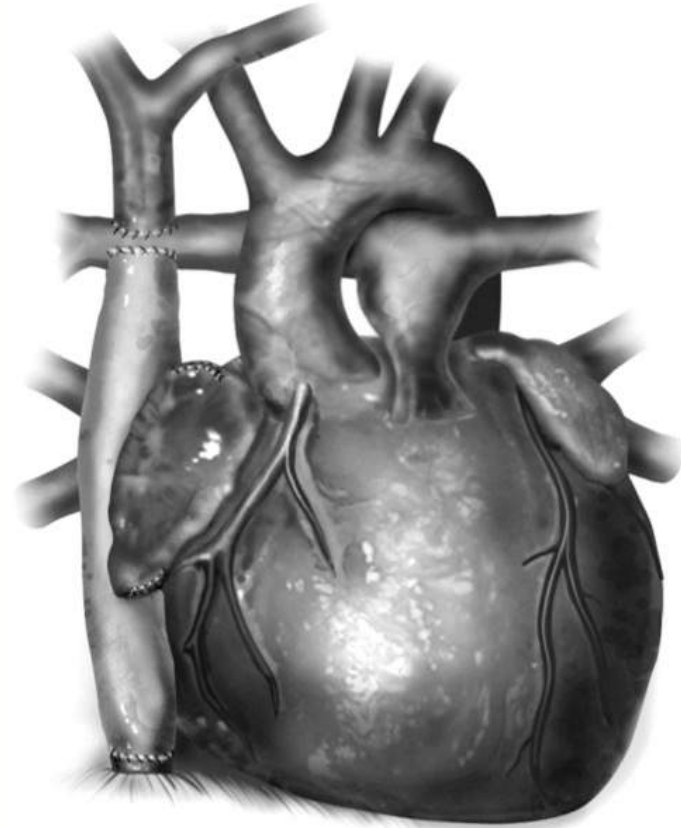


DOES PULMONARY VASODILATION IMPACT THE FONTAN CIRCULATION?

David J. Goldberg
Children's Hospital of Philadelphia
February 25, 2023



Yes

THANK YOU!



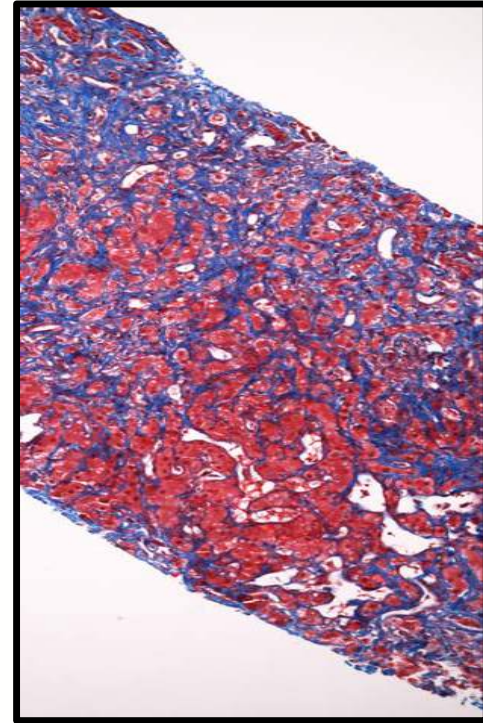
DISCLOSURES

The FUEL trial was conducted by the Pediatric Heart Network, funded by NIH / NHLBI, with financial support from the sponsor, Mezzion Pharma Co. Ltd.

