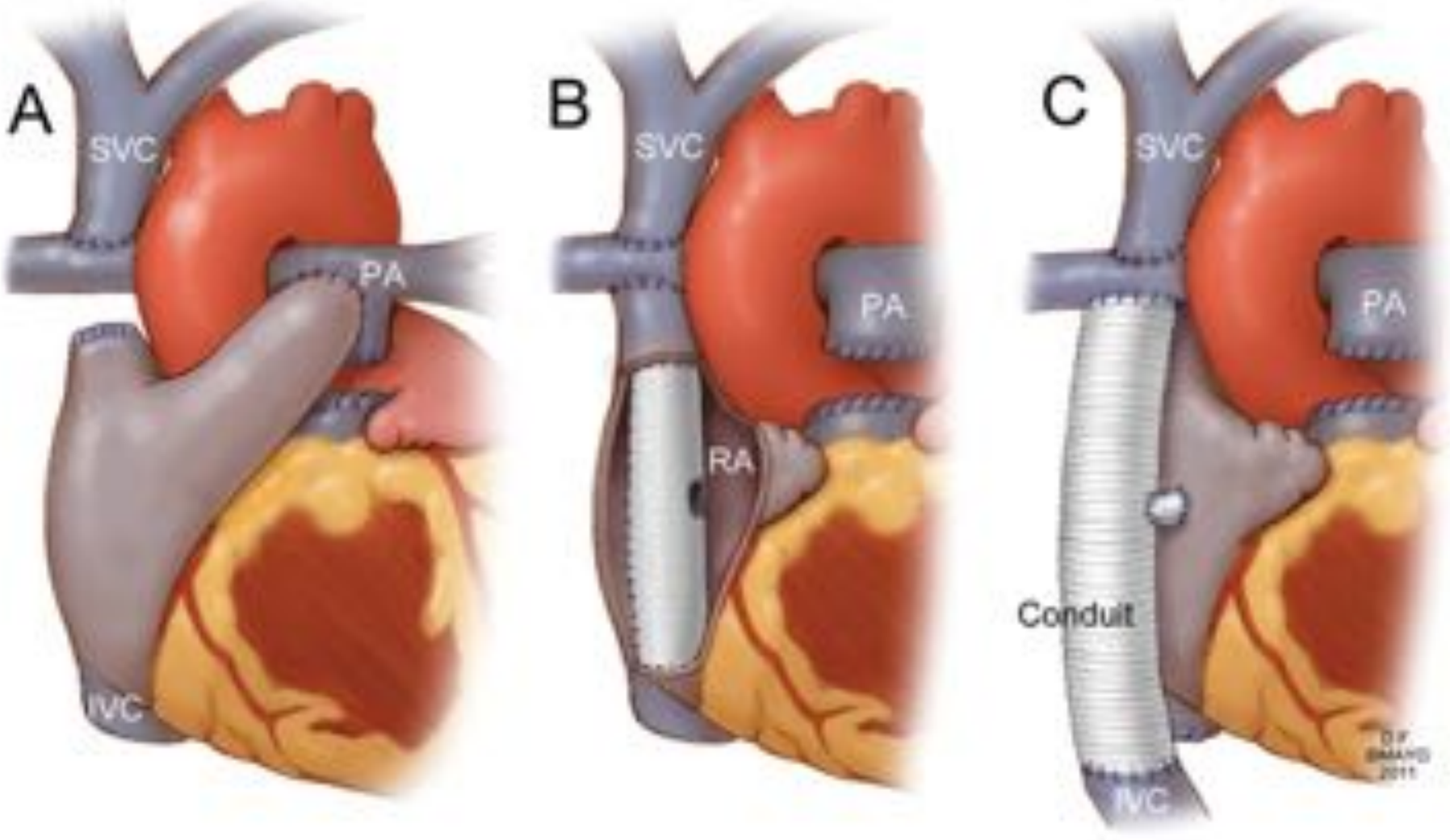
Partial cavopulmonary connection

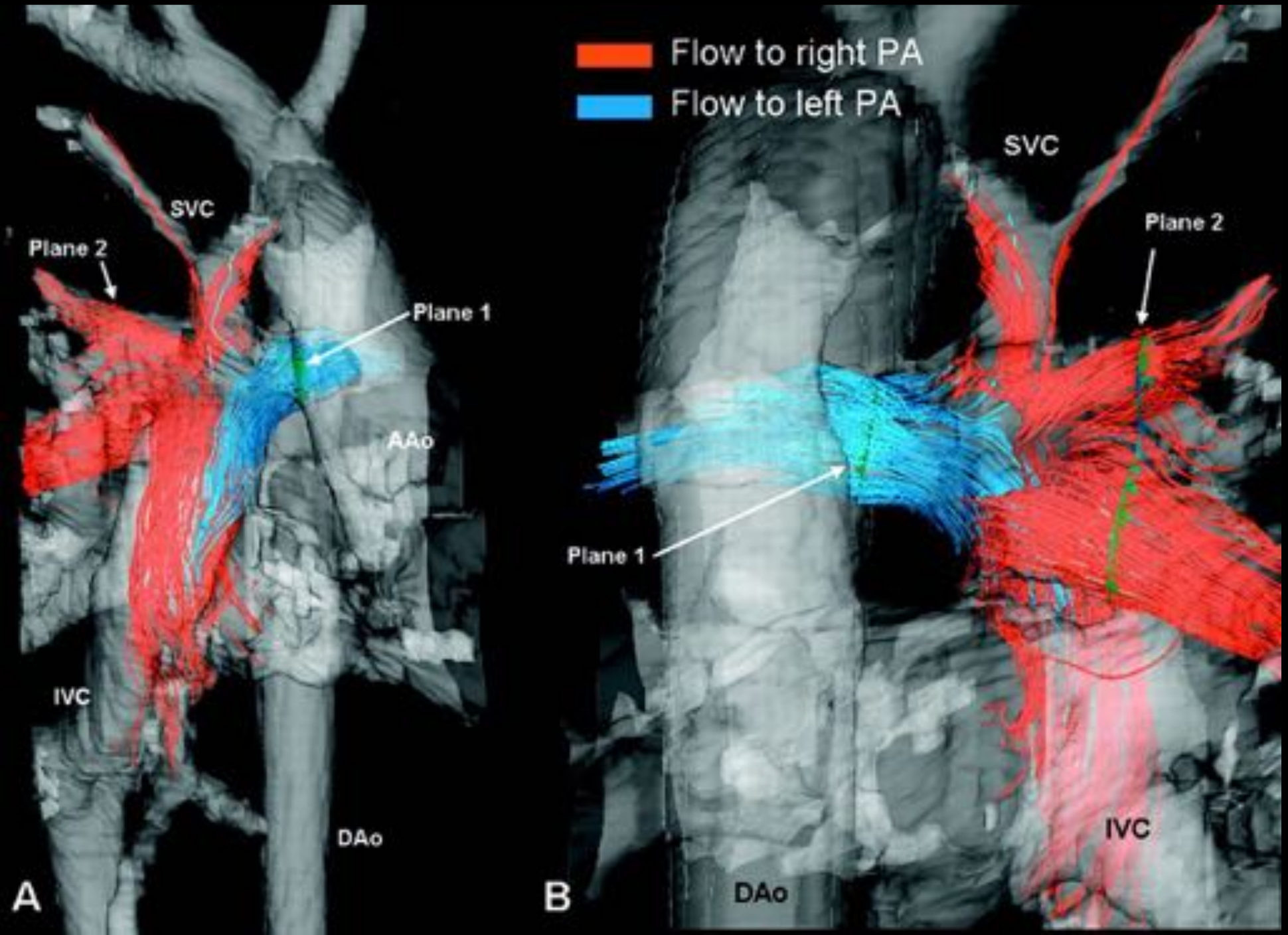


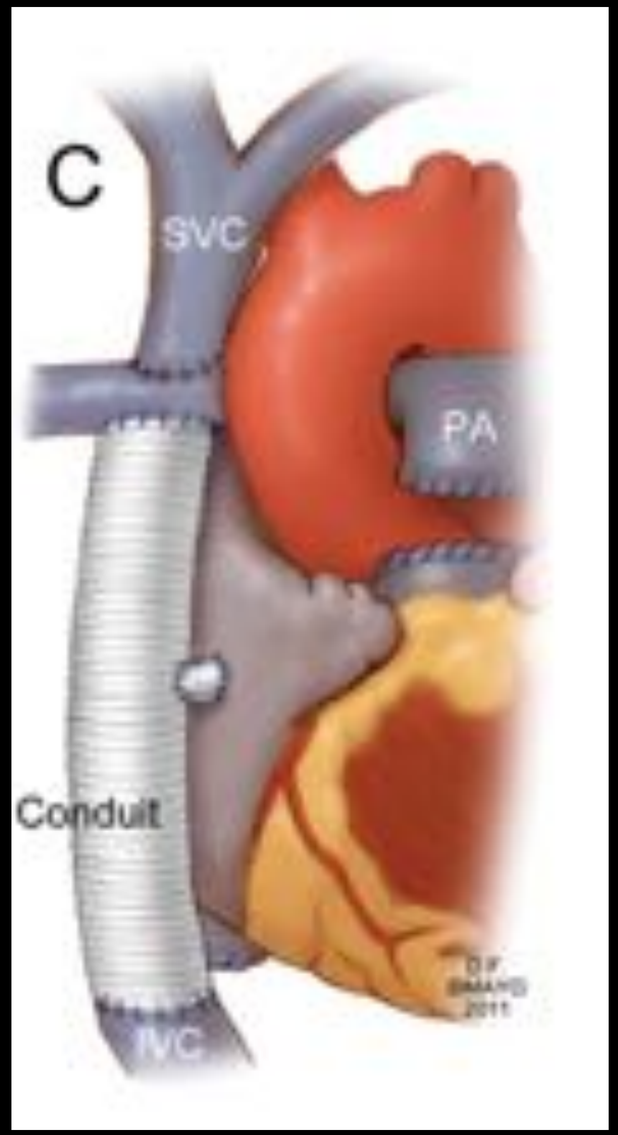
Partial cavopulmonary connection

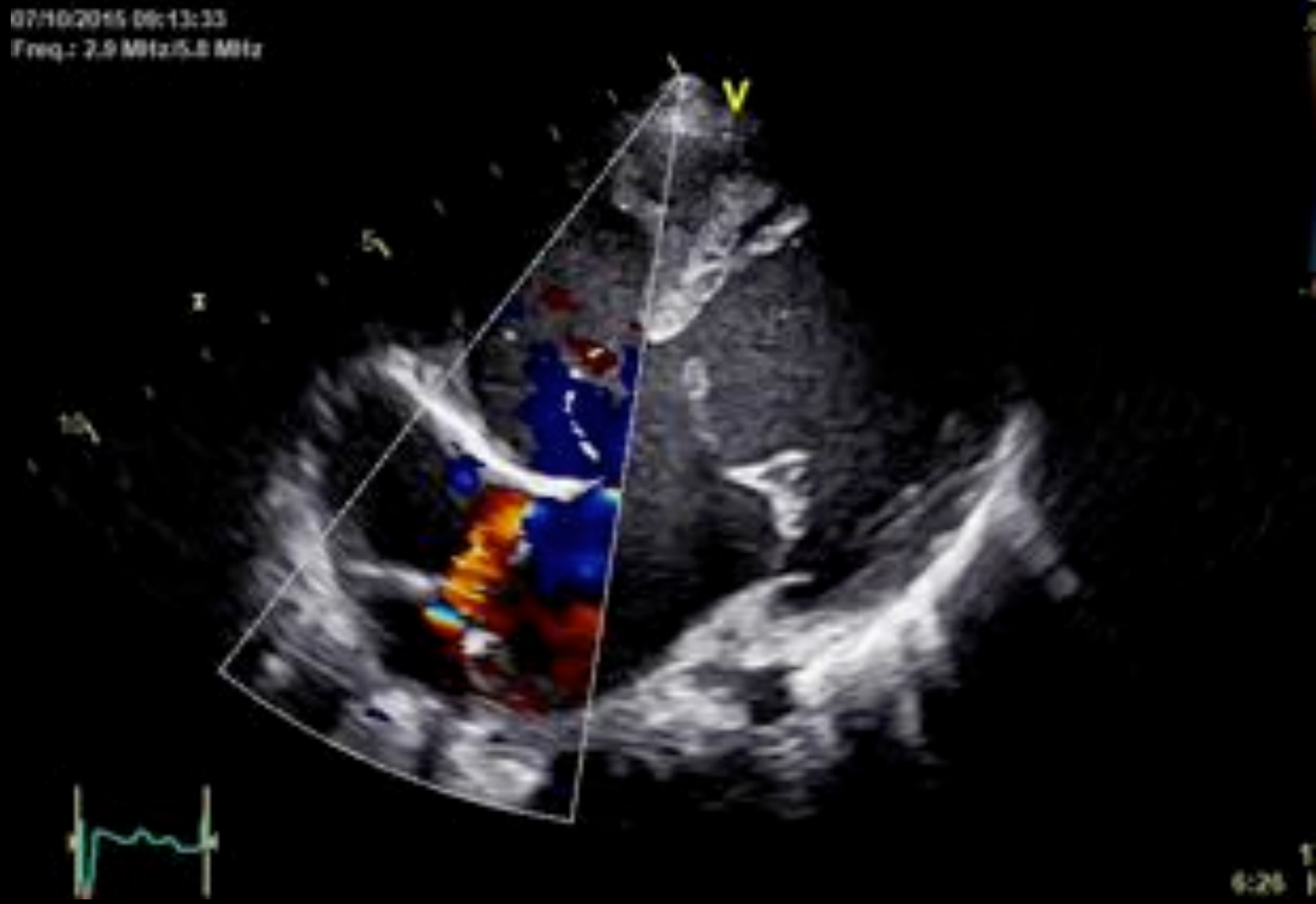
Partial CPC with additional food flow

Evaluation pre-TCPC


A
SVC
PA
IVC
B
SVC
PA
RA
C
SVC
PA
Conduit
IVC


Flow to right PA
Flow to left PA
SVC
Plane 2
Plane 1
AAo
IVC
DAo
A
B
SVC
Plane 2
