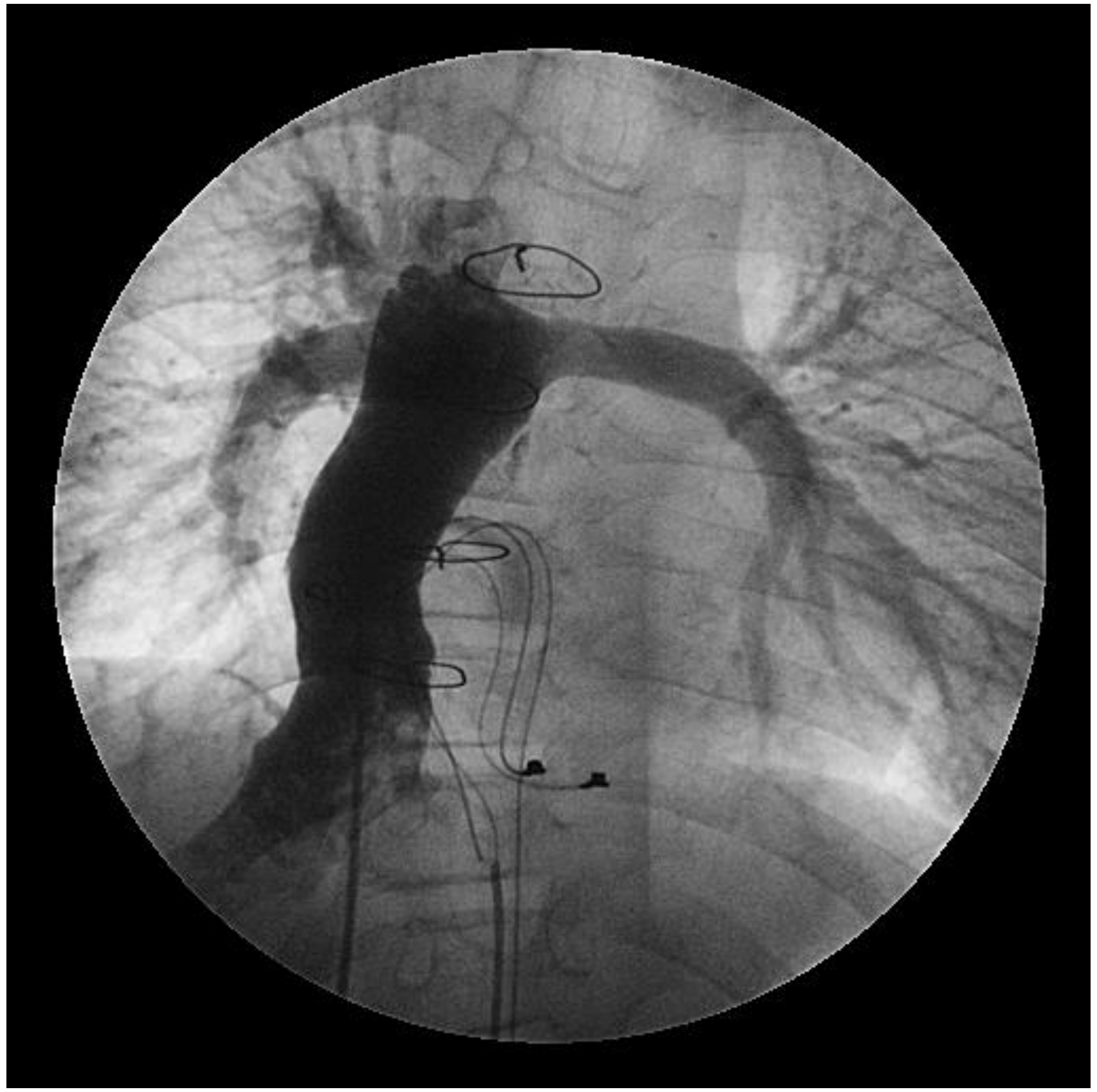
Role of pulmonary vasodilators in the Fontan setting

Michael Cheung

Melbourne

Fontan circuit



Low resistance to adequate pulmonary blood flow is critical

- Central PA anatomy (size and distortion)
- Intrapulmonary vessel (arborisation and flow)
- Unobstructed pulmonary venous flow (anatomical/physiological)
- Normal capillary bed

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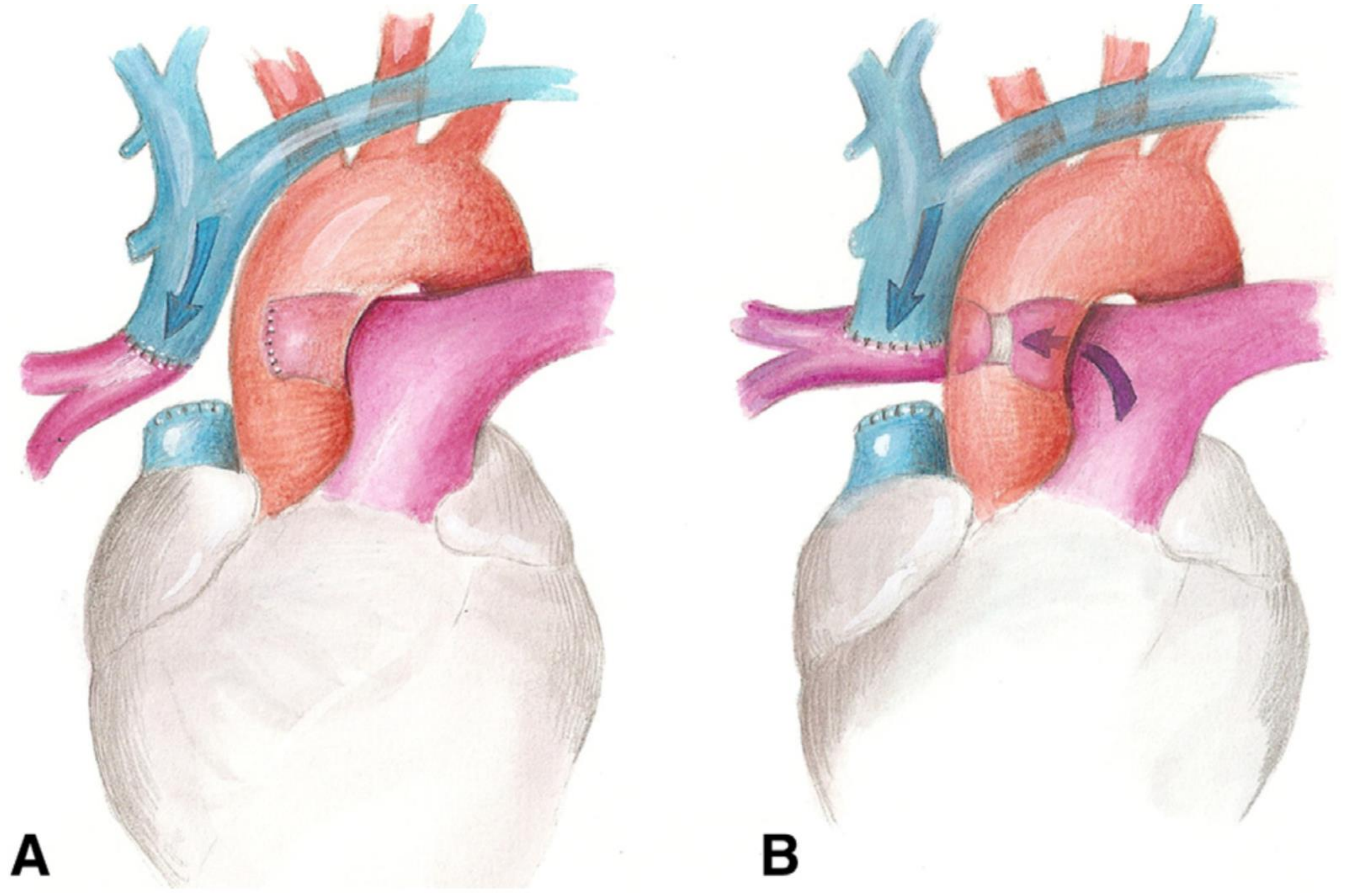
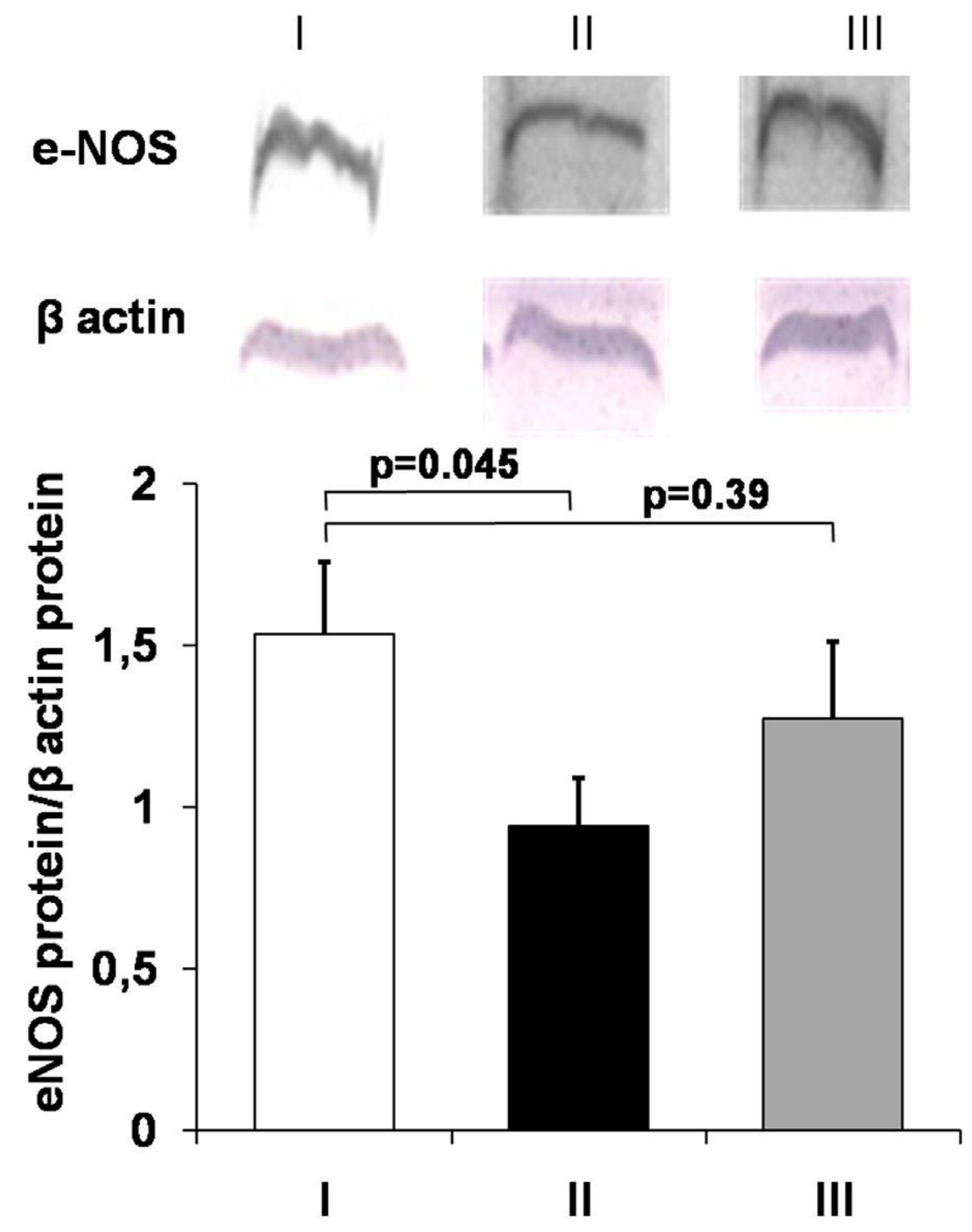
Elevated resistance to flow? Goldilocks and her bears