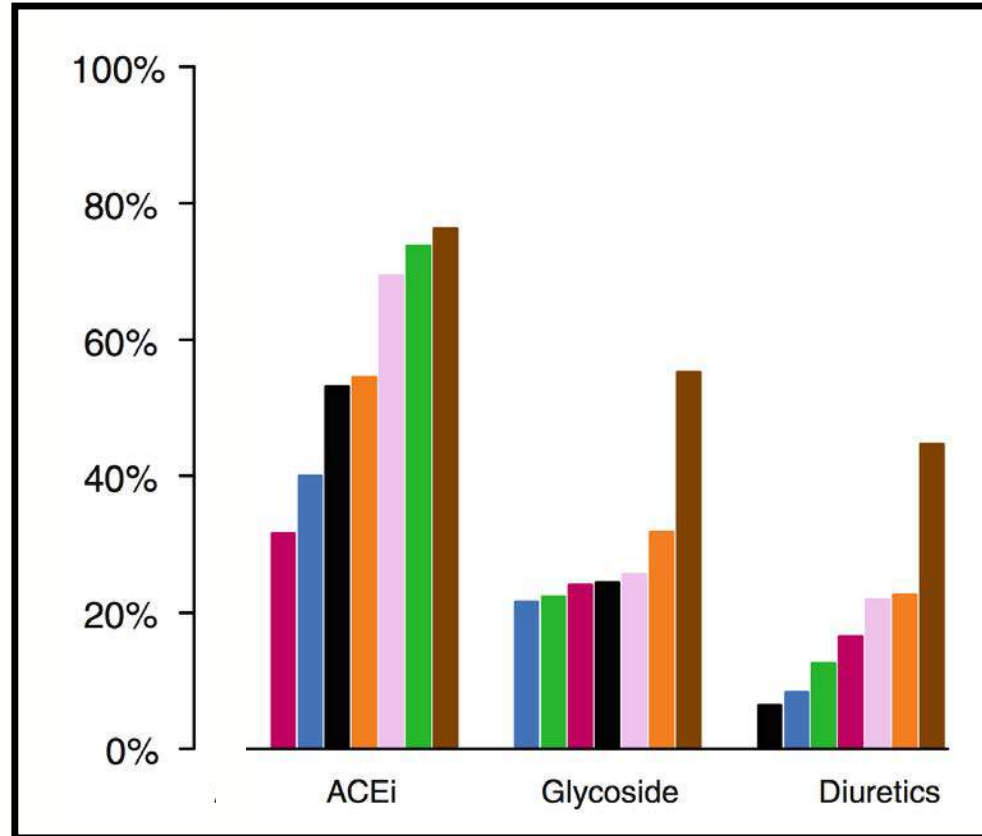
The off-label use of vasodilators will be discussed

Co-inventor on patents regarding the use of udenafil in adolescents who have undergone Fontan palliation