Plane 1
IVC
DAo


C
SVC
PA
Conduit
IVC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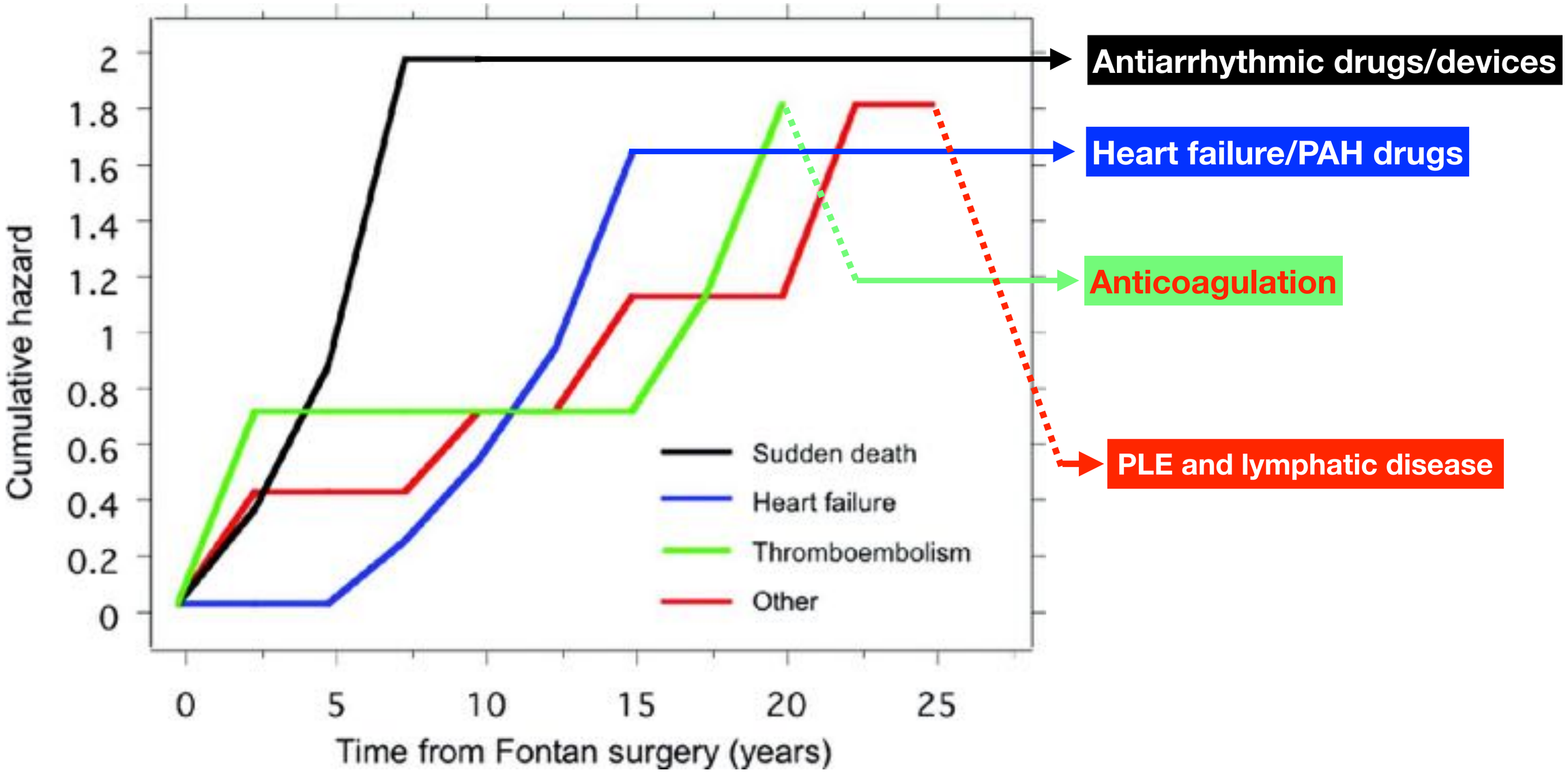
Freq.: 2.9 MHz/5.8 MHz
V

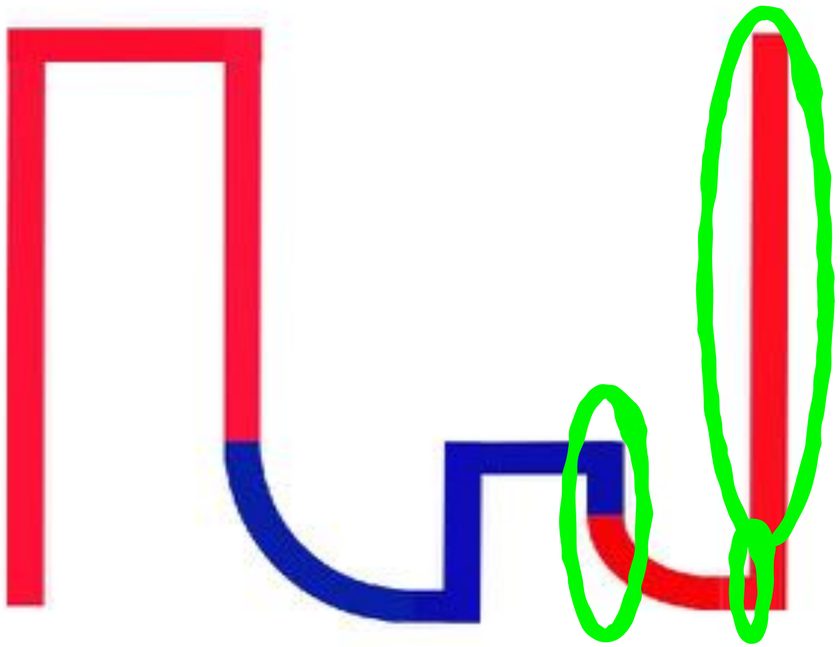
Cumulative hazard by mode of death



Khairy, P. et al. Circulation 2008;117:85-92

Critical bottlenecks in various circulations

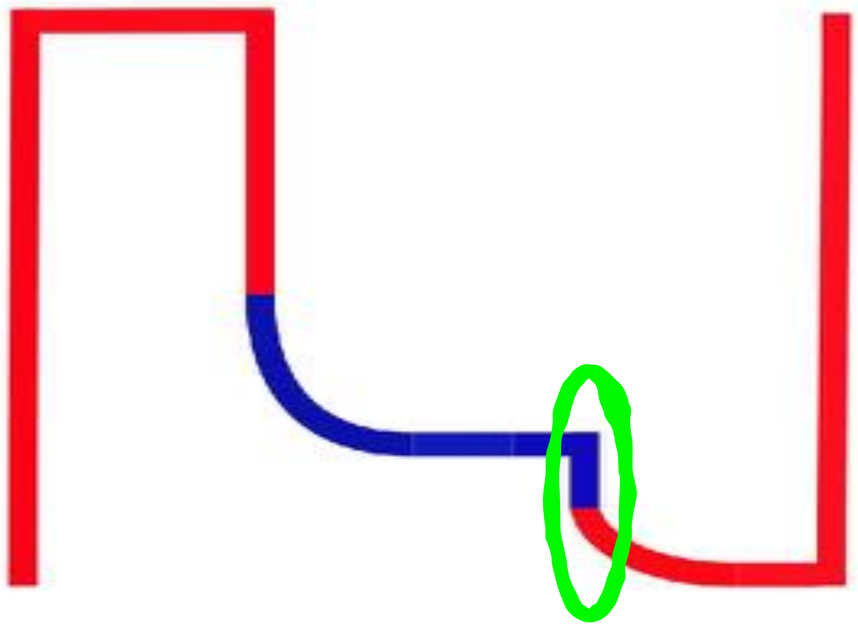
The Fontan circulation - a new portal system



