Nuove frontiere nella terapia dell'ipertensione arteriosa polmonare: al di là dei farmaci

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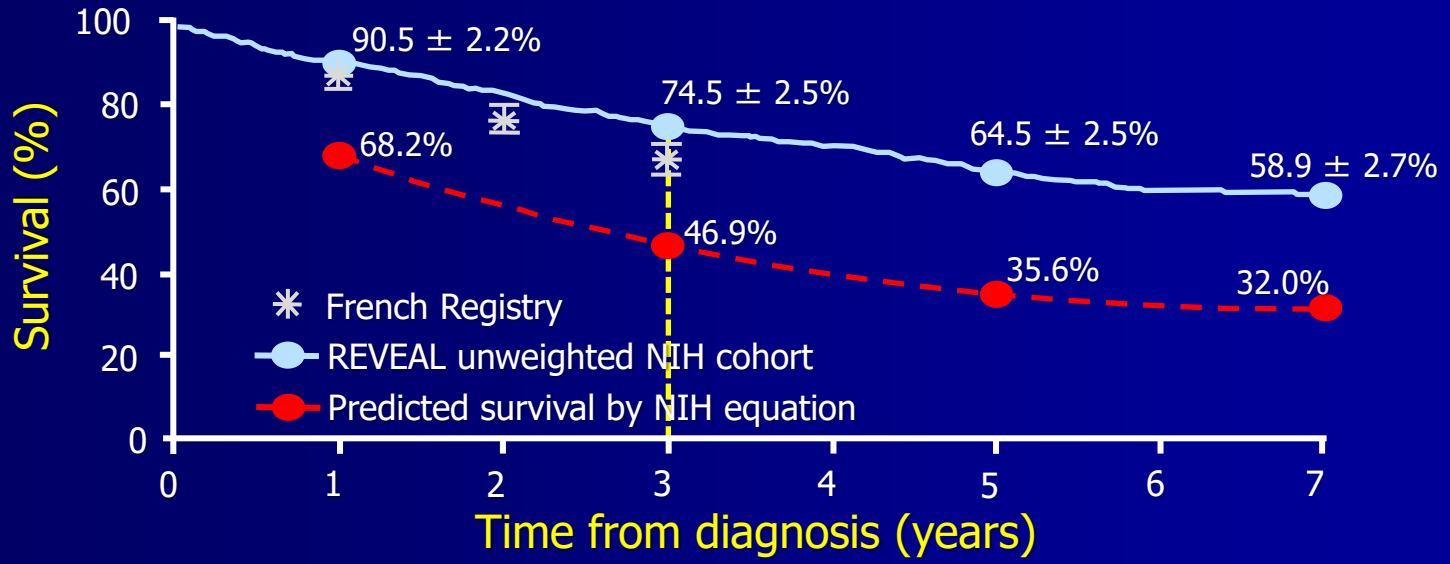
Disclosure information last 5y
Michele D'Alto, MD, PhD, FESC, FACC

Member of advisory board:
Actelion-Janssen, Bayer, GlaxoSmithKline, Merck Sharp and Dohme, United Therapeutics.

Speaker/travel fees:
Actelion-Janssen, Bayer, Boehringer-Ingelheim, Dompè, Ferrer, GlaxoSmithKline, Merck Sharp and Dohme, United Therapeutics.

Although outcome has improved over the past years long-term prognosis remains unsatisfactory



Benza RL, *et al. Chest* 2012

Nuovi farmaci o nuove strategie terapeutiche?

Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension

N. Galiè, J.A. Barberà, A.E. Frost, H.-A. Ghofrani, M.M. Hoeper, V.V. McLaughlin, A.J. Peacock, G. Simonneau, J.-L. Vachiery, E. Grünig, R.J. Oudiz, A. Vonk-Noordegraaf, R.J. White, C. Blair, H. Gillies, K.L. Miller, J.H.N. Harris, J. Langley, and L.J. Rubin, for the AMBITION Investigators*

Initial tadalafil and ambrisentan combination therapy in pulmonary arterial hypertension: cLinical and haemodYnamic long-term efficacy (ITALY study)

Michele D'Alto[a], Emanuele Romeo[a], Paola Argiento[a], Giuseppe Paciocco[b], Renato Prediletto[c], Stefano Ghio[d], [illegible]hele Correale[e], Francesco Lo Giudice[f], Roberto Badagliacca[g], Alessa[illegible]co[d] and Carmine Dario Vizza[g]

Hemodynami[illegible] assessment 2 years after the initiation [illegible] upfront ambrisentan–tadalafil in pulmonary arterial hypertension

Michele D'Alto, MD, PhD,[a,b] Roberto Badagliacca, MD, PhD,[b,c] Francesco Lo Giudice, MD, PhD,[b,d] Paola Argiento, MD, PhD,[a,b] Gavino Casu, MD,[b,e] Marco Corda, MD,[b,f] [illegible]chele Correale, MD,[b,g] Stefano Ghio, MD,[b,h] Alessandr[illegible][b,h] Mariangela Lattanzio, MD,[b,i] Valentina Mercurio, MD, [illegible]ciocco, MD, PhD,[b,k] Silvia Papa, MD,[b,c] Renat[illegible] MD,[b,l] Emanuele Romeo, MD, PhD,[a,b] Maria Giovanna Russo, MD, [illegible] Alessandro Tayar, MD,[d] Patrizio Vitulo, MD, PhD,[b,m] Carmine Dario Vizza, MD, PhD,[b,c] Paolo Golino, MD, PhD,[a] and Robert Naeije, MD, PhD[n]

