Faire un Fontan prépare l'inéluctable

Fontan circulation : A predicted steady decline

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

Francis Fontan

The faith in the future

Eur J Cardiothorac Surg 1988;2:1-7.

Francis Bacon

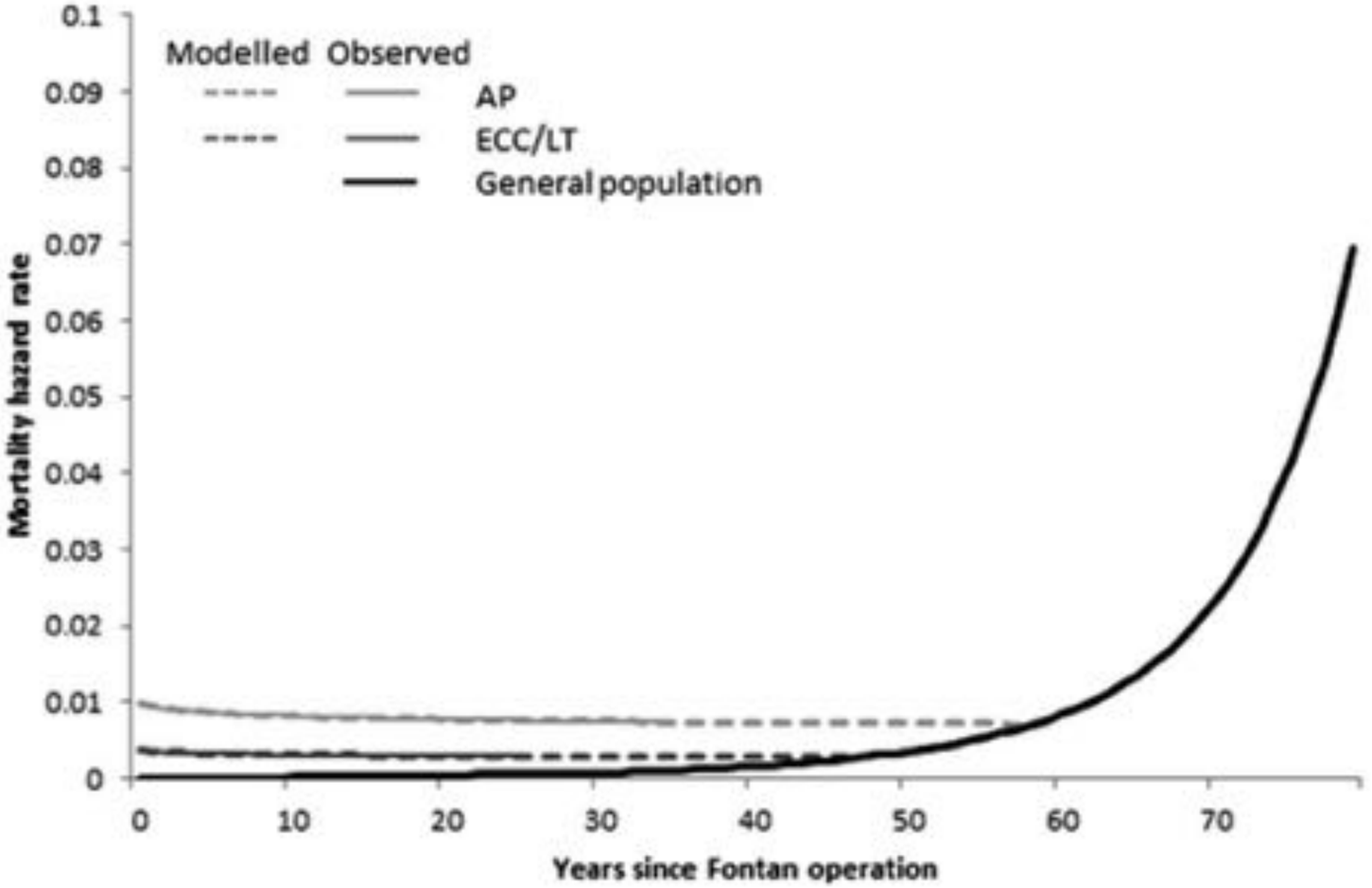
What is future ?

“une jeunesse presque éternelle, la guérison de maladies réputées incurables, l’amélioration des capacités cérébrales, …”

Marc Gewillig

Multiple bottleneck / New Portal System

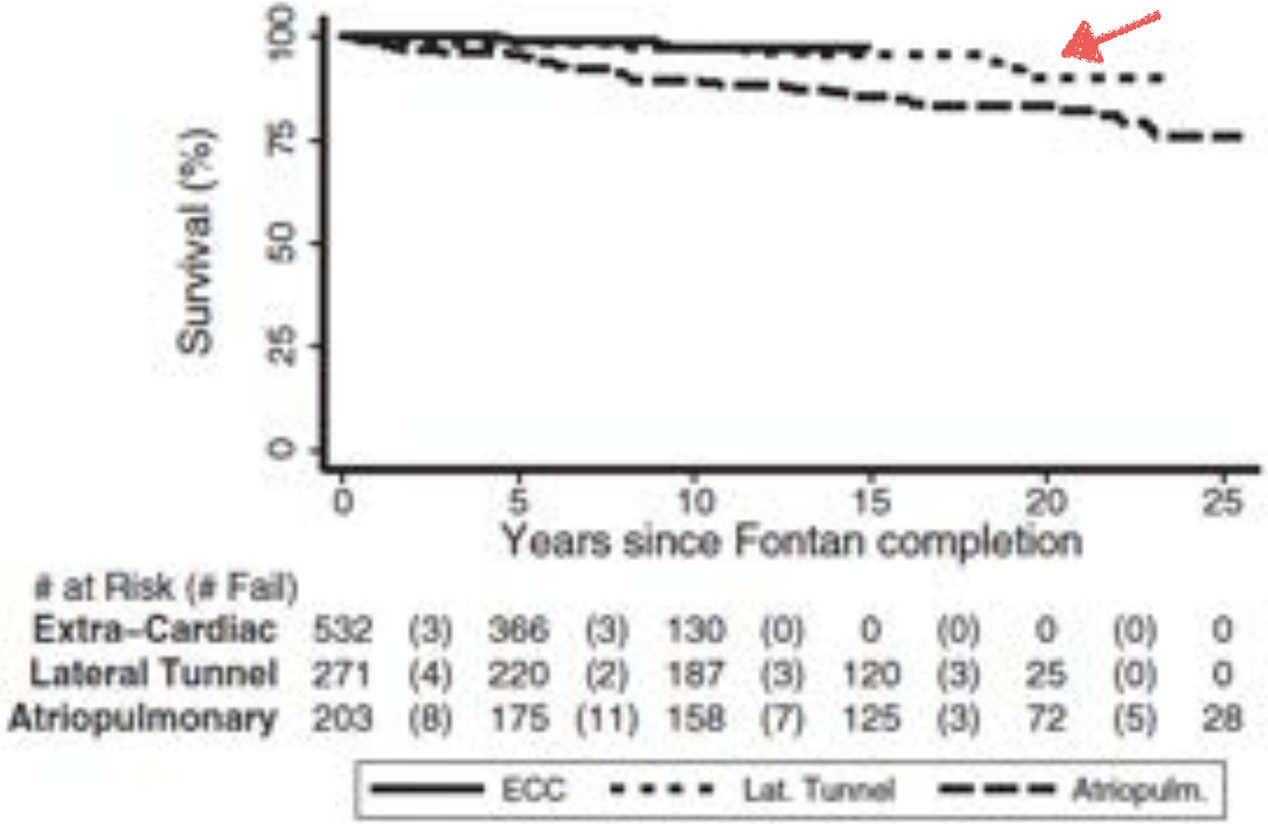
Current trends in the epidemiology of the Fontan population



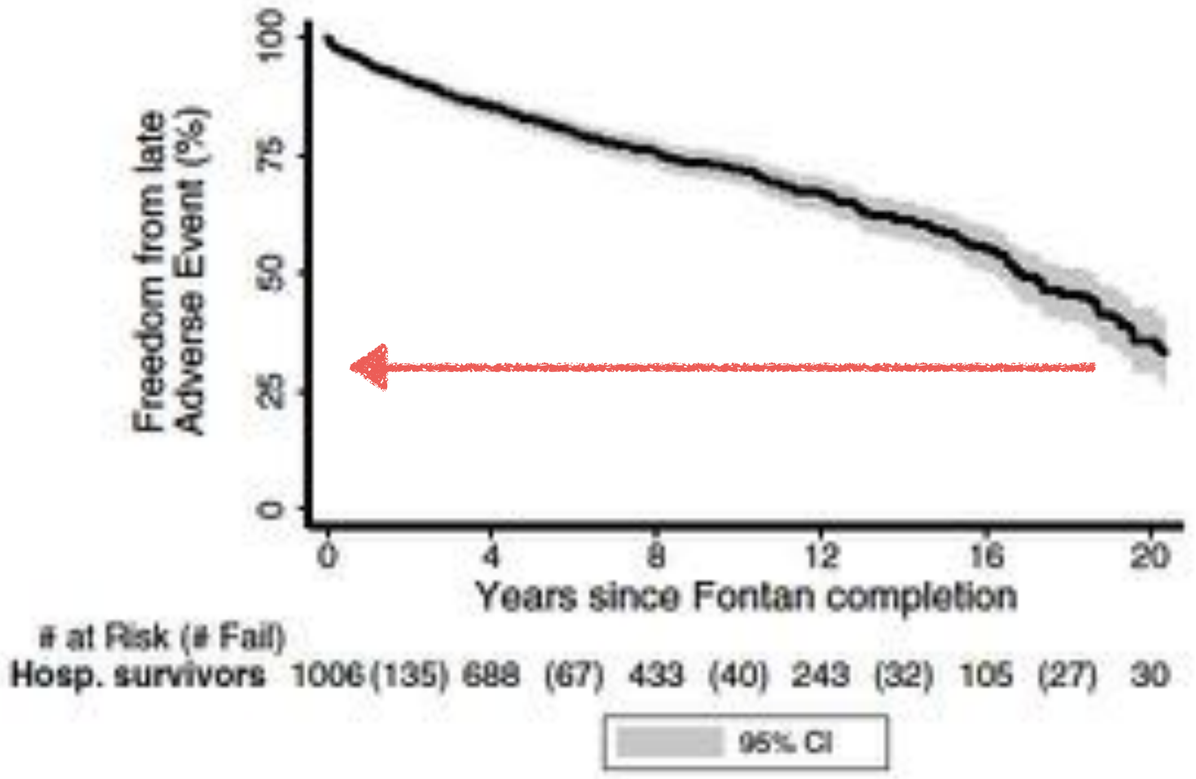
- **75.000 living people in the world**
- **Increasing prevalence**
  - 2014 ***4.5/100.000***
  - 2025 ***5.8/100.000***
  - 2045 ***7.2/100.000***
- **Aging population**
  - 2015 ***18 years***
  - 2025 ***23 years***
  - 2045 ***31 years***

Schilling C et al. Int J Cardiol 2017

The « success » of the modern management of univentricular hearts



Mortality/Survival



Morbidity

d'Udekem Y et al. Circulation 2014

Is the Fontan circulation
intrinsically incompatible
with a long near-normal life ?

Preliminary questions

Do we fully understand the physiological mechanisms of this circulation ?

Have we yet identified those who are at risk of early failure ?

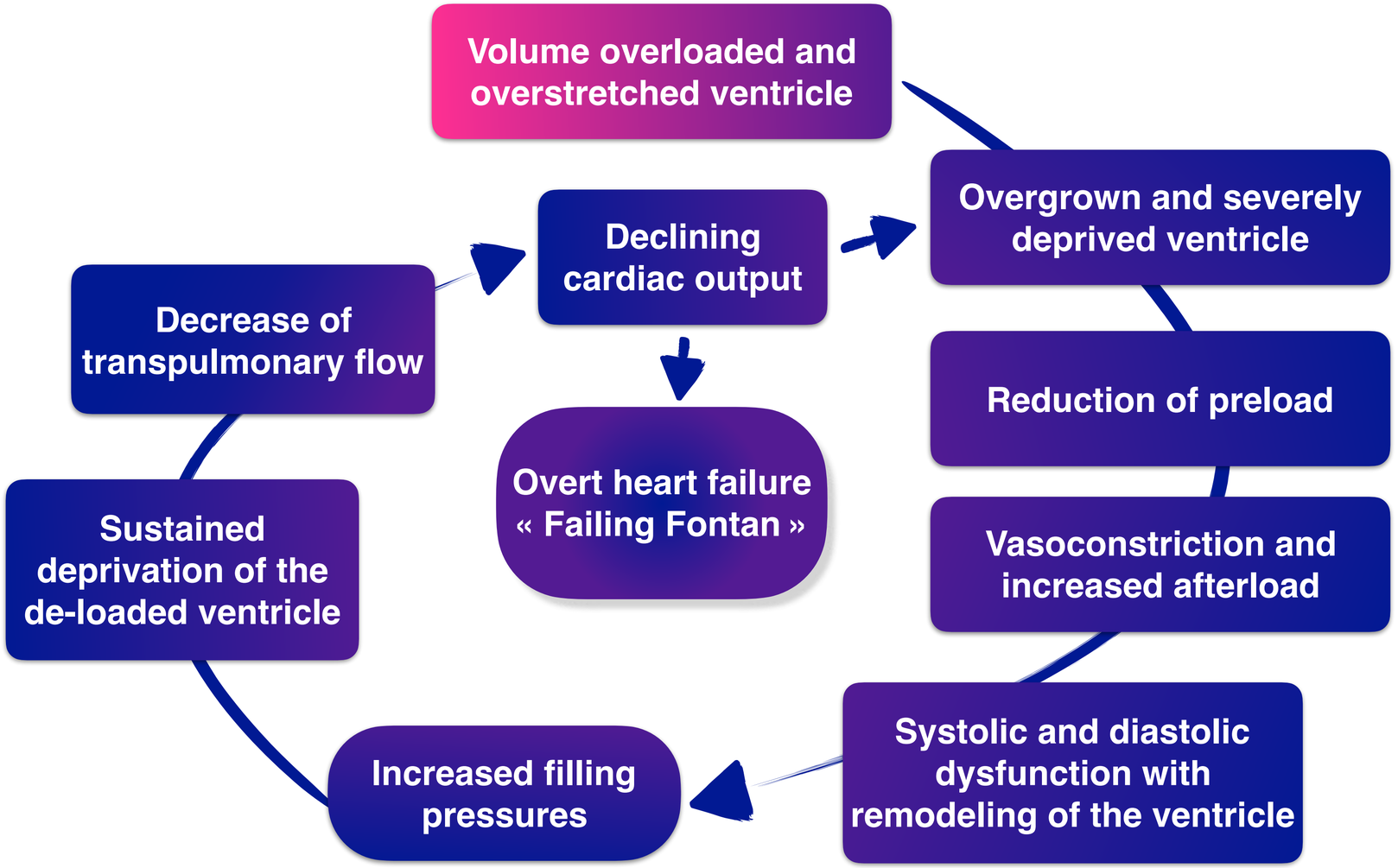
Do we have many ideas on the best way to follow them ?

Have we yet determined which treatment will best preserve their life ?

Have we yet established to what extent end-organ damage may affect their outcomes ?