Cardiomyopathies

Pulmonary hypertension

Mitral stenosis

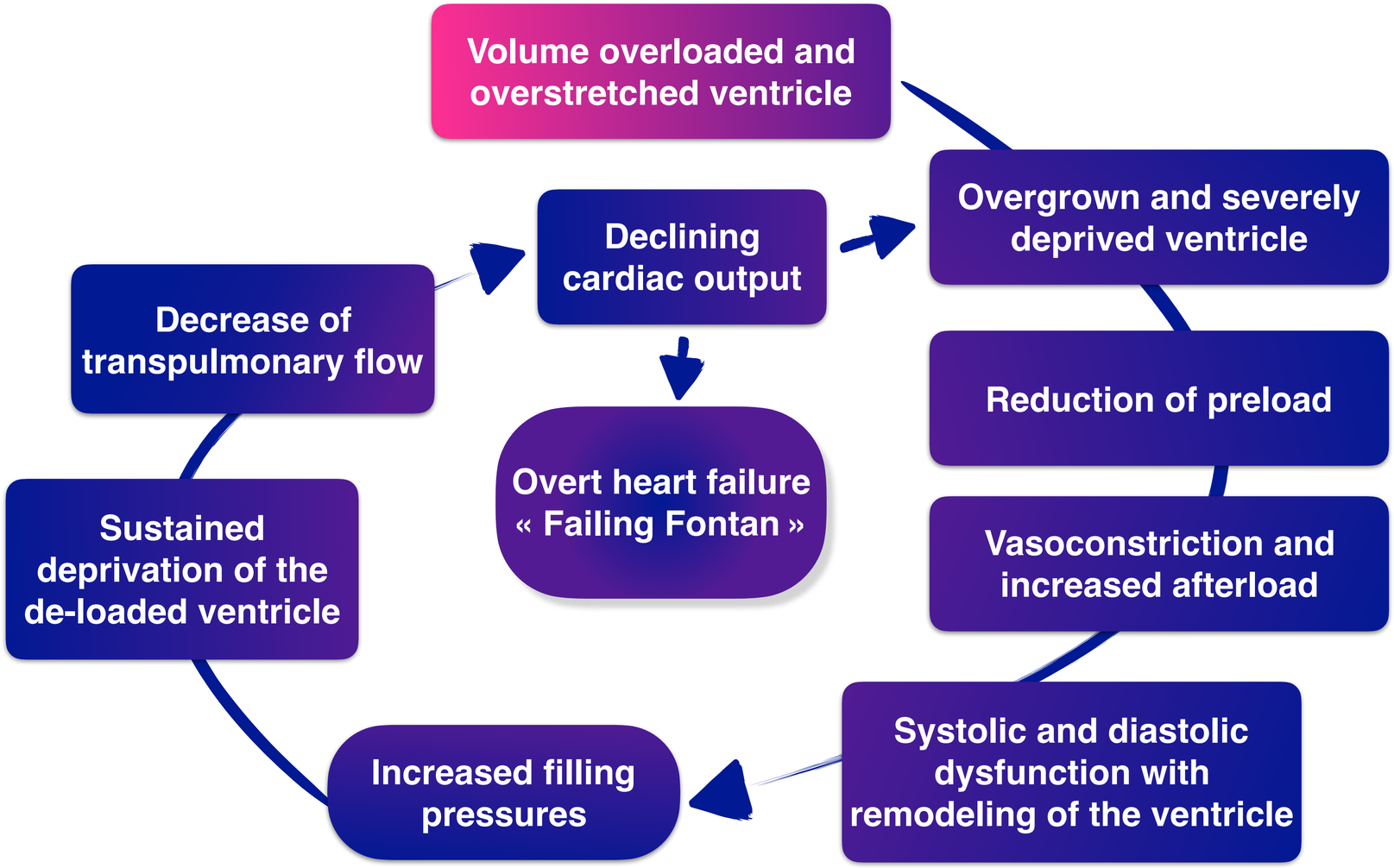


Fontan TCPC

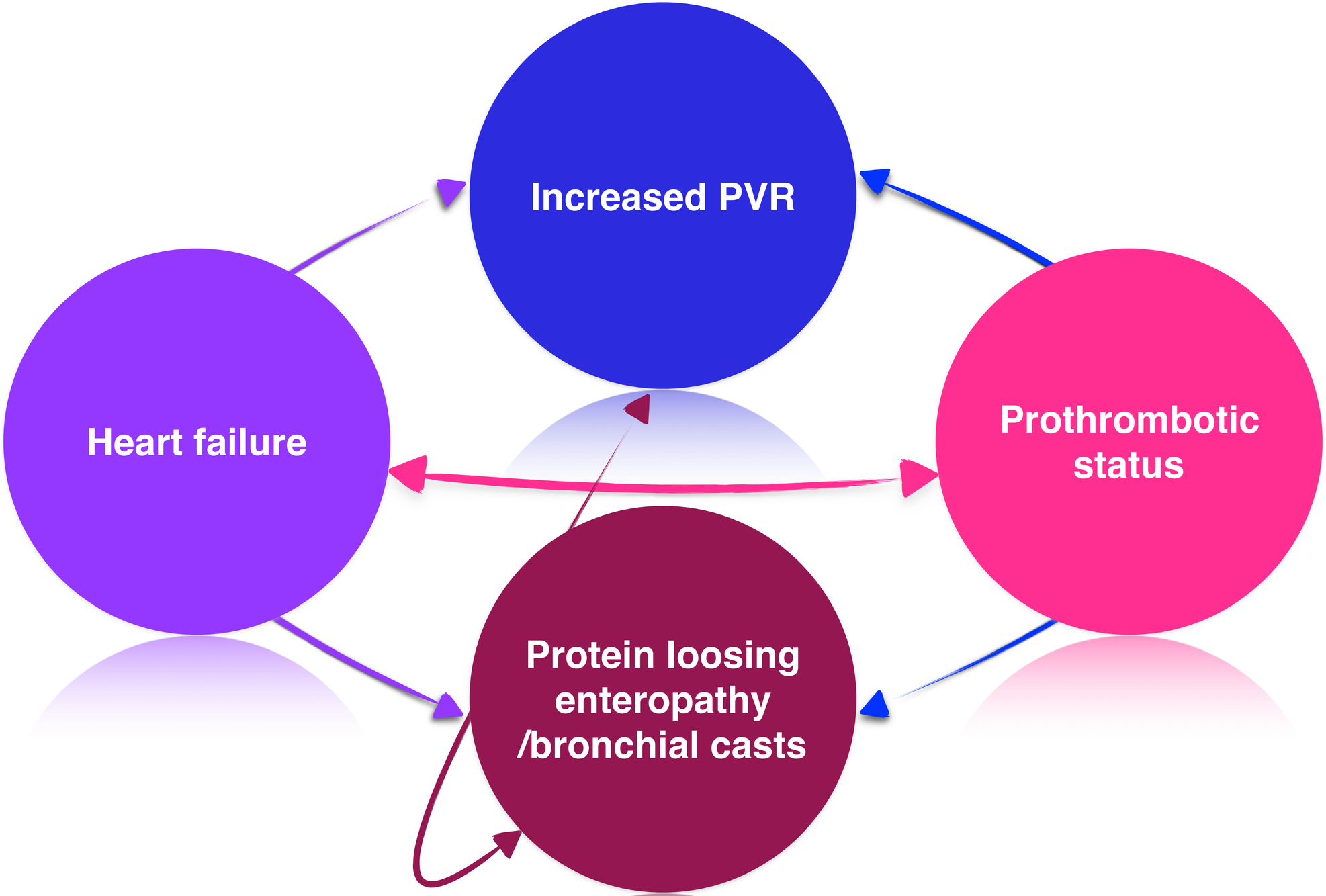
Courtesy Marc Gewillig

The Fontan circulation - a new portal system

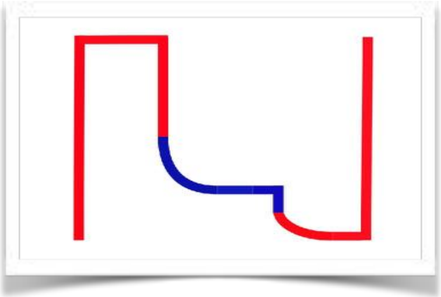
The vicious circle to failing Fontan



Adapted from Marc Gewillig-Heart 2016


Increased PVR
Heart failure
Prothrombotic status
Protein loosing enteropathy /bronchial casts

Optimization of the Neo-portal Fontan system



- **Connection**
  - No gradient
  - Minimal turbulence & flow collision; hepatic X-factor to both lungs
- **Lungs**
  - ***Total PVR as low as possible***
    - ✓ capacitance
    - ✓ recruitment
  - ***Reasons increased PVR***
    - ✓ Hypoplasia, stenosis, kink, loss of segments
    - ✓ Collateral flow
    - ✓ **Pulmonary vascular disease**
    - ✓ **(micro)Thrombi**
- **Ventricular succion**