Risk Reduction and Right Heart Reverse Remodeling by Upfront Triple Combination Therapy in Pulmonary Arterial Hypertension

Michele D'Alto, MD, PhD; Roberto Badagliacca, MD, PhD; Pa[illegible]nto, MD, PhD; Emanuele Romeo, MD, PhD; Andrea Farro, MD; Silvia Papa, MD; Berardo Sarubbi[illegible] Giovanna Russo, MD; Carmine Dario Vizza, MD, PhD; Paolo Golino, [illegible]aeije, MD, PhD

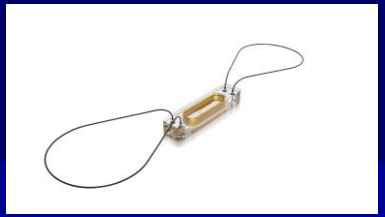
Influence of various therapeutic strategies on right ventricular morphology, function and hemodynamics in pulmonary arterial hypertension

Roberto Badagliacca, MD, PhD,[a] Amresh Raina, MD,[b] Stefano Ghio, MD,[c] Michele D'Alto, MD,[d] Marco Confalonieri, MD,[e] Michele Correale, MD,[f] Marco Corda, MD,[g] Giuseppe Paciocco, MD,[h] Carlo Lombardi, MD,[i] Massimiliano Mulè, MD,[j] Robe[illegible]ia, MD,[a] Laura Scelsi, MD,[c] Paola Argiento, MD,[d] S[illegible] MD,[a] Raymond L. Benza, MD,[b] and Carmine Dario Vizza, [illegible]

Upfront combination therapy reduces right ventricular volumes in pulmonary arterial hypertension

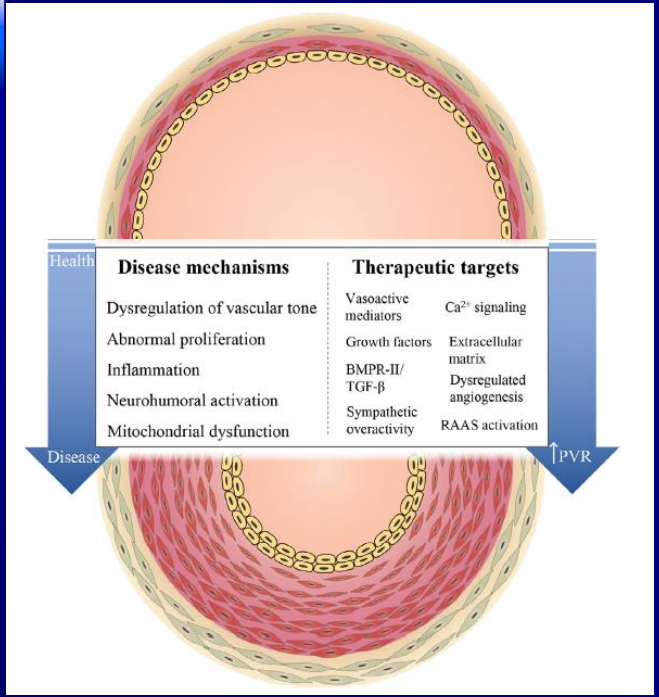
Mariëlle C. van de Veerdonk[1,2], Anna E. Huis in t Veld[1], J. Tim Marcus[3], Nico Westerhof[1], Martijn W. Heymans[4], Harm-Jan Bogaard[1] and Anton Vonk-Noordegraaf[1]

Agenda



- ~~Rehabilitation~~
- ~~Continuous PAP monitoring system~~
- Pulmonary artery denervation (PADN)
- Right-to-left shunt: atrial flow regulator (AFR), Potts, PDA stenting

The role of sympathetic nervous system activation (SNA)



A Constantine et al, Trends in Cardiovasc Med 2021;31:252–260

Major drivers of PAH:
- Endothelial dysfunction
- PA smooth muscle proliferation
- Vasoconstriction

As pulmonary vascular disease progresses…
compensatory **activation** of:
- **sympathetic nervous system**
- **renin-angiotensin-aldosterone-system**