The Fontan circulation - a new portal system

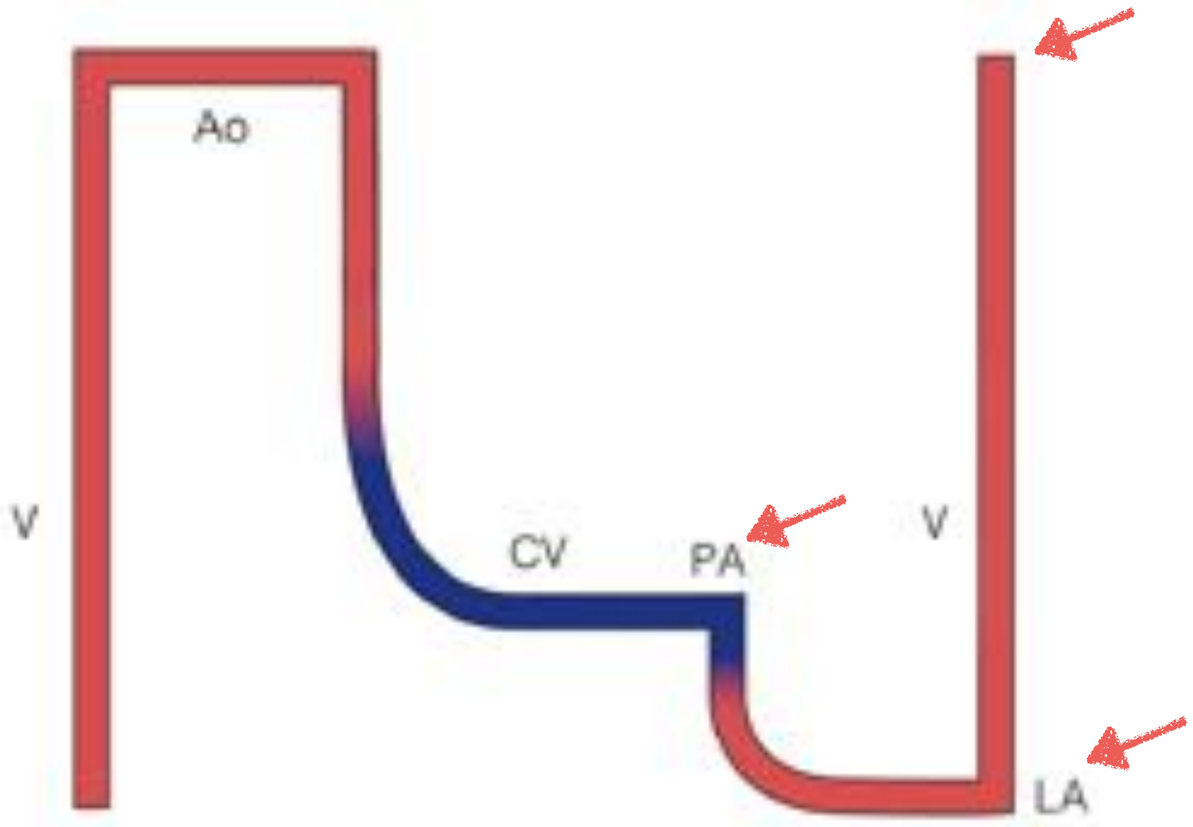
The vicious circle to failing Fontan

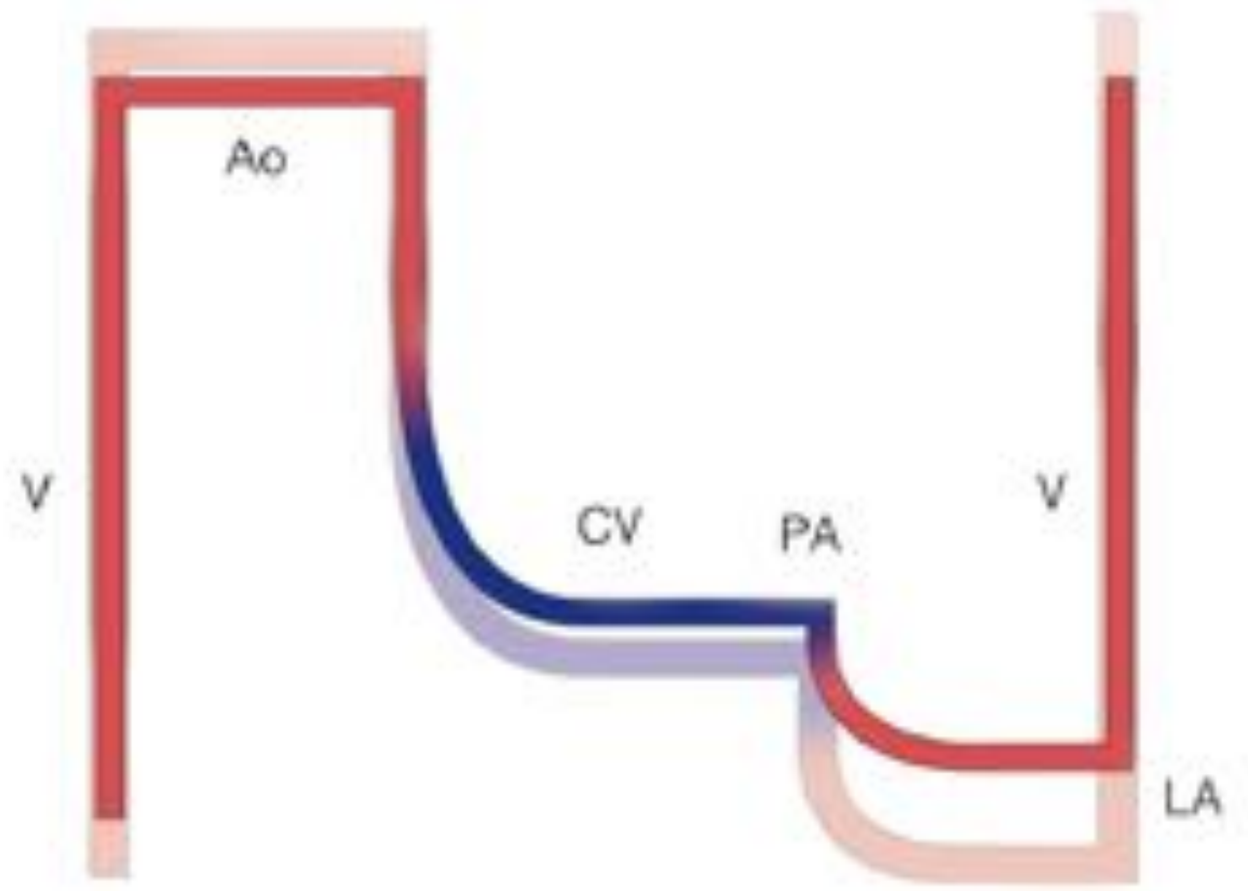


Adapted from Marc Gewillig-Heart 2016

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

M3C

Marc Gewillig-Heart 2016

The rationale for using PAH drugs in the Fontan circulation

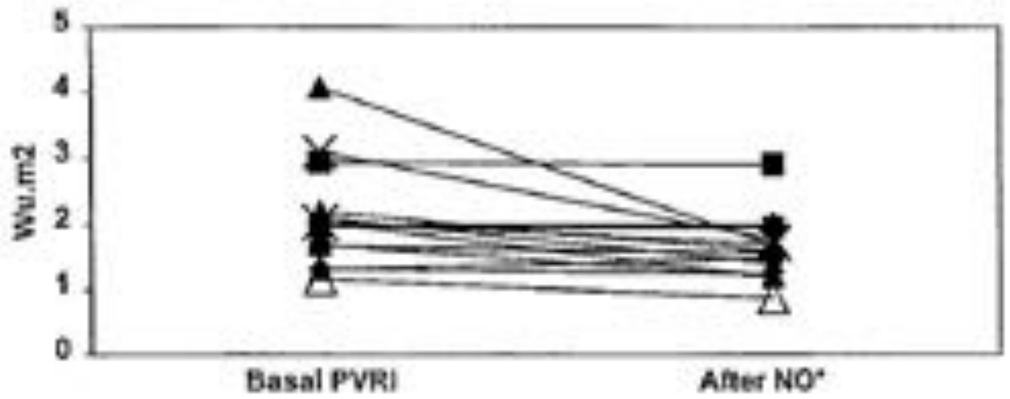


Figure 4. Effect of exogenous NO on PVRI late after Fontan operation. NO caused a significant drop of mean PVRI in the study group (*P=0.016).

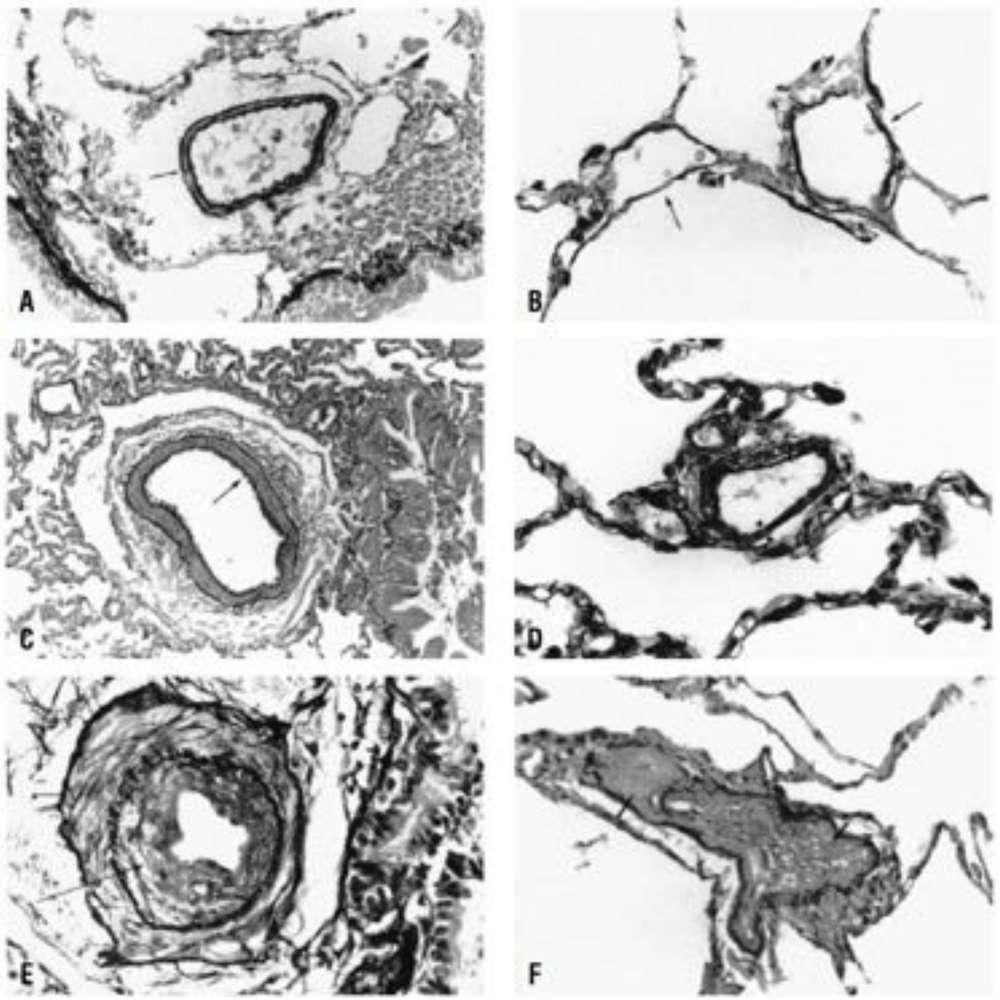
- Fontan patients have elevated PVRi
- Patients in NYHA 1 have a significantly lower mean PVRI (1.72+-0.38 WU.m2) compared with patients in NYHA 2 and 3 (2.82+/-0.88) (P=0.05)
- Significant drop in PVRi with NO°

Pulmonary endothelial dysfunction is related, at least in some part, to lack of pulsatility in the pulmonary circulation because of altered flow characteristics after Fontan operation

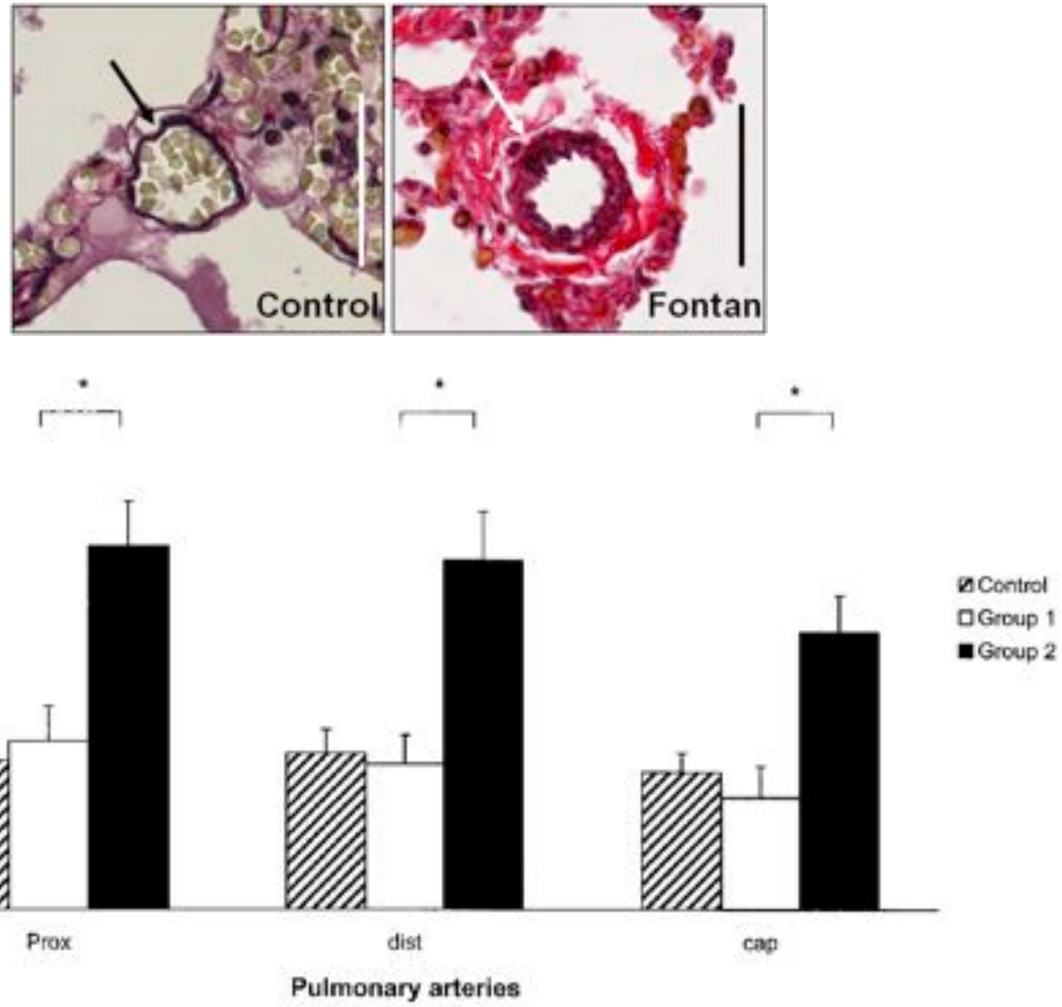
M3C

Khambadkone S et al. Circulation 2003;107:3204-8
Henaine R et al. J Thorac Cardiovasc Surg 2013;146:522-9

The rationale for using PAH drugs in the Fontan circulation



Remodeling of pulmonary arteries is present in half of patients with favorable hemodynamic at surgery and predicts outcome

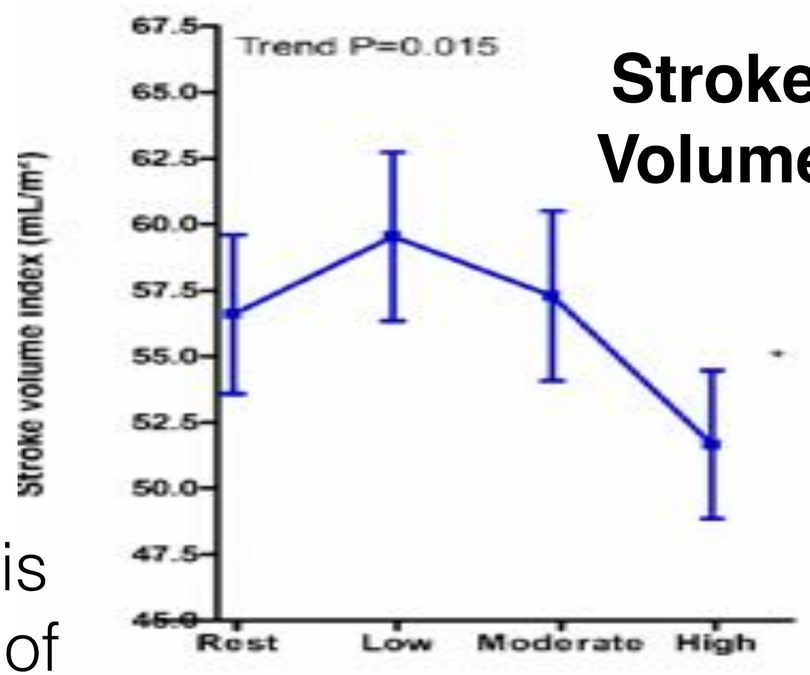


eNOS and ET1 expression is increased from baseline in « failed » Fontan procedures

