

# Trying to Find the Right Medication to Improve the Fontan Circulation

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The Children's Hospital of Philadelphia



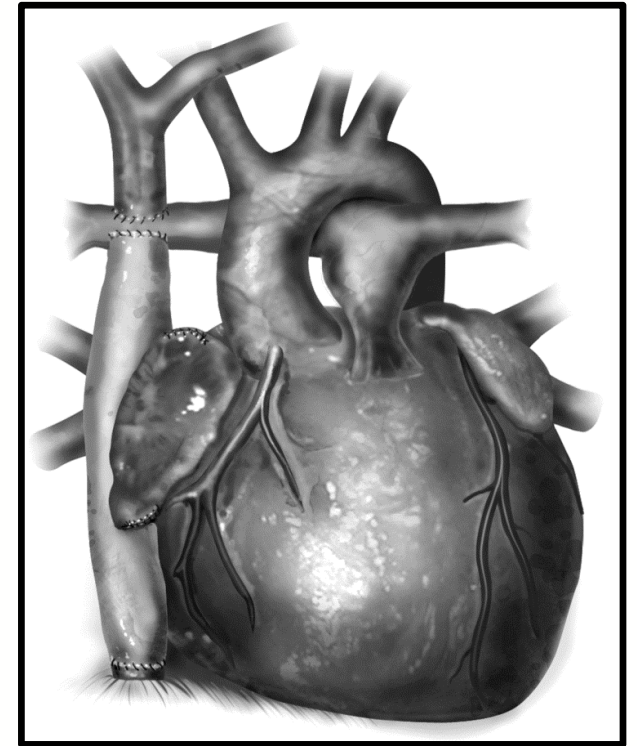
## Disclosures

- Co-PI on a study (FUEL) supported by NHLBI and Mezzion Pharma Co. Ltd.
- Protocol Development grant funded by Mezzion Pharma Co. Ltd.
- No personal financial disclosures

# Characteristics of the Fontan Circulation

Elevated central venous pressure and diminished cardiac output

1. Progressive decline in exercise capacity
2. Liver fibrosis / cirrhosis
3. Lymphatic insufficiency
4. Early death

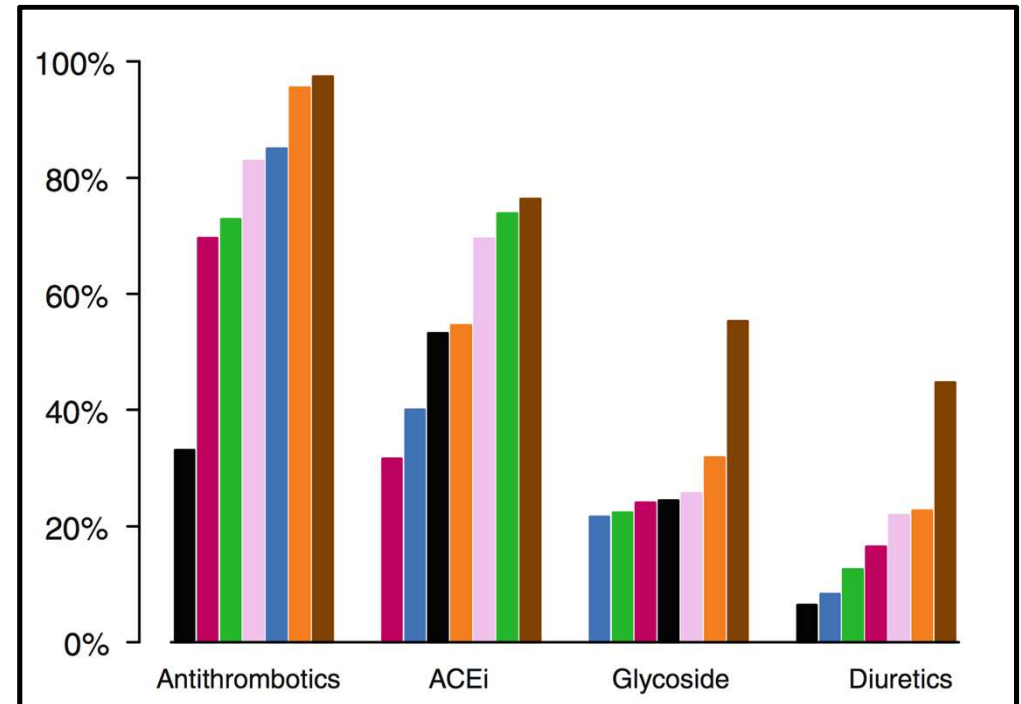


# Fontan Failure is Different from Heart Failure

- Underlying etiology is different
- Standard heart failures therapies may not be relevant
- Need therapy targeted to unique characteristics of the Fontan circulation

# Medical Therapy for the Fontan

- No consensus on appropriate medical treatment
- Significant variability in approach between centers