B-blockers
RAAS drugs

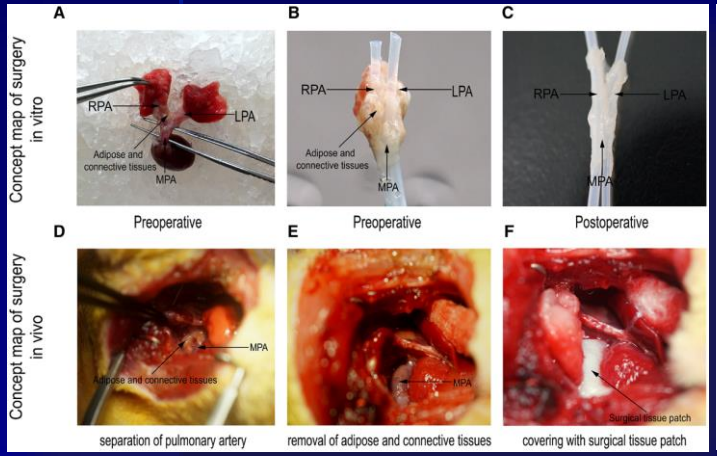
35 male rats
(Sprague Dawley)

Transthoracic Pulmonary Artery Denervation for Pulmonary Arterial Hypertension

Sympathetic Nerve Distribution and Pulmonary Artery Remodeling

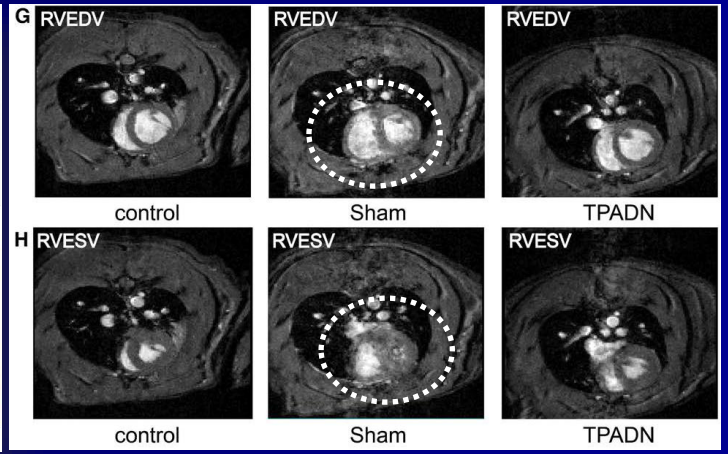
Yuan Huang, Yi-Wei Liu, Hai-Zhou Pan, Xiao-Ling Zhang, Jun Li, Li Xiang, Jian Meng, Pei-He Wang, Jun Yang, Zhi-Cheng Jing, Hao Zhang

Arterioscler Thromb Vasc Biol. 2019;39:704-718



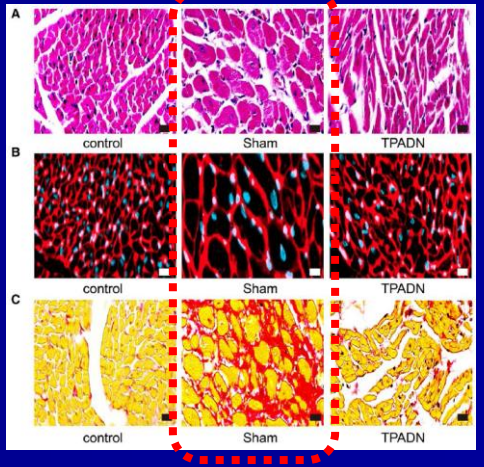
Technique

PAH



PA denervation reduced RV volumes

PAH

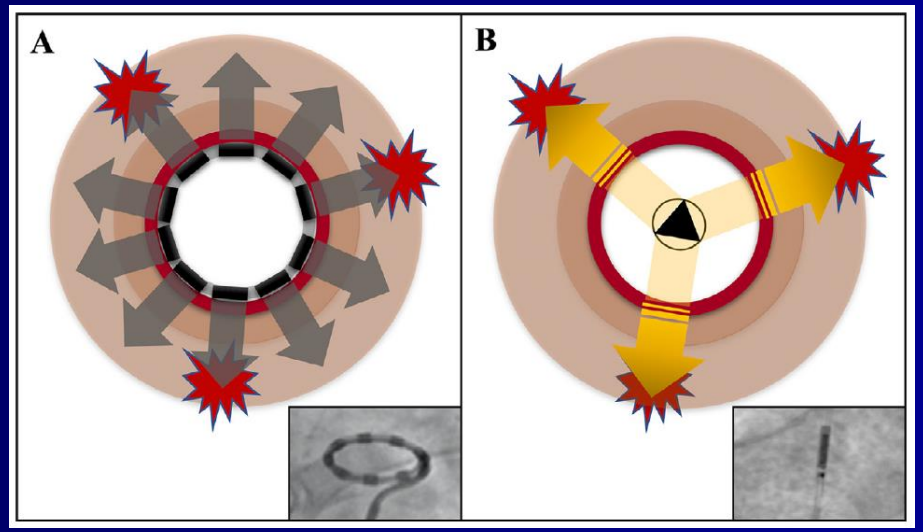


PA denervation attenuated RV hypertrophy and fibrosis

- **Better effort tolerance**
- **Better haemodynamics**

Interventional options for pulmonary artery denervation (PADN)

Catheter-based approaches



radiofrequency ablation

high-energy endovascular ultrasound

A Constantine et al, Trends in Cardiovasc Med 2021

Circulation: Cardiovascular Interventions
Volume 10, Issue 10, October 2017
https://doi.org/10.1161/CIRCINTERVENTIONS.117.005812