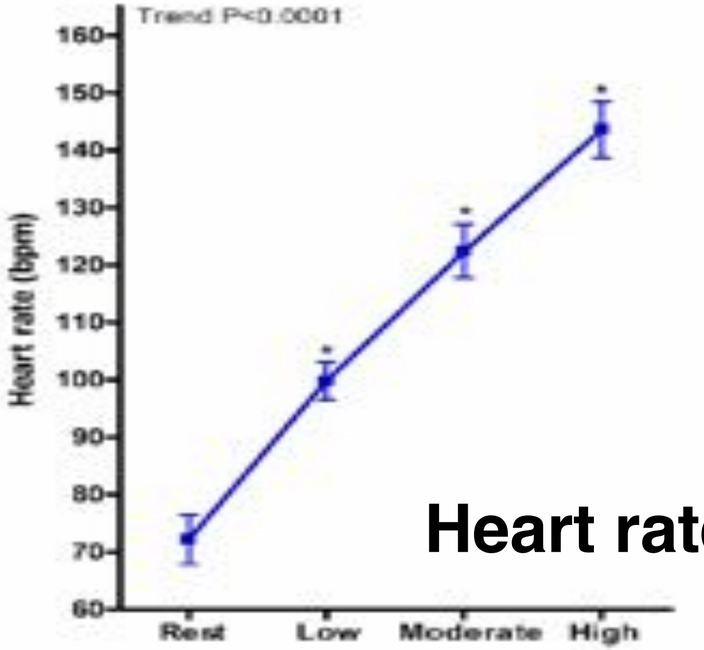
Juaneda E, Hawaorth S. Br Heart J 1984
Levy M et al. J Thorac Cardiovas Surg 2002;123:263
Levy M et al. J Thorac Cardiovasc Surg 2003;125:1083

Fontan Ergo MRI

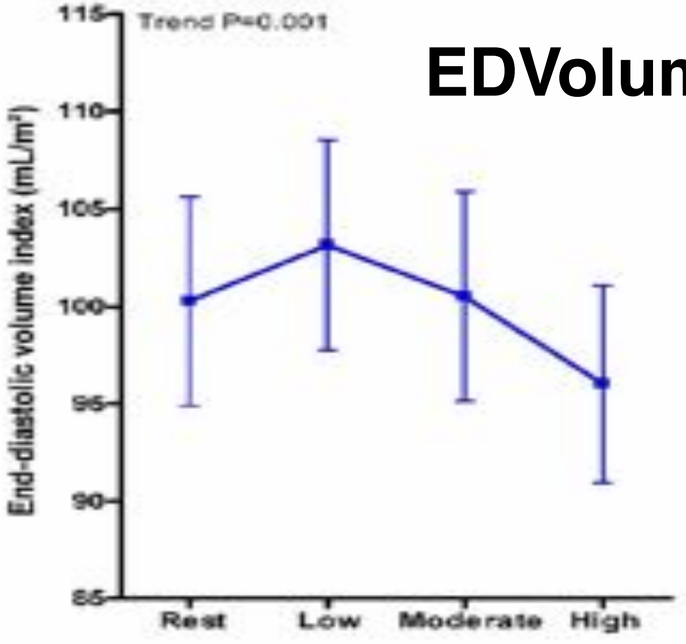
Stroke volume decrease is related to impaired filling of the single ventricle at exercise



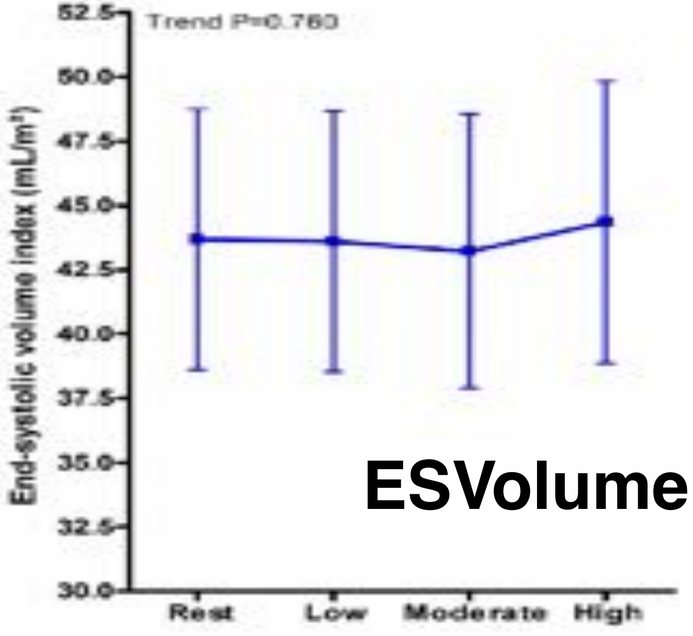
Stroke Volume



Heart rate



EDVolume



ESVolume

The rationale for using PAH drugs in the Fontan circulation

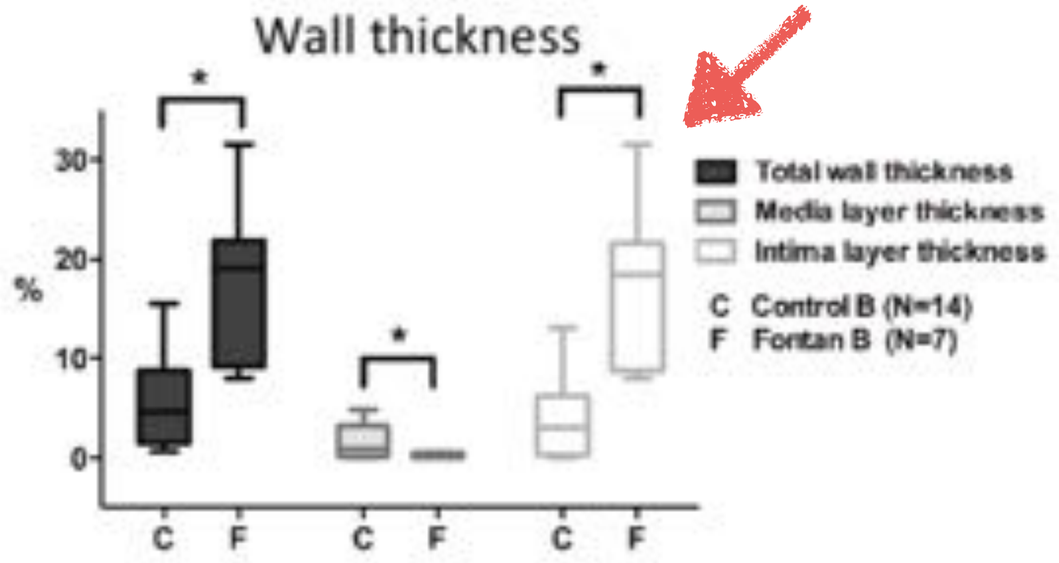
Post-transplantation PVR is elevated (2.0 Wood units · m2) in the majority of survivors past initial hospitalization (mean 3.3+/-1.7 Wood units · m2).

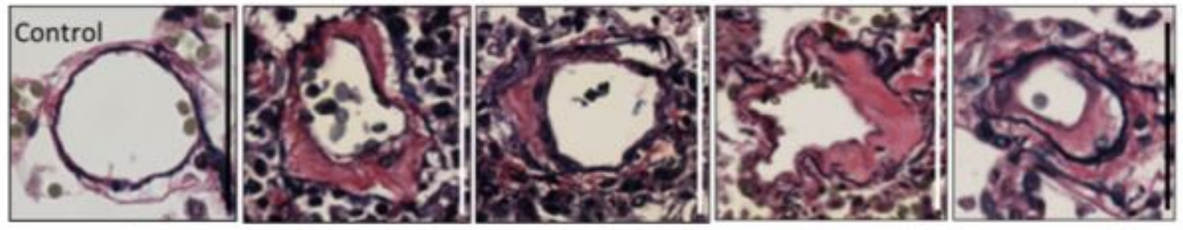
Only patients with early Fontan failures (<1 year) had normal post-transplantation PVR.

In paired comparisons, post-transplantation transpulmonary gradient was increased by a mean of 6.8 mm Hg (P=0.0001) relative to pretransplantation value.

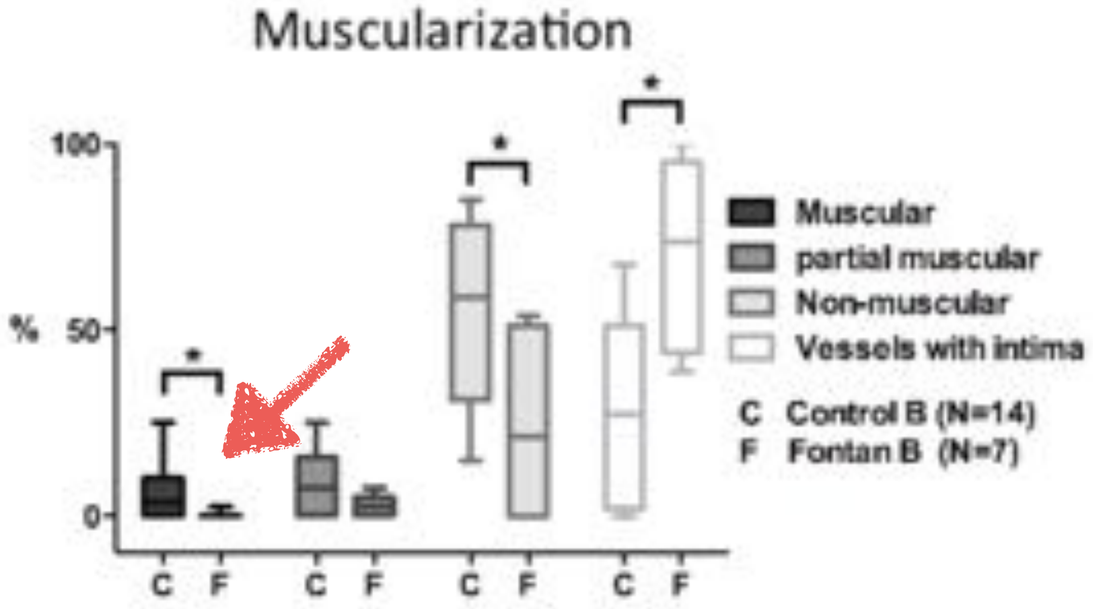
Mitchell M et al. J Thorac Cardiovas Surg 2004;128:693

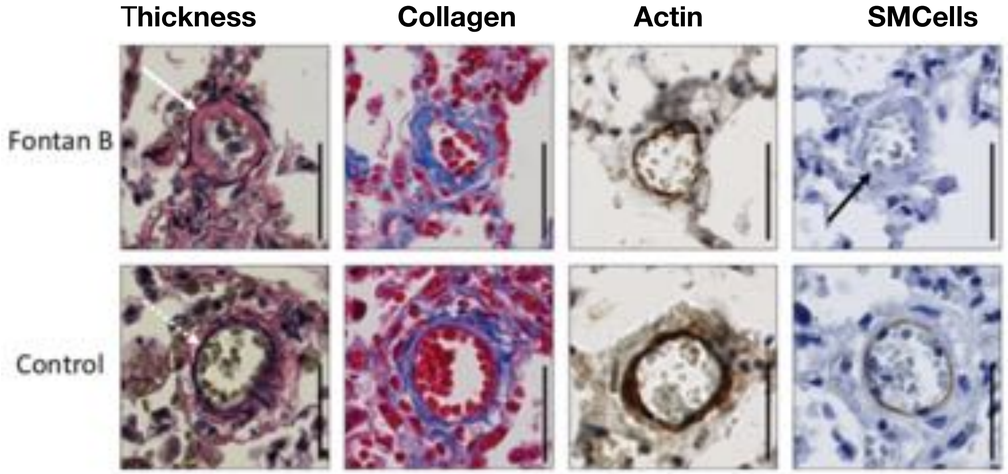
The unusual remodeling of intra-acinar pulmonary vessels in TCPC





eccentric acellular intima fibrosis in the intra-acinar pulmonary vessels





Ridderbos FJS et al.

Is the Fontan circulation
a unique condition or a multiform situation
that should be analyzed individually to
predict outcomes ?

Patients characteristics

Different categories

Non modifiable

-underlying genetic/extracardiac conditions

Time-dependent

-age and weight

-symptoms

Anatomical characteristics

Non modifiable

-type of UVH

Time-dependent/modifiable factors

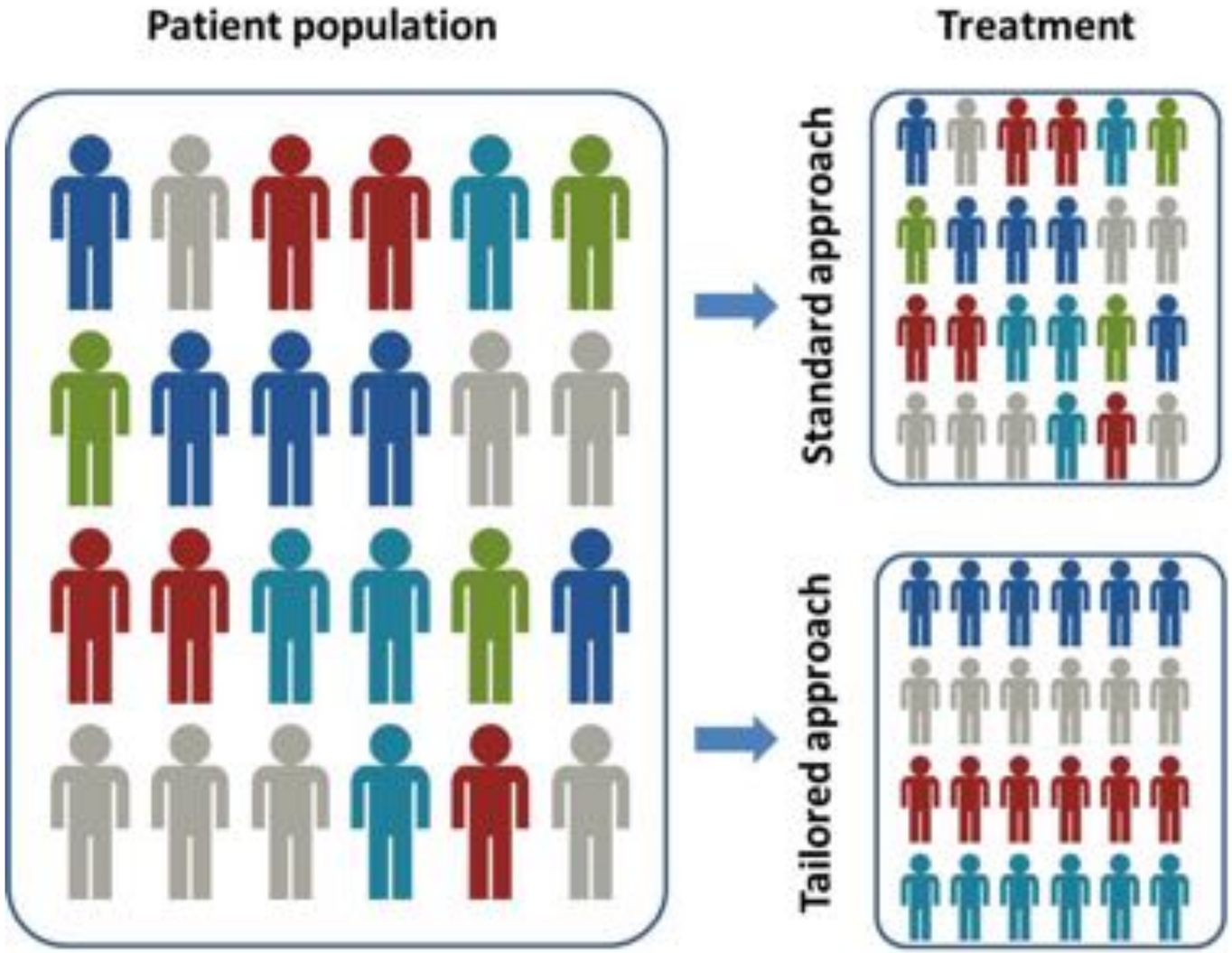
-outflows anatomy

-pulmonary artery branches (size, contiguity)