NEED FOR MEDICAL THERAPY



FONTAN MEDICAL THERAPY



FLUID DYNAMICS

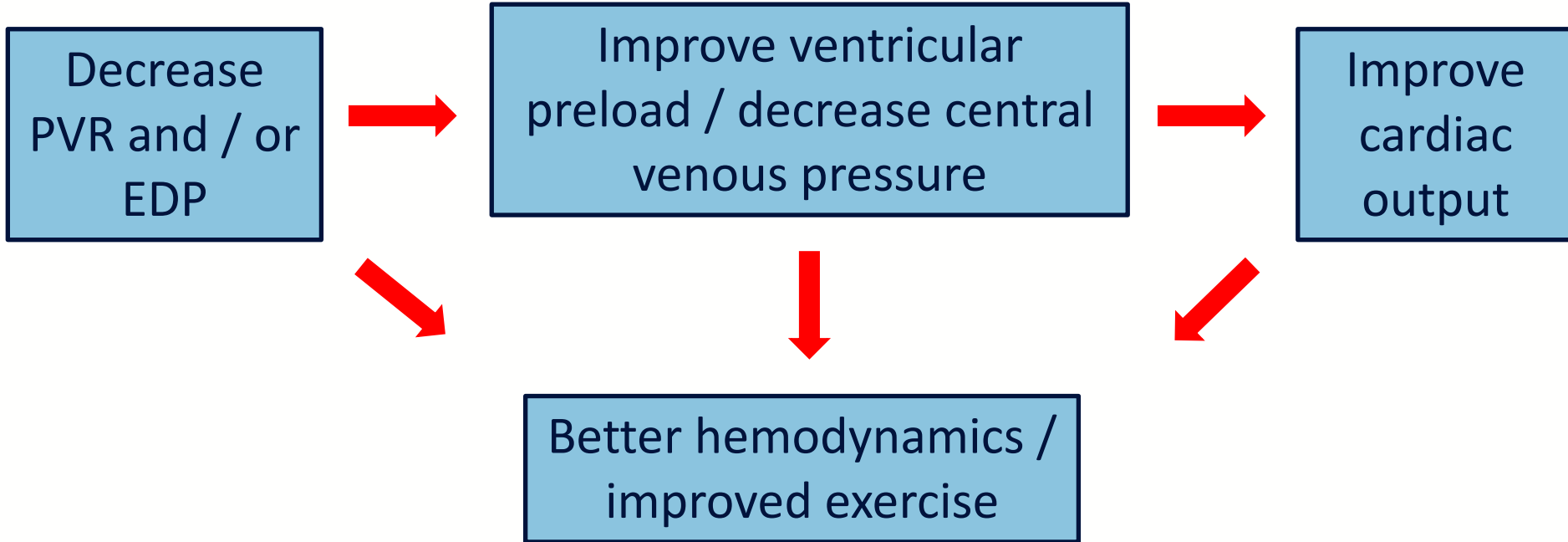


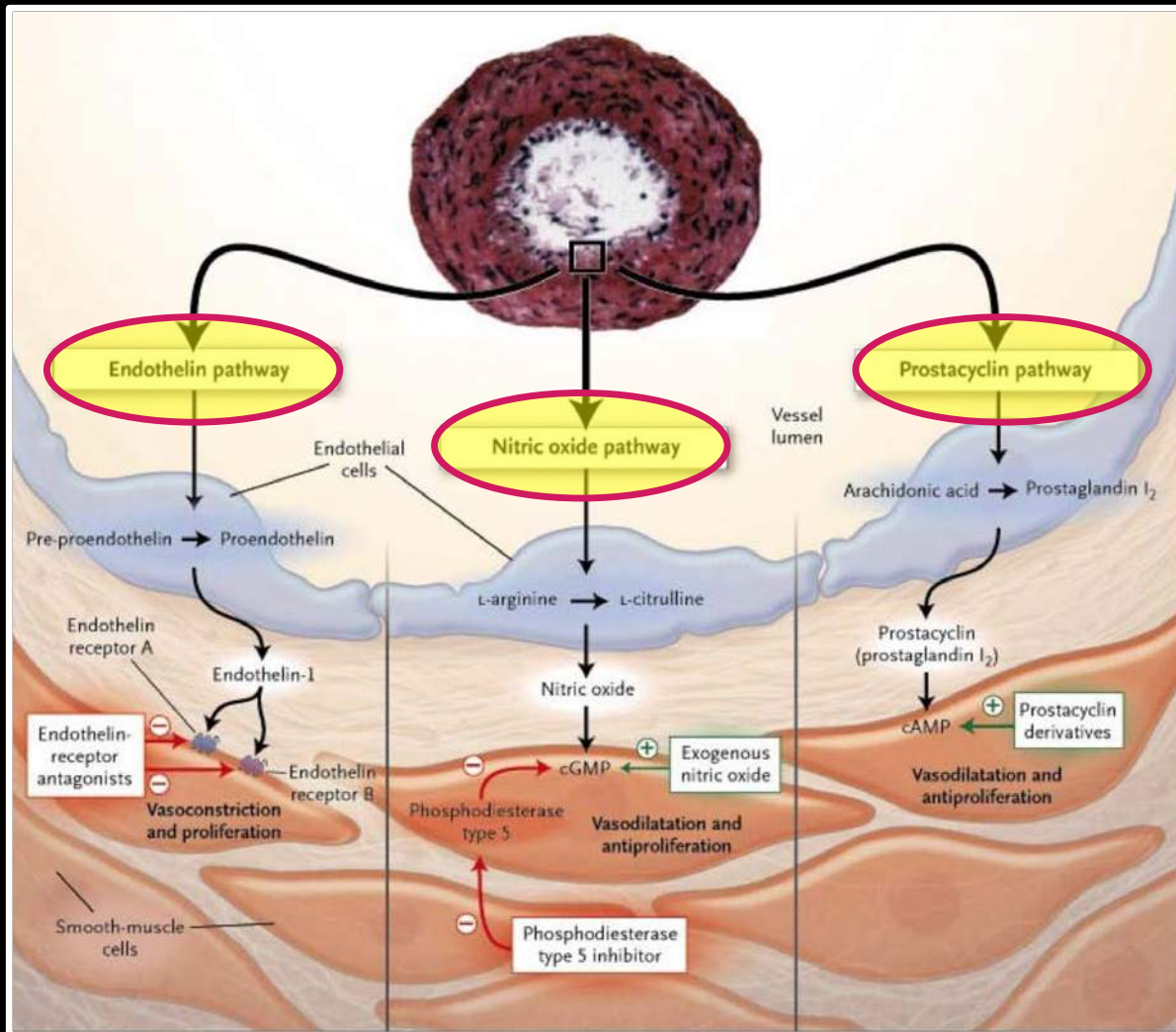
Jean Léonard Marie Poiseuille (1797-1869)