We know excessive PBF is bad
Low/non-pulsatile flow also bad

Pig model, 3 months



PVR
Group A; Right lung PVR 2x greater than left lung
Group B; Left/right lungs PVR no different



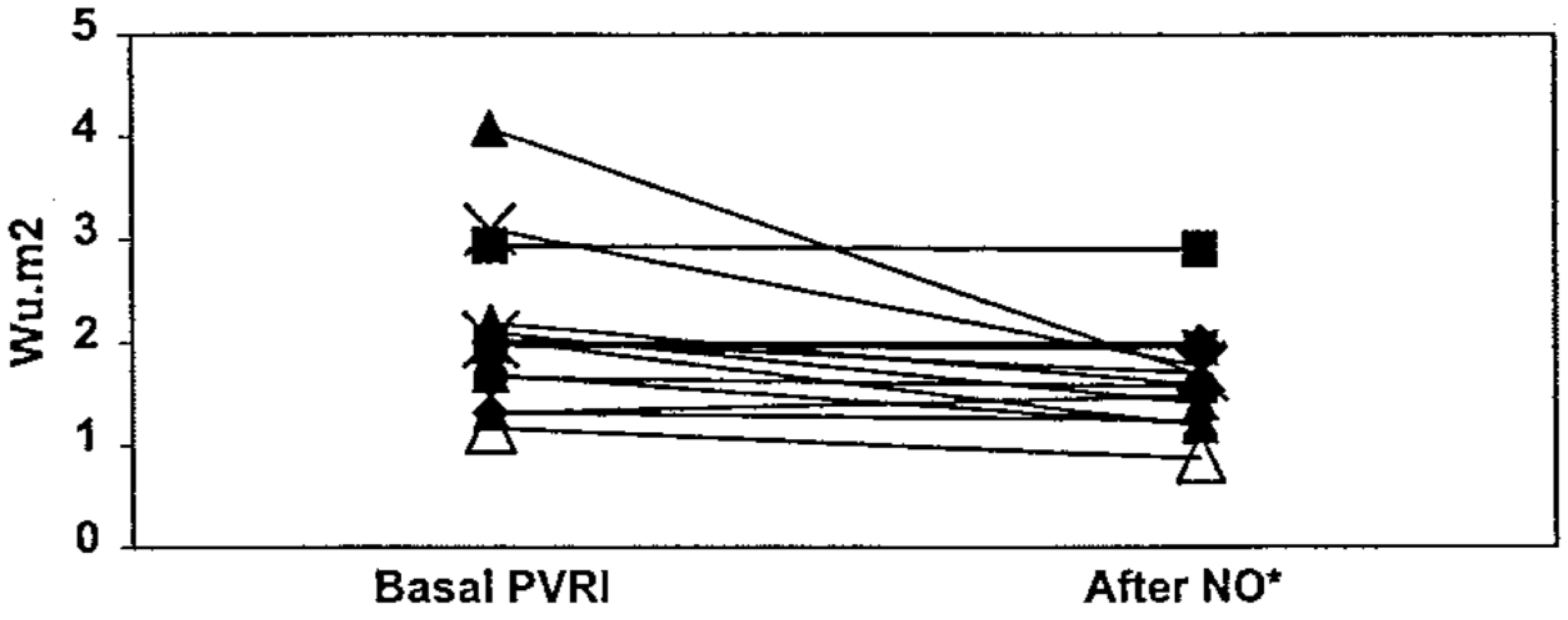
eNOS Right lung
I; sham
II; Non-pulsatile
III; Slight pulsatility

Henaine et al

J Thorac Cardiovasc Surg 2013;146:522-9

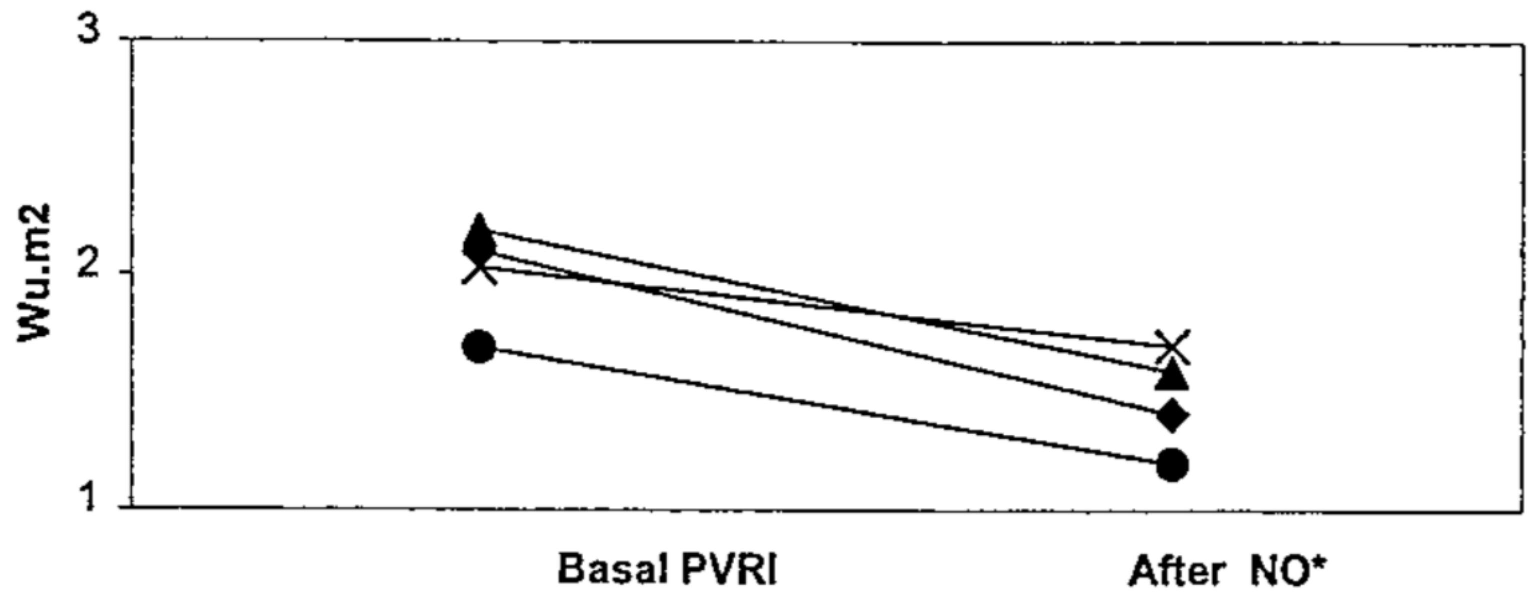
Endothelial function

15 Fontan patients aged 7-17 years

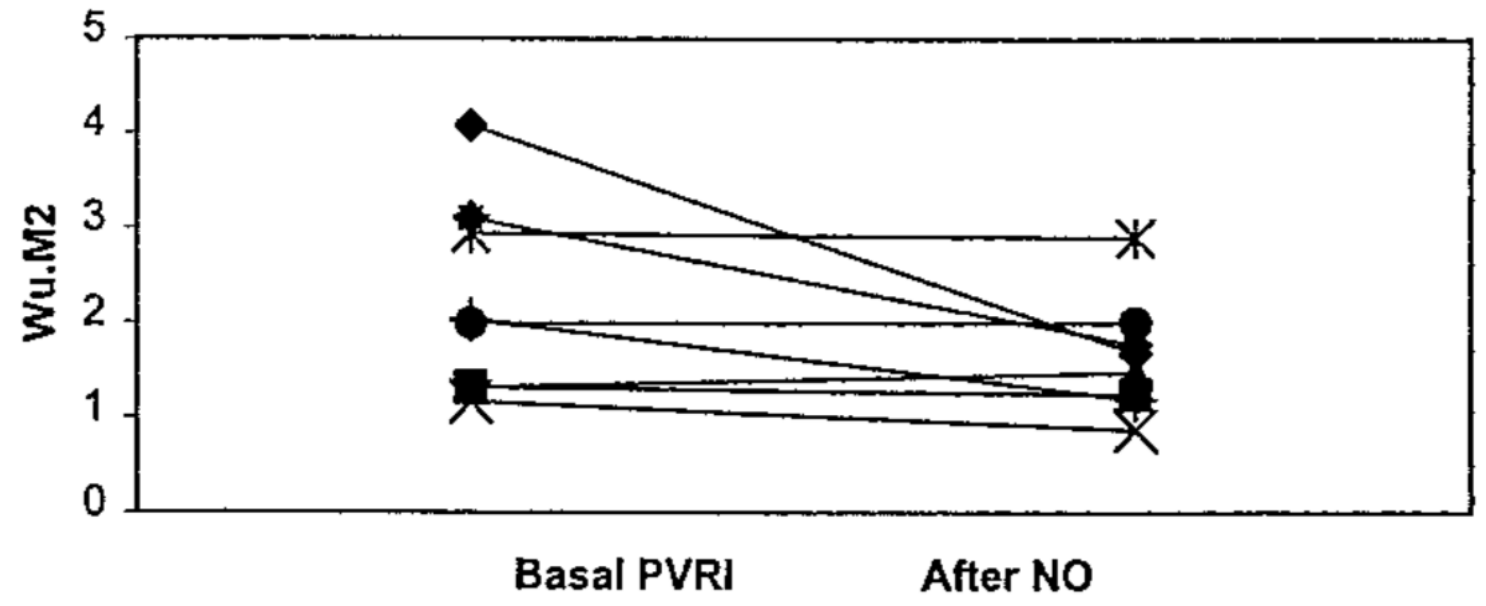


All subjects; fall in PVR (p=0.016)