-AV valves function

-arrhythmias

UVH/Fontan(s) *or* one patient/one F-UVH

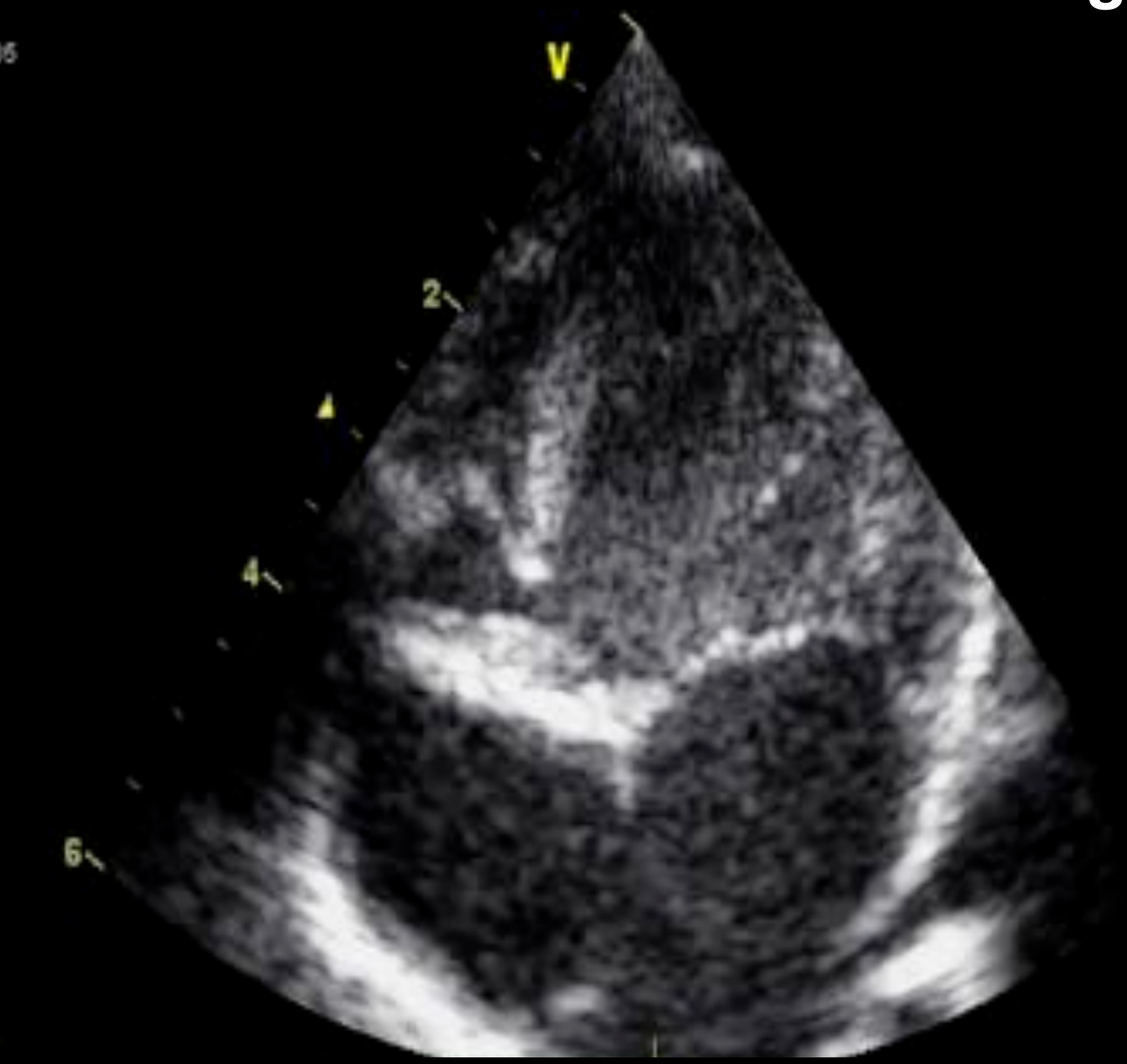


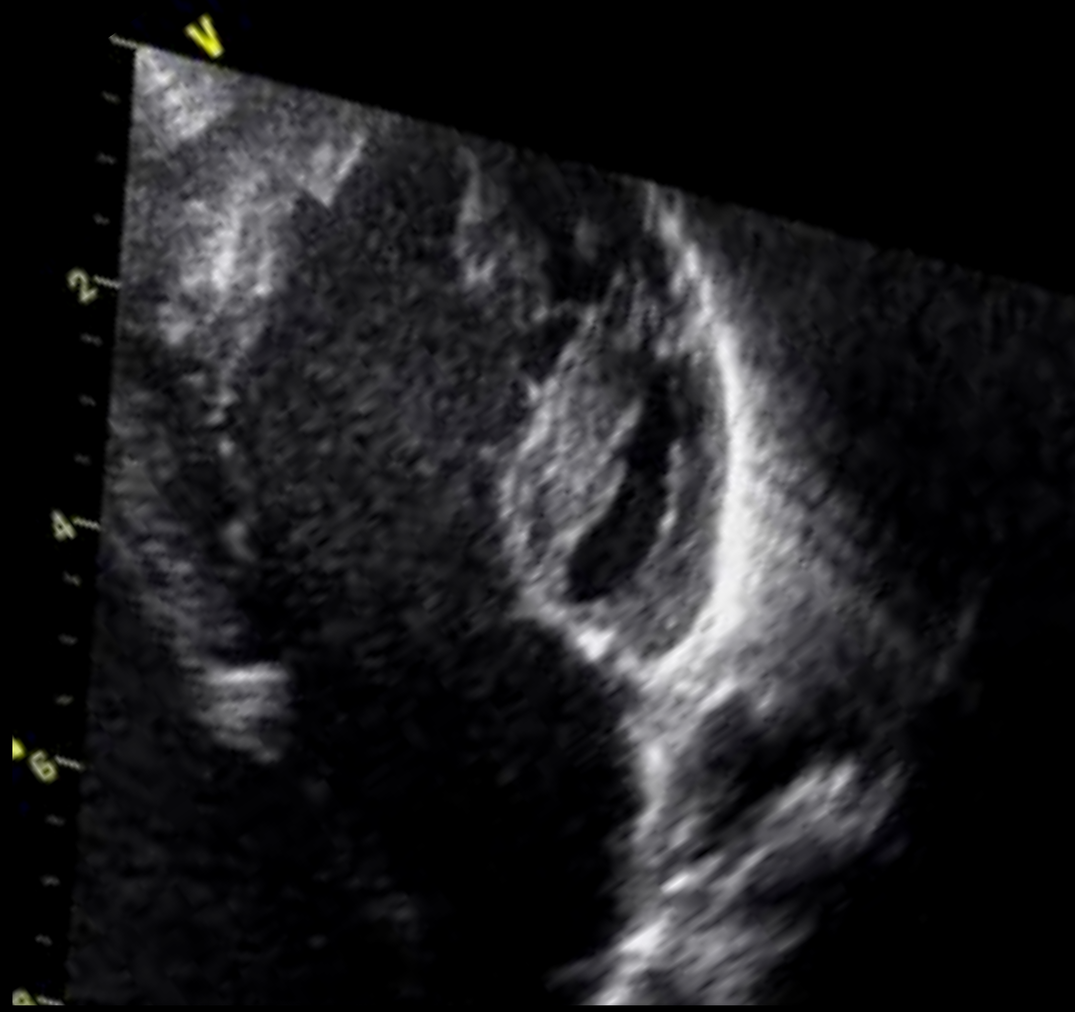
Low mortality
Tolerated morbidity (early and late)

Reduced mortality?
Reduced morbidity (early and late)
Improve patients reported outcomes

Patients & Strategies & Alternative techniques

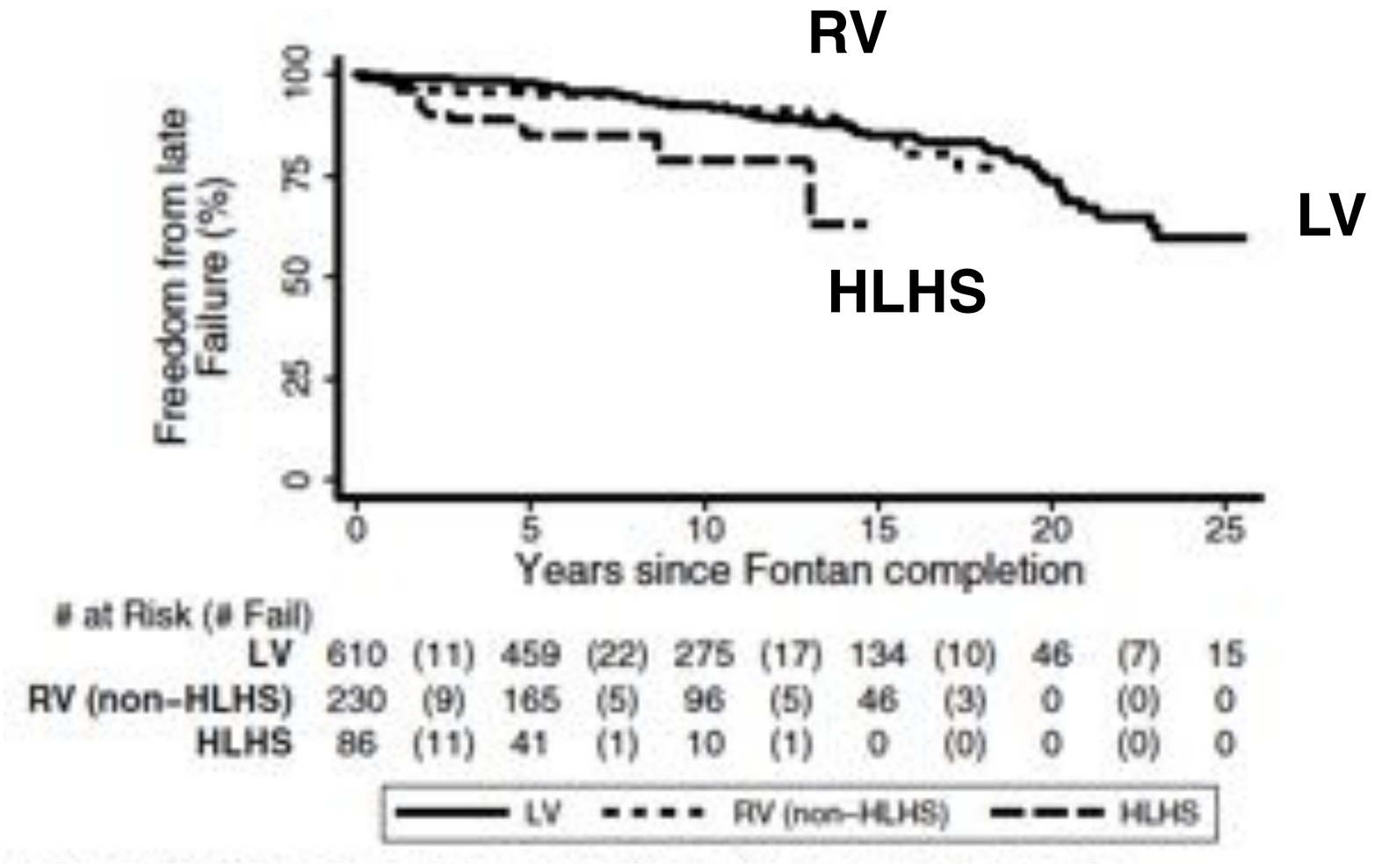
Right vs. Left



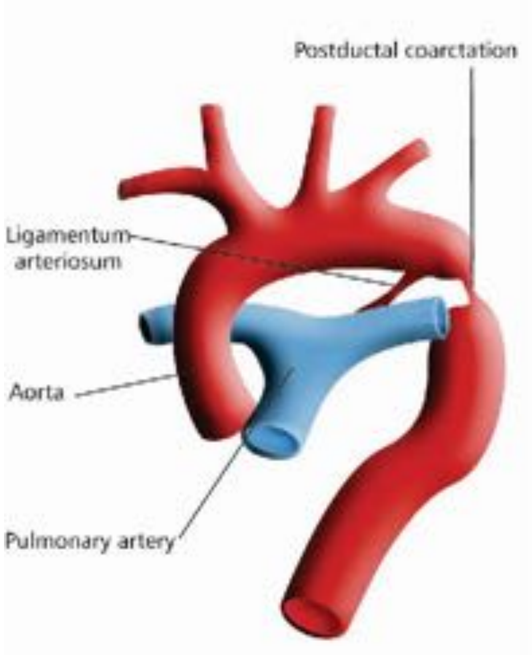


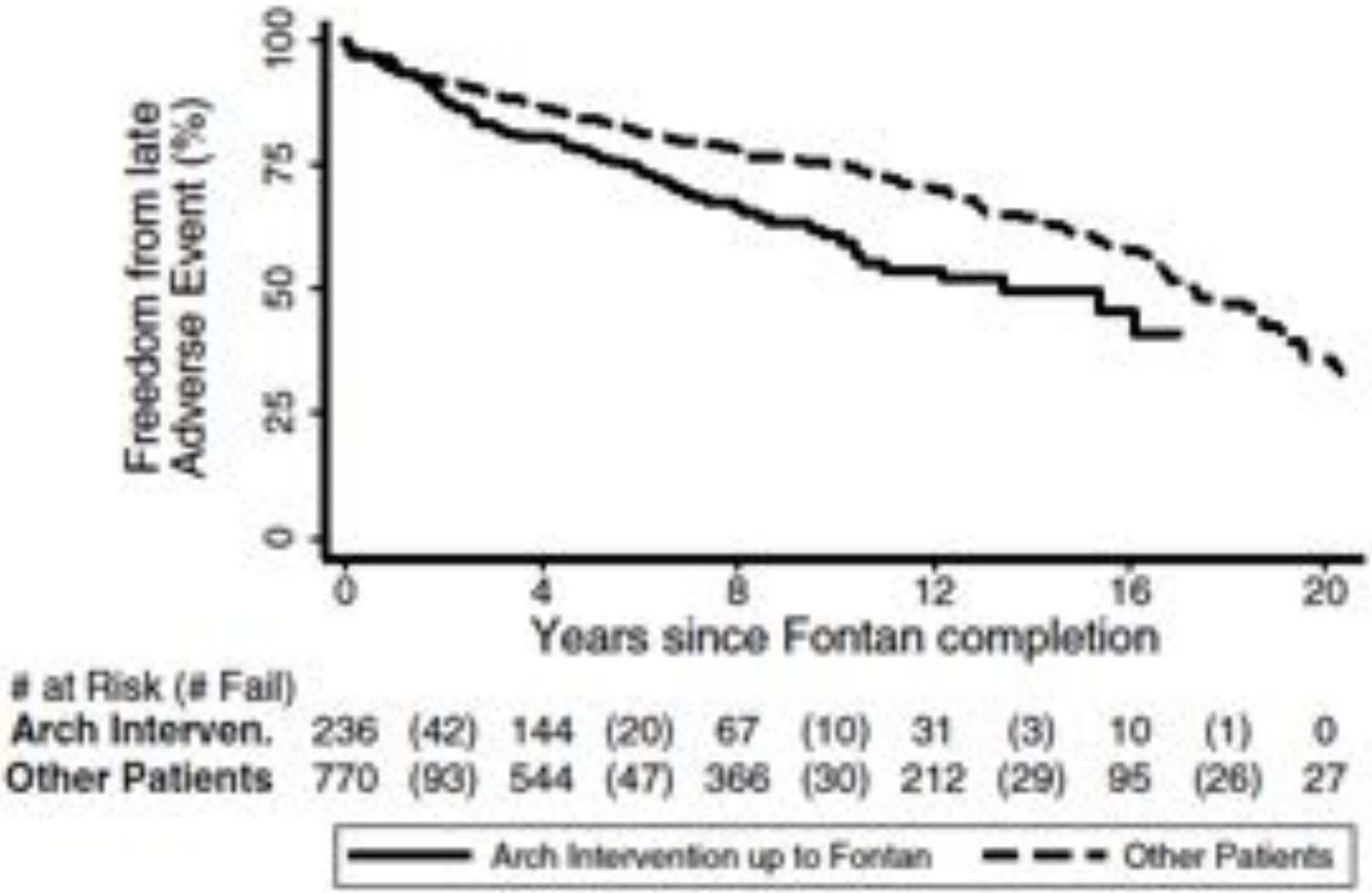
Atz AM et al. JACC 2017

Comparative freedom from failure (death, heart transplantation, reoperation for the Fontan circuit, poor functional status) for patients with and without HLHS