$$R_p = \Delta P / Q_p$$

$$\downarrow R_p = \downarrow \Delta P / \uparrow Q_p$$

FONTAN MEDICAL THERAPY





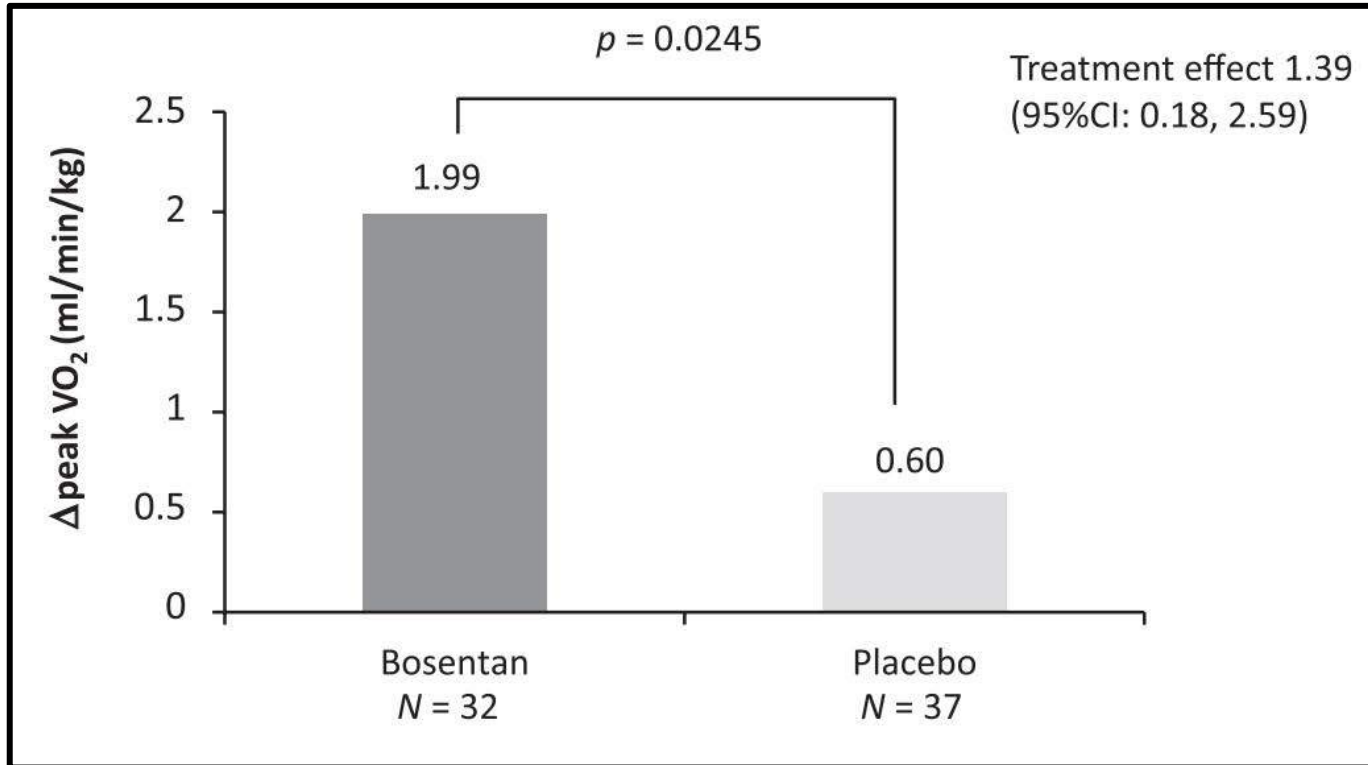
Humbert, et al
Treatment of
Pulmonary Arterial
Hypertension
New England Journal
of Medicine, 2004

2013 – JONATHAN RHODES (N=18)

Effect of iloprost on indices of aerobic function (outlier excluded).

Exercise parameter	Median (IQR)			p-value
	Placebo	Iloprost	Iloprost-induced change	
Peak O ₂ pulse (mL/b)	10.8 (2.9)	11.8 (3.8)	1.2 (0.9)	0.0002
Peak V _{O2} (mL/kg/min)	27.6 (10.2)	30.2 (8.8)	1.6 (2.0)	0.0040
%Predicted peak V _{O2} (%)	68.6 (18.6)	69.5 (19.8)	3.9 (6.8)	0.0203
Peak work rate (W/kg)	2.1 (1.0)	2.0 (0.8)	0.0 (0.3)	0.7148
V _{O2} at VAT (mL/kg/min)	14.2 (5.9)	16.9 (5.4)	0.4 (2.0)	0.1040

2008 – TEMPO TRIAL (N=75)