Initial procedure



PA band

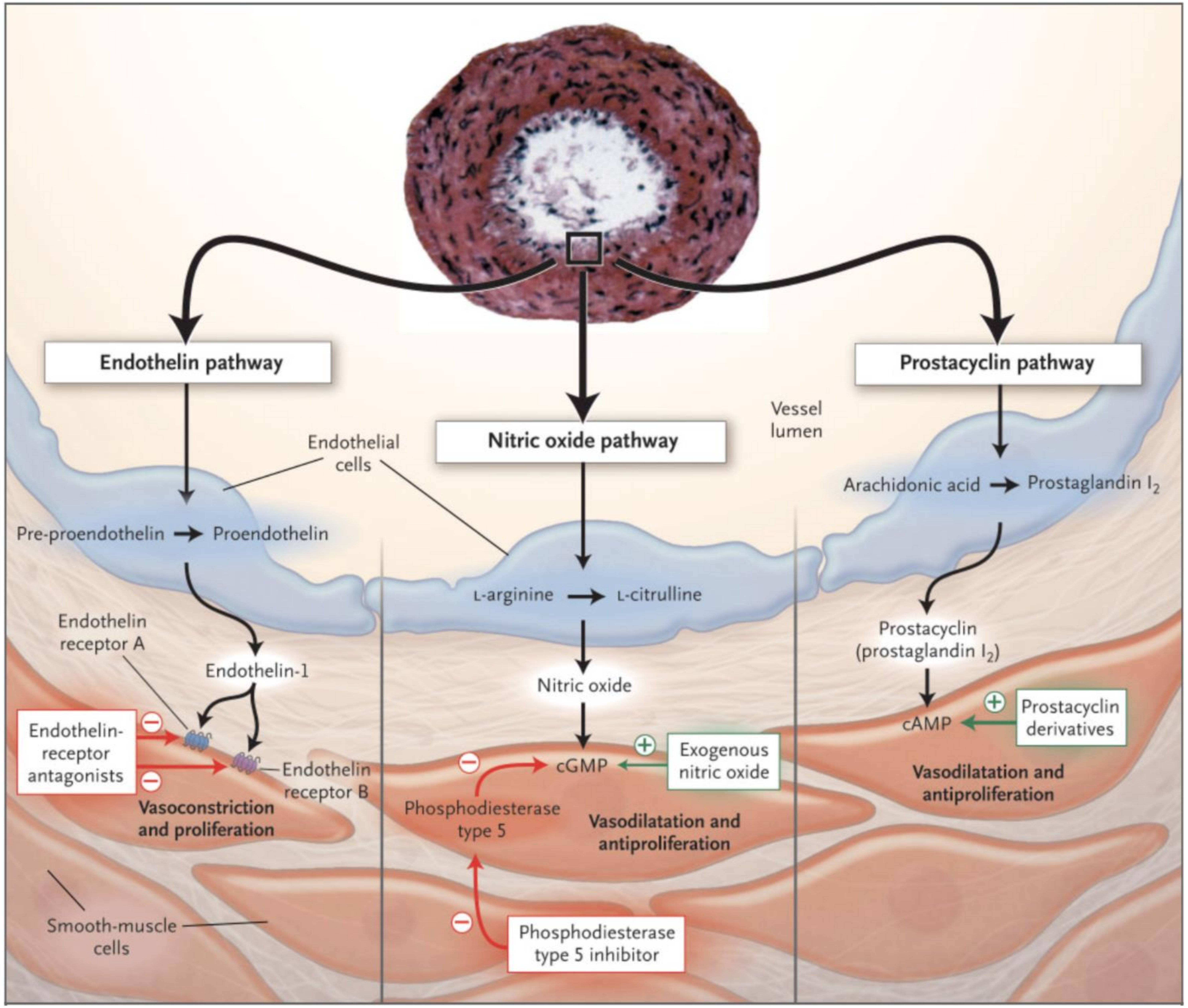


BT shunt

Greater effect of NO in pts with previous pulsatile flow (p=0.006)

Khambadkone et al Circulation 2001

Pulmonary arterial hypertension specific therapy



Supportive therapy
- hydration
- anticoagulation
- Iron supplementation

NO

PDE5 inhibition
- sildenafil/vardenafil/tadalafil

soluble Guanylate Cyclase stimulation
- Riociguat

ERA
- bosentan/ambrisentan/macitentan

PGI
- Prostacyclin (IV/subcut/nebulised)
- Selexipag

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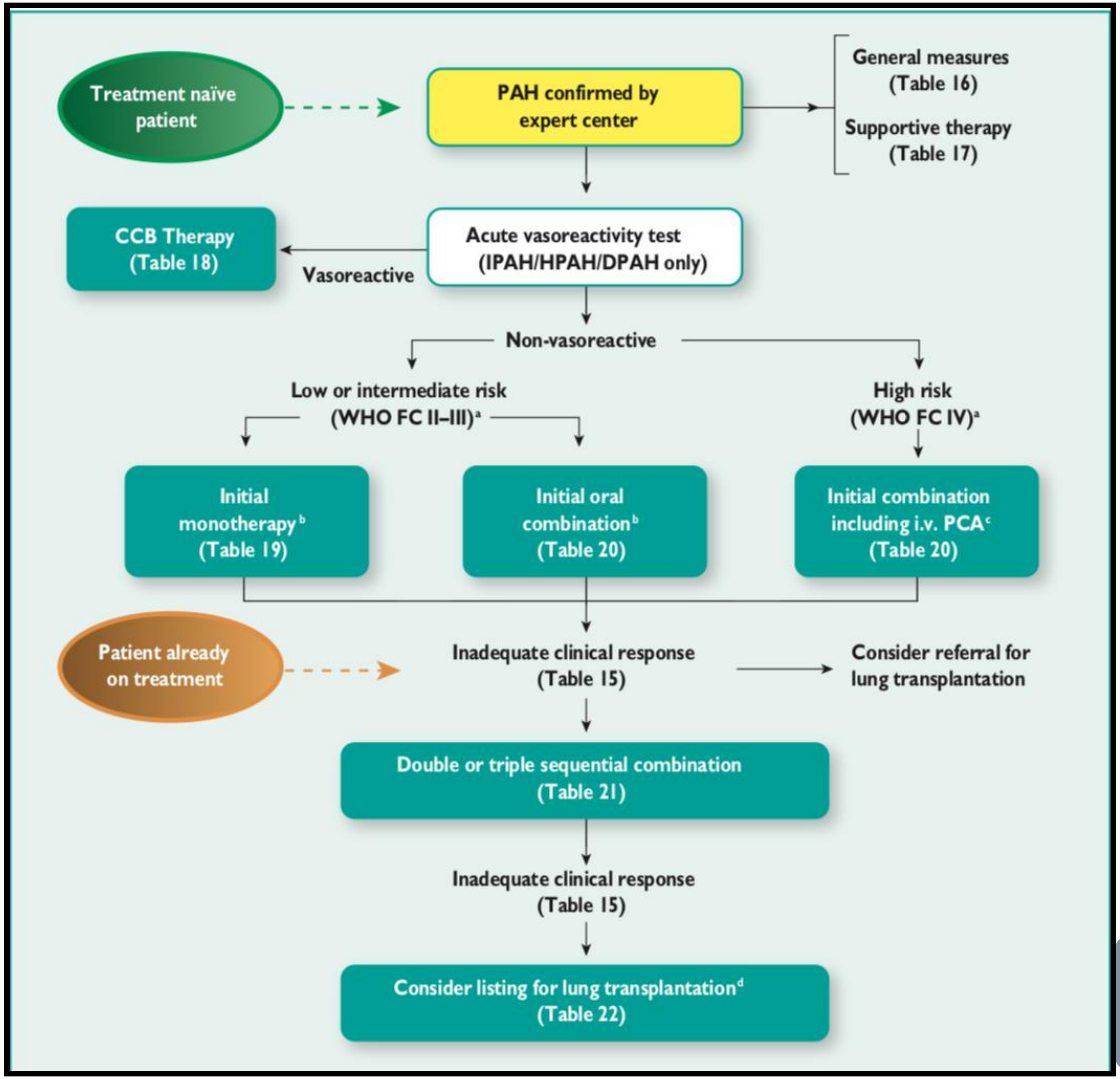
N Engl J Med 2004; 351:1425-1436

Pulmonary arterial hypertension specific therapy

2015 ESC/ERS Guidelines for the diagnosis and treatment of PAH



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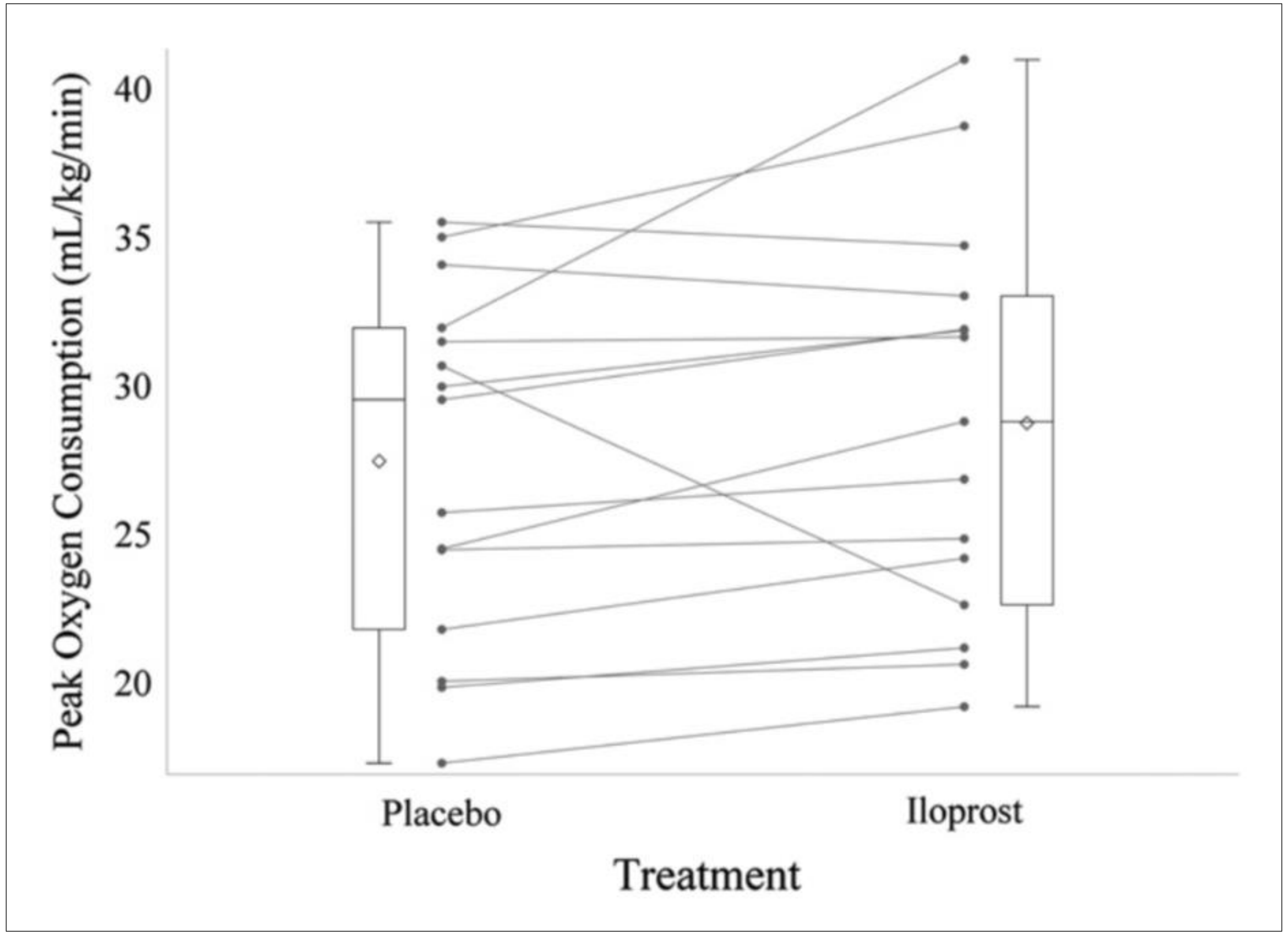
Prostacyclin; *Studies in Fontan patients*



- 2 exercise tests done 1/12 apart
- Randomised to single dose inhaled prostacyclin vs placebo
- Improved VO2max
- All patients with baseline VO2 <30ml/kg/min improved with iloprost c/f placebo
- No change in spirometry