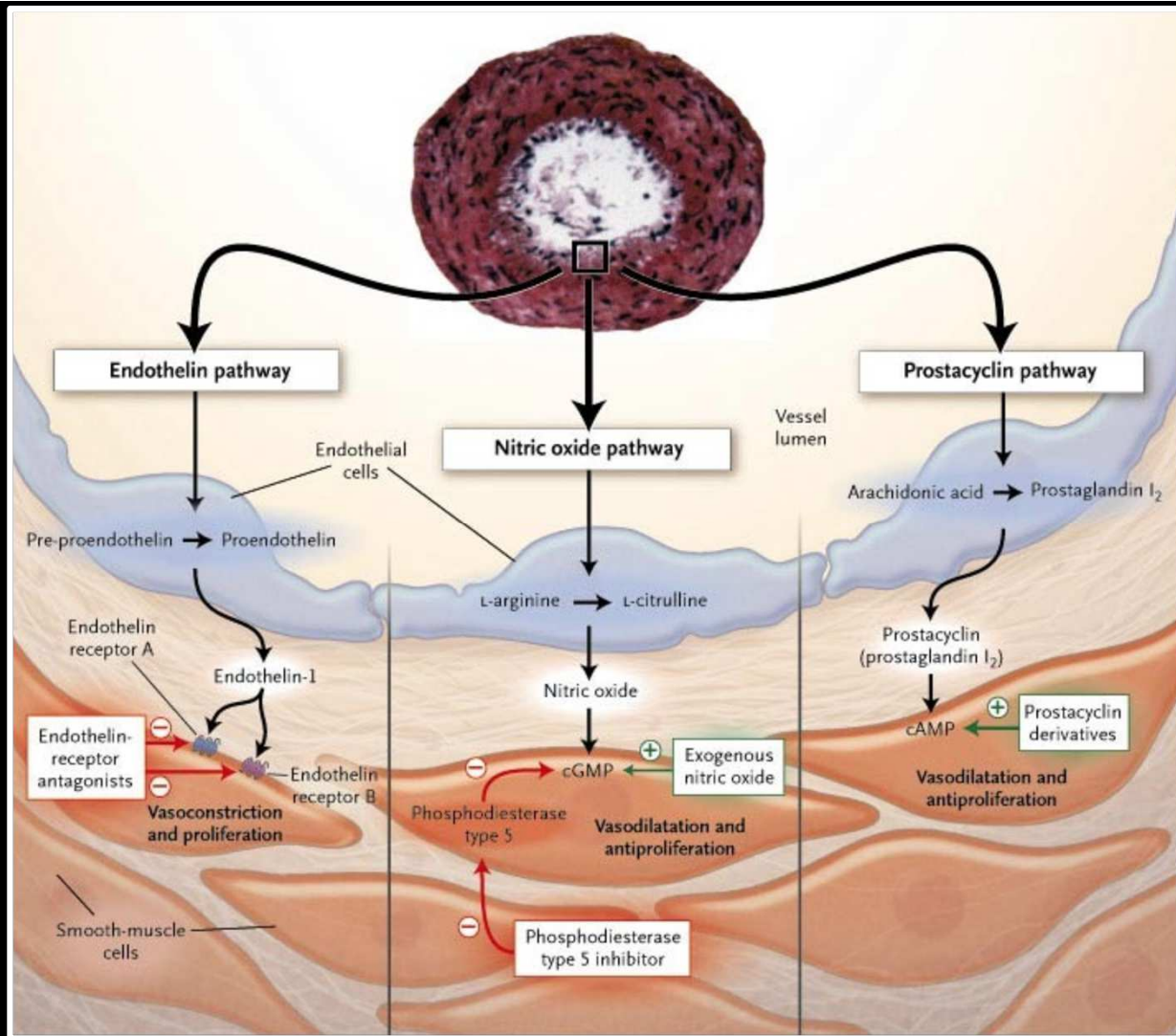
Anderson et al  
(Pediatric Cardiol 2010)

# Medical Therapy for the Fontan

- Testing medical therapies is a challenge
  - Single ventricle heart disease is rare
  - Fontan failure is chronic and slowly progressive
  - Low incidence of hard endpoints (death / transplant)
- Exercise capacity
  - Readily measured, used clinically, associated with outcome
  - $\text{VO}_2$  max of 45% predicted threshold for symptoms