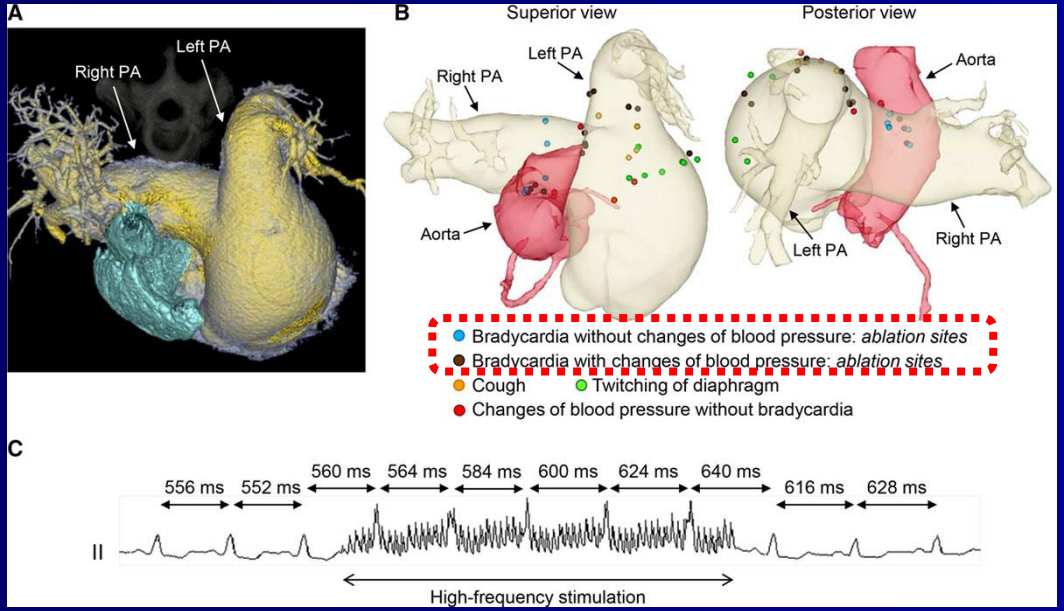
CASE REPORTS IN INTERVENTIONAL CARDIOLOGY

Pulmonary Artery Denervation by Determining Targeted Ablation Sites for Treatment of Pulmonary Arterial Hypertension

Taishi Fujisawa, MD, Masaharu Kataoka, MD, Takashi Kawakami, MD, Sarasa Isobe, MD, Kazuaki Nakajima, MD, Akira Kunitomi, MD, Shin Kashimura, MD, Yoshinori Katsumata, MD, Takahiko Nishiyama, MD, Takehiro Kimura, MD, Nobuhiro Nishiyama, MD, Yoshiyasu Aizawa, MD, Mitsushige Murata, MD, Keiichi Fukuda, MD, and Seiji Takatsuki, MD

Targeting the ablation sites for PADN

High-output burst electric stimulation applied to the pulmonary artery to determine **ablation sites based on the autonomic responses**



Pulmonary Artery Denervation to Treat Pulmonary Arterial Hypertension

The Single-Center, Prospective, First-in-Man PADN-1 Study (First-in-Man Pulmonary Artery Denervation for Treatment of Pulmonary Artery Hypertension)

Shao-Liang Chen, MD,*† Feng-Fu Zhang, MD,* Jing Xu, MD,* Du-Jiang Xie, MD,* Ling Zhou, MD,* Thach Nguyen, MD,‡ Gregg W. Stone, MD§

Nanjing, China; Hobart, Indiana; and New York, New York

JACC 2013

2013: first-in-man experience with PADN

- 13 patients with idiopathic PAH not responding adequately to medical therapy

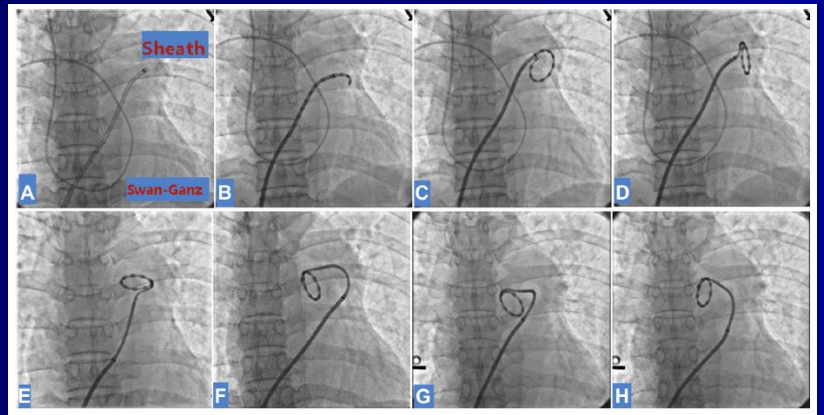


Figure 2 An 8-F Long Sheath Was Inserted Through the Femoral Vein and Advanced to the MPA

- mPAP from 55±5 mmHg to 36±5 mmHg, ($p<0.01$)
- 6MWT from324±21 m to 491±38 m ($p<0.005$)
- Tei index from 0.7±0.04 to 0.50±0.04 ($p<0.001$).