Median VO2max 30.2 vs 27.6 mL/min/kg

$p=0.004$

Rhodes Int J Card 2013

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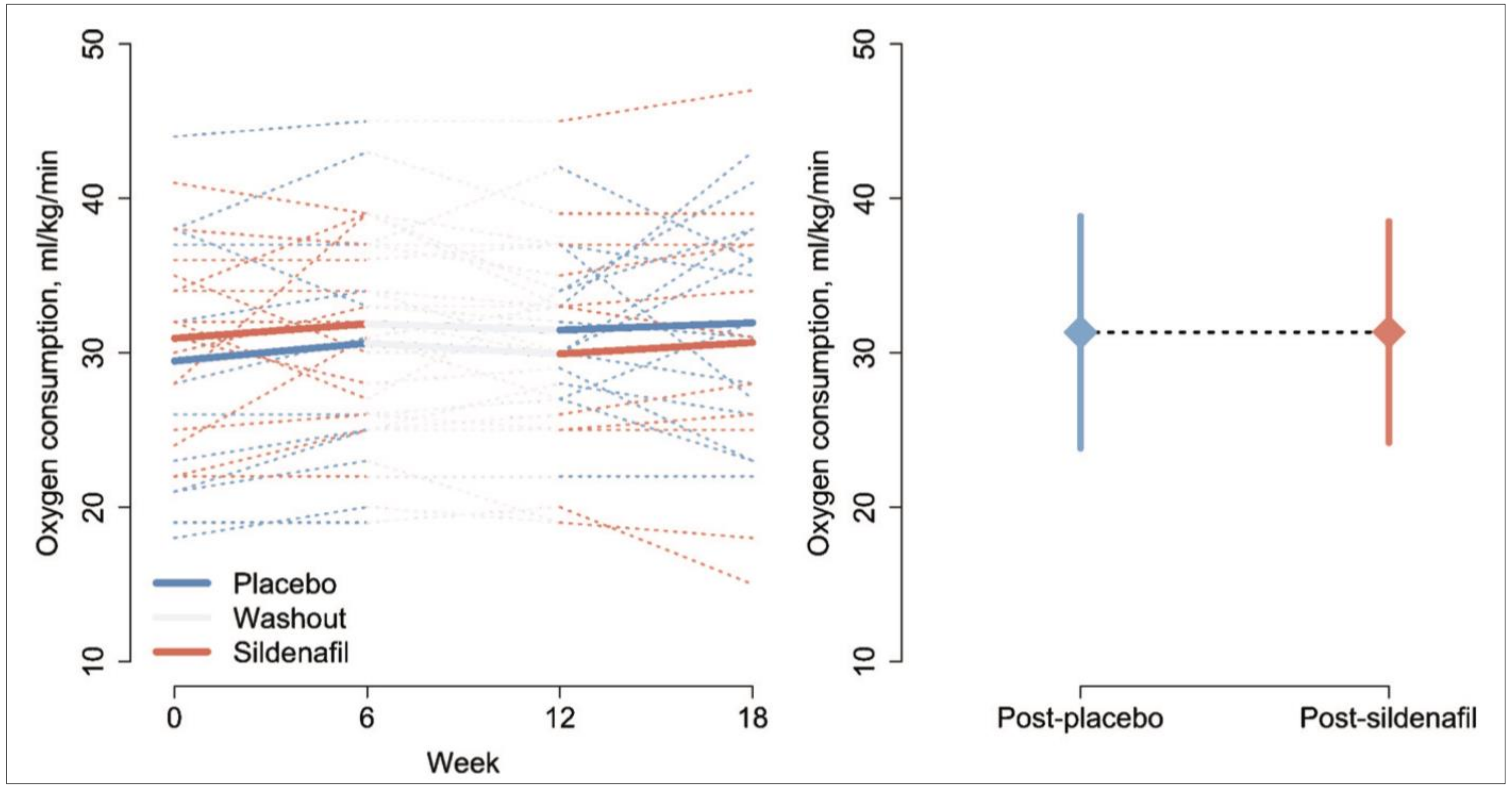
Sildenafil; *Studies in Fontan patients*

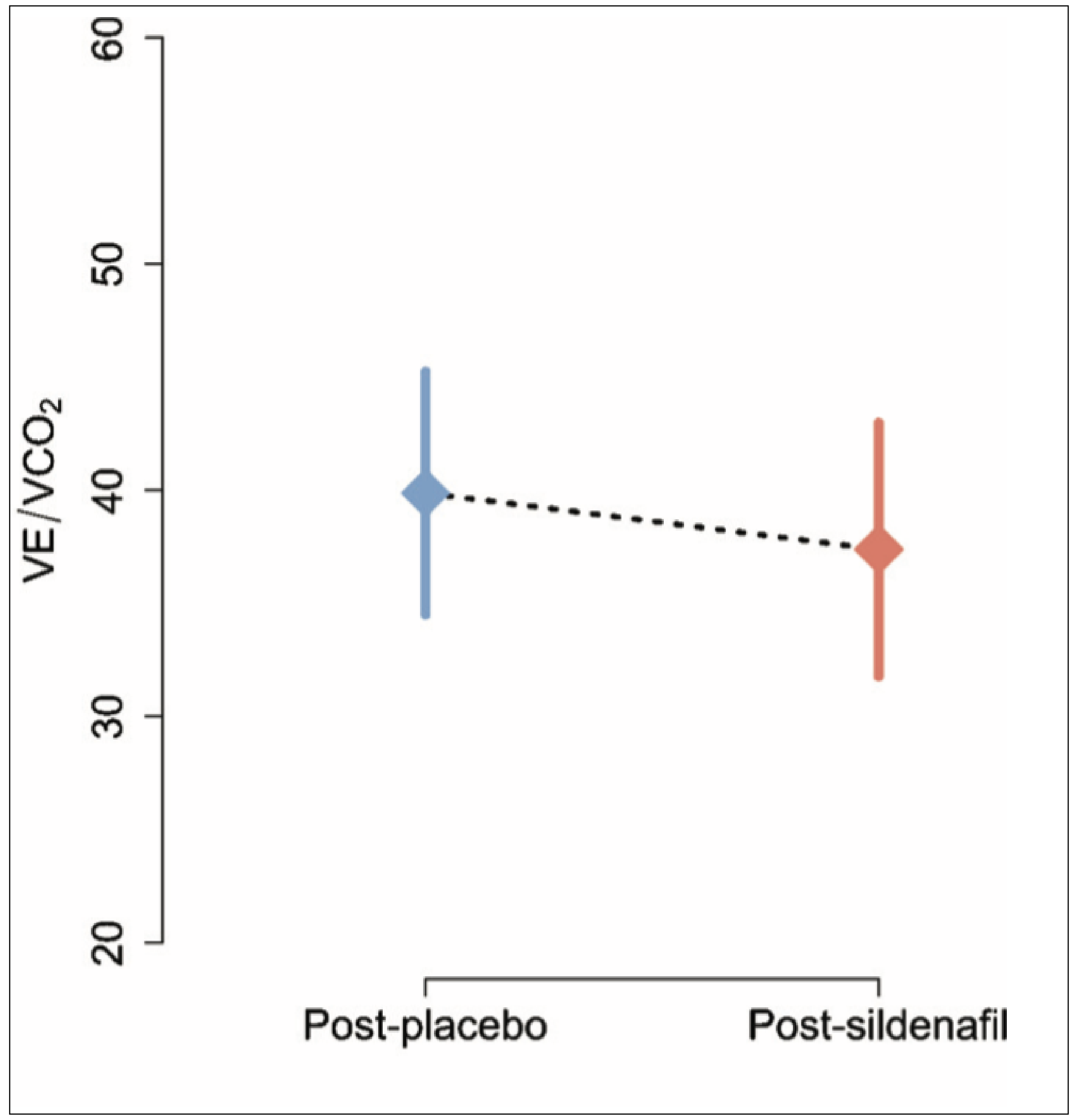
Impact of Oral Sildenafil on Exercise Performance in Children and Young Adults After the Fontan Operation

A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial

David J. Goldberg, MD; Benjamin French, PhD; Michael G. McBride, PhD;
Bradley S. Marino, MD, MPP, MSCE; Nicole Mirarchi, MA; Brian D. Hanna, MD, PhD;
Gil Wernovsky, MD; Stephen M. Paridon, MD; Jack Rychik, MD

27 patients
Mean age 15 +/-5 years
6 weeks of sildenafil,/placebo crossover trial
CPET assessment
Mean VO2 max @ baseline 30.5ml/kg/min





Whole group data
Improved ventilatory efficiency @ AT
(p=0.03)

Greater effect in those with BNP>100 pg/mL

No change in VO2 max

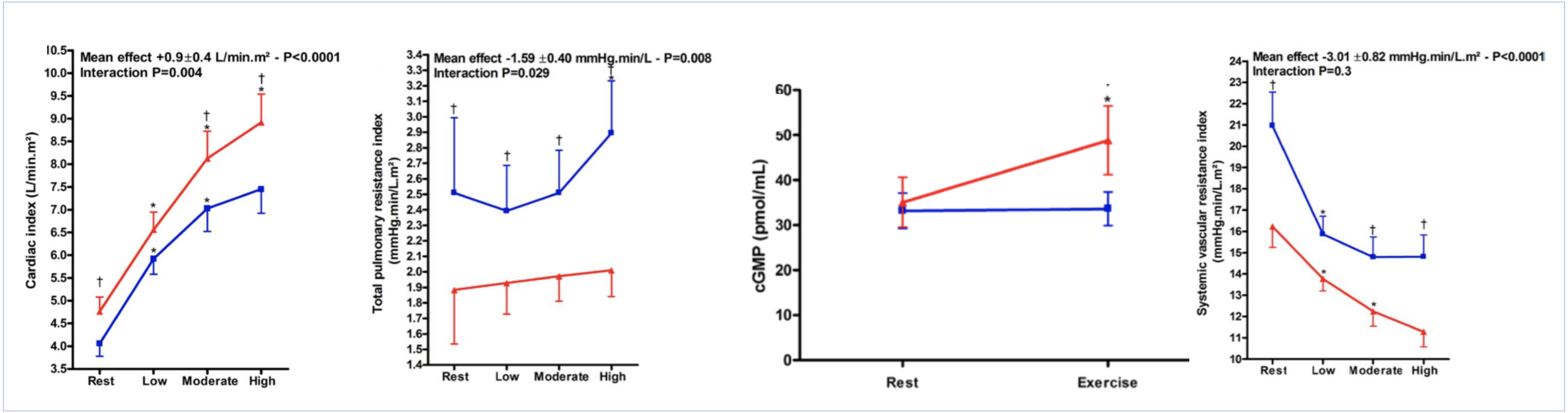
Circulation 2011;123:1185

Sildenafil; *Studies in Fontan patients*

Sildenafil Improves Exercise Hemodynamics in Fontan Patients

Alexander Van De Bruaene, MD, PhD*; Andre La Gerche, MD, PhD*; Guido Claessen, MD; Pieter De Meester, MD; Sarah Devroe, MD; Hilde Gillijns, BSc; Jan Bogaert, MD, PhD; Piet Claus, PhD; Hein Heidbuchel, MD, PhD; Marc Gewillig, MD, PhD*; Werner Budts, MD, PhD*

Adults (n=10)
Single dose of sildenafil (50mg) pre-exercise
Exercise MRI and SVC/radial artery catheter