# Medical Therapy for the Fontan

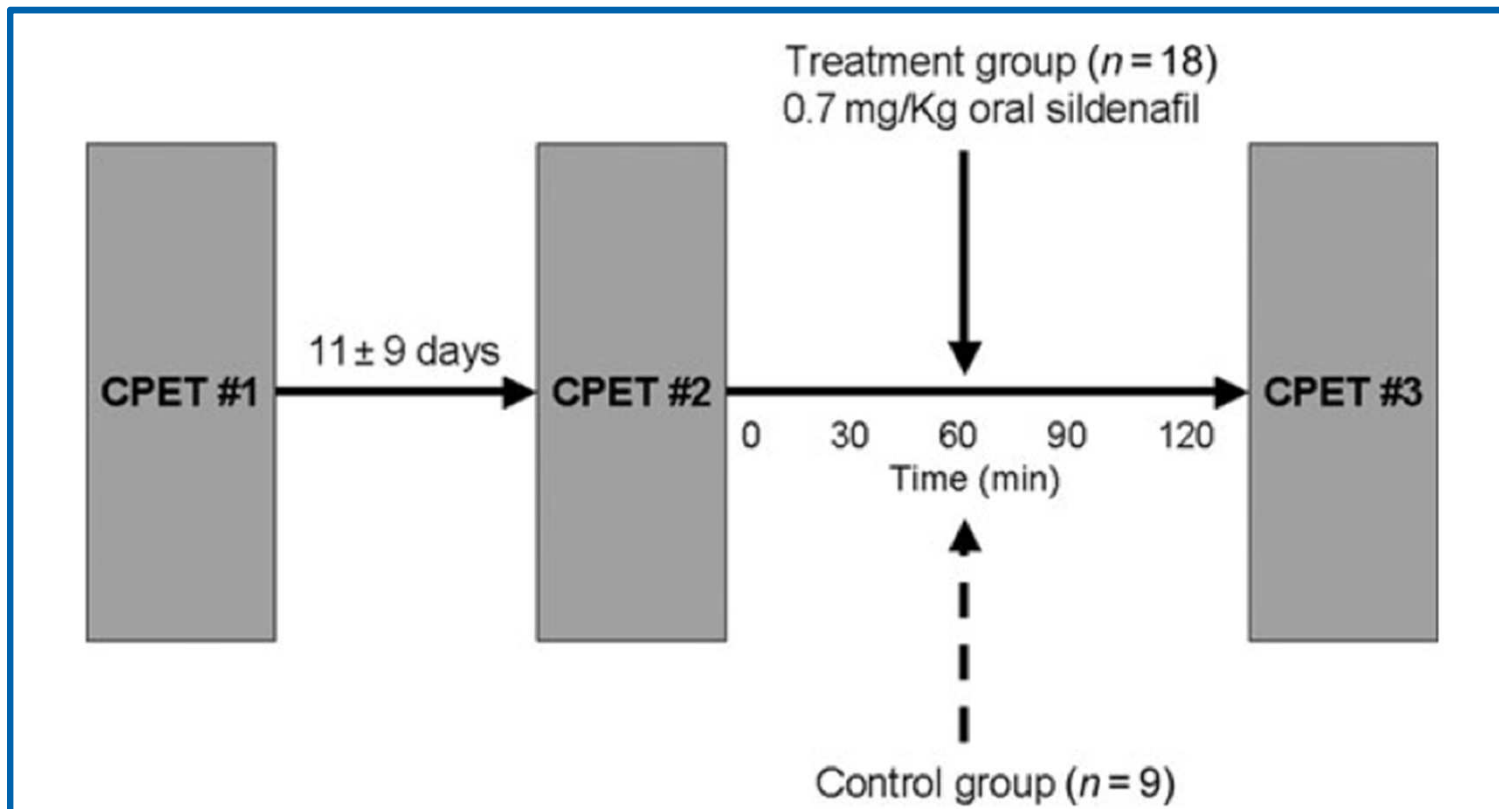
- Decrease pulmonary vascular resistance
  1. Reduce the  $\Delta P$  needed to drive flow through the pulmonary bed -> decreased systemic venous pressure
  2. Allow for improved pulmonary blood flow -> increased preload -> increased cardiac output



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



## 2008 – Alessandro Giardini



## 2008 – Alessandro Giardini

**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 <sup>2</sup> ) | 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 <sup>2</sup> )     | 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 <sub>2</sub> (%)                  | 90 ± 6     | 90 ± 5    | 91 ± 6    | 91 ± 5    | 86 ± 8        | 87 ± 7    | 88 ± 8    | 88 ± 8    |