Anatomical solutions

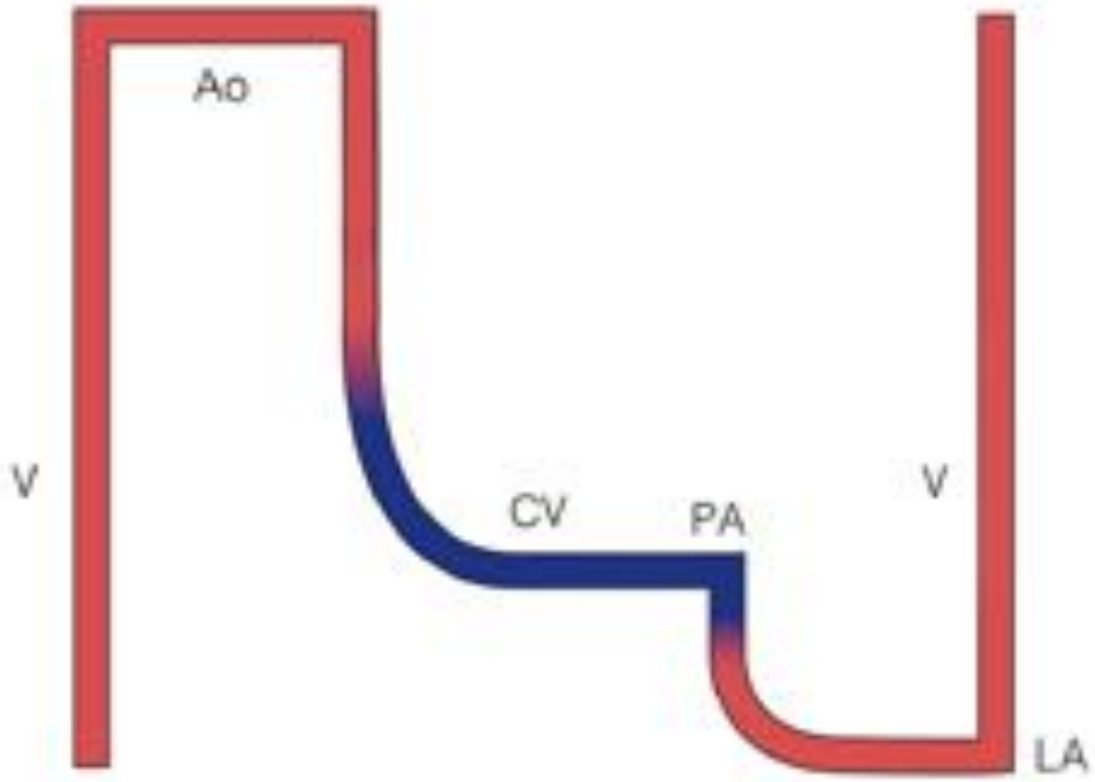
PAH drugs

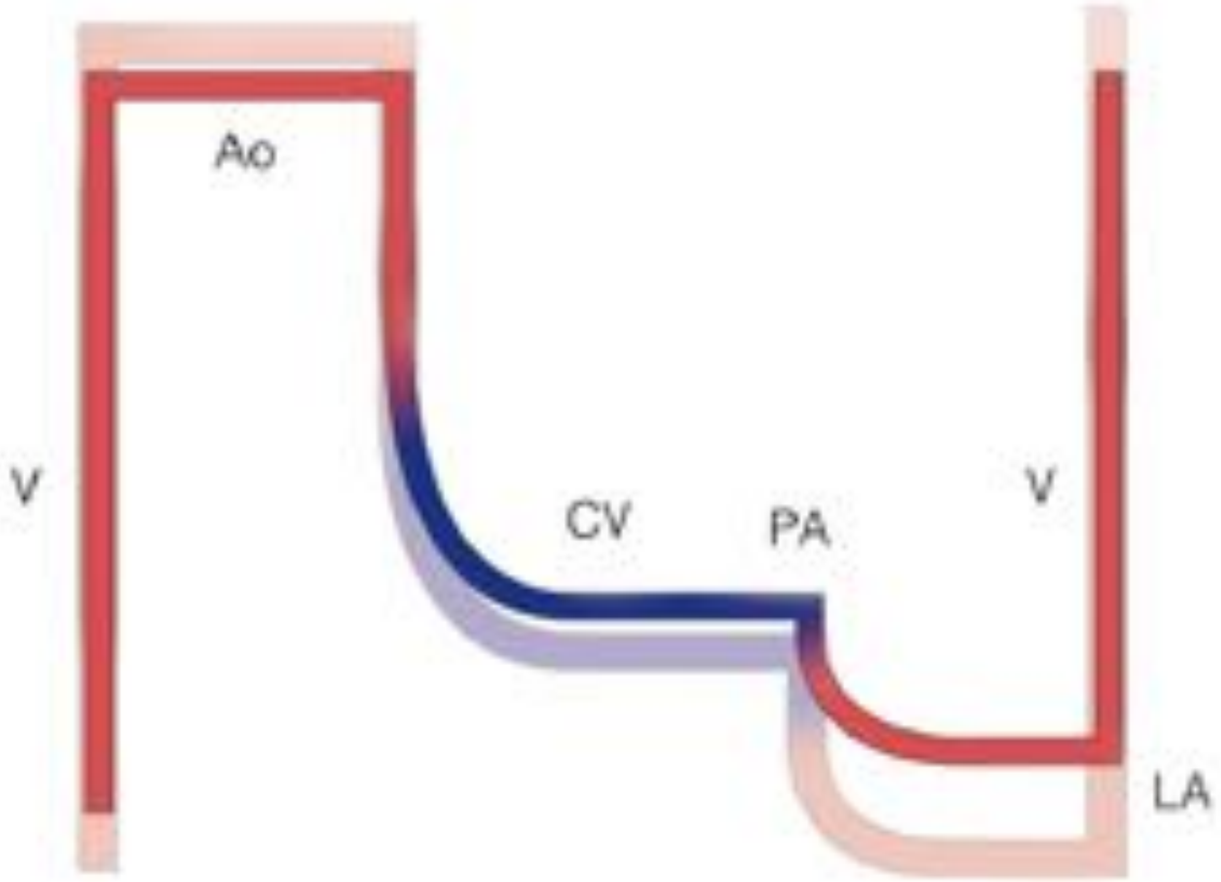
Anticoagulants

Lusitropic drugs

The Fontan circulation - a new portal system

Changes with aging - Preventing strategies



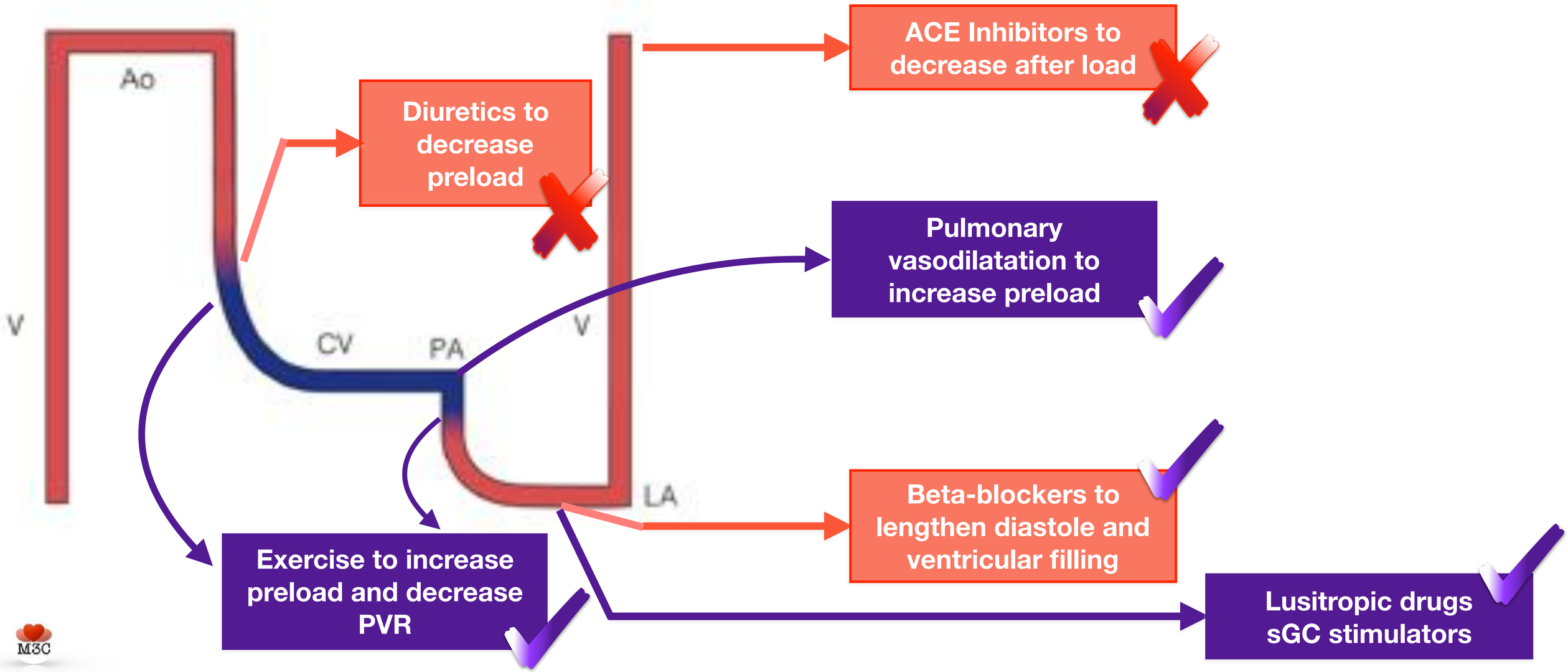


The lack of a robust definition of Fontan failure has contributed to the limited understanding of the prevalence of HF in Fontan-palliated SVs

Marc Gewillig-Heart 2016

Heart failure drugs in Fontan circulation

Potentially a wrong reasoning and a predictable minimal effect



Heart failure drugs in Fontan circulation

Fontan patients with reduced EF are different from those with preserved EF

- In a group of Fontan patients undergoing transplantation, **patients with preserved EF had significantly worse outcomes than those with reduced EF** suggesting that important mechanisms other than systolic dysfunction contributed to heart failure in the former group.

- This also suggests that **preventive treatment with heart failure drugs** aiming to prevent deleterious remodeling of the SV **is not beneficial**.

Griffiths ER, Kaza AK, Wyler von Ballmoos MC, Loyola H, Valente AM, Blume ED, del Nido P. Evaluating failing Fontans for heart transplantation: predictors of death. Ann Thorac Surg. 2009;88:558–563.

ACE inhibitors in univentricular hearts

- *Therapies for HF with reduced EF have not shown a mortality benefit in patients with HF with preserved EF. No evidence that preventive treatment is useful in UVH with preserved SV-EF.*

- Enalapril in children with single ventricle : **no changes** in HF severity neither improve growth, ventricular function nor death/transplantation at one year. [1]

- Enalapril did not alter systemic vascular resistance, resting cardiac index, diastolic function, or exercise capacity in adults with Fontan.[2,3]

- **There are no data evaluating ACE inhibitors in adults with SV and symptomatic HF.**

1-Hsu DT, Zak V, Mahony L, et al; Pediatric Heart Network Investigators. Enalapril in infants with single ventricle: results of a multicenterrandomized trial. Circulation. 2010;122:333–340.
2-Kouatli AA, Garcia JA, Zellers TM, Weinstein EM, Mahony L. Enalapril does not enhance exercise capacity in patients after Fontan procedure. Circulation 1997; 96:1507–1512.
3-Vonder Muhll I, Liu P, Webb G. Applying standard therapies to new targets: the use of ACE inhibitors and B-blockers for heart failure in adults with congenital heart disease. Int J Cardiol. 2004;97(suppl 1):25–33.

Beta-blockers in univentricular hearts

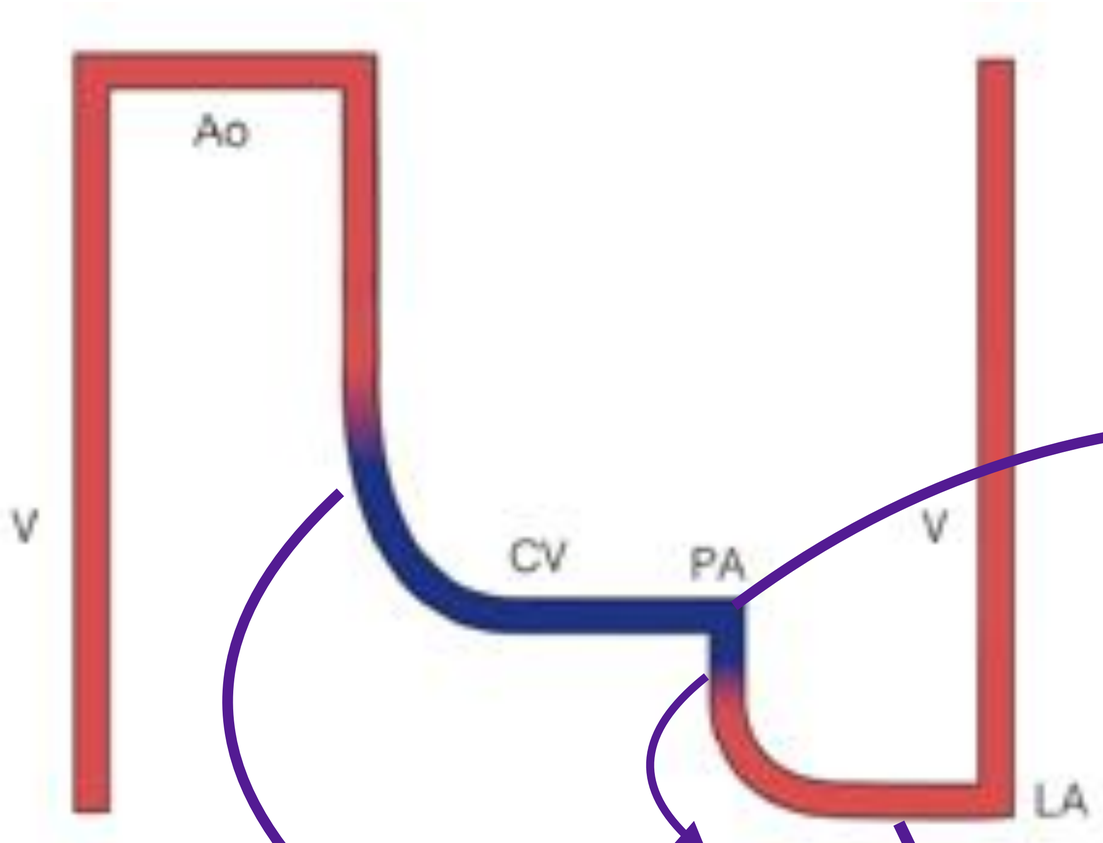
- Retrospective study of 51 patients of varying ages and nature of intervention (unoperated, after Glenn shunt, and after Fontan), **carvedilol** together with standard medical therapy **reduced the symptoms of HF and improved clinical parameters**.

- In a multicenter, double-blind, placebo-controlled study of **carvedilol** in children with systemic ventricular dysfunction, β-blockers **appeared to have a negative or neutral effect in patients with SV** compared with patients with cardiomyopathies and no structural heart defects.

1. Shaddy RE, Boucek MM, Hsu DT, Boucek RJ, Canter CE, Mahony L,Ross RD, Pahl E, Blume ED, Dodd DA, Rosenthal DN, Burr J, LaSalle B, Holubkov R, Lukas MA, Tani LY; Pediatric Carvedilol Study Group. Carvedilol for children and adolescents with heart failure: a randomized controlled trial. JAMA. 2007;298:1171–1179.
2. Ishibashi N, Park IS, Waragai T, Yoshikawa T, Murakami Y, Mori K, Mimori S, Ando M, Takahashi Y, Doi S, Mizutani S, Nakanishi T. Effect of carvedilol on heart failure in patients with a functionally univentricular heart. Circ J. 2011;75:1394–1399.