Pulmonary Vascular Disease

OPEN

Hemodynamic, Functional, and Clinical Responses to Pulmonary Artery Denervation in Patients With Pulmonary Arterial Hypertension of Different Causes

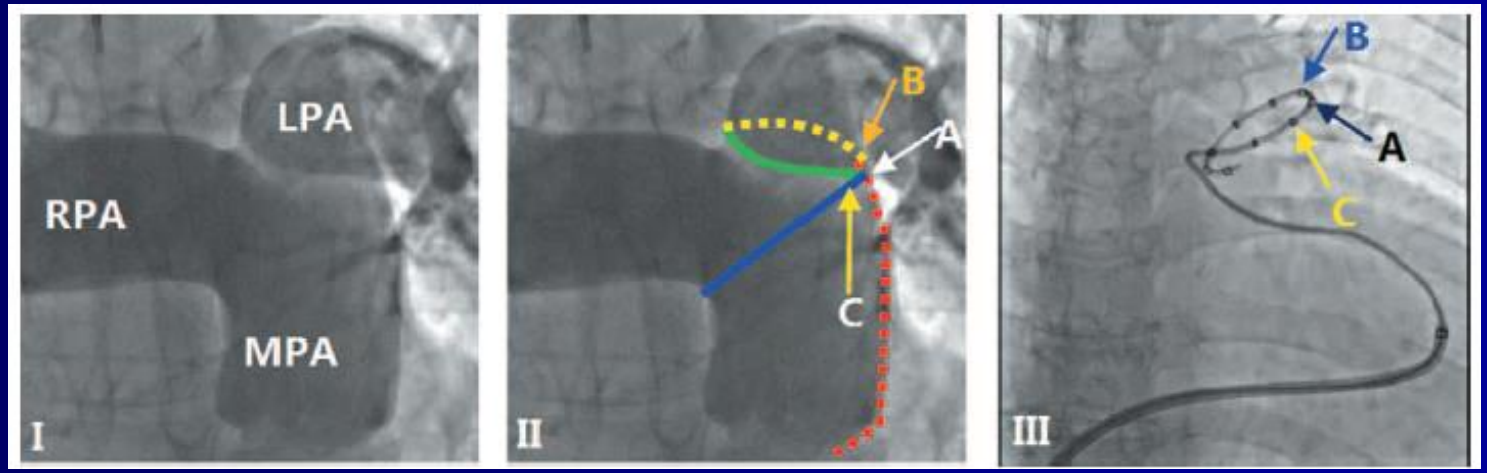
Phase II Results From the Pulmonary Artery Denervation-1 Study

Shao-Liang Chen, MD; Hang Zhang, MD; Du-Jiang Xie, MD; Juan Zhang, MD; Ling Zhou, MD; Alexander M.K. Rothman, MD; Gregg W. Stone, MD

Circ Cardiovasc Interv 2015

PADN for patients with different PH forms

- 66 patients with different forms of PH

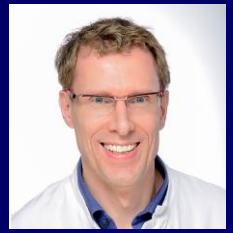


- 94% mPAP reduction >10% (mPAP -7 mmHg)
- Mean 6MWT increase: +95 m

Letter by Hoeper and Galiè Regarding Article, "Hemodynamic, Functional, and Clinical Responses to Pulmonary Artery Denervation in Patients With Pulmonary Arterial Hypertension of Different Causes: Phase II Results From the Pulmonary Artery Denervation-1 Study"

To the Editor:

Hoeper M, Galie N, Circ Cardiovasc Interv 2015



Weaknesses of the study

- Serious **concerns about the withdrawal** of targeted therapies for investigative reasons (unethical!)
- **No control group**
- All-cause **mortality 12%** (procedure? Drugs withdrawal?)
- **Incorrect PH classification** (PAH group II doesn't exist)
- Medications do not meet current standards of care (i.e. **prostacyclin analogues in 89% of Gr2 PH patients**)

Pulmonary Artery Denervation Significantly Increases 6-Min Walk Distance for Patients With Combined Pre- and Post-Capillary Pulmonary Hypertension Associated With Left Heart Failure

The PADN-5 Study

Zang H, JACC Cardiovasc Interv 2015

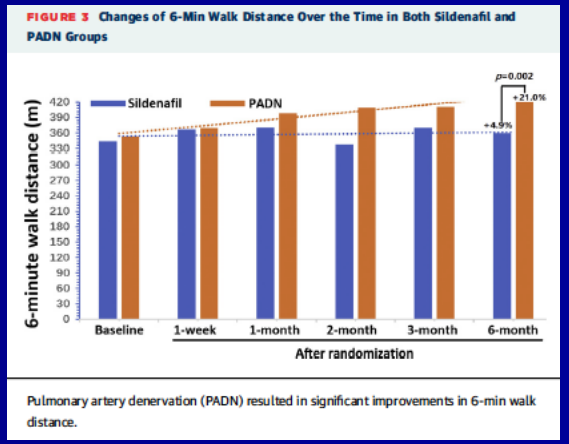
PADN for patients with Combined post and pre-capillary PH (Cpc-PH)

New-onset HF randomized to **PADN + sildenafil** (n = 48) or **sham denervation + sildenafil** (n = 50).