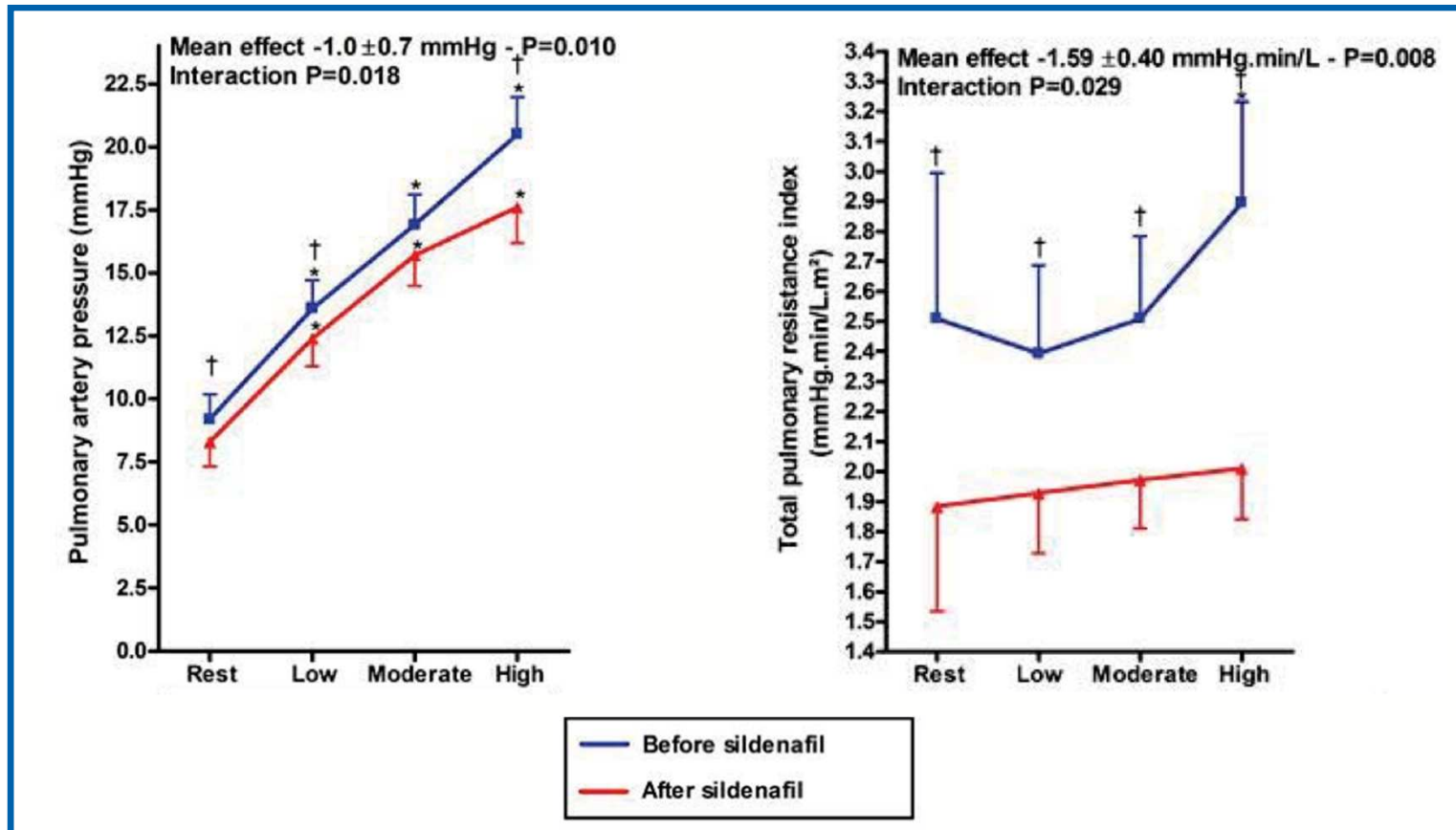
Data are presented as mean ± SD. PBF, pulmonary blood flow; SO<sub>2</sub>, arterial oxygen saturation.