Heart failure drugs in Fontan circulation

Potentially efficient therapies



Pulmonary vasodilatation to increase preload

Exercise to increase preload and decrease PVR

Lusitropic drugs sGC stimulators

Pulmonary vasodilator in univentricular hearts

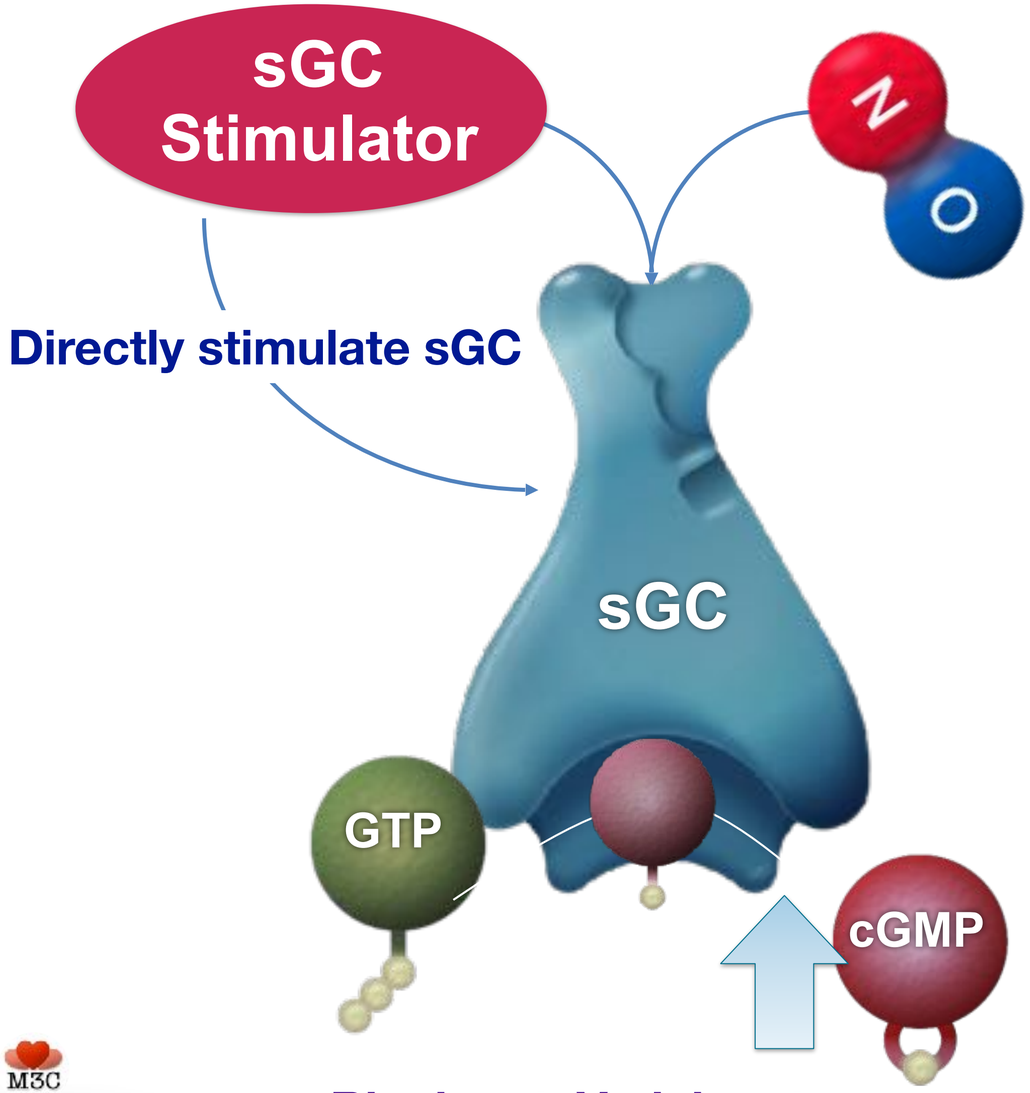
- The objective is to lower pulmonary vascular resistance and to improve ventricular preload.
- Although theoretically the results were beneficial, small series show mixed results.

- ***Phosphodiesterase-5 inhibitors***
  - A single dose improved peak VO2 during exercise with a measurable increase in both pulmonary and systemic blood flow at peak exercise.
  - Others series showed a favorable impact on the Doppler-derived myocardial performance index and systolic arterial and ventricular elastance.
  - With longer therapy, **a double-blind, placebo-controlled crossover trial showed an improvement in the ventilatory efficiency slope during cardiopulmonary exercise testing**, although other parameters were not improved.
- ***Endothelin receptor antagonists***
  - Limited improvements in ventricular function were described in 1 study, but other pilot studies found no benefit.
  - **TEMPO study : improvement of Peak VO2** (and WHO-FC)

Giardini A, et al. Effect of sildenafil on haemodynamic response to exercise and exercise capacity in Fontan patients. Eur Heart J. 2008;29:1681–1687.
Van De Bruaene A, et al. Sildenafil improves exercise hemodynamics in Fontan patients. Circ Cardiovasc Imaging. 2014;7:265–273.
Goldberg DJ, et al. Impact of sildenafil on echocardiographic indices of myocardial performance after the Fontan operation. Pediatr Cardiol. 2012;33:689–696.
Shabanian R, et al. Sildenafil and ventriculo-arterial coupling in Fontan-palliated patients: a noninvasive echocardiographic assessment. Pediatr Cardiol. 2013;34:129–134.
Goldberg DJ, et al. Impact of oral sildenafil on exercise performance in children and young adults after the Fontan operation: a randomized, double-blind, placebo-controlled, crossover trial. Circulation. 2011;123:1185–1193.
Bowater SE, et al The safety and effects of bosentan in patients with a Fontan circulation. Congenit Heart Dis. 2012;7:243–249.
Ovaert C, et al. The effect of bosentan in patients with a failing Fontan circulation. Cardiol Young. 2009;19:331–339.
Schuuring MJ, et al. Impact of bosentan on exercise capacity in adults after the Fontan procedure: a randomized controlled trial. Eur J Heart Fail. 2013;15:690–698.
Hebert A et al. Circulation. 2014;130:2021-2030.

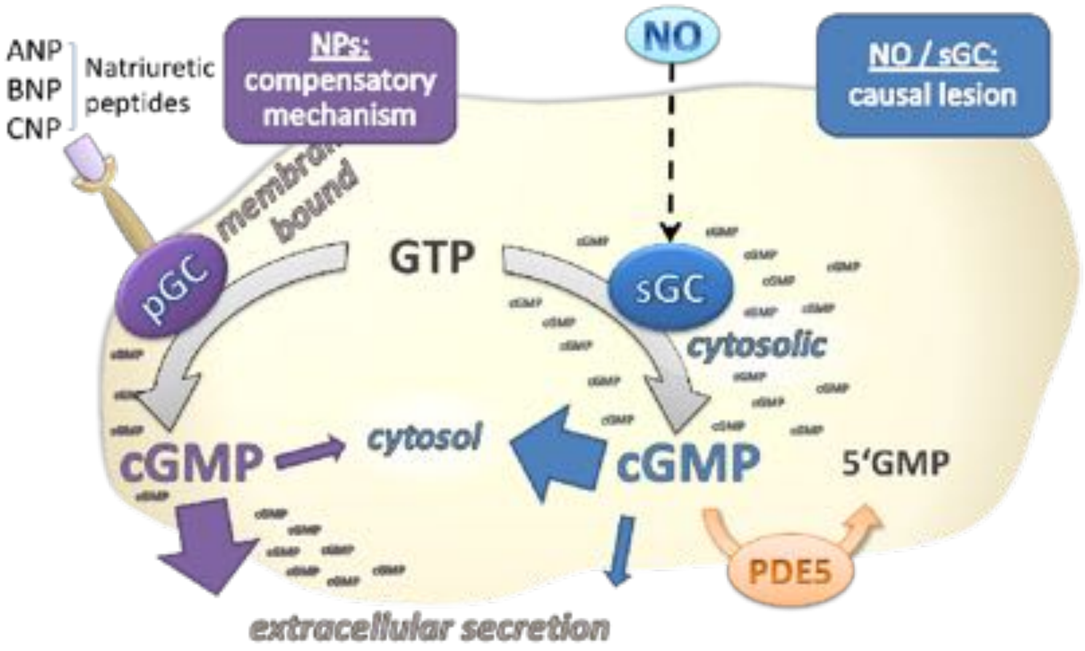
Lusitropic drugs in univentricular hearts

Enhances sensitivity of sGC to NO



Riociguat, Vericiguat

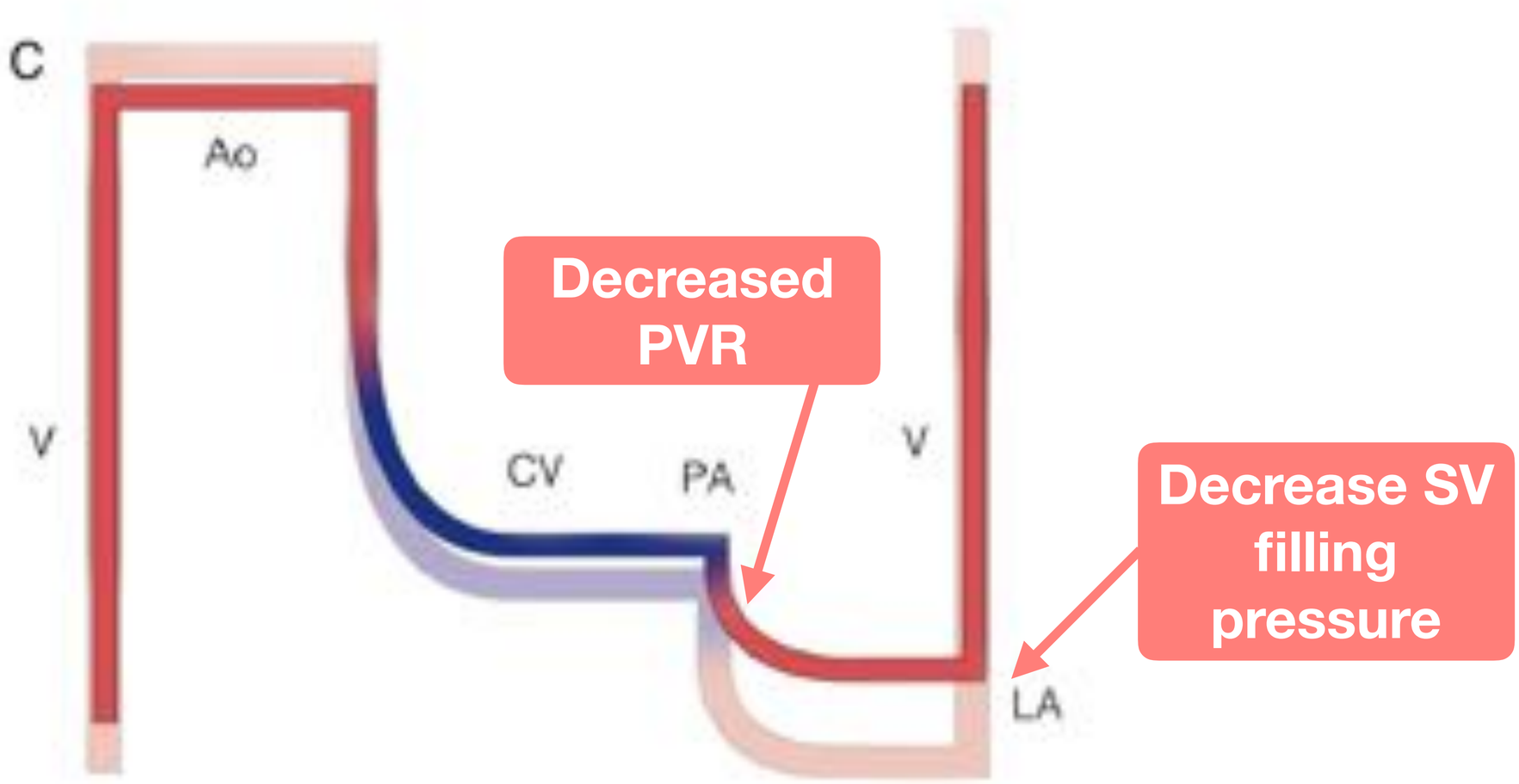
Different cGMP-augmenting pathways targeted in clinical trials



sGC stimulators, PDE-5 inhibitors, Neprilysin inhibitors (LCZ)

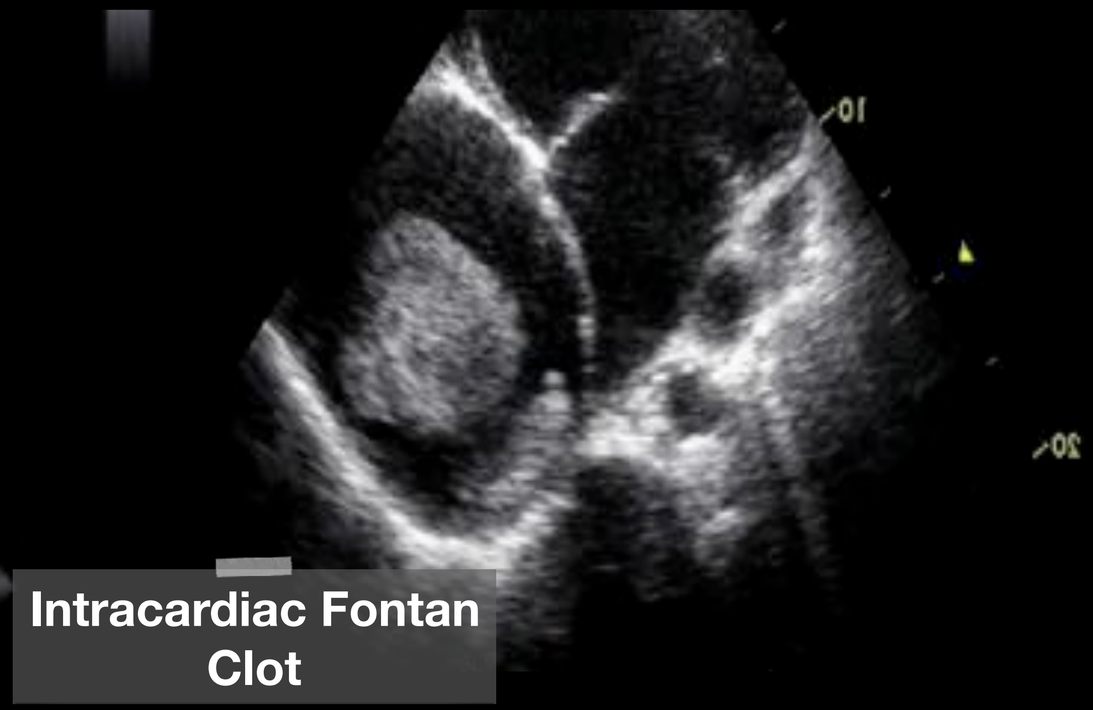
ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CNP, c-type natriuretic peptide; NO, nitric oxide; PDE5, phosphodiesterase-5; pGC, particulate guanylyl cyclase; sGC, soluble guanylyl cyclase. modified after Senni et al., Eur Heart J. 2014 Oct 21;35(40):2797-815
Stasch JP et al. Nature 2001;410:212–15;
Greene SJ et al. J Am Heart Assoc 2013;2:e000536;