2008 – TEMPO TRIAL (N=75)

Bosentan and Anemia

Hemoglobin mmol/L	32	37	<0.0001*
Baseline	9.6 (9.3 to 9.9)	9.5 (9.2 to 9.8)	
EOS	9.3 (9.0 to 9.5)	9.8 (9.5 to 10.1)	
Change*	-0.3 (-0.5 to -0.1) *	0.3 (0.1 to 0.5)*	

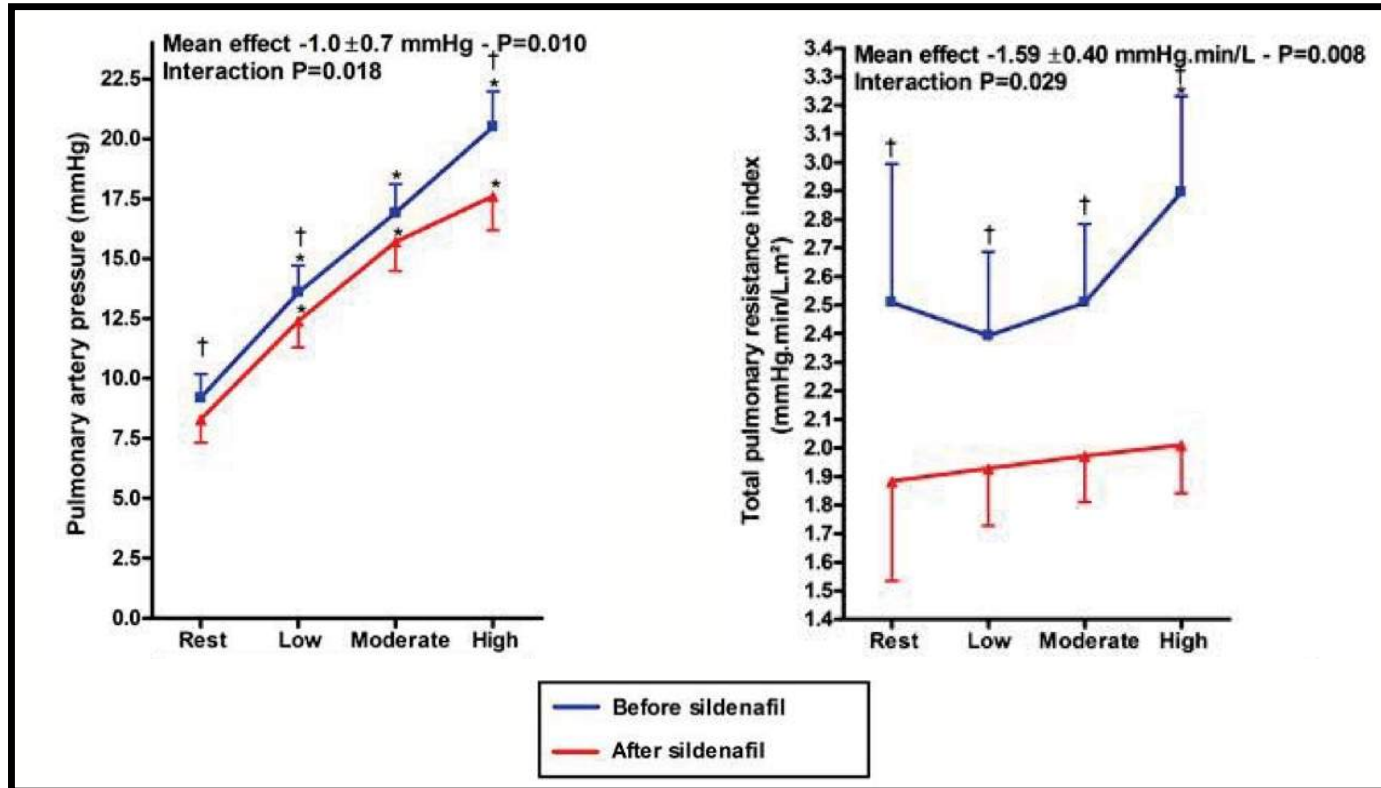
2008 – ALESSANDRO GIARDINI (N=27)

Table 2 Change in cardiopulmonary and haemodynamic variables observed in exercise test nos 2 vs. 3 in the sildenafil treatment and in the control group at each exercise stage