## 2013 – Jonathan Rhodes

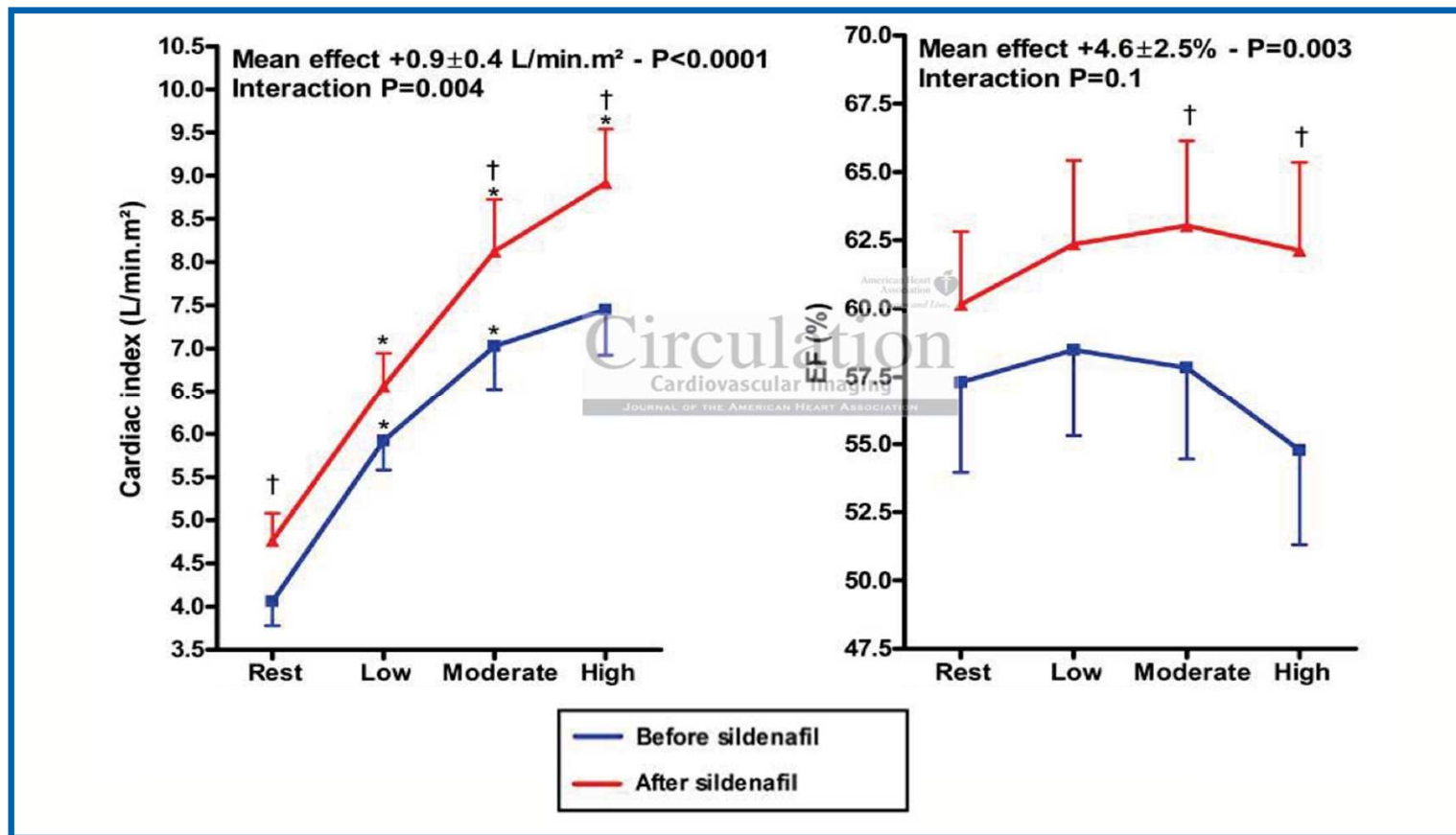
Effect of iloprost on indices of aerobic function (outlier excluded).

| Exercise parameter                  | Median (IQR) |             |                         | p-value |
|-------------------------------------|--------------|-------------|-------------------------|---------|
|                                     | Placebo      | Iloprost    | Iloprost-induced change |         |
| Peak O <sub>2</sub> pulse (mL/b)    | 10.8 (2.9)   | 11.8 (3.8)  | 1.2 (0.9)               | 0.0002  |
| Peak V <sub>O2</sub> (mL/kg/min)    | 27.6 (10.2)  | 30.2 (8.8)  | 1.6 (2.0)               | 0.0040  |
| %Predicted peak V <sub>O2</sub> (%) | 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 <sub>O2</sub> at VAT (mL/kg/min)  | 14.2 (5.9)   | 16.9 (5.4)  | 0.4 (2.0)               | 0.1040  |

## 2013 – Alexander Van De Bruaene



## 2013 – Alexander Van De Bruaene



## 2012 – David Goldberg

|                          | Coefficient*<br>ml/kg/min | 95% Confidence<br>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<br>(BNP > 100) | 1.85                      | (0.59, 3.12)               | < 0.01  |
| VO2 at AT<br>(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