Improved cardiac output

Reduced PVR

Restored exercise induced cGMP release

SVR greater fall

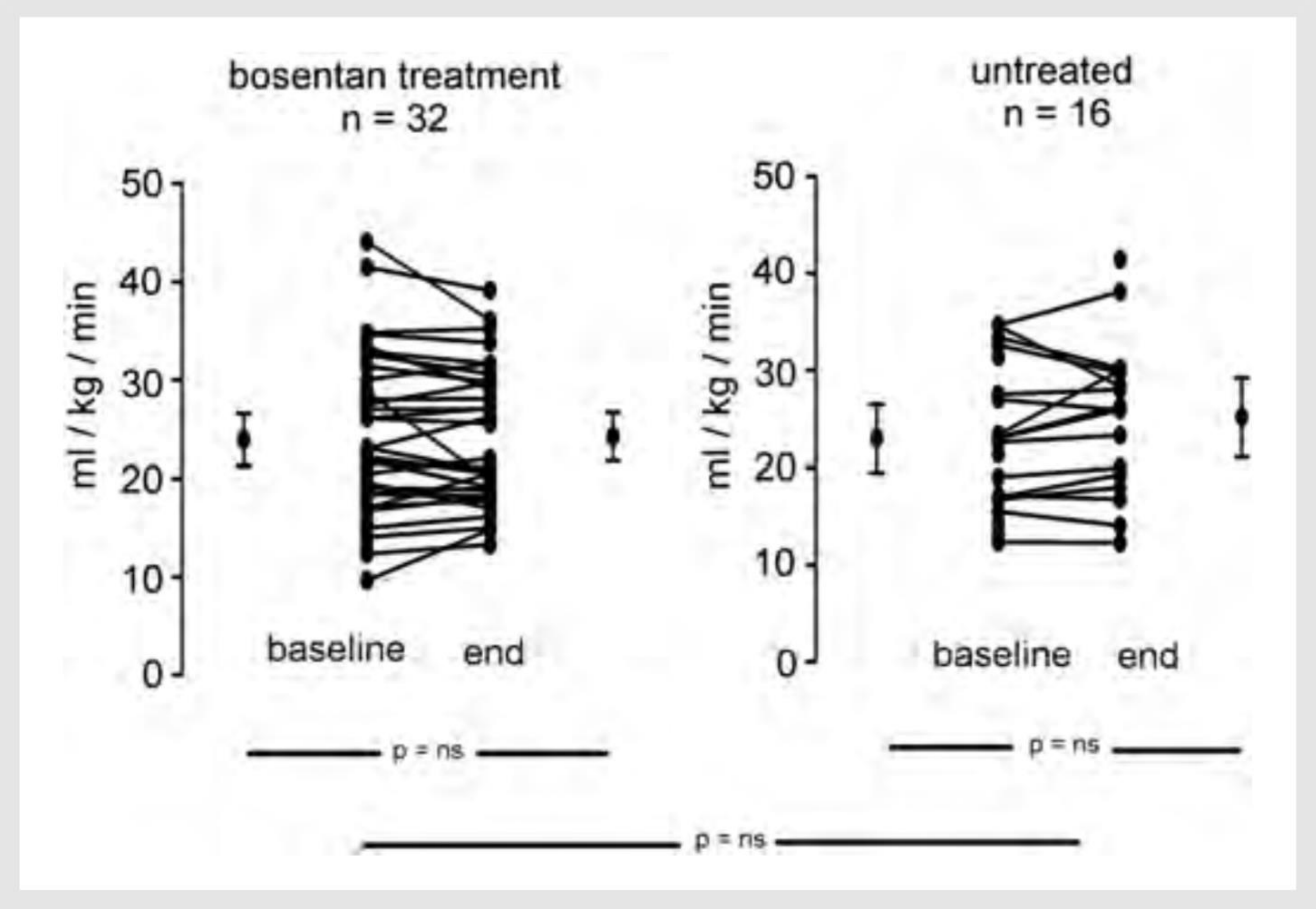
Before sildenafil
After sildenafil

Circ CV Imaging 2014;7:265-273

ERAs; *Studies in Fontan patients*

Impact of bosentan on exercise capacity in adults after the Fontan procedure: a randomized controlled trial Eur J Heat Failure 2013

Mark J. Schuuring[1,2†], Jeroen C. Vis[1†], Arie P.J. van Dijk[3], Joost P. van Melle[4], Hubert W. Vliegen[5], Petronella G. Pieper[4], Gertjan T. Sieswerda[6], Rianne H.A.C.M. de Bruin-Bon[1], Barbara J.M. Mulder[1,2], and Berto J. Bouma[1*]



The effect of bosentan in patients with a failing Fontan circulation

Caroline Ovaert,[1] Daisy Thijs,[2] Daniel Dewolf,[3] Jaap Ottenkamp,[4] Hugues Dessy,[5] Philip Moons,[6] Marc Gewillig,[2] Luc Mertens[2]

CITY 2009

N=9, median age 12 years (4-33 years)
"Failing" Fontan
4 months of Bosentan treatment
No difference in 6MWT/functional class

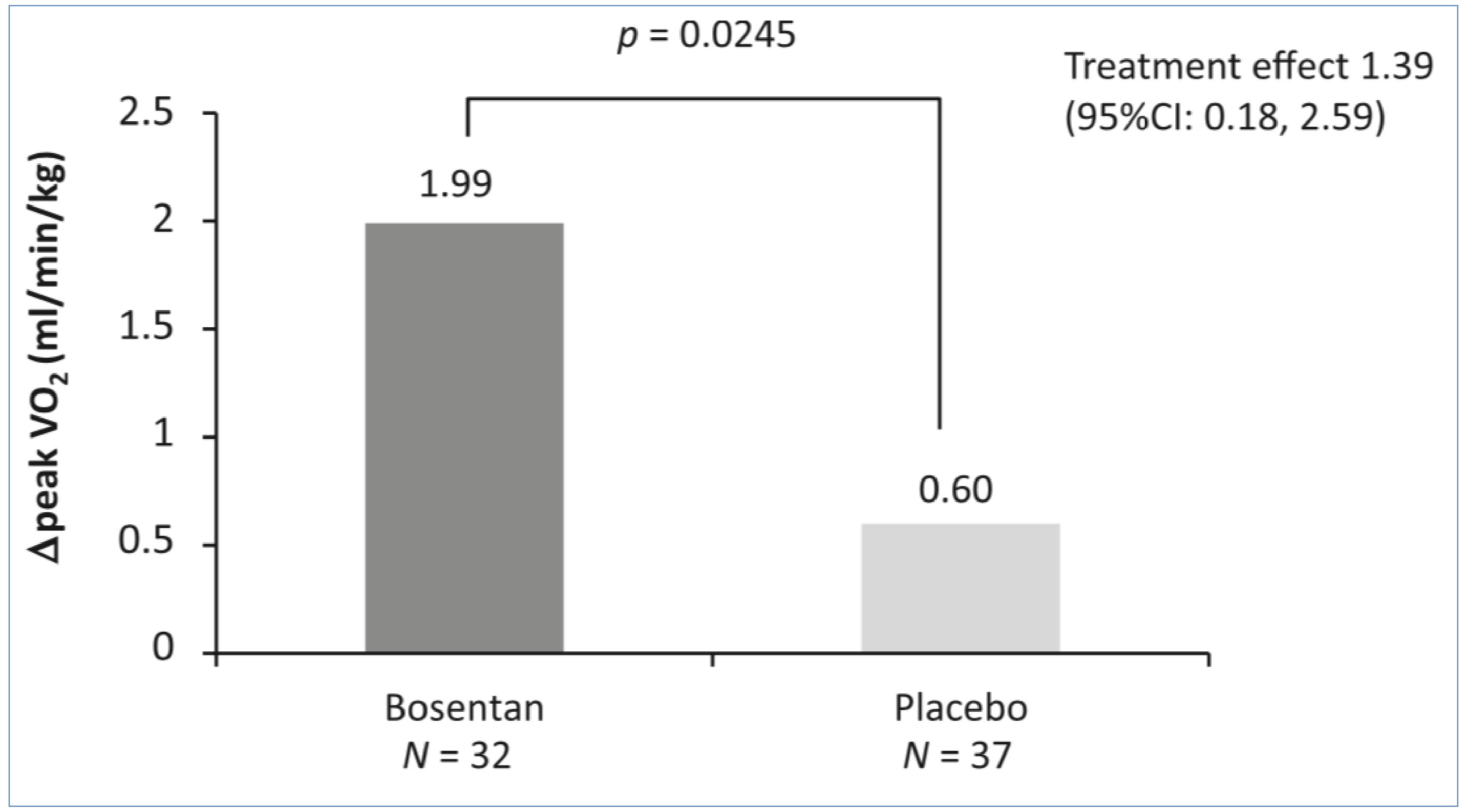
N=32, median age 29 years (18-56 years)
6 months of treatment
No change in VO2 max, SF-36 QoL, NT-proBNP

ERAs; *Studies in Fontan patients*

Bosentan Improves Exercise Capacity in Adolescents and Adults After Fontan Operation
The TEMPO (Treatment With Endothelin Receptor Antagonist in Fontan Patients, a Randomized, Placebo-Controlled, Double-Blind Study Measuring Peak Oxygen Consumption) Study

Anders Hebert, MD; Ulla R. Mikkelsen, PhD; Ulf Thilen, MD, PhD; Lars Idorn, MD, PhD; Annette S. Jensen, MD, PhD; Edit Nagy, MD, PhD; Katarina Hanseus, DMSc; Keld E. Sørensen, DMSc; Lars Søndergaard, DMSc

Circ 2014

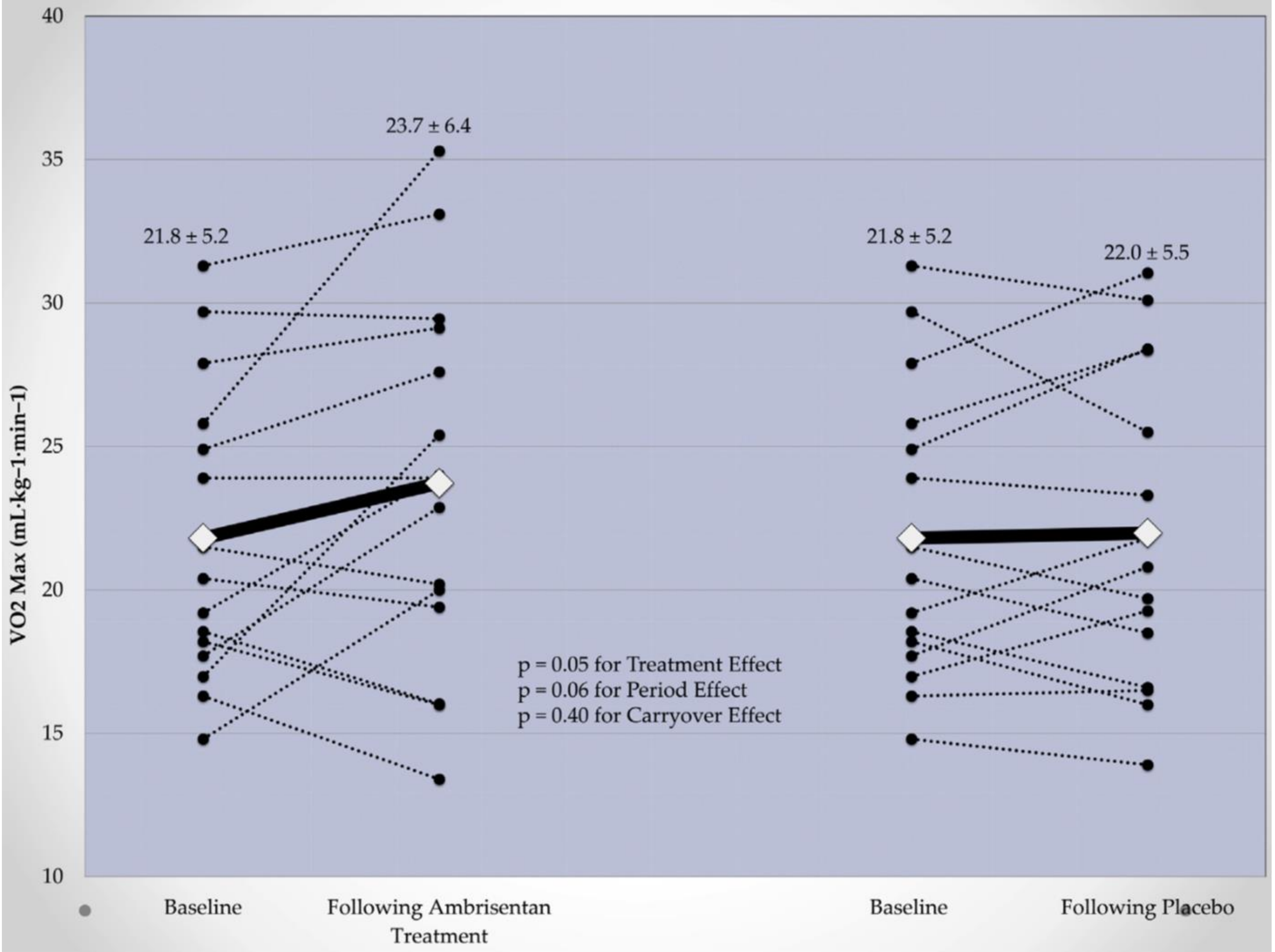


n=69, mean age 20 +/-7 years
14 weeks of treatment
Increase in VO2 max +1.4 ml/kg/min (~+5%)
Improved endurance +24 seconds
Reduced NT-proBNP
Improved FC in 9/32 Rx, 0/37 controls
No change in QoL (SF-36)