The RioFontan study : riociguat in patients with Fontan circulation



The antithrombotic treatment in Fontan circulation

Intracardiac Fontan Sludge



Intracardiac Fontan Clot

Predictors of thrombo-embolic deaths in survivors

Characteristic	Hazard ratio	*95%CI*	*P*
Univariate			
Atrial fibrillation	5.4	*1.0-29.4*	0.0529
Lack of aspirin or warfarin therapy	5.7	*1.0-32.3*	0.0515
RA pressure on follow-up, mmHg	1.26	*1.03-1.53*	0.0247
Thrombus within Fontan	4.9	*2.1-11.6*	0.0002
Multivariate			
Thrombus within Fontan	22.7	*4.3-120.0*	0.0002
Lack of aspirin or warfarin therapy	91.6	*4.2-2004.8*	0.0041

All but nothing

M3C

Effect of aspirin and warfarin therapy on TE events in patients with Fontan palliation

Meta-analysis

10 studies with 1200 patients, average F/U 7.1 yrs

Incidence of TE

OR 0.43 (0.19-0.93) for some vs. none
OR 0.36 (0.18-0.74) for ASA vs. none
OR 0.33 (0.17-0.63) for warfarin vs. none
OR 0.94 (0.61-1.44) for warfarin vs. ASA

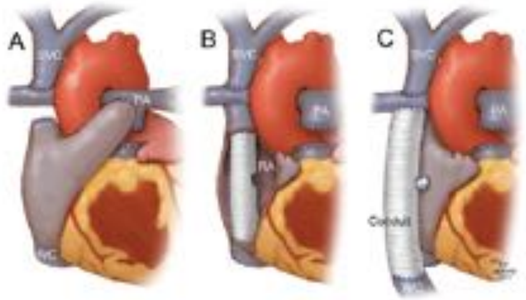
No difference for early or late TE

No difference for Fontan connection type

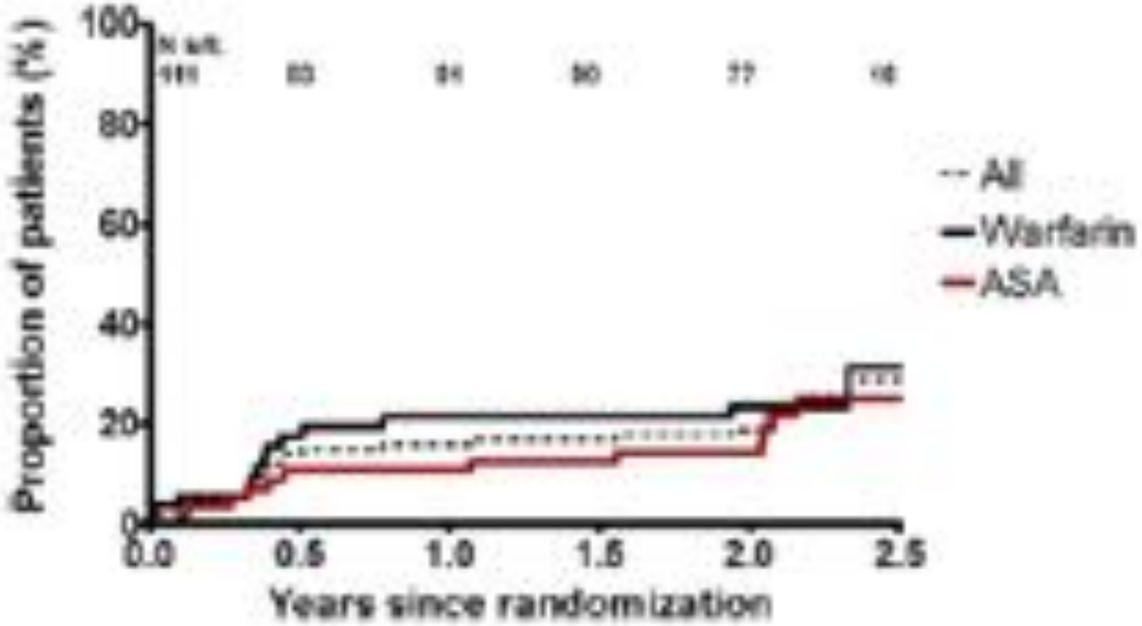
M3C

Alsaled et al. Heart 2015

A Multicenter, Randomized Trial Comparing Heparin/Warfarin and Acetylsalicylic Acid as Primary Thromboprophylaxis for 2 Years After the Fontan Procedure in Children



Thrombosis after randomization

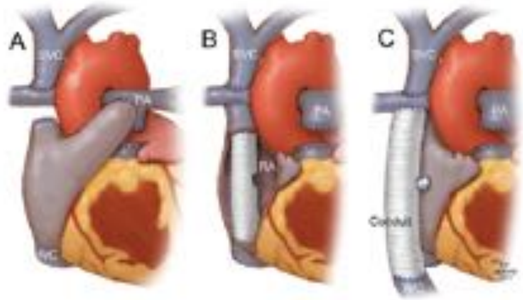


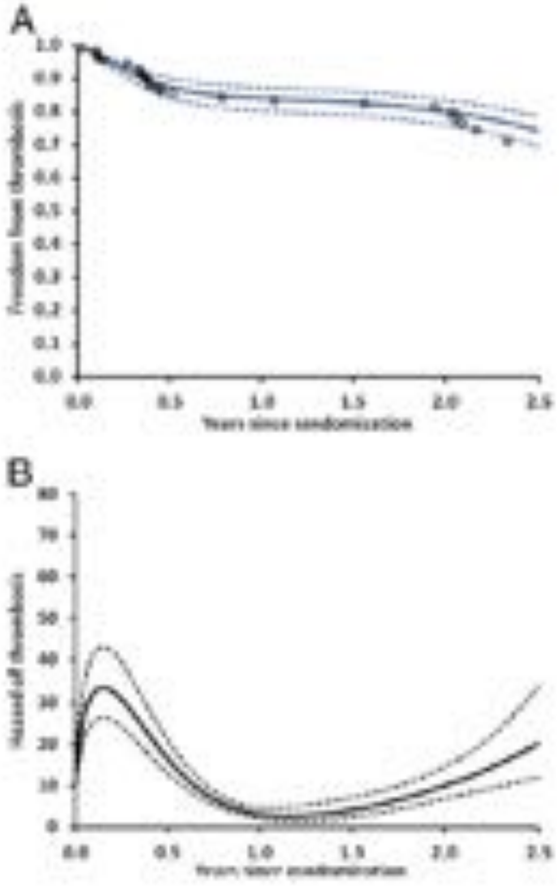
Kaplan-Meier estimate for the proportion of patients with thrombosis 2 years after randomization was 19% (24% in patients randomized to warfarin vs. 14% in patients randomized to aspirin). Hazard ratio for thrombosis for patients randomized to warfarin vs. acetylsalicylic acid (ASA) was 1.35 (95% confidence interval: 0.62 to 3.00), p 0.45.

Monagle P et al. J Am Coll Cardiol 2011;58:645-51

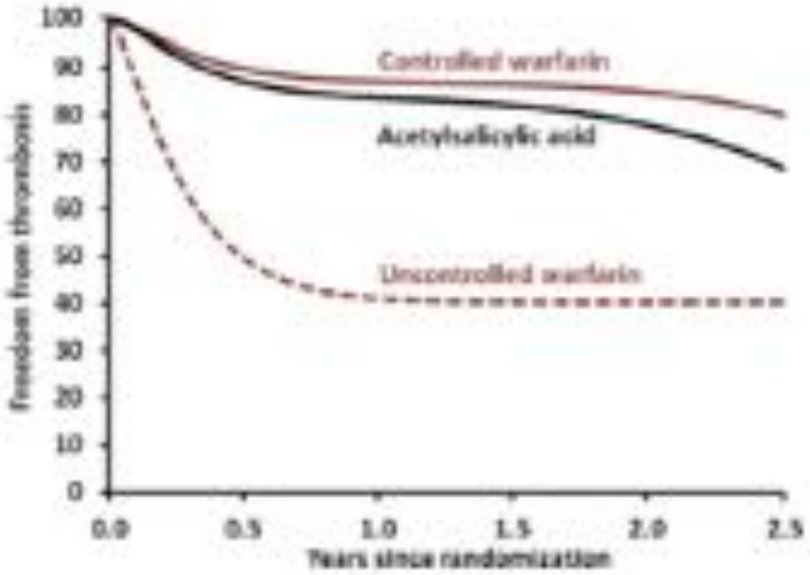
Factors Associated With Thrombotic Complications After the Fontan Procedure

A Secondary Analysis of a Multicenter, Randomized Trial of Primary Thromboprophylaxis for 2 Years After the Fontan Procedure





Time-related freedom from thrombosis was 69% (all venous, no arterial events), with 28% of thrombosis presenting with clinical signs or events



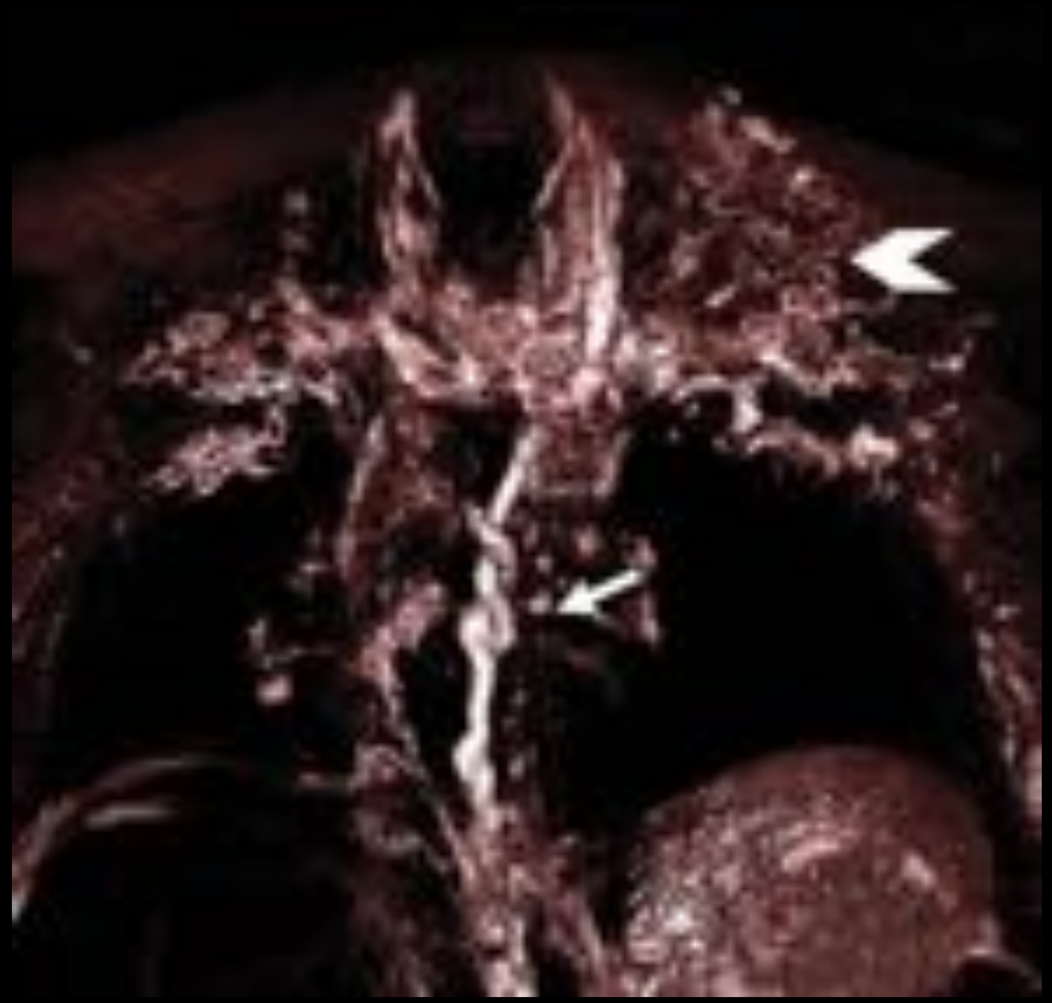
Freedom From and Hazard of Thrombosis Over Time in Patients After Fontan Surgery