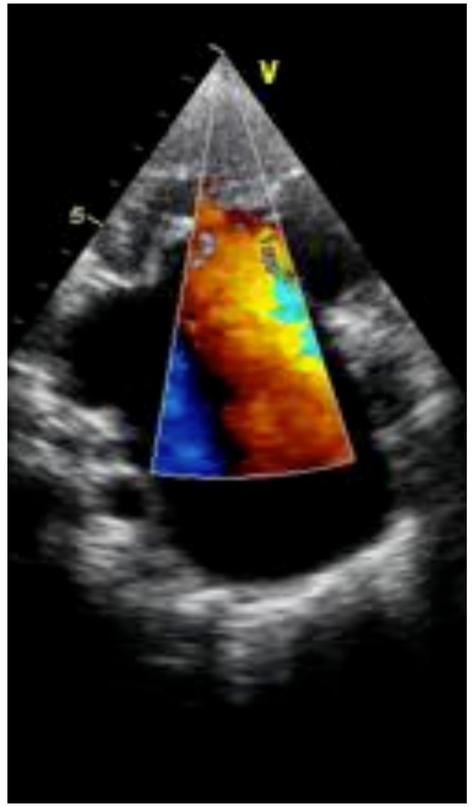


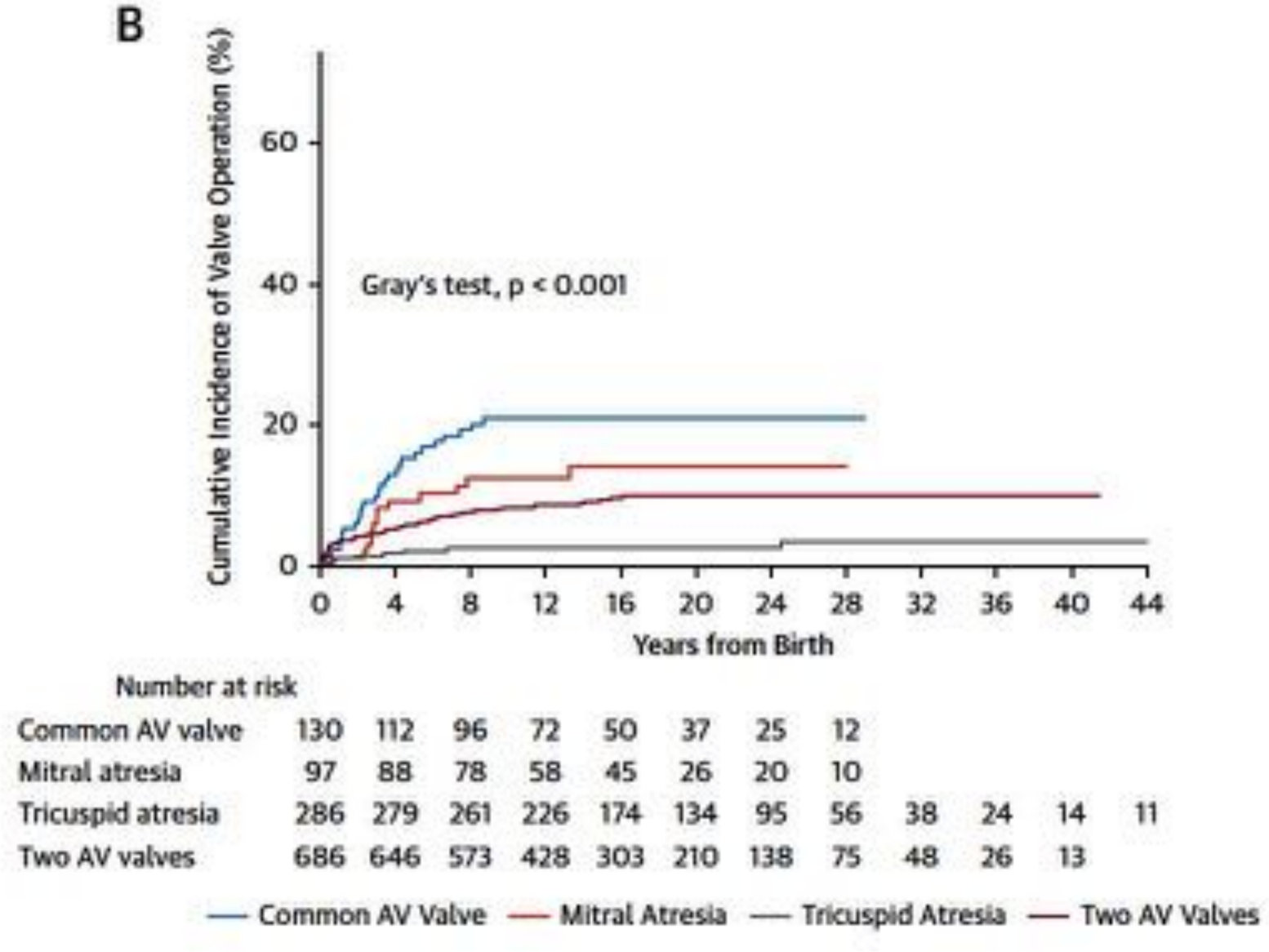
Comparative freedom from adverse events for patients with or without arch intervention before or at Fontan completion





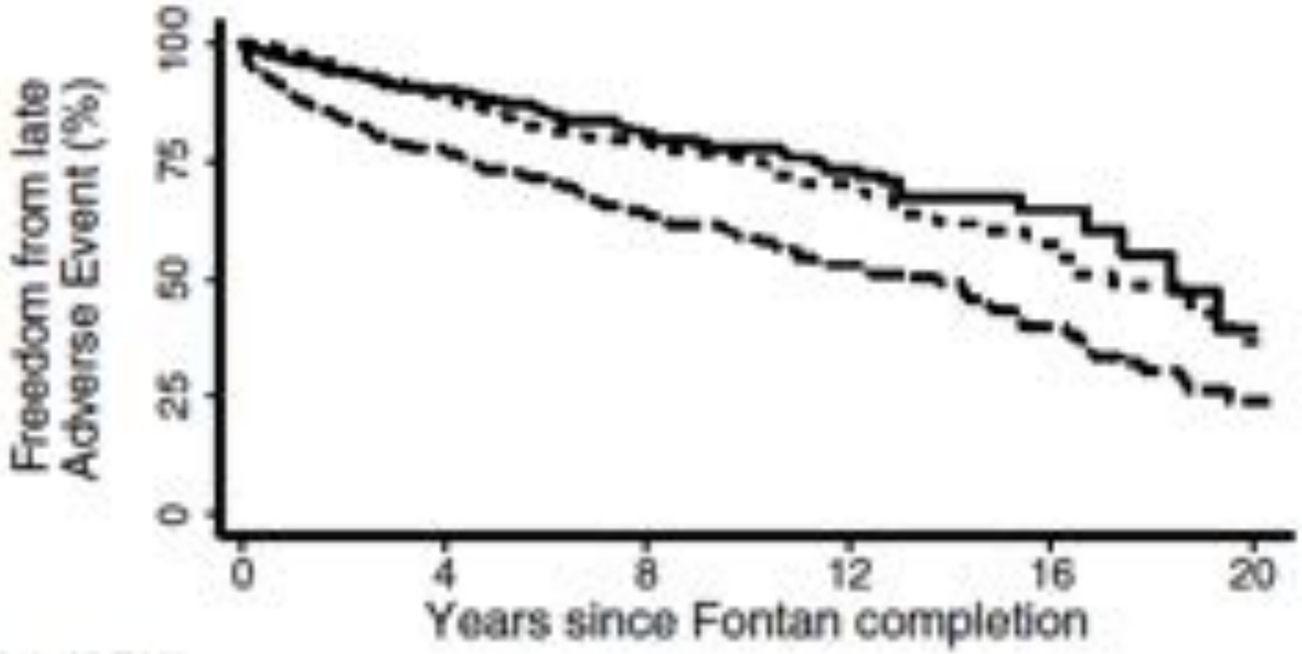
Cumulative incidence curve for estimated incidence of atrioventricular valve intervention (repair or replacement) stratified by valvular morphology for patients who underwent Fontan palliation





King G et al. JACC 2019

Impact of length of hospital stay on late failure and late occurence of adverse events



# at Risk (# Fail)											
LOS < 12 days	294	(28)	213	(17)	120	(8)	58	(5)	19	(4)	4
LOS 12–18 days	305	(33)	212	(19)	139	(13)	82	(12)	35	(9)	10
LOS > 18 days	279	(61)	181	(28)	108	(15)	60	(12)	26	(9)	7

< 12 days 12–18 days > 18 days

Clinical characteristic	All (N = 14)
Sex (female:male)	7:7
Age (y)	24 ± 5 (16-34)
BMI (kg/m^2)	23.0 ± 3.0 (16.7-27.8)
Predominant ventricular morphology	
Left	12 (86)
Right	1 (7)
Biventricular	1 (7)
Dominant cardiac defect	
Tricuspid atresia	10 (71)
Double-outlet left ventricle	2 (14)
Complex double-outlet right ventricle	2 (14)
Type of TCPC repair	
Atriopulmonary connection	3 (21)
Intracardiac lateral tunnel	7 (50)
Extracardiac conduit	3 (21)
Extracardiac conduit post-APC conversion	1 (7)
Patent fenestration	5 (36%)
Echocardiography	
Ventricular systolic function	
Normal	12 (86)
Mild to moderate impairment	2 (14)
Atrioventricular valve regurgitation	
None-trivial	8 (57)
Mild	6 (43)
Aortic regurgitation	
None-trivial	13 (93)
Mild	1 (7)

Super-Fontan

"Super-Fontans" shared some favorable anatomic characteristics, the multitude of potential impediments that affect these superior performers suggest that there are **important extracardiac factors contributing to superior exercise performance**:

-peripheral muscles

-thoracic muscles

-BMI

Cordina R et al. JTCVS 2017

How to prevent poor outcomes before Fontan completion?

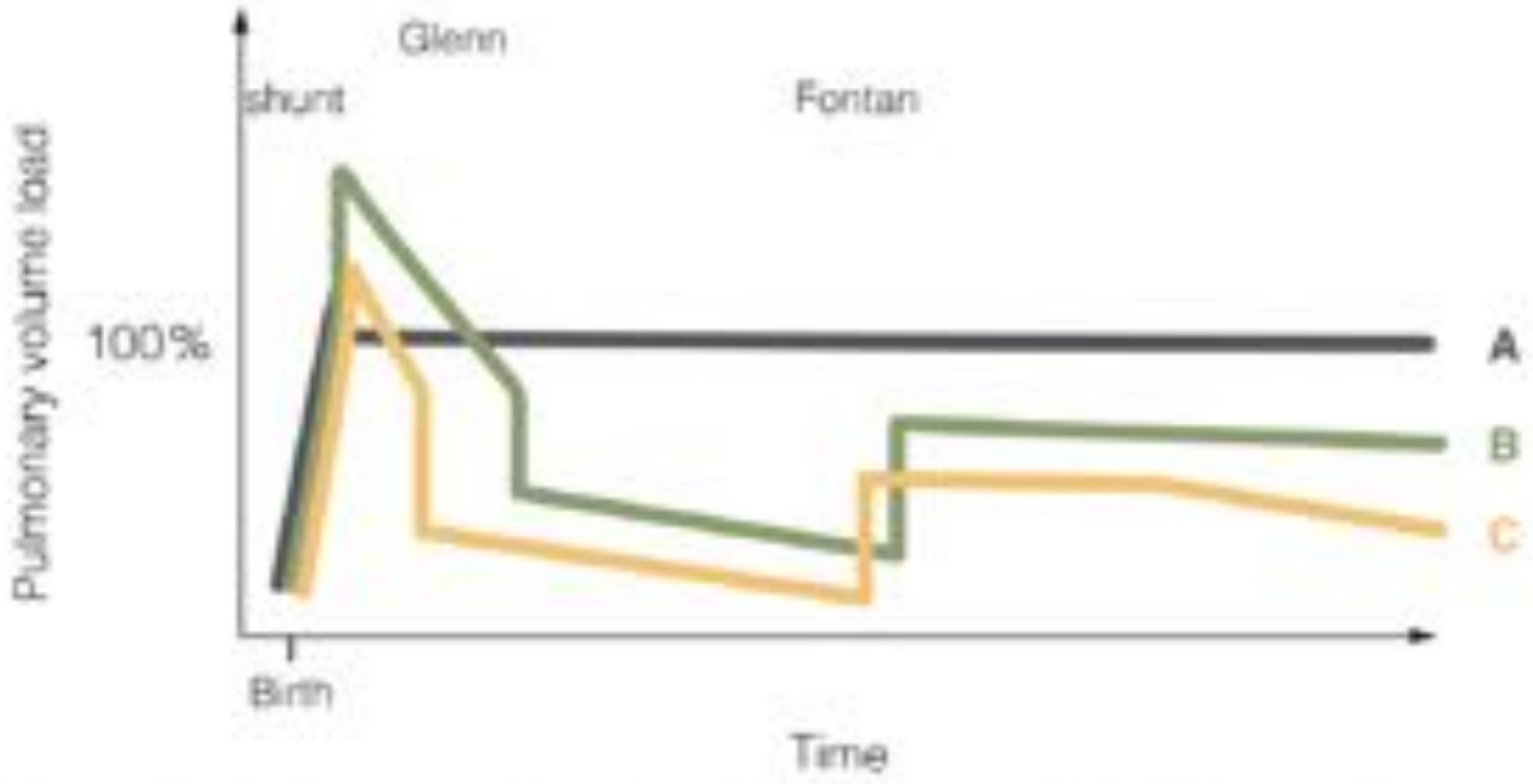
We need to address the modifiable factors pre- and post Fontan

- **Investigate strategies that will better preserve their ventricular/lung vasculature function before they reach Fontan**

- **Improve the factors that may adversely affect their outcomes**
  - mild distortion of their Fontan circuitry
  - hypoplastic pulmonary arteries
  - suboptimal arch anatomy
  - atrioventricular and semi-lunar valve regurgitation.

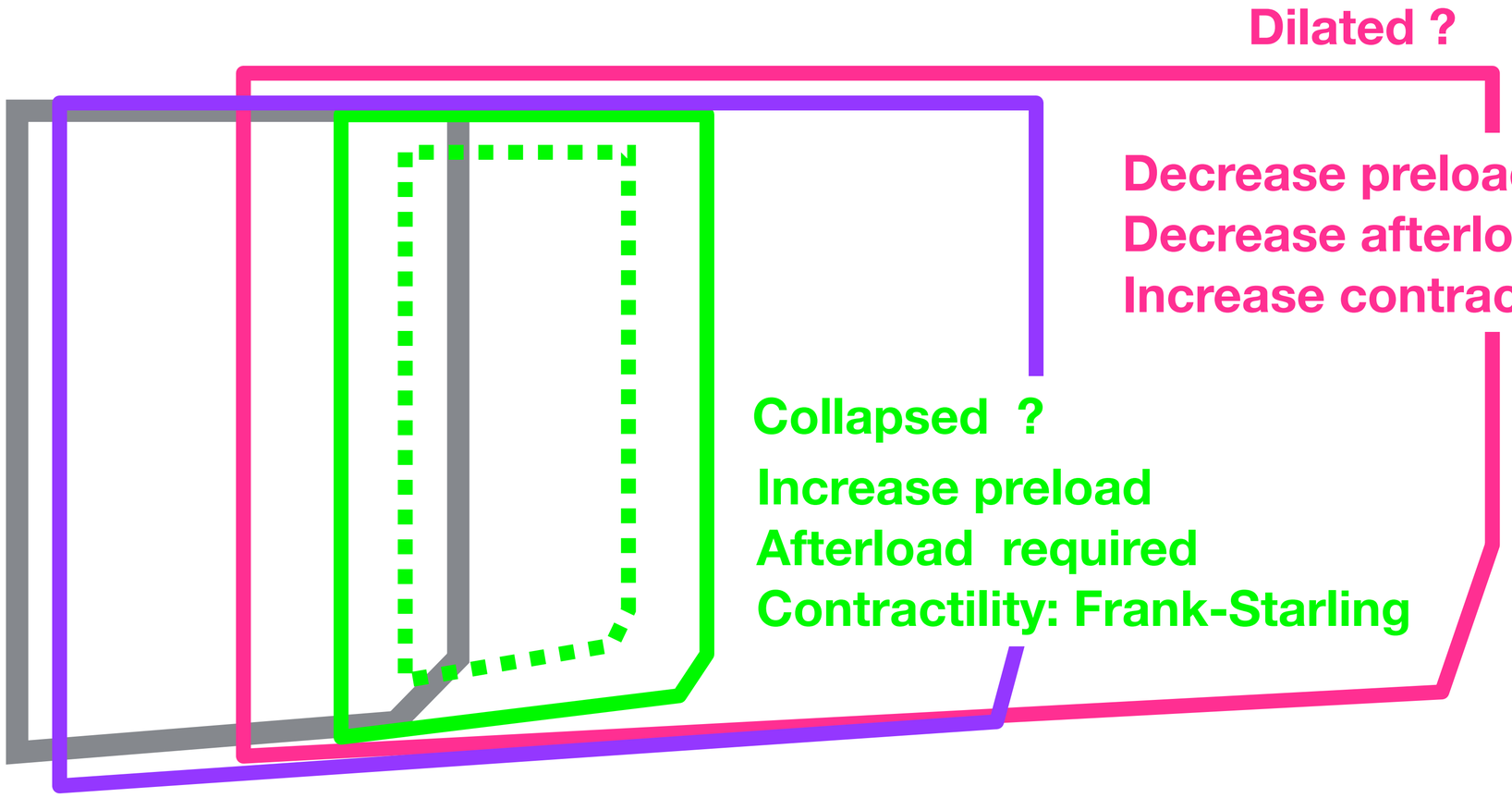
- **The incidence of these issues seems far more important than the number/risk of reinterventions performed in these patients.**