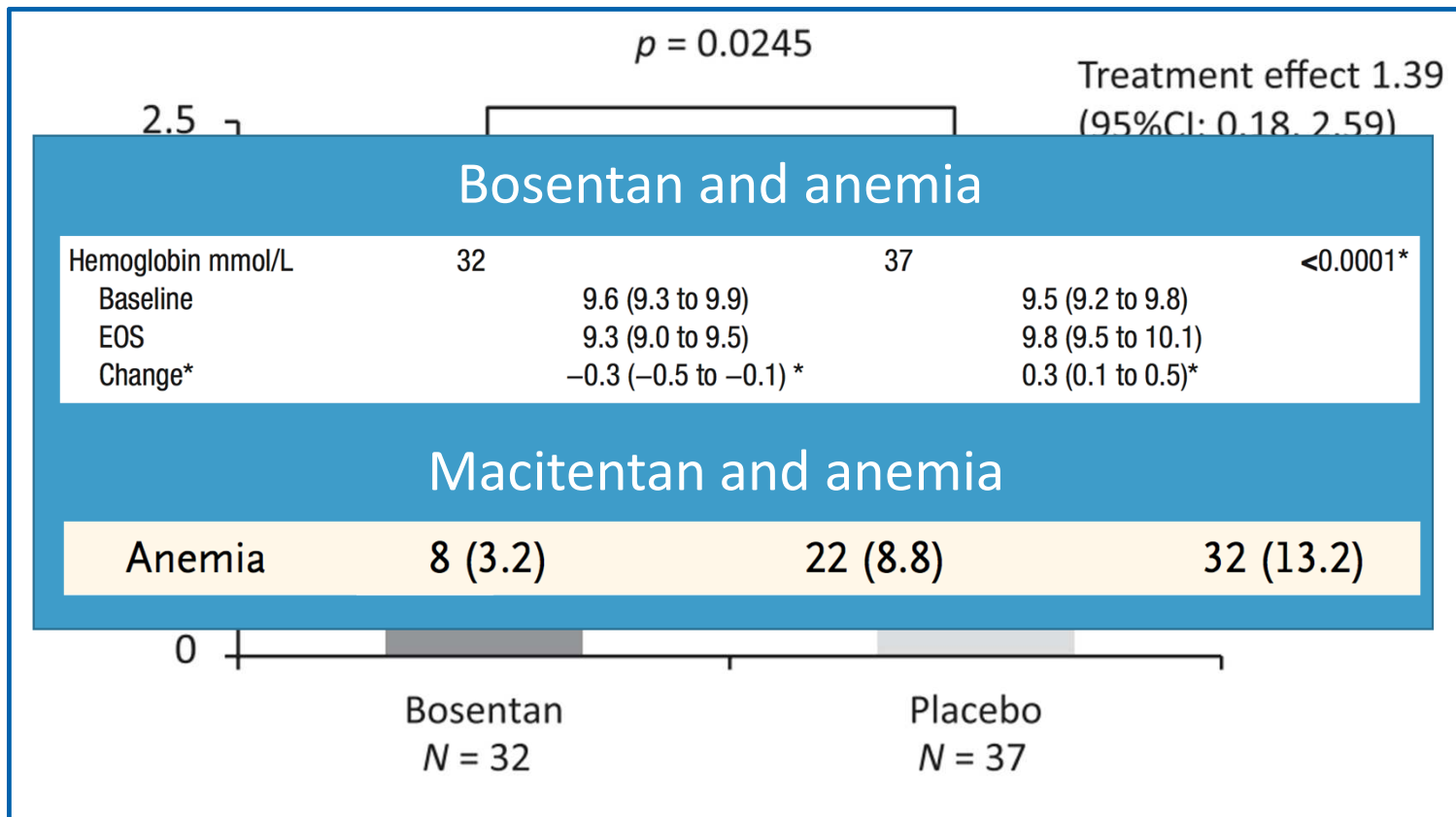
## 2012 – David Goldberg

|           | 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