- Exercise capacity improved in PADN+S patients: 6MWD +83 m vs +15 m (p< 0.001).
- Fall in PVR (6.4±3.2 to 4.2 ±1.5WU, p < 0.001)
- Fall in PAWP (22.2±6.6 to 16.1±6.2 mmHg, p = 0.01)

Concerns

- **Acute HF** (HF therapies up-titrated during the follow-up)
- **Sildenafil** is not standard practice (post-capillary PH)
- **Fall in PAWP is difficult to explain**



Pulmonary artery denervation: lights and shadows

- safety and feasibility procedure
- positive (yet not conclusive) signals of efficacy

- carefully designed large multicentre randomized trials
- clarify the technique's mechanisms of action
- how can PADN influence the severe, fixed, obstructive PAH lesions?
- long-term results
- variable degrees of delayed reinnervation (see heart Tx) possible

Reverse Potts shunt or PDA stenting as palliation for severe PAH in childhood: transforming a IPAH in CHD-PAH…

Two boys with supra-systemic PAH (TGA after ASO) and right ventricular failure (4 and 14 yo).

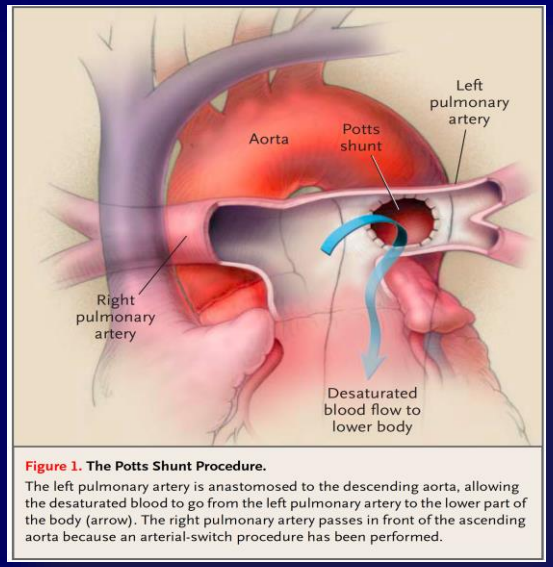
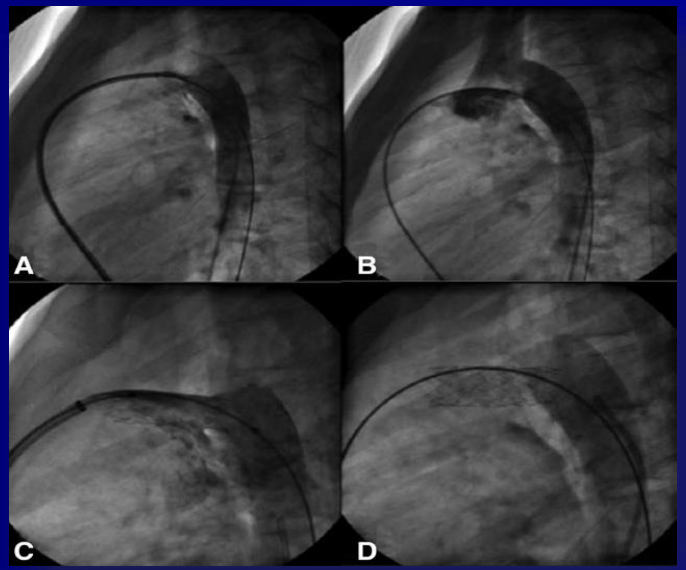


Figure 1. The Potts Shunt Procedure.
The left pulmonary artery is anastomosed to the descending aorta, allowing the desaturated blood to go from the left pulmonary artery to the lower part of the body (arrow). The right pulmonary artery passes in front of the ascending aorta because an arterial-switch procedure has been performed.

Blanc J et al. N Engl J Med 2004;350:623

Three boys with supra-systemic PAH and right ventricular failure (2-9 yo).



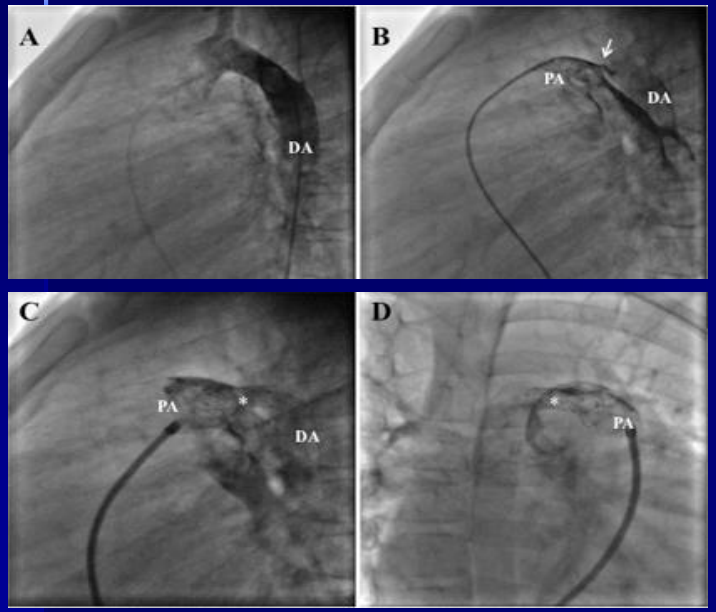
Boudjemline Y et al, Can J Cardiol 2017;33(9):1188-1196