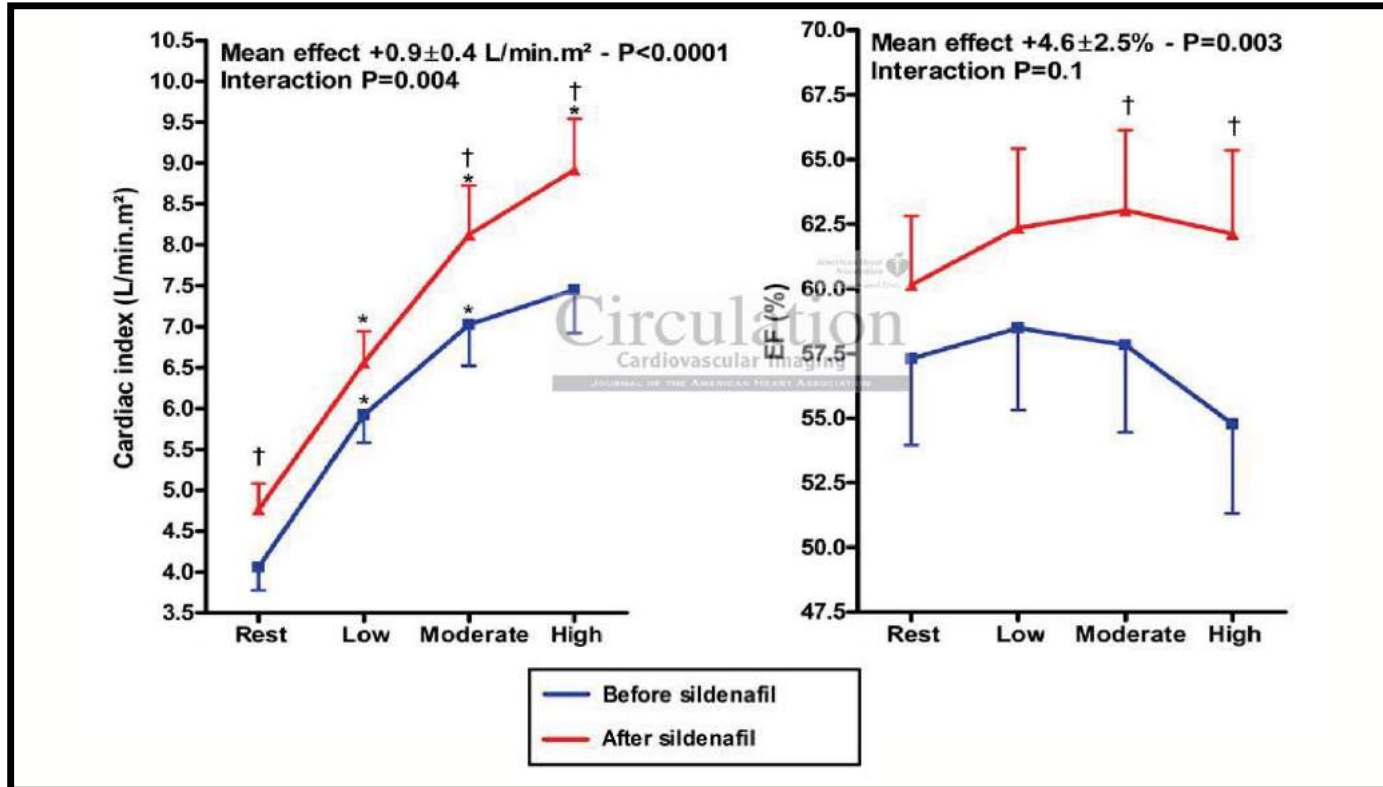
Variable	Rest				Peak exercise			
	Sildenafil		Control		Sildenafil		Control	
	Before	After	Before	After	Before	After	Before	After
Cardiac index (L/min/m ²)	2.9 ± 0.8	3.7 ± 1.0	2.9 ± 0.9	2.9 ± 0.9	5.1 ± 0.9	5.6 ± 0.9	5.1 ± 0.9	5.2 ± 0.9
PBF index (L/min/m ²)	2.2 ± 0.6	2.8 ± 0.5	2.4 ± 0.5	2.4 ± 0.6	4.2 ± 0.5	4.7 ± 0.6	4.4 ± 0.6	4.4 ± 0.6
Heart rate (b.p.m.)	81 ± 10	83 ± 11	80 ± 12	82 ± 13	136 ± 23	137 ± 24	132 ± 22	133 ± 21
Systolic blood pressure (mmHg)	109 ± 17	100 ± 11	111 ± 21	109 ± 14	126 ± 18	122 ± 18	136 ± 17	138 ± 14
Diastolic blood pressure (mmHg)	71 ± 13	67 ± 13	72 ± 16	70 ± 11	73 ± 12	70 ± 11	77 ± 13	78 ± 10
SaO ₂ (%)	90 ± 6	90 ± 5	91 ± 6	91 ± 5	86 ± 8	87 ± 7	88 ± 8	88 ± 8

Data are presented as mean ± SD. PBF, pulmonary blood flow; SO₂, arterial oxygen saturation.