Effect of *Ambrisentan* on Exercise Capacity in Adult Patients After the Fontan Procedure

Ari M. Cedars, MD[a,*], Joshua Saef, MD[b], Linda R. Peterson, MD[b], Andrew R. Coggan, PhD[b], Eric L. Novak, MA[b], Debra Kemp, RN[b], and Philip A. Ludbrook, MD[b]

AmJ Card 2016



n=19, aged 18-35 years
8 with reduced systolic function
Randomised to ambrisentan or placebo12 weeks
Improved VO2 max and Ve/VO2

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ERAs; *Studies in Fontan patients*

Endothelin inhibitors lower pulmonary vascular resistance and improve functional capacity in patients with Fontan circulation

Gabriella Agnoletti, PhD,[a] Simona Gala, MD,[a] Francesca Ferroni, MD,[a] Roberto Bordese, MD,[a] Lorenzo Appendini, MD,[b] Carlo Pace Napoleone, MD,[c] and Laura Bergamasco, PhD[b]

All had PVRi>2 Woods units

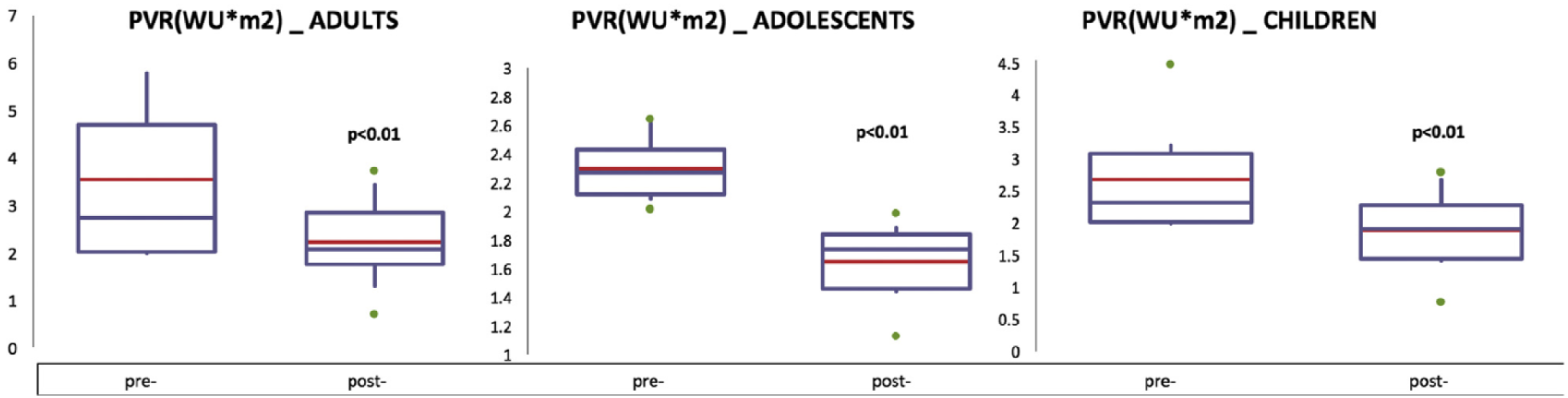
6 children (9 yo)

8 adolescents (17 yo)

7 adults (26 yo)

Bosentan in under 18, macitentan in adults

6/12 treatment



Reduced PVR in >70% of subjects

Improved FEV1 and FVC in under 18s

Adolescents and adults increase cardiac output

JTCVS 2017;153:1468

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Combination therapy; *Studies in Fontan patients*

Sildenafil reduces pulmonary vascular resistance in single ventricular physiology

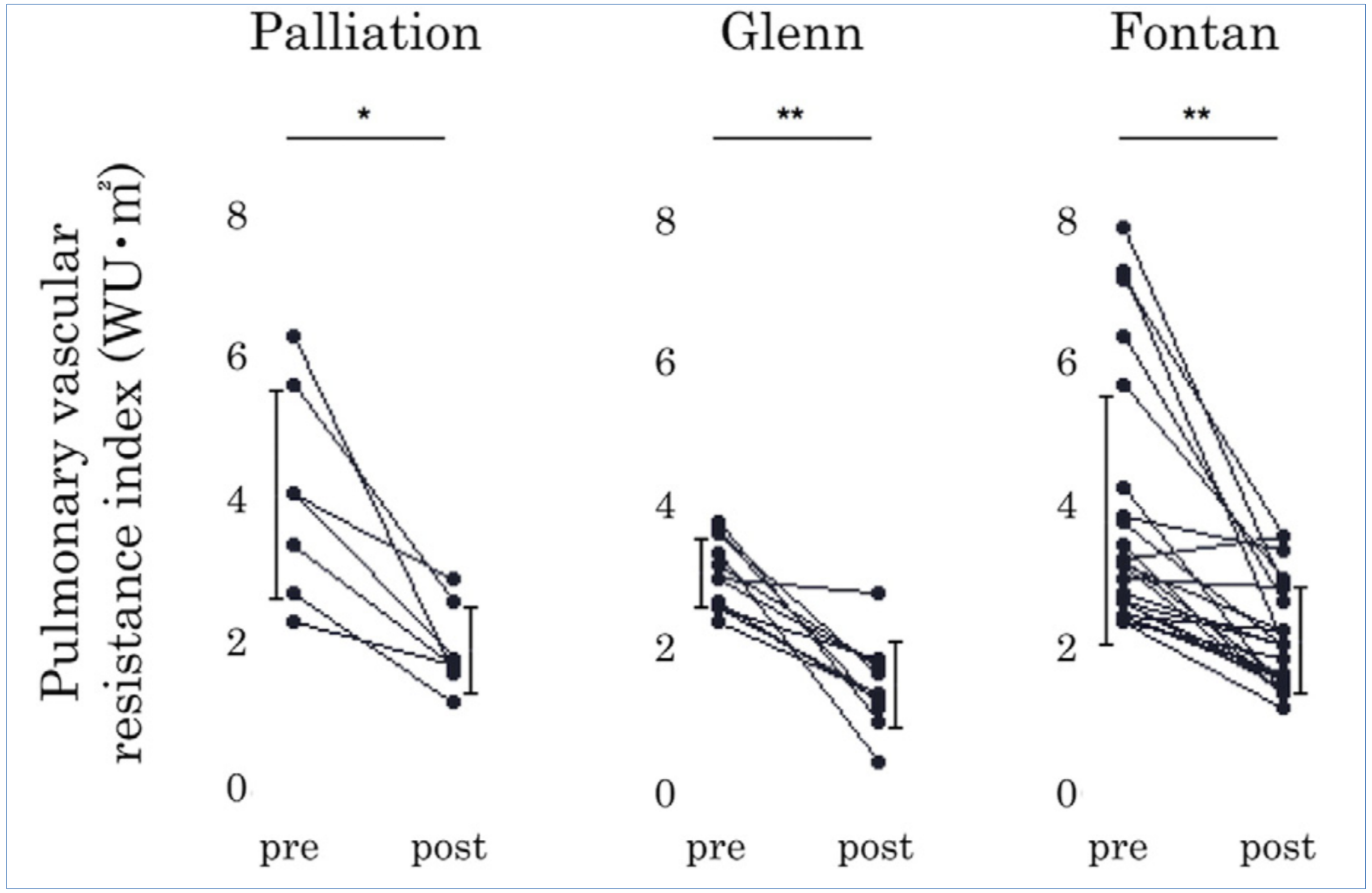
Hiroki Mori, In-Sam Park, Hiroyuki Yamagishi, Makoto Nakamura, Shiro Ishikawa, Kiyohiro Takigiku, Satoshi Yasukochi, Tomotaka Nakayama, Tsutomu Saji, Toshio Nakanishi *

Baseline characteristics.

	ALL (n = 42)	Group 1 (n = 7)	Group 2 (n = 11)	Group 3 (n = 24)
Medical therapy				
Furosemide	20	3	4	13
Spironolactone	21	2	4	15
Trichlormethiazide	2	0	0	2
ACE inhibitors/ARB	16	2	4	10
Carvedilol	3	0	2	1
Digoxin	5	0	0	5
Aspirin	20	3	8	9
Warfarin	8	1	3	4
Anti-arrhythmia drug	1	0	0	1
Bosentan	4	0	1	3
Beraprost sodium	8	1	2	5
Home oxygen therapy	6	0	5	1

Group 1 shunted; mean 1 year old
Group 2 Glenn; mean 7 years old
Group 3 Fontan; mean 13 years old