Patent ductus arteriosus stenting for palliation of severe pulmonary arterial hypertension in childhood

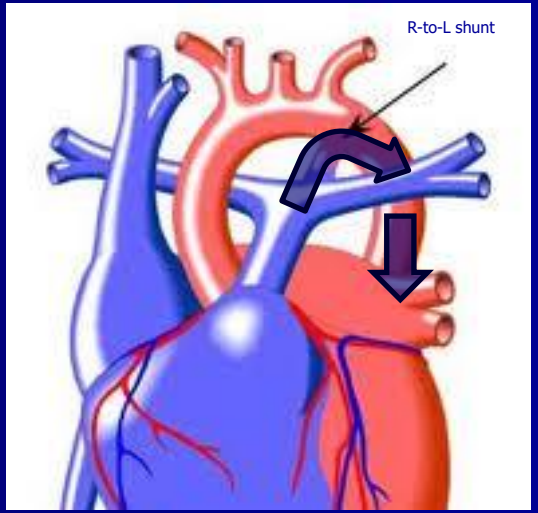
Michele D'Alto,[1] Giuseppe Santoro,[1] Maria T. Palladino,[1] Francesco Parisi,[2] Maria G. Russo[1]

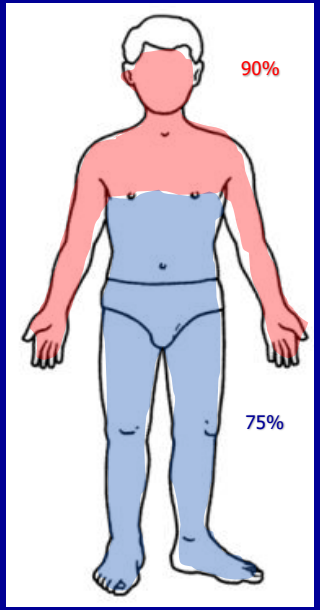
Cardiology in the young, 2015

Tiny PDA (white arrow) with exclusive right-to-left shunt



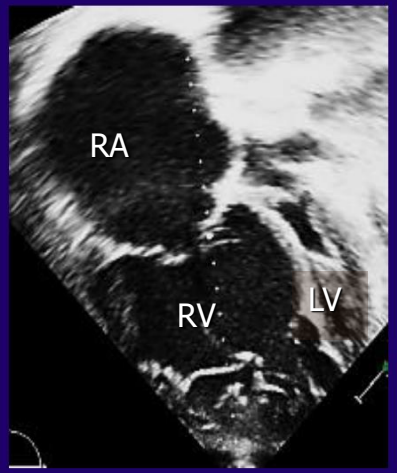
After stent deployment in the arterial duct, a significant increase in right-to-left shunt was obtained.



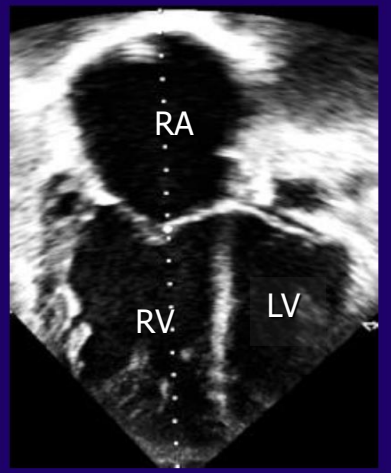


Atrial flow regulator (AFR) device (Occlutech®) in PAH

Pre- AFR



Post- AFR



Modified from J. Vettukattil, Grand rapid, MI, USA

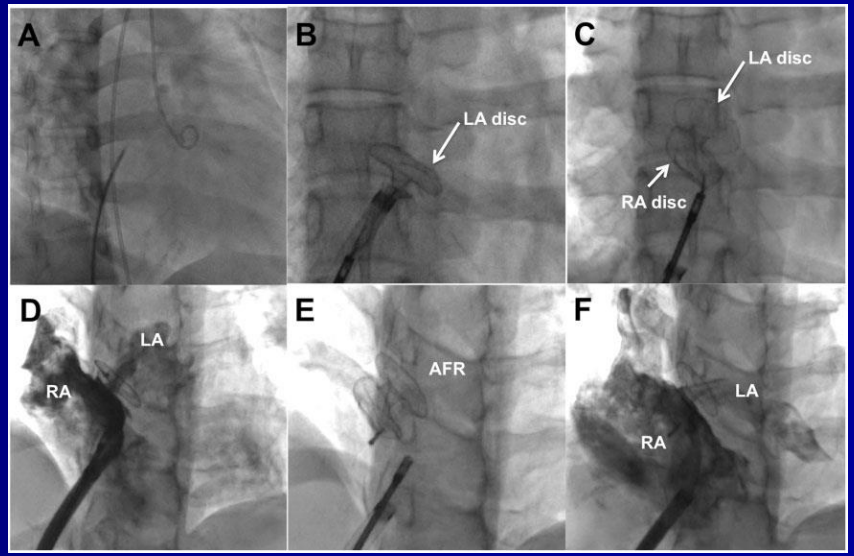
Study of the effect of Occlutech Atrial Flow Regulator on symptoms, hemodynamics, and echocardiographic parameters in advanced pulmonary arterial hypertension