2013 – ALEXANDER VAN DE BRAUENE



2013 – ALEXANDER VAN DE BRAUENE



2008 – SILDENAFIL AFTER FONTAN

	Coefficient* ml/kg/min	95% Confidence Interval	p-value
VO2 max	-0.39	(-2.69, 1.92)	0.73
VO2 at AT	1.38	(-0.19, 2.96)	0.08
VO2 at AT (BNP > 100)	1.85	(0.59, 3.12)	< 0.01
VO2 at AT (LV and MV)	1.77	(0.58, 2.97)	< 0.01

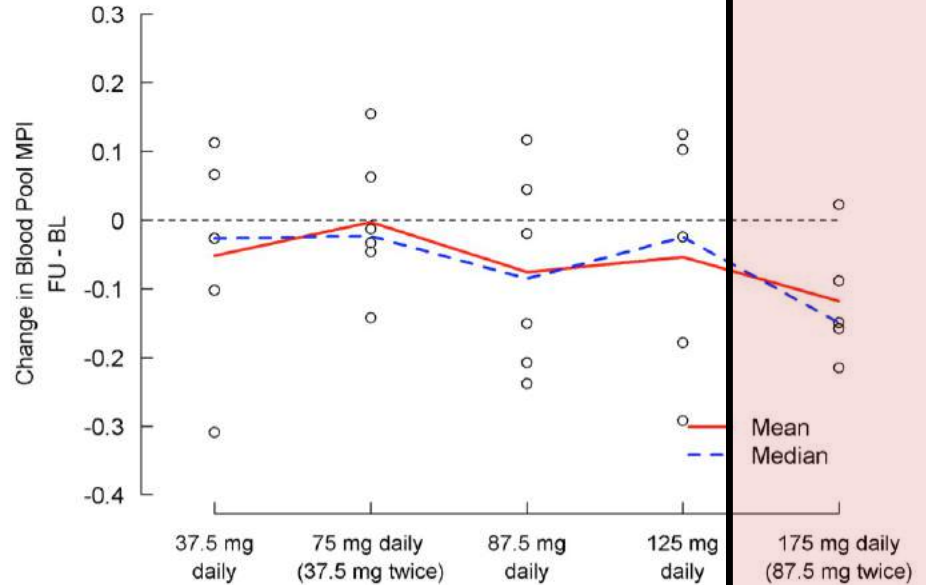
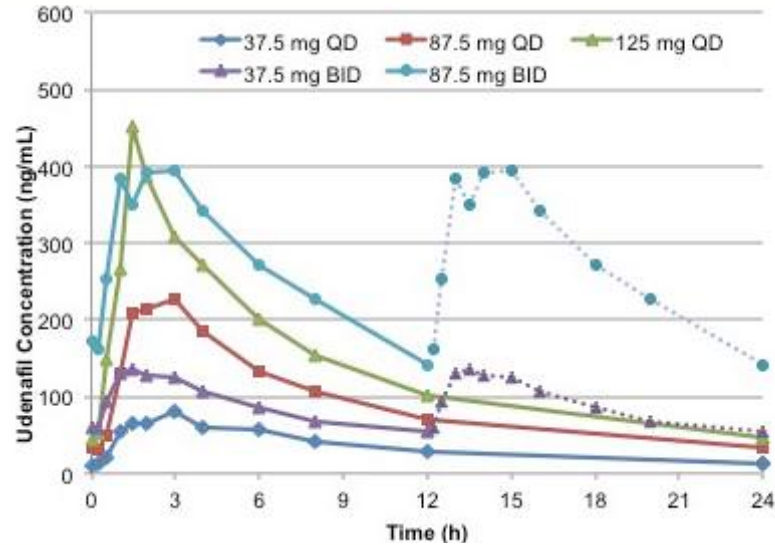
* Each regression coefficient corresponds to the difference in the average post-phase outcome between Sildenafil and placebo; adjusted for pre-phase values, study period, and treatment sequence