## 2014 – Anders Hebert

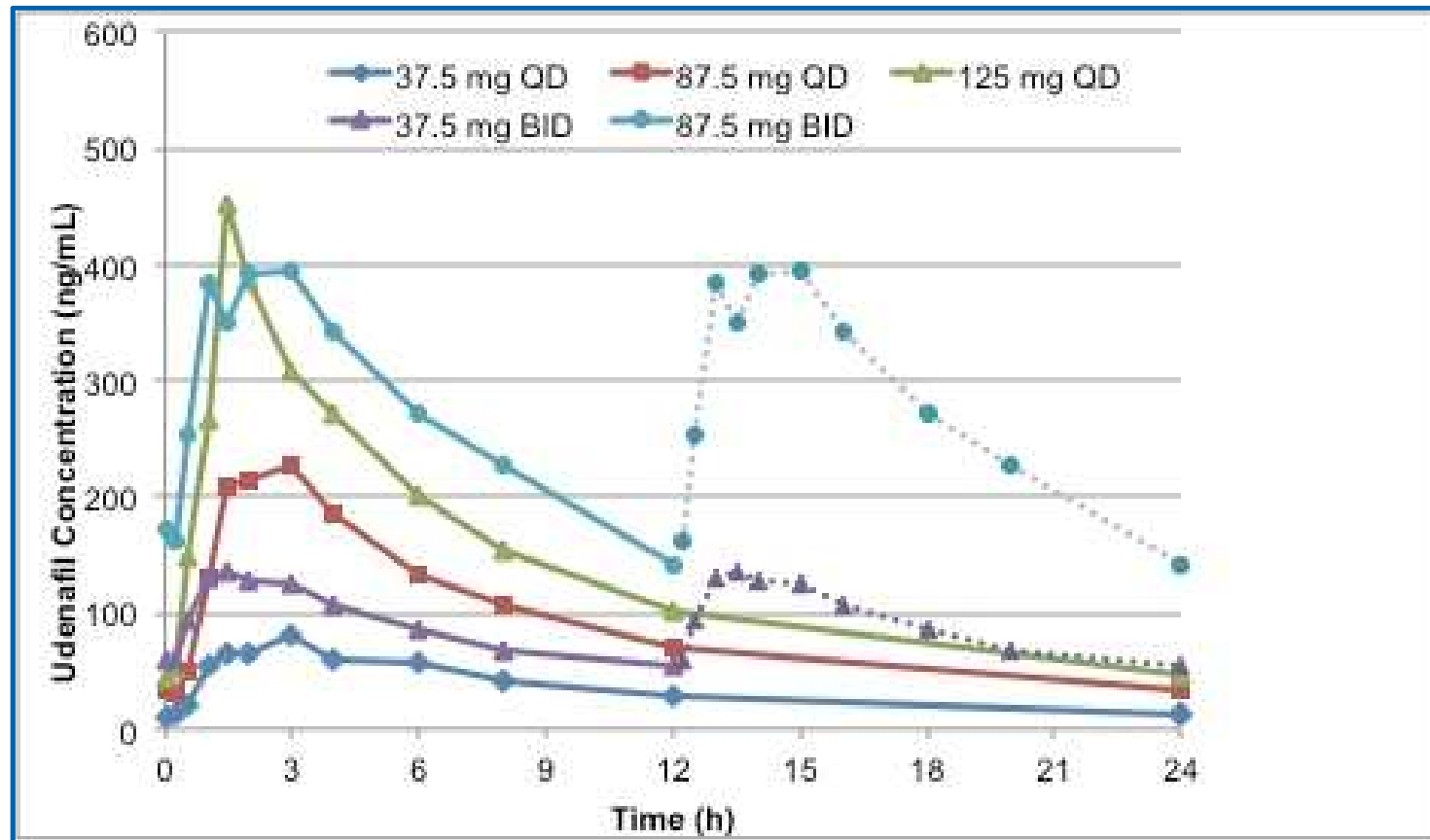




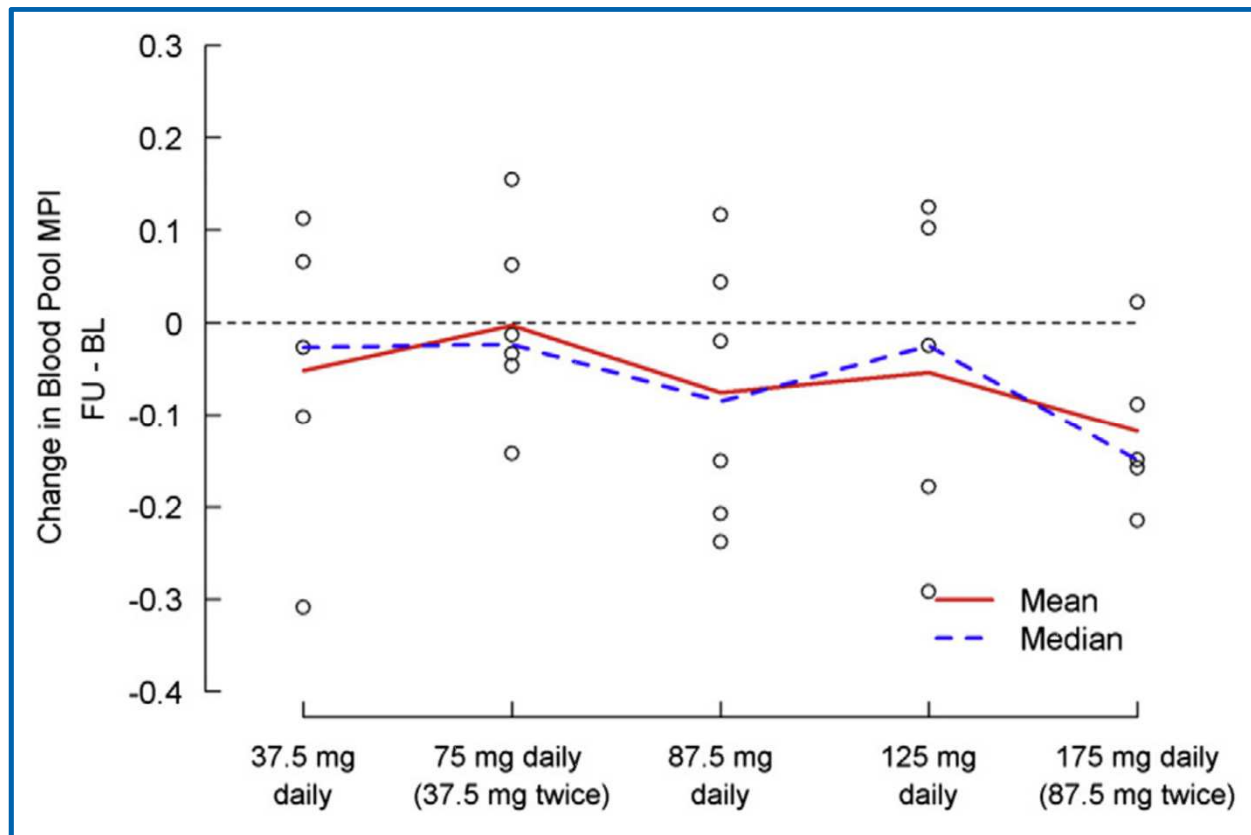
## **Pediatric Heart Network / Mezzion Pharma**