Kothandam Sivakumar, Gopalavilasam R. Rohitraj, Monica Rajendran and Nithya Thivianathan
Department of Pediatric Cardiology, Institute of Cardio Vascular Diseases, Madras Medical Mission, Chennai, India

Pulmonary Circulation 2021;11(1):1–10

- **39 PAH patients (9 children)**
  - 34/39 **syncope**
  - 27/39 **right-heart failure**
- **No procedural complications**
- 37 months follow-up

- **6MWD** increased (310±58 vs 376±182)
- **None developed syncope**
- **SpO_2** reduced (96±6% vs 92±5%)
- **RAP** reduced (9.5 vs 6.9 mmHg)
- **CI** increased (2.4±0.8 vs 3.0±1.0 L/min/m^2)



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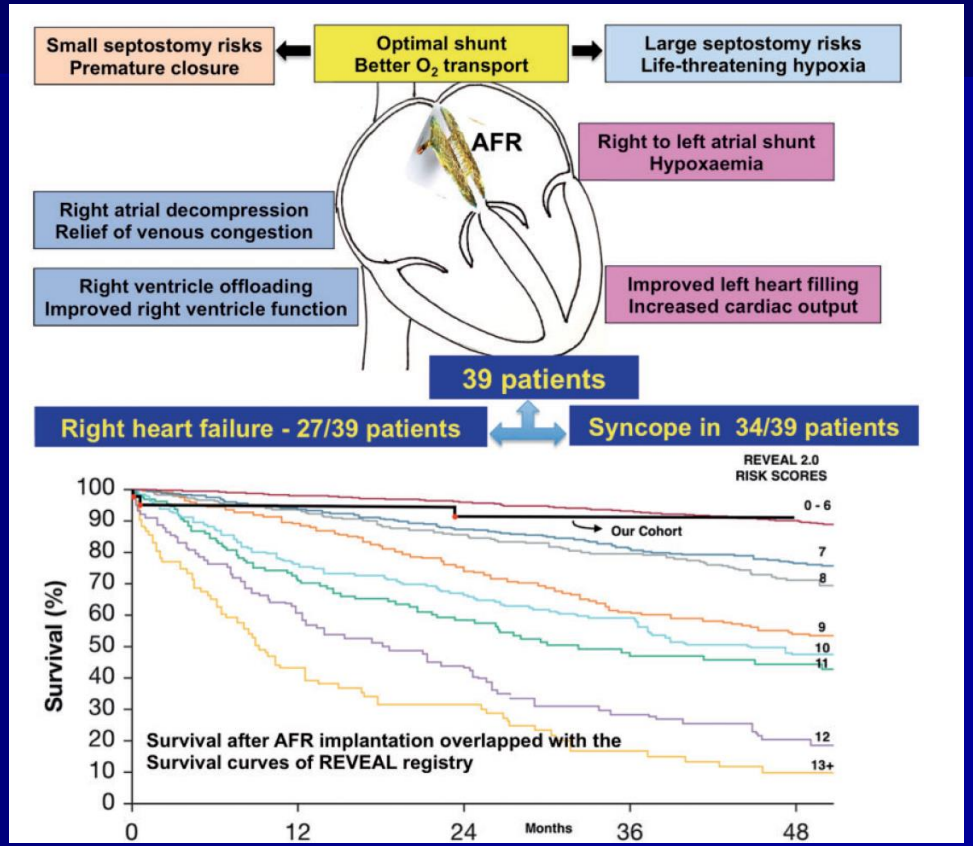

REVEAL score < 6 4/39 patients	• Predicted 1-year survival - 93% • Actual survival post AFR at 27 months: 100%(4/4)
REVEAL score 6-12 29/39 patients	• Predicted 1-year survival - 70% • Actual survival post AFR at 27 months:100%(29/29)
REVEAL score >12 6/39 patients	• Predicted 1-year survival - 40% • Actual survival post AFR at 27 months: 50%(3/6)

Potts shunt and AFR device in PAH

- Surgical and percutaneous **Potts shunt** leads to a significant desaturation of the lower limbs (**brain circulation oxygenation preserved**).
- **Percutaneous Potts shunt needs a PDA** (complications with covered stents in absence of PDA).

- **AFR** offers a **safe and controlled septostomy** in adults and children.
- Patients show **acute benefits** in symptoms, RV function haemodynamics and survival.

- **Early implantation is better** than high-risk procedures at a very advanced stage (timing!!!).


The Future
NEXT EXIT


New
techniques