Freedom From Thrombosis Over Time Stratified by Thromboprophylaxis Choice and Effectiveness

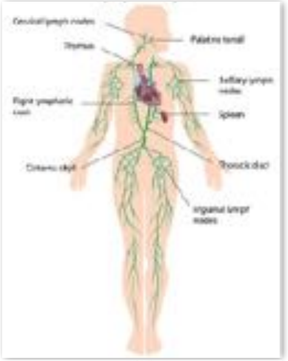
McCrindle BW et al. J Am Coll Cardiol 2013;61:346-53

The lymphatics in Fontan circulation

Bronchial casts



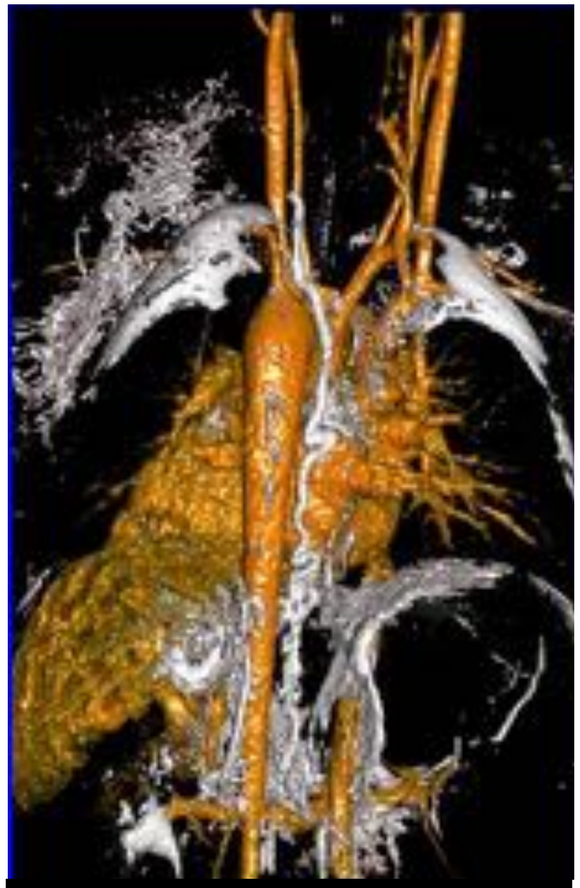
Lymphatics



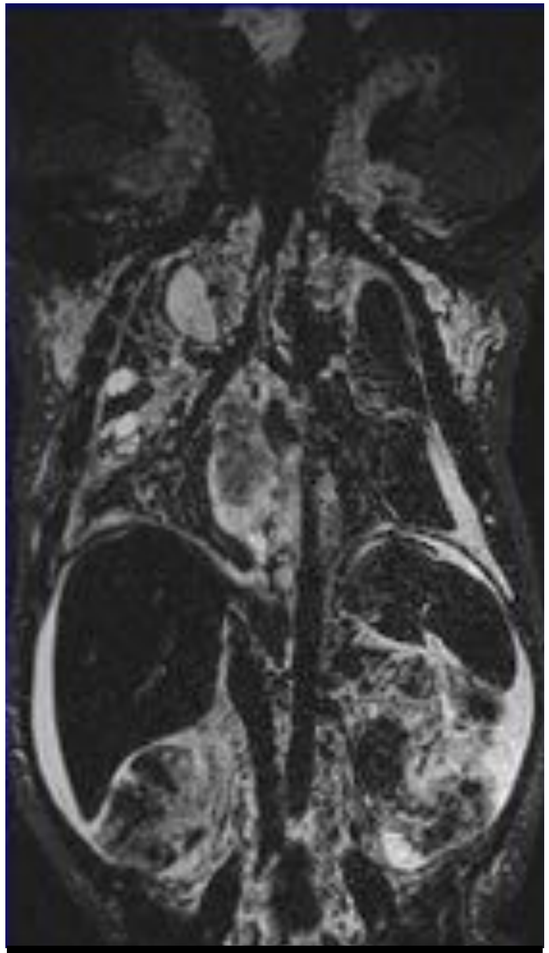
T2 imaging of lymphatic circulation

The new horizon for the treatment of PLE/bronchial casts

Lymphangectasia collaterals

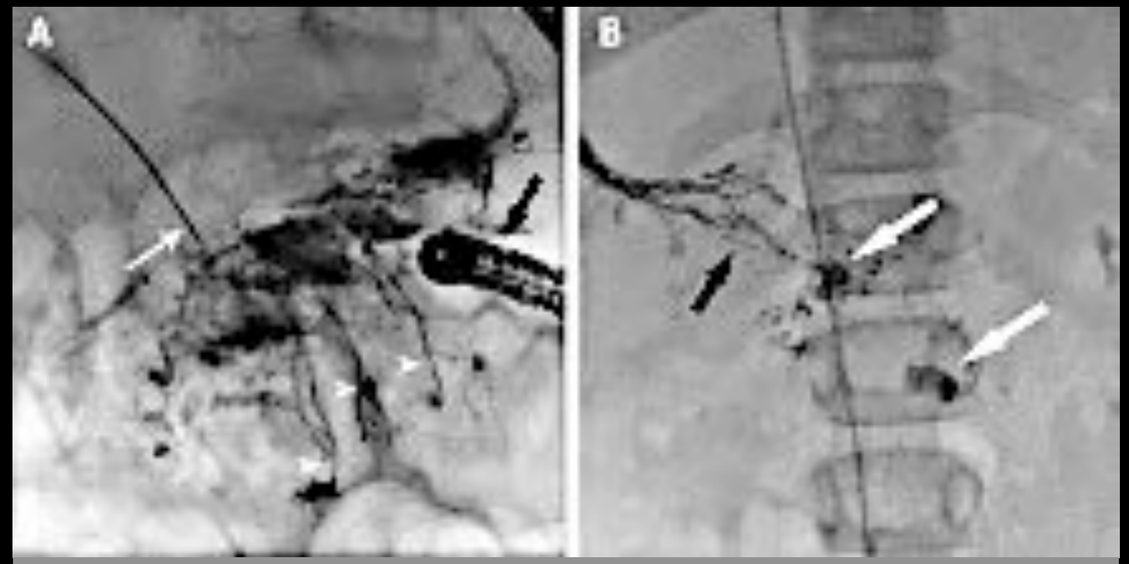


Thoracic duct dilation & tortuosity



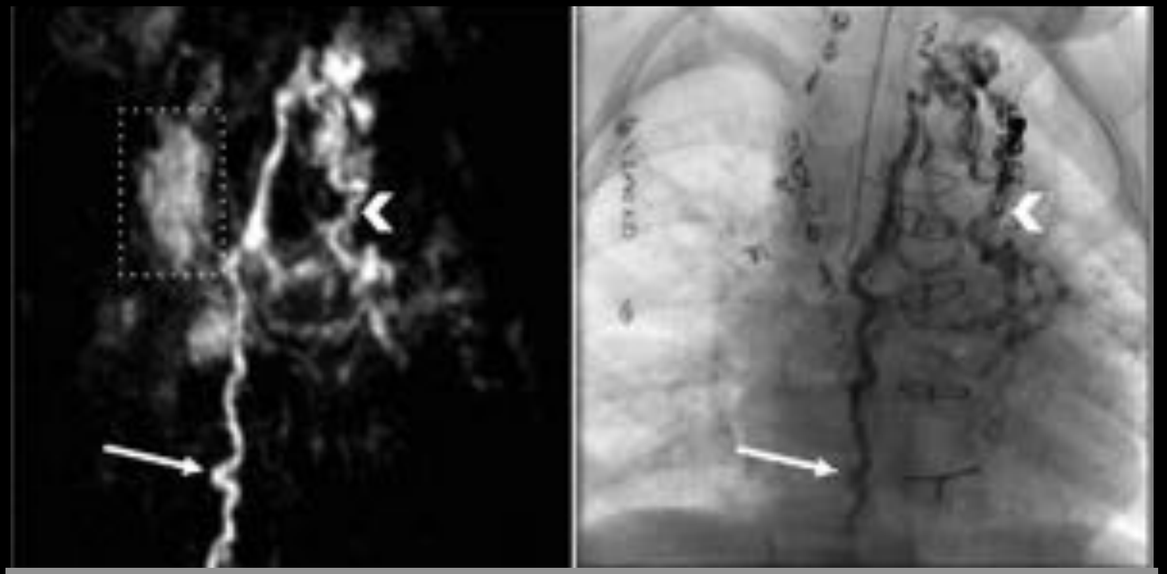
Tissue edema

Dori Y et al. AJR 2014;203:426

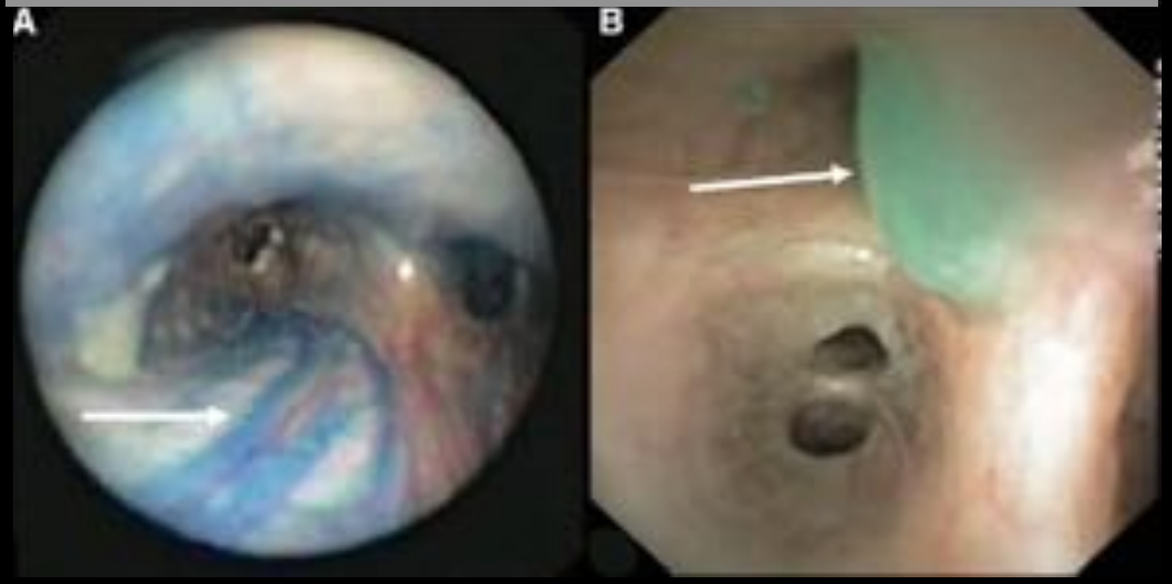


PLE Hepatic lymphogram & endoscopy

Itkin M et al. JACC 2017



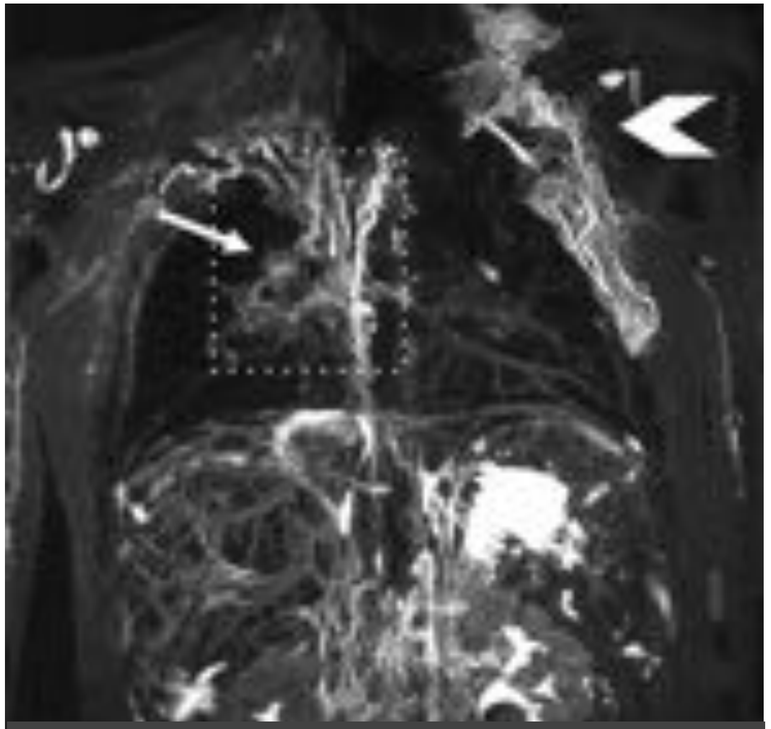
Plastic bronchitis lymphogram & bronchoscopy



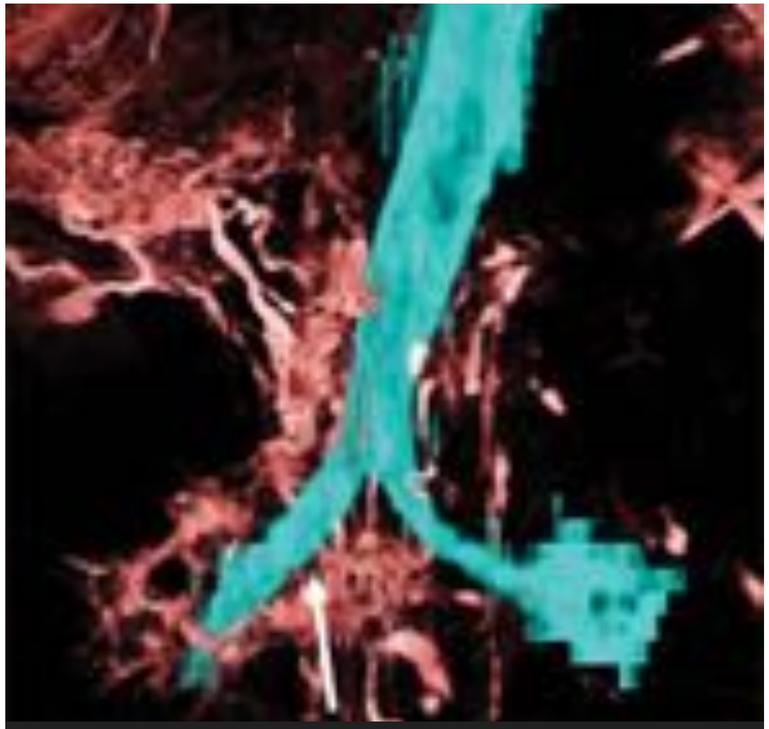
Dori Y et al. Circulation 2016

Lymphatic interventional catheterization

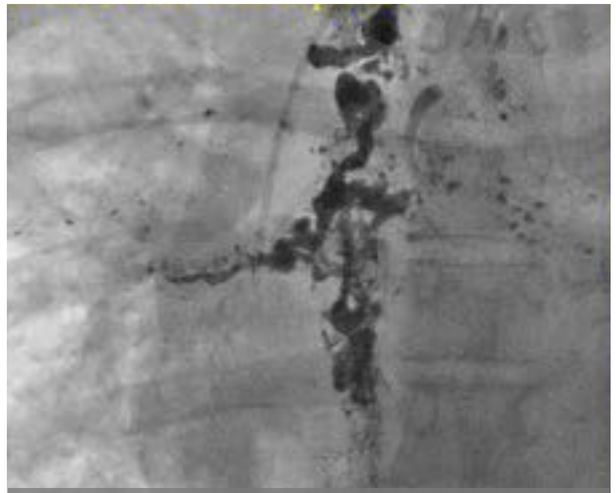
The new horizon for the treatment of PLE/bronchial casts



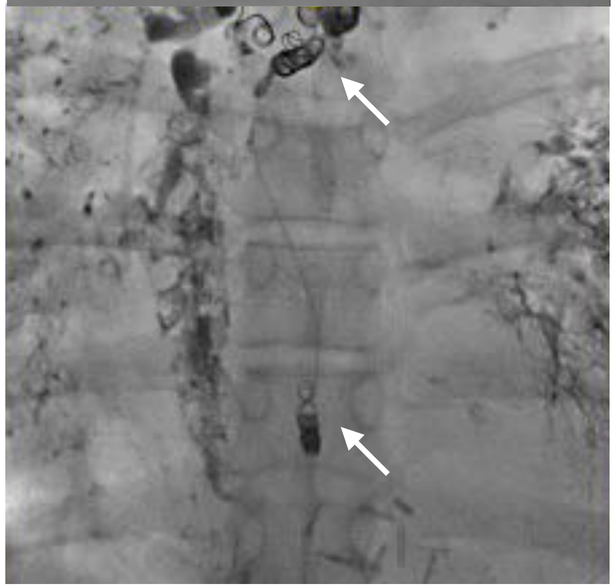
Leak in right lung



Leak into right bronchus



Embolisation coils & glue

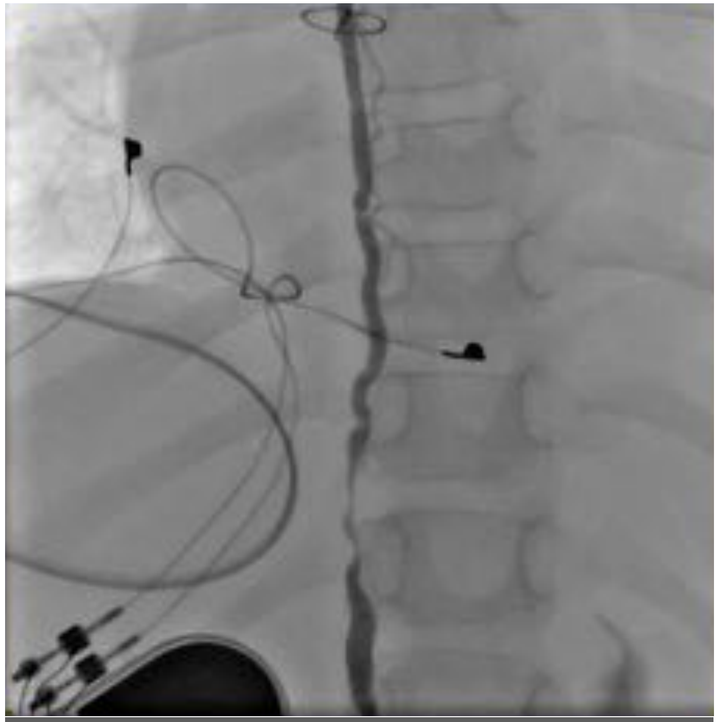