Children
PVR >2.5 WU
Sildenafil added to Rx



Significant fall in PVR in all 3 groups

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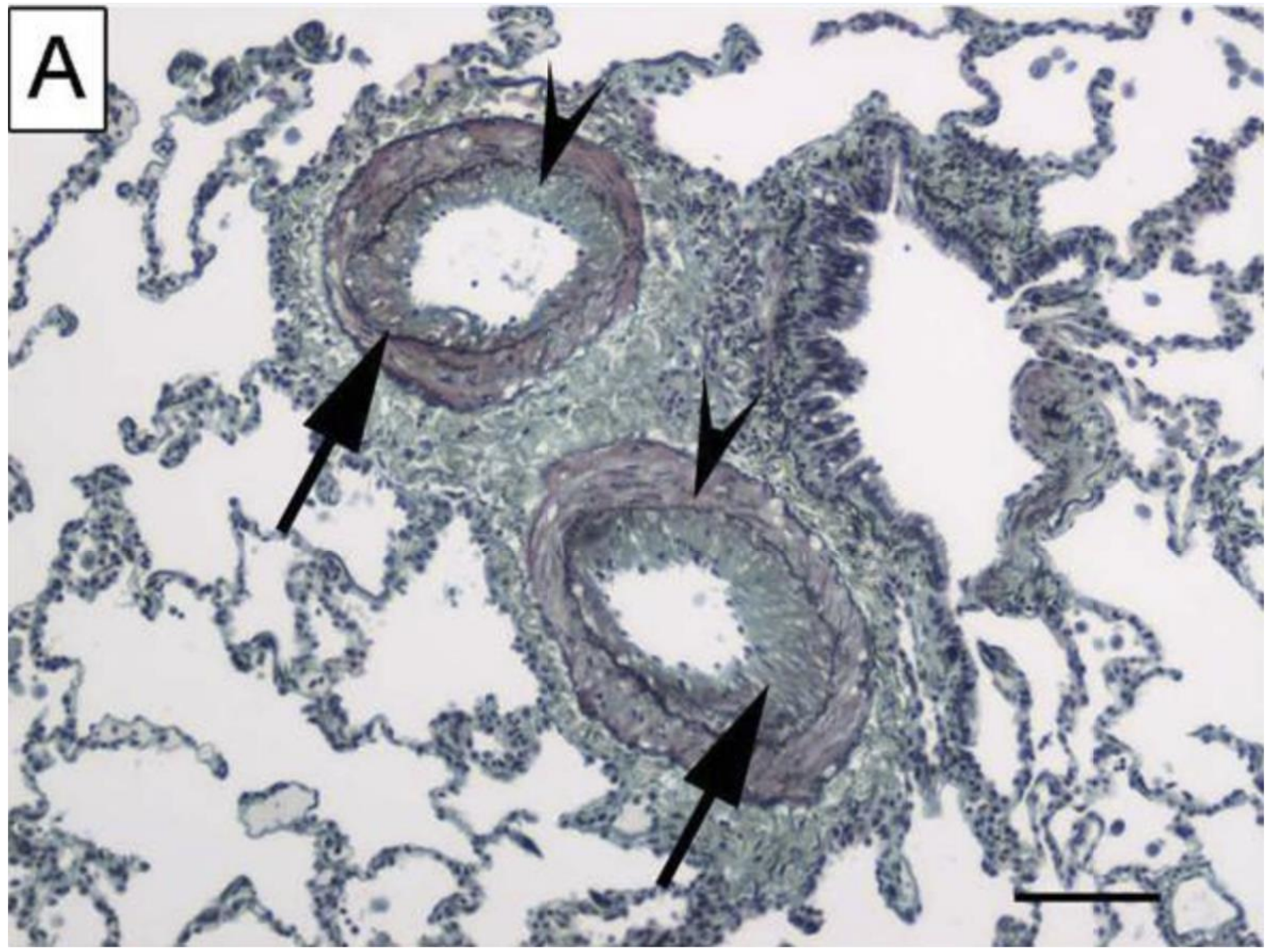
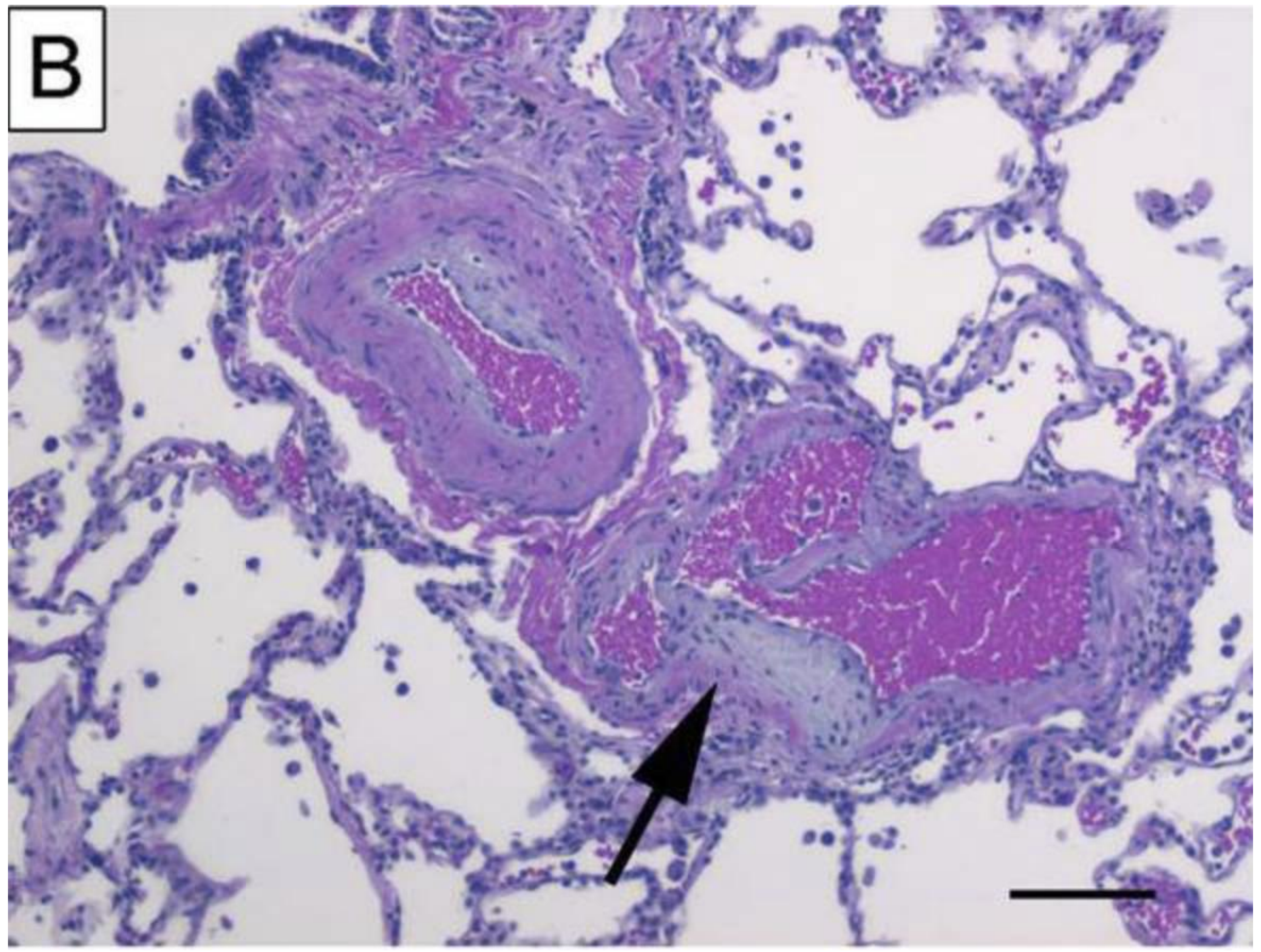
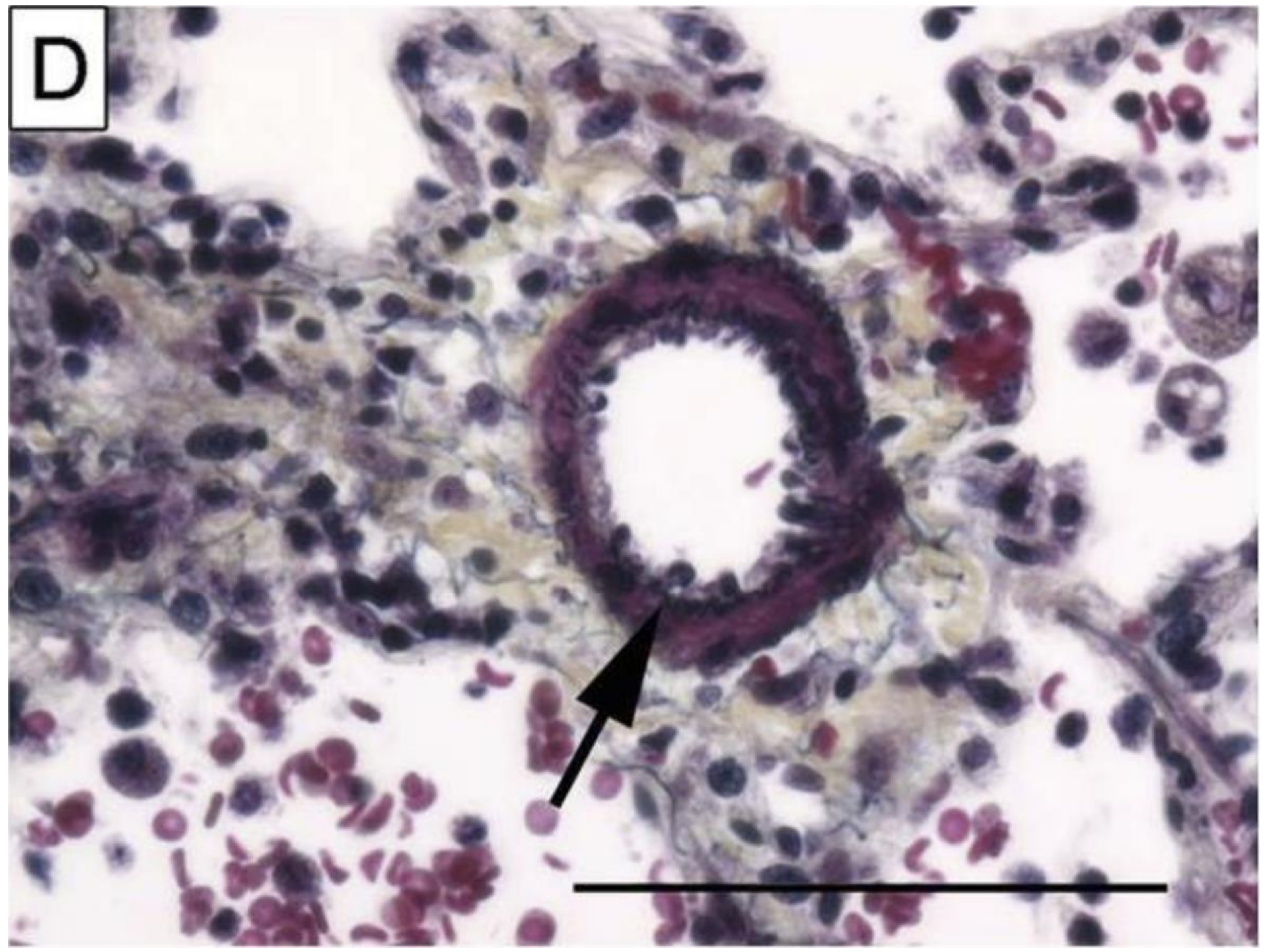
IPAH; *histology*