Pulmonary volume load in Fontan



Gewillig M, Brown SC. Heart 2016

A ventricle with a history



Normal LV
UVH fetal
UVH shunted
UVH Fontan-Failing Fontan

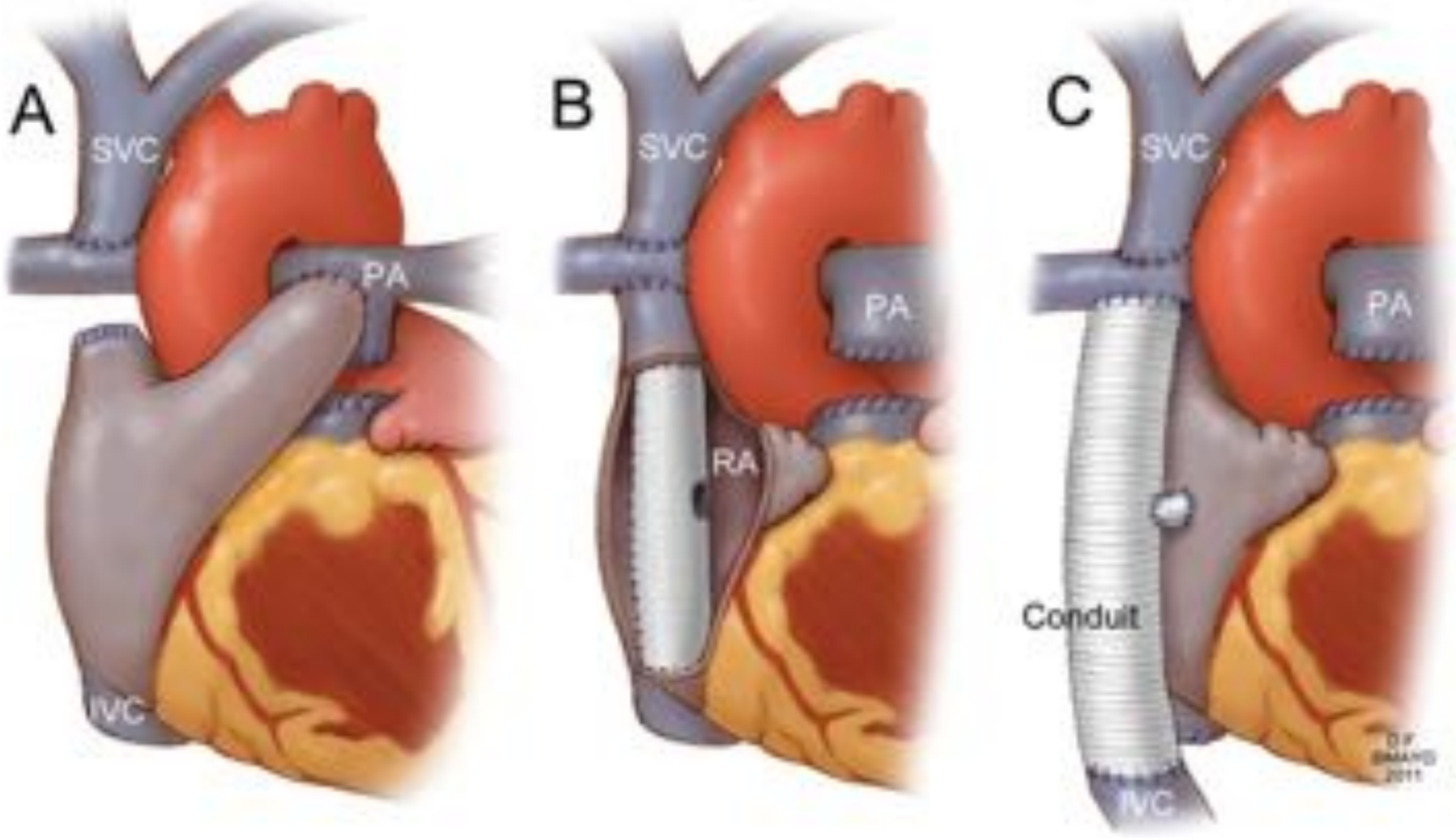
Gewillig M, Brown SC. Heart 2016

Paradoxical decisions

- Maintain chronic increased preload : high Qp/Qs
  - but AV valve, UVH remodeling…
- Additional source of blood flow : antegrade flow, BT shunt
  - but increased P blood flow, PVR increase …
- Tolerate AV valve regurgitation
  - How long, chronic diastolic overload, risk of reoperation…
- Delay TCPC
  - Start the counter, not too long …

How to prevent poor outcomes after Fontan completion?

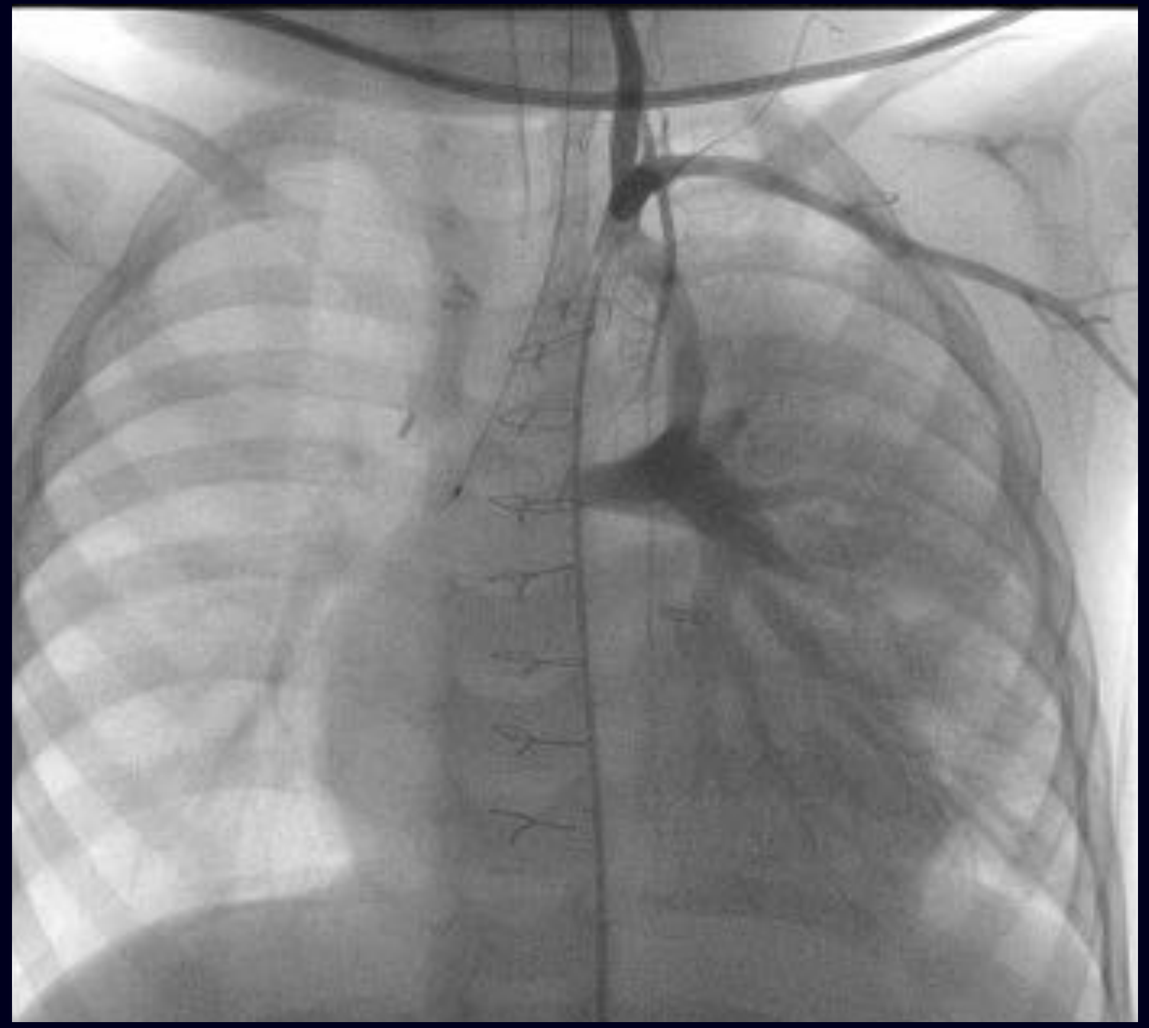
TCPC program



HLHS, 3 years pre-Fontan

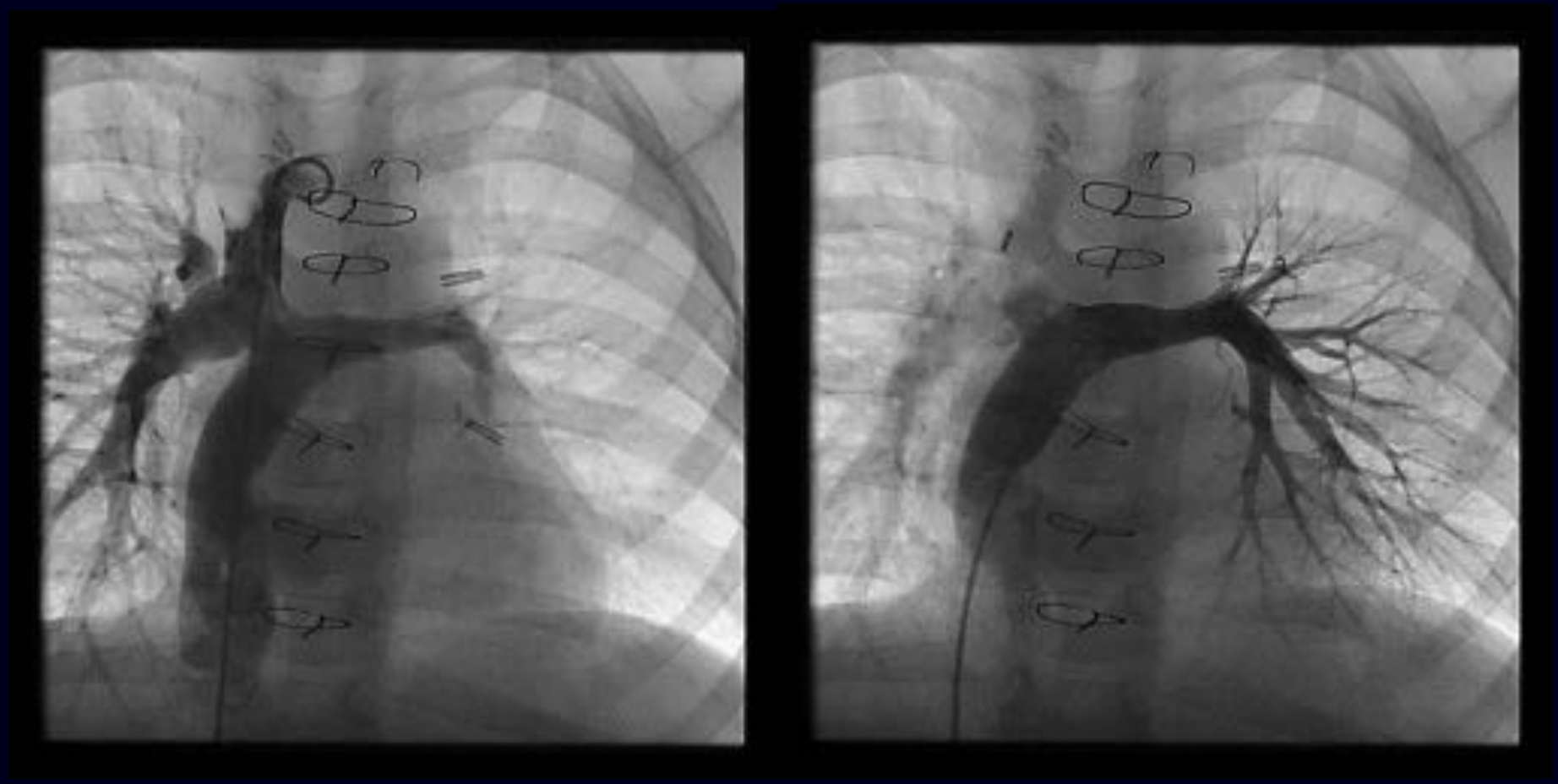
Status PO Norwood 3.0 central shunt; PO Glenn