15 years TCPC, plastic bronchitis

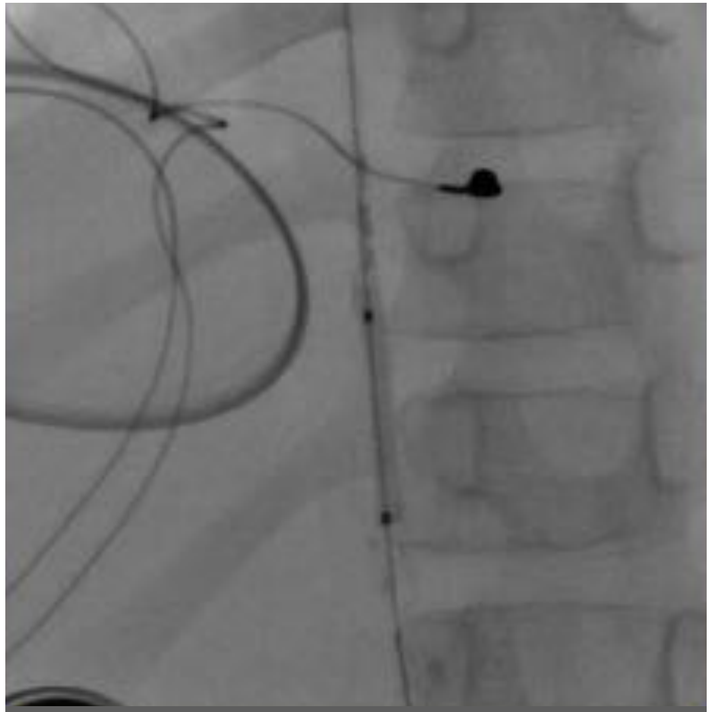
Dori Y et al. AJR 2014;203:426

Lymphatic interventional catheterization

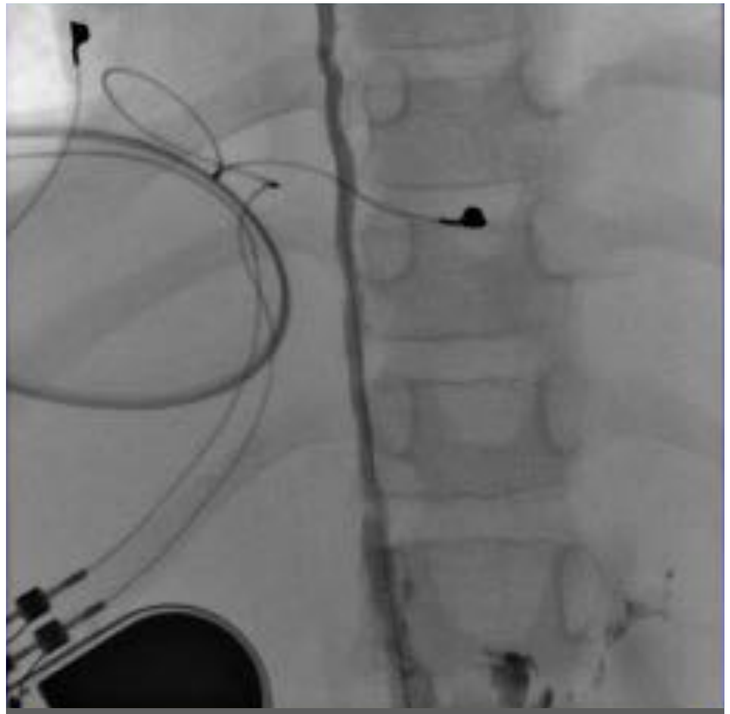
The new horizon for the treatment of PLE/bronchial casts



Stenosis of the thoracic duct



Balloon dilatation of the thoracic duct



Control after dilatation of the thoracic duct

23 years TCPC, PLE

Dori Y et al. AJR 2014;203:426

1-Sequentially phenotyping patients is the key to define the baseline and follow-up predictors of outcome

2-Phenotyping patients and building large registries are the keys to identify real surrogates (therapeutic targets)

3-Treatment of heart failure in Fontan circulation uses different paradigms than for HF with reduced EF

4-Thromboprophylaxis should be given to ALL patients and if given appropriately monitored

5-The « lympho-cardiology imaging/intervention » is the new horizon to improve PLE/bronchial casts

Collective ignorance is the motivation
Curiosity is the strength
Research is the path

Individual experience is the brake
Indifference is the weakness
Authority argument is the threat

Thank you

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