Thickened intima and media

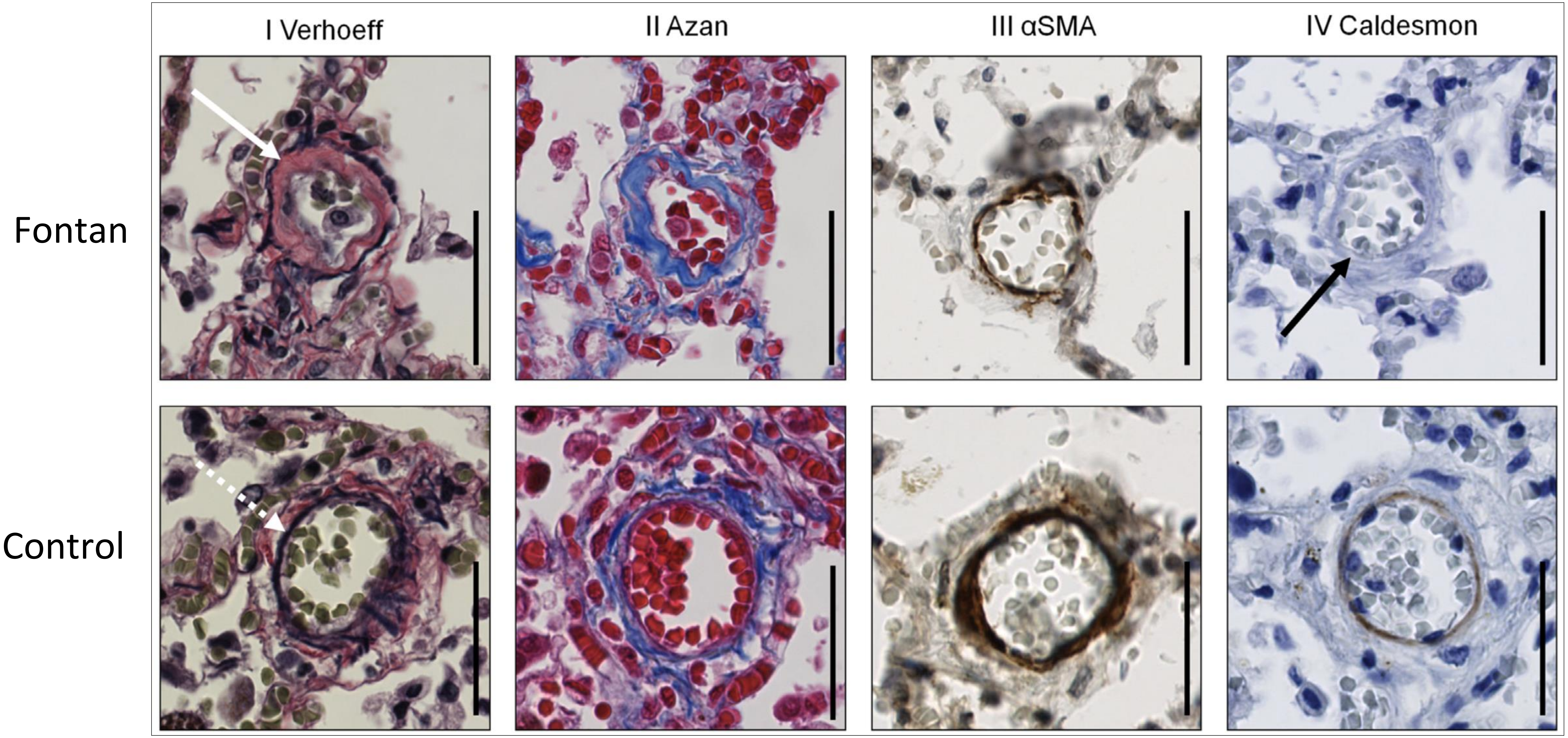


Eccentric intimal thickening

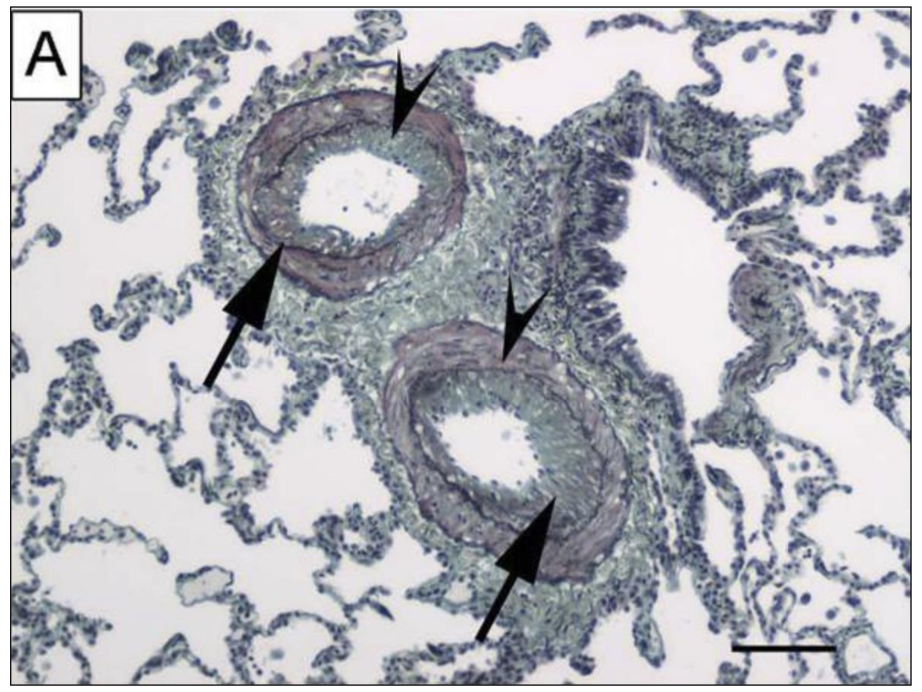


Muscularised small artery

Histology of vessels; *postmortem lung specimens*



PAH



Thicker walls

More collagen

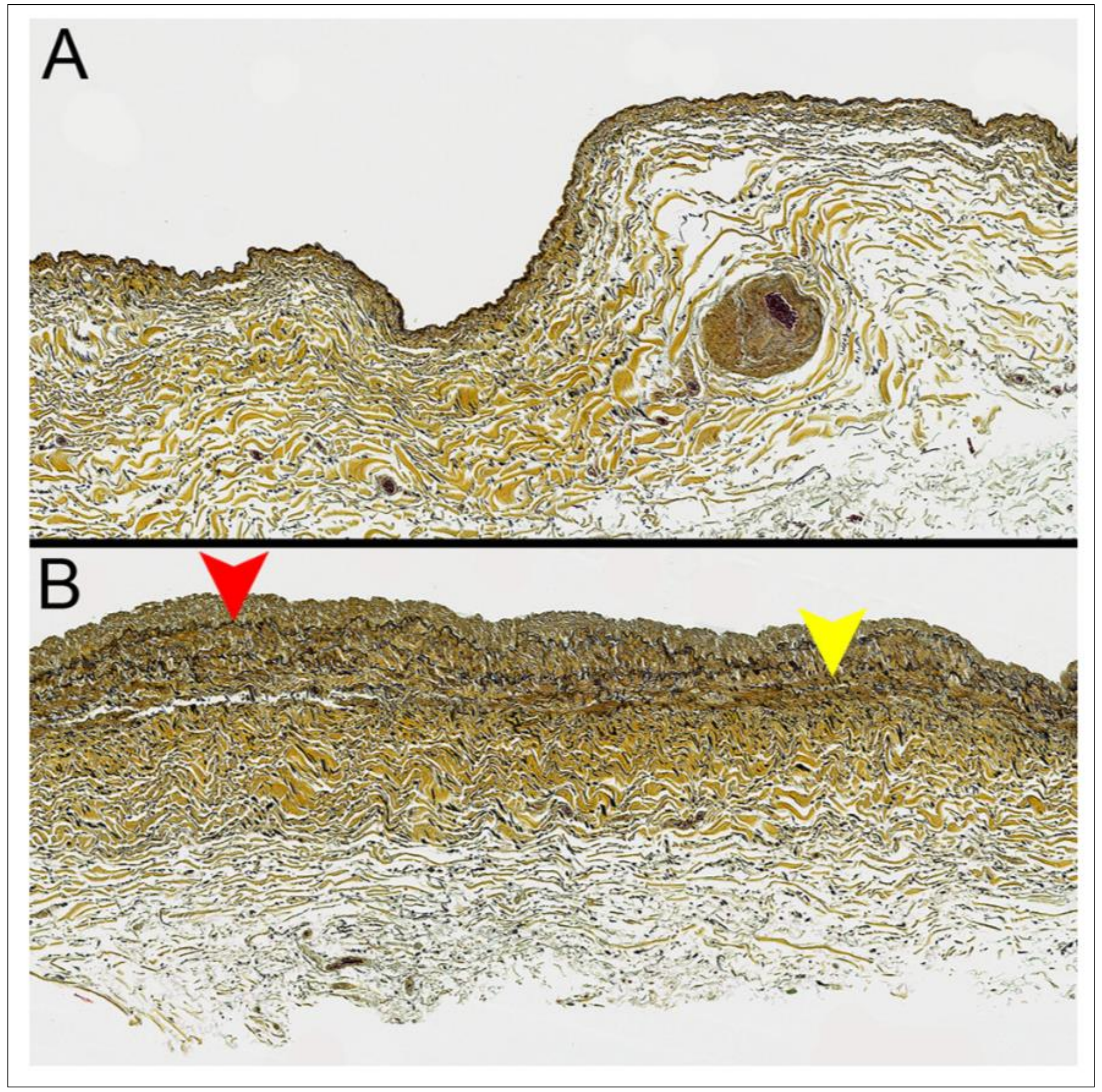
Thin layer of actin

Minimal smooth muscle

Intrapulmonary arteries of Fontan patients (aged 20-35 years)
Acellular fibrosis with collagen deposition

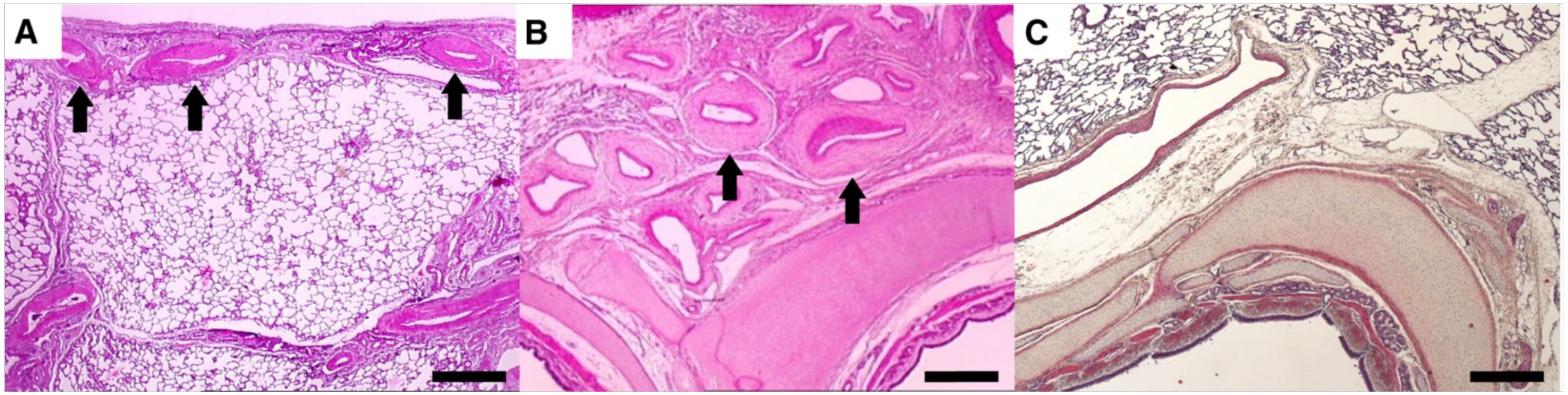
Ridderbos JHLTx 2015

Histology of vessels; *pulmonary veins*



Pulmonary veins humans
A control
B Fontan; fibromuscular intimal proliferation and medial muscularisation (yellow arrow)
Hays et al Heart 2017

Low flow lung
Control lung



Pulmonary veins; pig model of low flow
A subpleural venous hyperplasia
B venous hyperplasia between alveolar lobules
C control lung

Henaine et al JTCVS 2013;146:522-9

Summary

Lack of pulsatile/low pulmonary blood flow induces

- endothelial dysfunction
- structural changes arteries and veins
- Changes seem different to pulmonary arterial hypertension with acellular fibrosis and collagen deposition

Variable results of studies

Which patients benefit and why?

- Baseline PVR > 2 WU showed greater response to NO *Khambadkone*
- Previously banded patients greater response *Khambadkone*
- 71% of patients had fall in PVR with ERAs, all subjects had baseline PVR > 2 WU *Agnoletti*
- BNP > 100 had greater response to sildenafil *Goldberg*
- VO2 max < 30mL/min/kg had greater response to nebulised prostacyclin *Rhodes*
- Perhaps improved Ve/VCO2 is opening capillaries and improving V/Q mismatch? *Goldberg*
- Is some of the effect is in altering systemic vascular resistance? *Van De Bruane*

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