HLHS, 3 years pre-Fontan



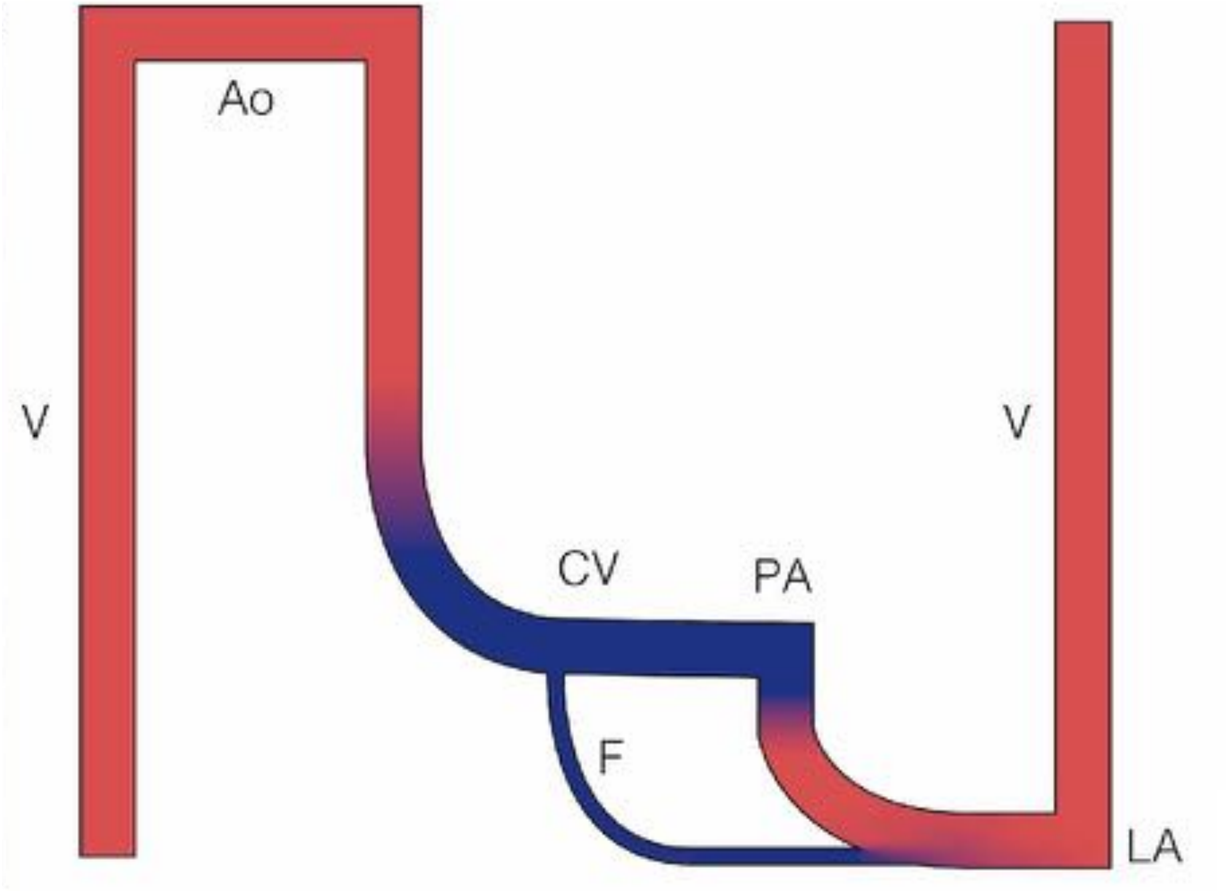
6 mm GT mBT shunt , clip on central PA

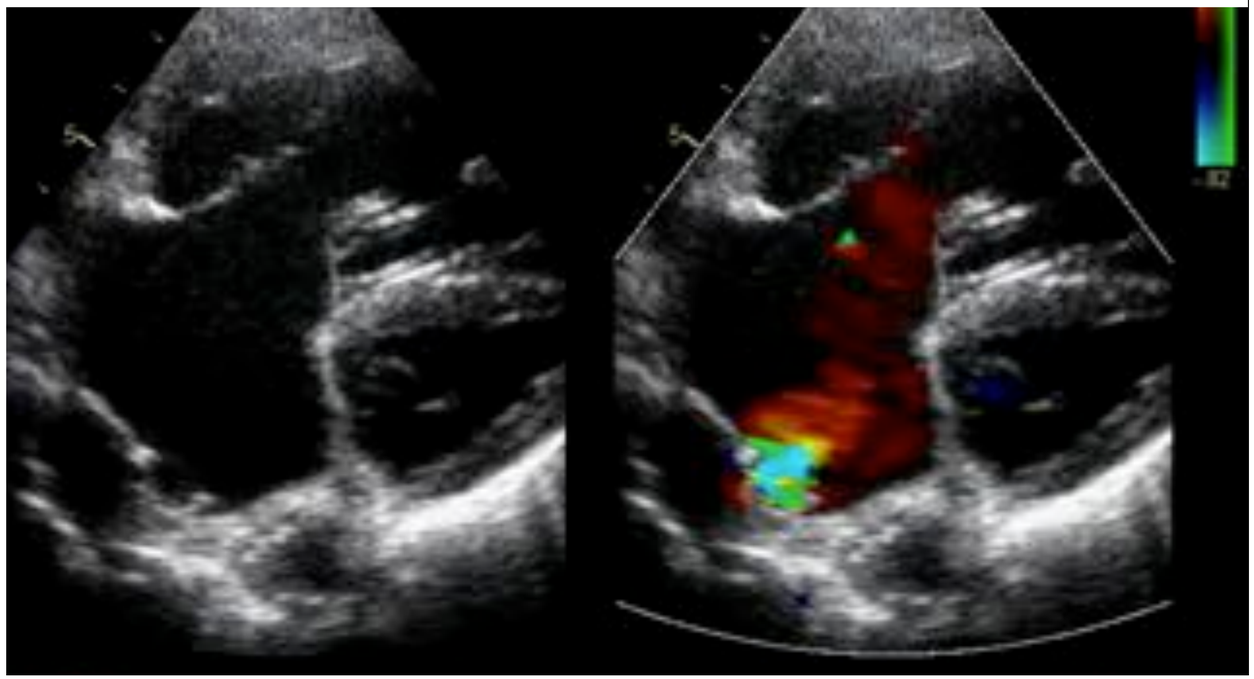
HLHS, 1 year post-Fontan



Le PA reconstructed with 12 GT

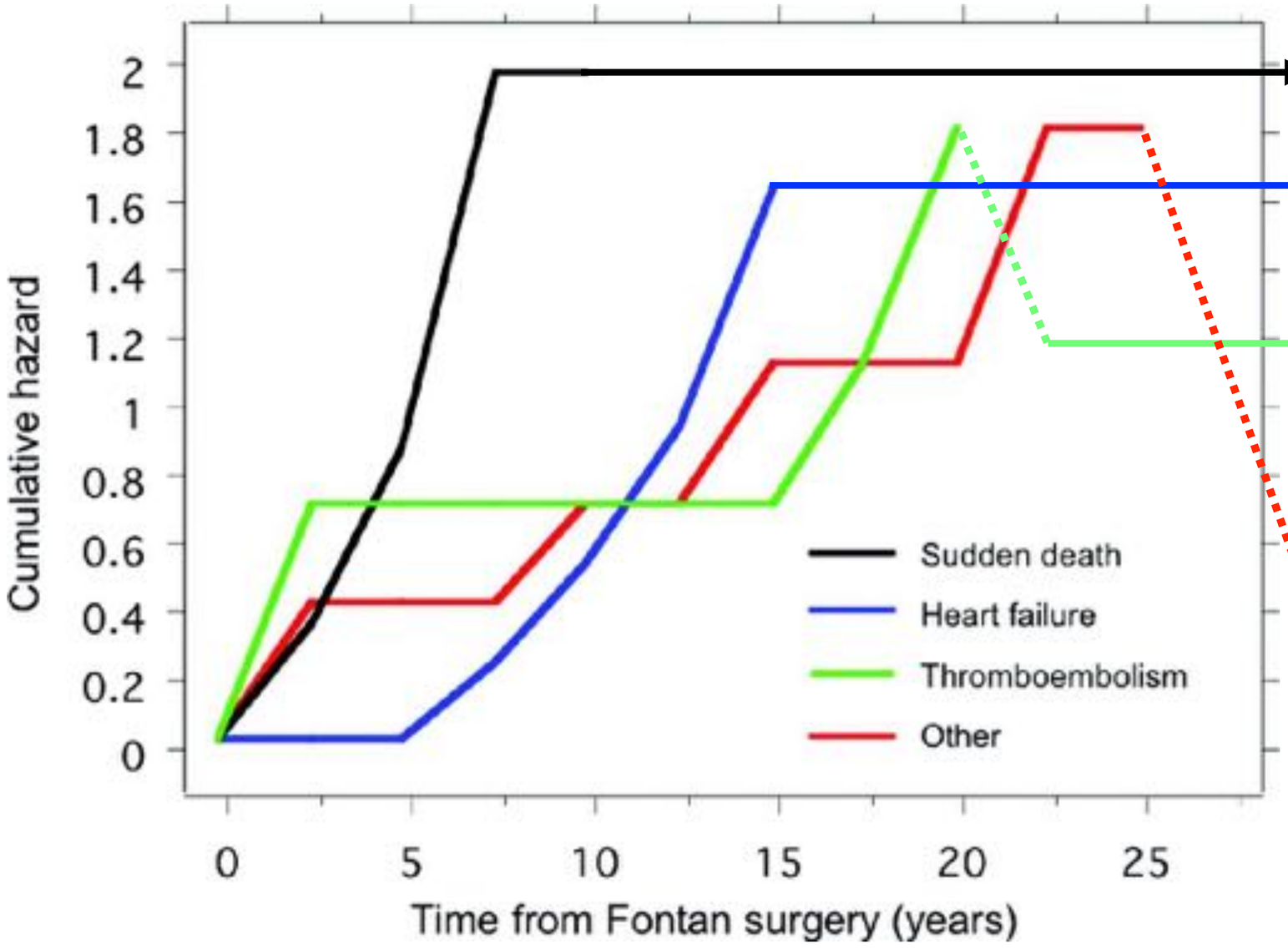
Should we close fenestrations to prevent stroke ?
or leave them open to improve cardiac output ?





How to prevent poor outcomes after Fontan completion with medical treatment ?

Cumulative hazard by mode of death



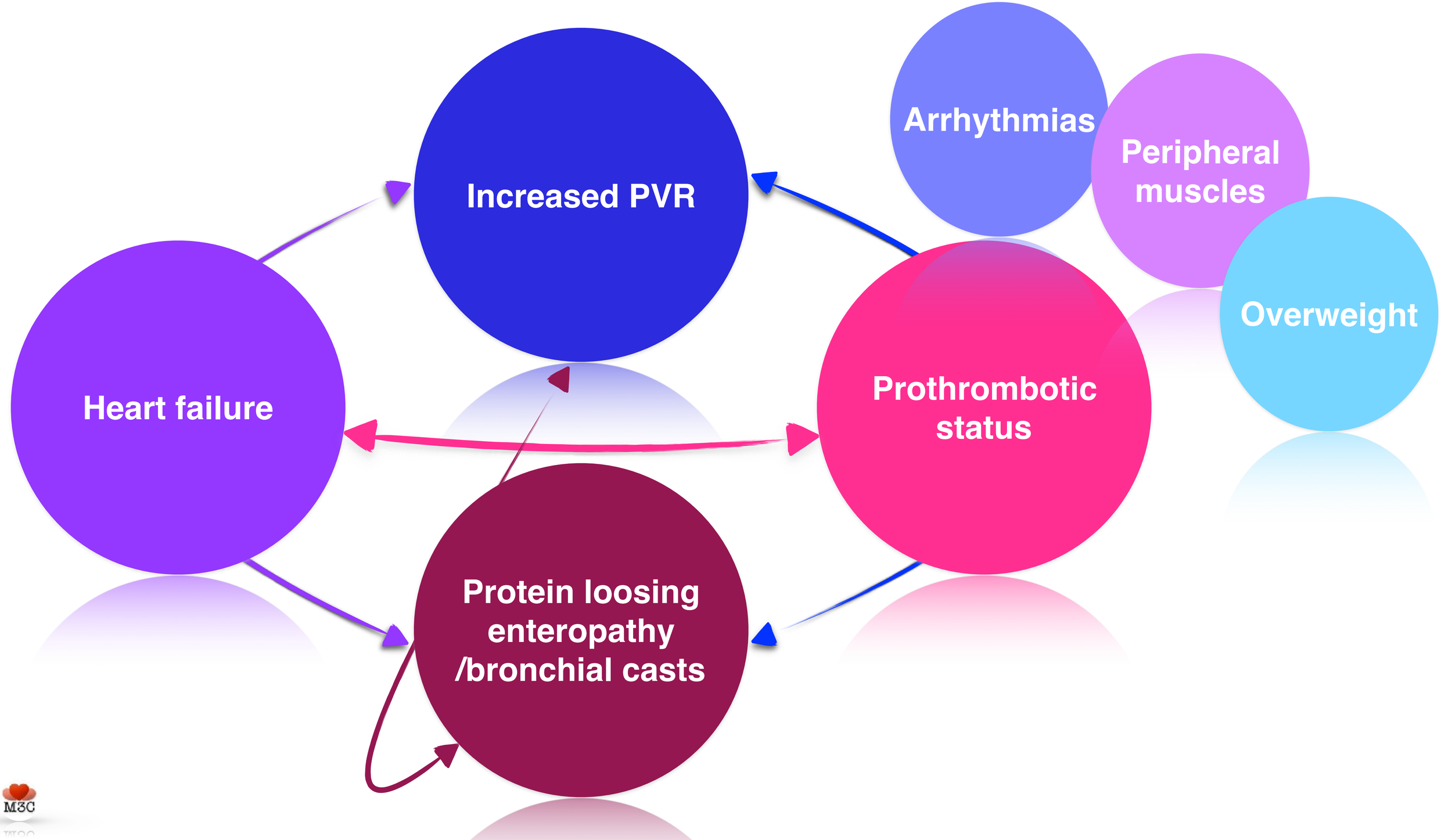
Antiarrhythmic drugs/devices

Heart failure/PAH drugs

Anticoagulation

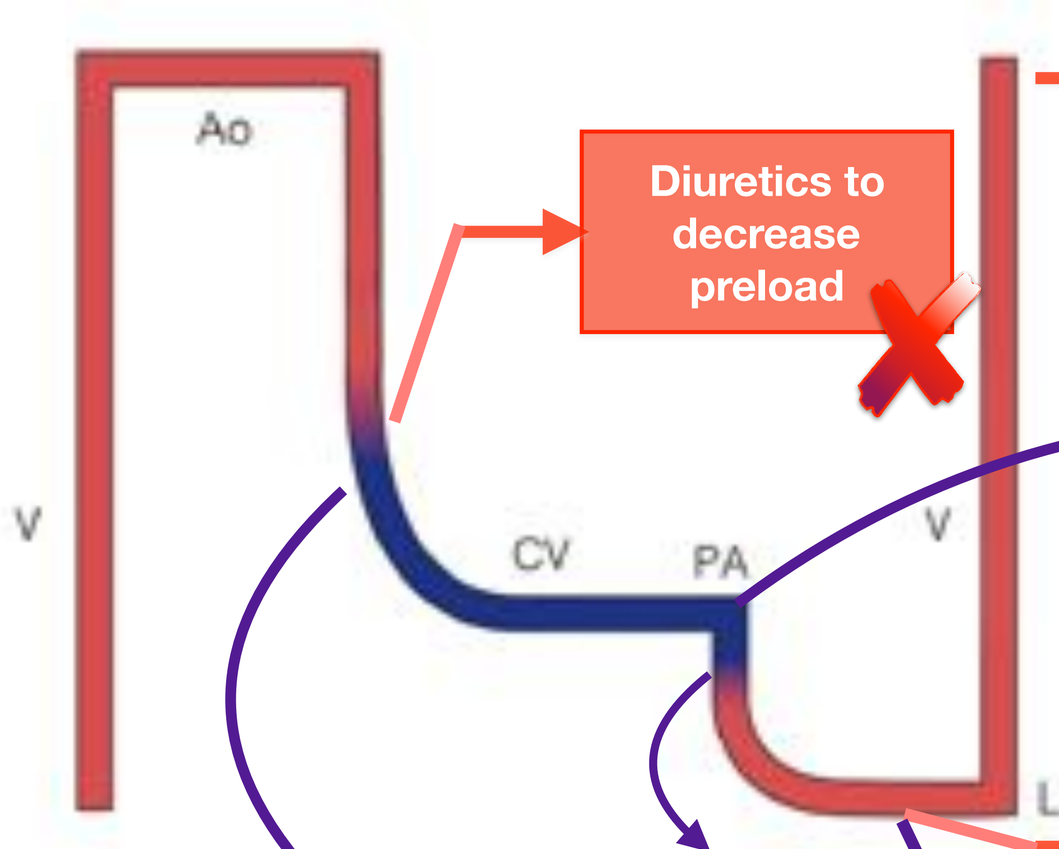
PLE and lymphatic disease

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


Increased PVR
Arrhythmias
Peripheral muscles
Overweight
Heart failure
Prothrombotic status
Protein loosing enteropathy /bronchial casts

Heart failure drugs in Fontan circulation

Potentially a wrong reasoning and a predictable minimal effect



Diuretics to decrease preload

ACE Inhibitors to decrease after load

Wilson TG et al. Int J Cardiol 2016

Pulmonary vasodilatation to increase preload

Exercise to increase preload and decrease PVR

Beta-blockers to lengthen diastole and ventricular filling

Lusitropic drugs sGC stimulators

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.***

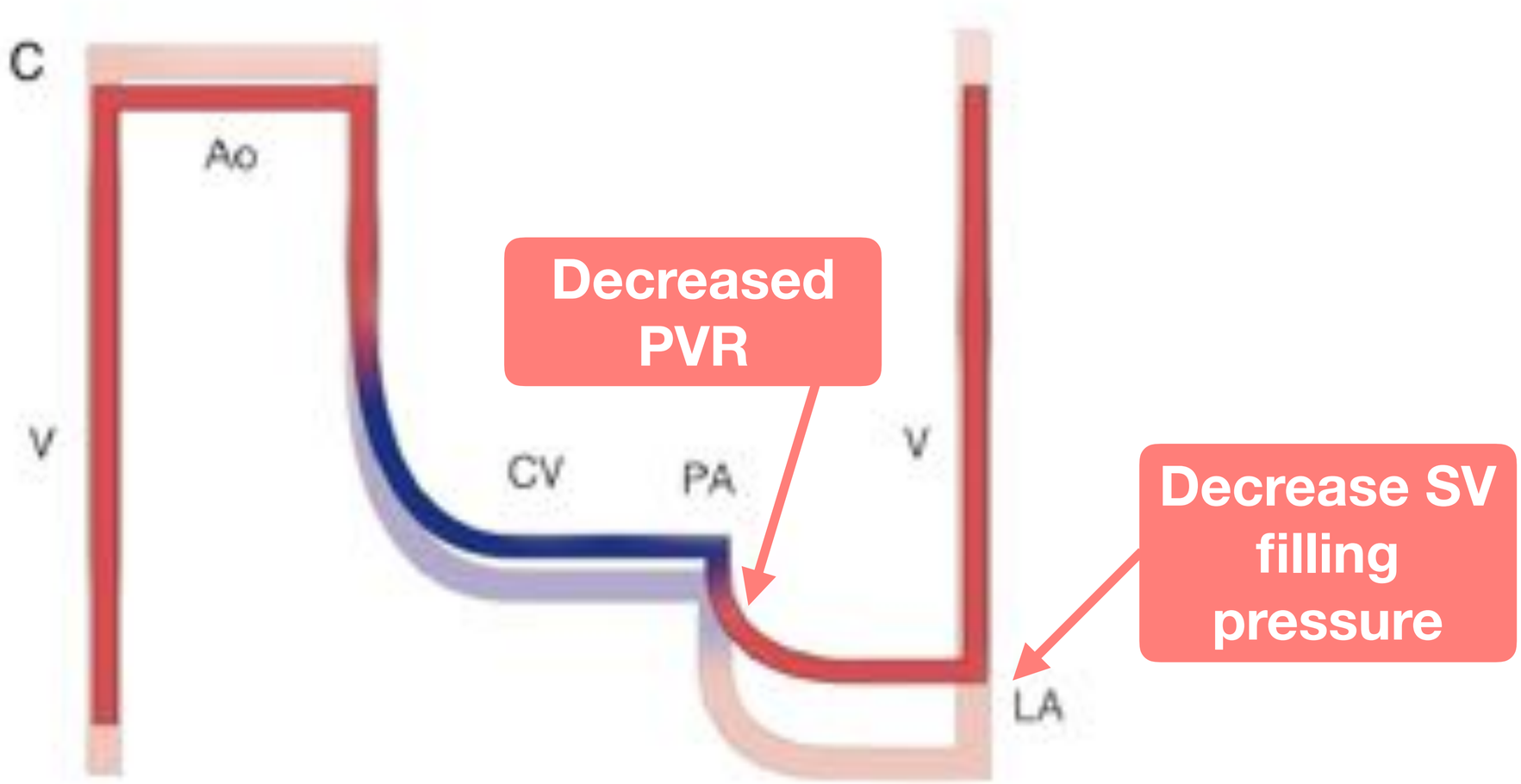
- Enalapril in children with single ventricle : **no changes** in HF severity neither improve growth, ventricular function nor death/transplantation at one year. [1]

- 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.