2008 – SILDENAFIL AFTER FONTAN

	Coefficient*	95% Confidence Interval	p-value
MPI	-0.050	(-0.093, -0.007)	0.02
VTI x HR	83.1	(-59, 225)	0.24
E:A ratio	0.10	(-0.10, 0.29)	0.31

* Each regression coefficient corresponds to the difference in the average post-phase outcome between Sildenafil and placebo; adjusted for pre-phase values, study period, and treatment sequence

UDENAFIL – PHASE I/II



UDENAFIL – PHASE III – FUEL TRIAL

Primary Aim: Determine the effect of six months of treatment with udenafil (87.5 mg bid) on exercise capacity in adolescents with single ventricle heart disease

Secondary Aims:

- Effect on ventricular performance
- Effect on peripheral arterial tonometry
- Effect on serum BNP level

UDENAFIL – PHASE III – FUEL TRIAL

	Udenafil (n=200)	Placebo (n=200)	
	Wk 26 – Baseline	Wk 26 – Baseline	p-value
Peak VO ₂ (ml/kg/min)	-0.23	-0.89	0.092
VO ₂ at VAT (ml/kg/min)	-0.07	-0.68	0.012
Work at VAT (watts)	3.46	0.31	0.029
VE/VCO ₂ at VAT	-0.76	-0.05	0.011
MPI	-0.02	-0.01	0.024

UDENAFIL – FUEL TRIAL - SUBGROUP

Analysis limited to those with a baseline percent predicted peak $VO_2 < 80\%$

	Udenafil (n=200)	Placebo (n=200)	
	Wk 26 – Baseline	Wk 26 – Baseline	p-value
Peak VO_2 (ml/kg/min)	0.23	-0.89	0.023
VO_2 at VAT (ml/kg/min)	0.11	-0.66	0.022
Work at VAT (watts)	3.80	0.26	0.032
VE/ VCO_2 at VAT	-0.61	0.05	0.053
MPI	-0.03	0.01	0.006

UDENAFIL – FUEL FALD

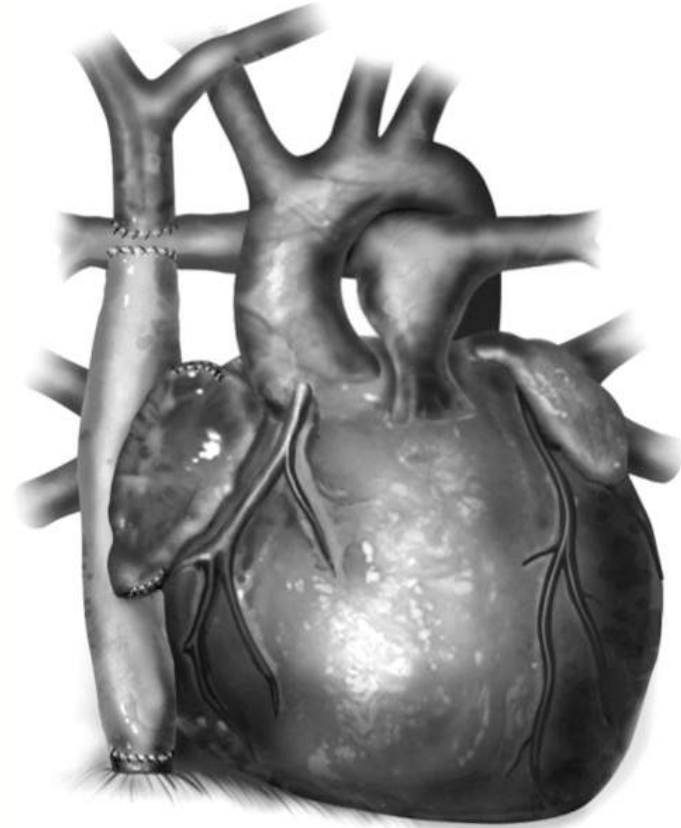
FUEL FALD: Assessment of liver stiffness and biomarkers associated with liver fibrosis following 12 months of udenafil therapy

UDENAFIL – FUEL FALD

	Baseline	Wk 52	p-value	Ongoing fibrosis
ELF Score	10.4 ± 0.95	9.8 ± 0.8	<0.0001	Improved
ELF Components				
HA	85.8 ± 64.1	41.3 ± 24.7	<0.0001	Improved
PIIINP	31.5 ± 19.7	26.6 ± 14.4	<0.0001	Improved
TIMP-1	205.8 ± 39	216.5 ± 51.1	0.052	Not Improved

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