Impedance of Pulmonary vasculature and ventricular succion



sGC insufficiency in heart failure

DILATE: Effects of single doses of riociguat in Heart Failure with preserved EF and PH

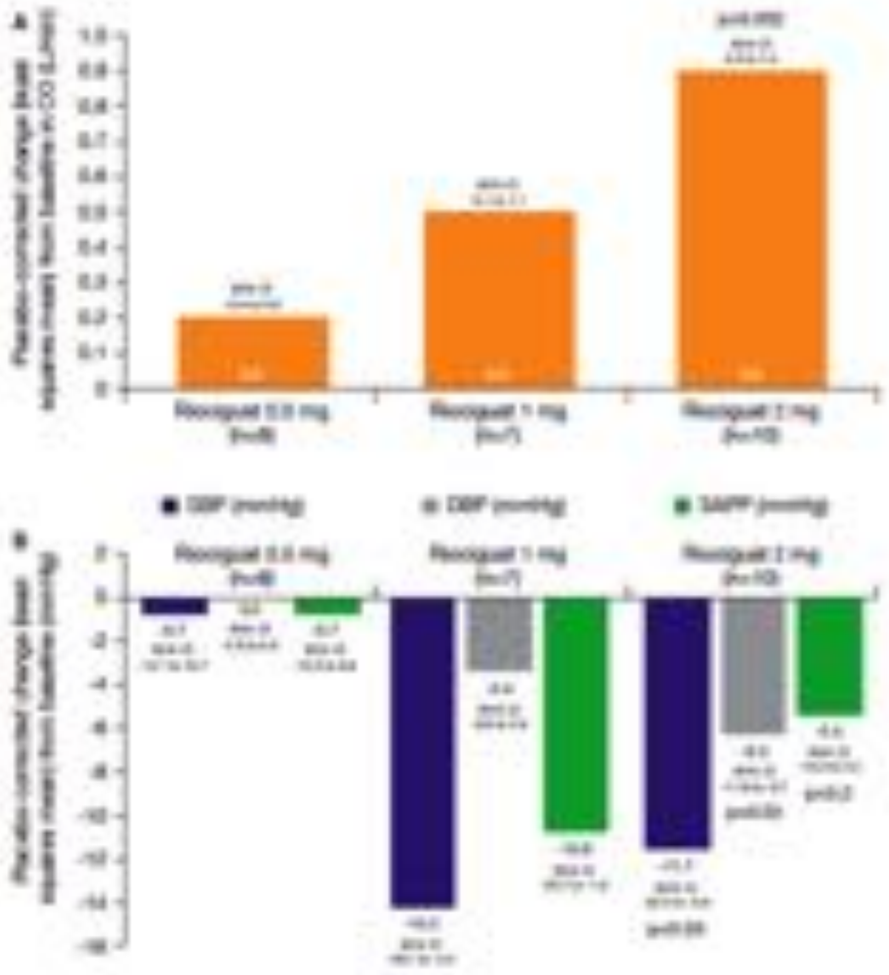


Figure 4. Placebo-corrected change (least squares mean) from baseline over the 6-hour period after study drug administration in selected hemodynamic parameters. (A) cardiac output (CO); (B) systolic blood pressure (SBP); diastolic blood pressure (DBP); and systemic arterial pulse pressure (SAPP).

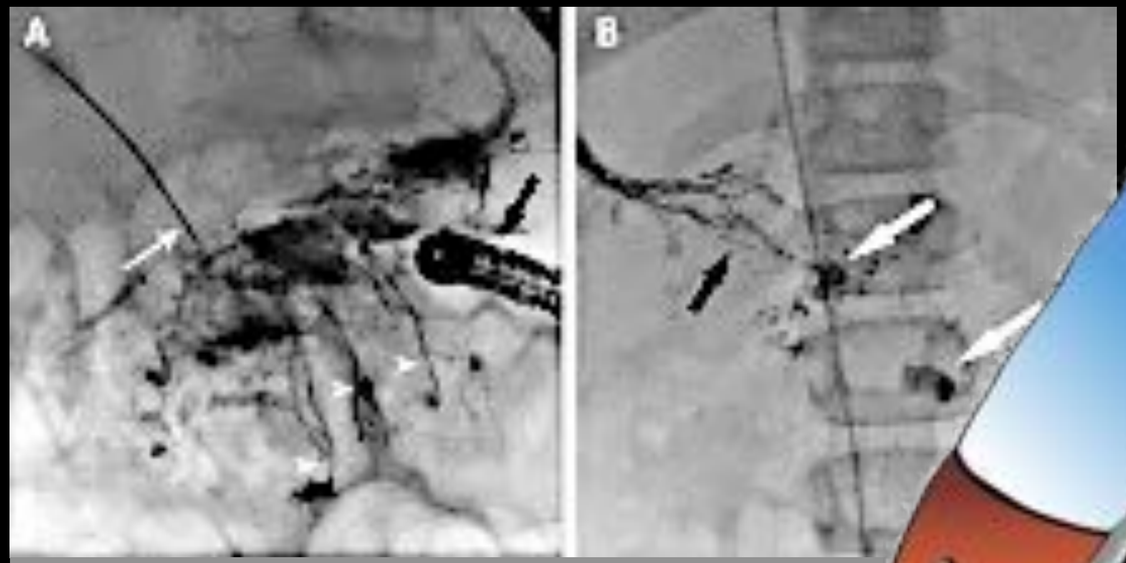
Conclusions

- Single doses of riociguat were well tolerated and showed favorable hemodynamic and echocardiographic effects in patients with HFpEF and PH.
- Despite the primary endpoint of the study—peak decrease in mPAP from baseline up to 6 hours after administration of study drug—not being met, riociguat 2 mg significantly increased SV and cardiac index, and decreased systolic BP, SVR, and RVED area, without altering HR, TPG, or PVR.
- The ventricular filling required to establish an increased SV was not accompanied by increased PAWP, indicating that riociguat might improve diastolic function via a change in relaxation and/or distensibility of the LV.
- Chronic, large-scale, placebo-controlled studies are required to further assess the long-term clinical safety and efficacy of riociguat, started at lower doses and carefully up-titrated, in this population.

Bonderman et al., Chest. 2014 Nov;146(5):1274-85

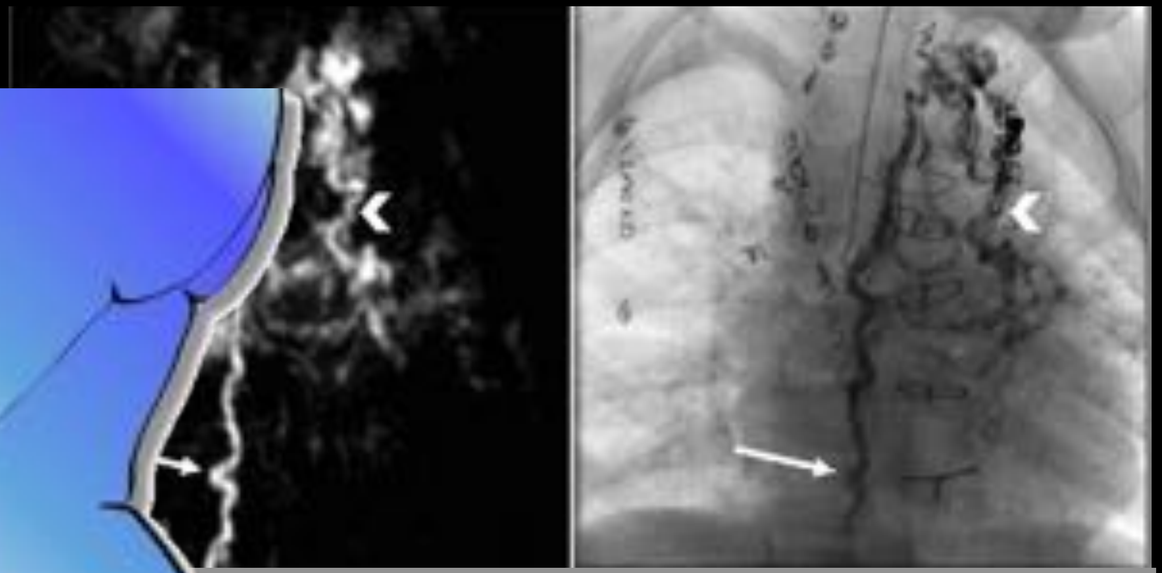
Significant predictors of late death after Fontan

- prolonged pleural effusions post Fontan surgery (HR 1.18, 95%CI 1.09-1.29, p<0.001),
- **protein losing enteropathy (HR 2.19, 95%CI 1.69-2.84, p<0.001),**
- increased ventricular end diastolic volume (HR 1.03 per 10ml/BSA increase, 95%CI 1.02-1.05, p<0.001)
- and having a permanent pacemaker (HR 12.63, 95%CI 6.17-25.86, p<0.001).

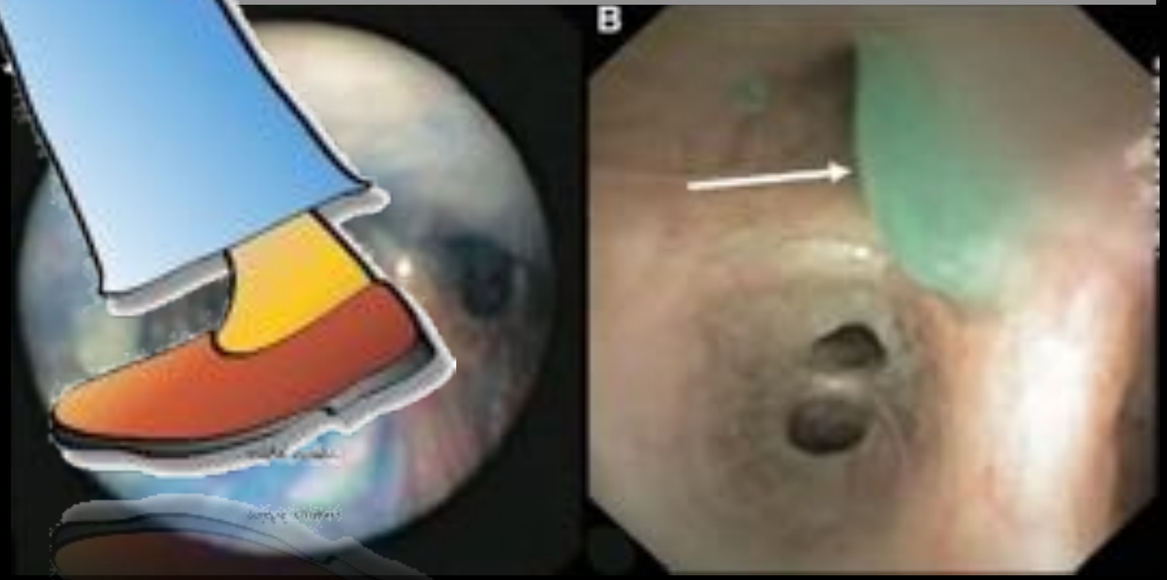


PLE Hepatic lymphogram & endos

Itkin M et al. JACC 2017

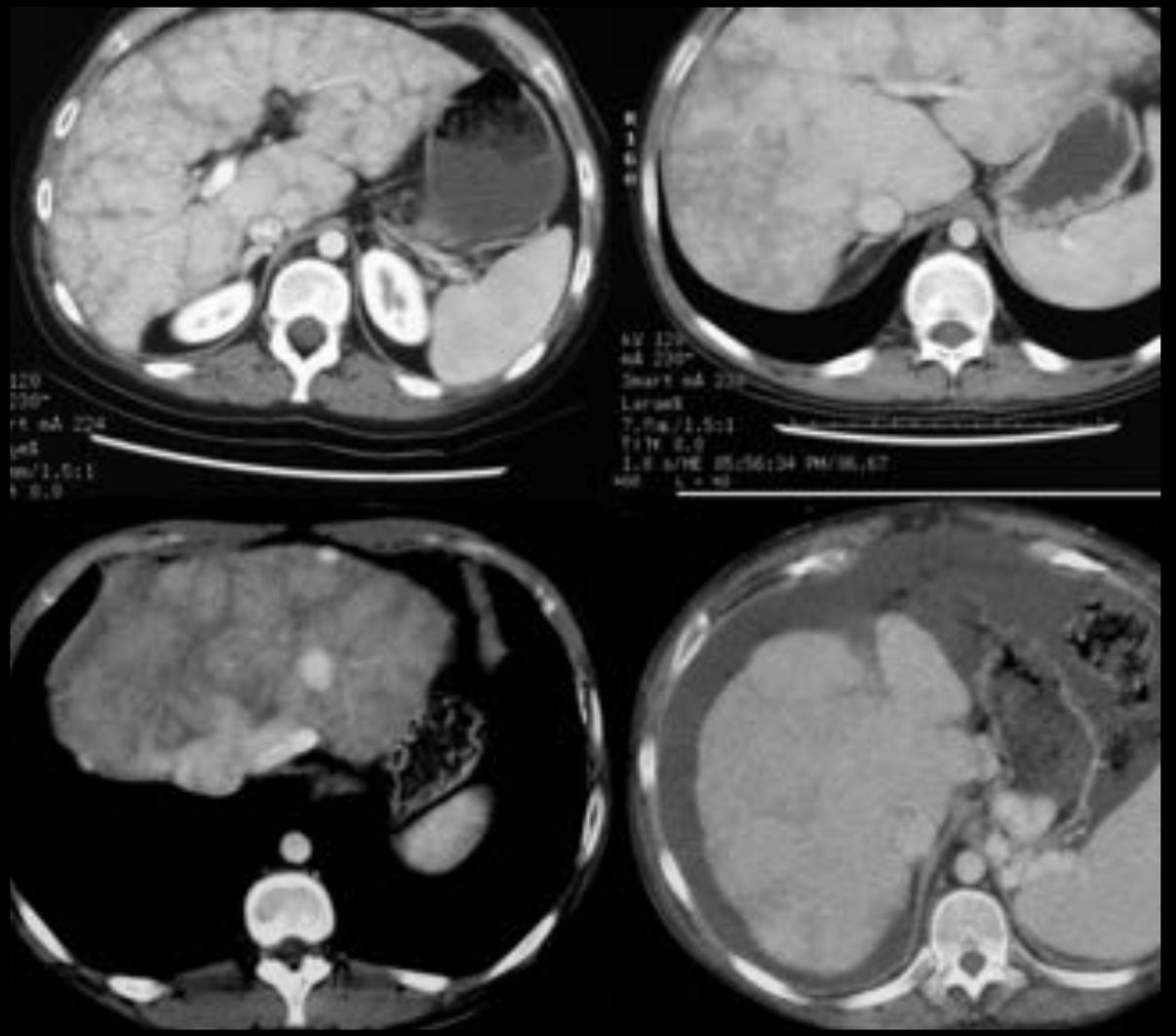


bronchitis lymphogram & bronchoscopy



Dori Y et al. Circulation 2016

Liver and Fontan



Fontan will ineluctably fail

- Prevent failure by agressive management
- Truly evaluate preventive strategies pre- and post-Fontan
- Adapt to patients individual characteristics
- Involve/educate patients to delay failure
- Tailor follow-up to patients characteristics