- Unique collaboration between NHLBI and pharma
- Program to evaluate udenafil in adolescents with Fontan physiology
- Phase I/II pharmacokinetic / dose-finding study

## 2017 – Pediatric Heart Network / Mezzion Pharma



# 2017 – Pediatric Heart Network / Mezzion Pharma



# Fontan Udenafil Exercise Longitudinal Trial

## FUEL Trial

- Phase III clinical trial designed to evaluate the effect of udenafil on adolescents with Fontan over a 6 month period
  - Exercise capacity, ventricular performance, peripheral vascular function, brain-type natriuretic peptide
- 12 month open label safety extension study (FUEL-OLE)
- FUEL FALD: impact of udenafil on liver stiffness

| Enrollment by Site and Month as of 02/20/2018 |             |                |            |            |            |            |            |            |        |        |        |            | FUEL  | OLE      |
|---|-------------|----------------|------------|------------|------------|------------|------------|------------|--------|--------|--------|------------|-------|----------|
| Site #  | Name        | Date Activated | Q3<br>2016 | Q4<br>2016 | Q1<br>2017 | Q2<br>2017 | Q3<br>2017 | Q4<br>2017 | Jan-18 | Feb-18 | Mar-18 | Q1<br>2018 | Total | Enrolled |
| 110   | SickKids    | 3/16/2017      |            |            |            | 1          | 8          | 2          |        |        |        | 0          | 11    | 0        |
| 120   | BCH         | 8/25/2016      |            | 4          | 4          | 5          | 1          | 7          |        |        |        | 0          | 21    | 3        |
| 130   | CHONY       | 8/5/2016       |            | 1          | 2          | 2          | 2          |            |        |        |        | 0          | 8     | 3        |
| 140   | CHC         |                |            |            |            |            |            |            |        |        |        |            |       | 17       |
| 150   | Duk         |                |            |            |            |            |            |            |        |        |        |            |       | 0        |
| 160   | MU          |                |            |            |            |            |            |            |        |        |        |            |       | 3        |
| 170   | Uta         |                |            |            |            |            |            |            |        |        |        |            |       | 8        |
| 180   | CHL         |                |            |            |            |            |            |            |        |        |        |            |       | 0        |
| 200   | CHV         |                |            |            |            |            |            |            |        |        |        |            |       | 9        |
| 210   | UM          |                |            |            |            |            |            |            |        |        |        |            |       | 10       |
| 220   | CCH         |                |            |            |            |            |            |            |        |        |        |            |       | 16       |
| 221   | Rile        |                |            |            |            |            |            |            |        |        |        |            |       | 4        |
| 230   | CHC         |                |            |            |            |            |            |            |        |        |        |            |       | 8        |
| 240   | JHM         |                |            |            |            |            |            |            |        |        |        |            |       | 0        |
| 260   | Was         |                |            |            |            |            |            |            |        |        |        |            |       | 3        |
| 270   | TCH         |                |            |            |            |            |            |            |        |        |        |            |       | 8        |
| 310   | Ner         |                |            |            |            |            |            |            |        |        |        |            |       | 5        |
| 330   | Van         |                |            |            |            |            |            |            |        |        |        |            |       | 0        |
| 370   | Sea         |                |            |            |            |            |            |            |        |        |        |            |       | 3        |
| 380   | Ced         |                |            |            |            |            |            |            |        |        |        |            |       | 0        |
| 390   | Rad         |                |            |            |            |            |            |            |        |        |        |            |       | 2        |
| 420   | CNM         |                |            |            |            |            |            |            |        |        |        |            |       | 2        |
| 460   | Mer         |                |            |            |            |            |            |            |        |        |        |            |       | 7        |
| 470   | CHC         |                |            |            |            |            |            |            |        |        |        |            |       | 0        |
| 480   | Pho         |                |            |            |            |            |            |            |        |        |        |            |       | 6        |
| 490   | Nebraska    | 8/3/2017       |            |            |            |            |            |            |        |        |        |            |       | 2        |
| 500   | Ohio**      | 8/10/2017      |            |            |            |            |            | 1          |        | 1      |        | 1          | 2     | 0        |
| 510   | Edmonton**  | 7/18/2017      |            |            |            |            | 2          | 4          |        | 1      |        | 1          | 7     | 0        |
| 530   | Seoul Nat'l | 7/12/2017      |            |            |            |            | 4          | 9          | 1      |        |        | 1          | 14    | 0        |
| 540   | Sejong      | 8/3/2017       |            |            |            |            | 3          | 6          | 3      |        |        | 3          | 12    | 0        |
| Total   |             |                | 28         | 58         | 58         | 54         | 70         | 70         | 14     | 5      | 0      | 19         | 357   | 119      |

30 sites

360 of 400 Participants

119 FUEL OLE Participants

3 FUEL FALD Participants

# PDE-5 and Ventricular Function

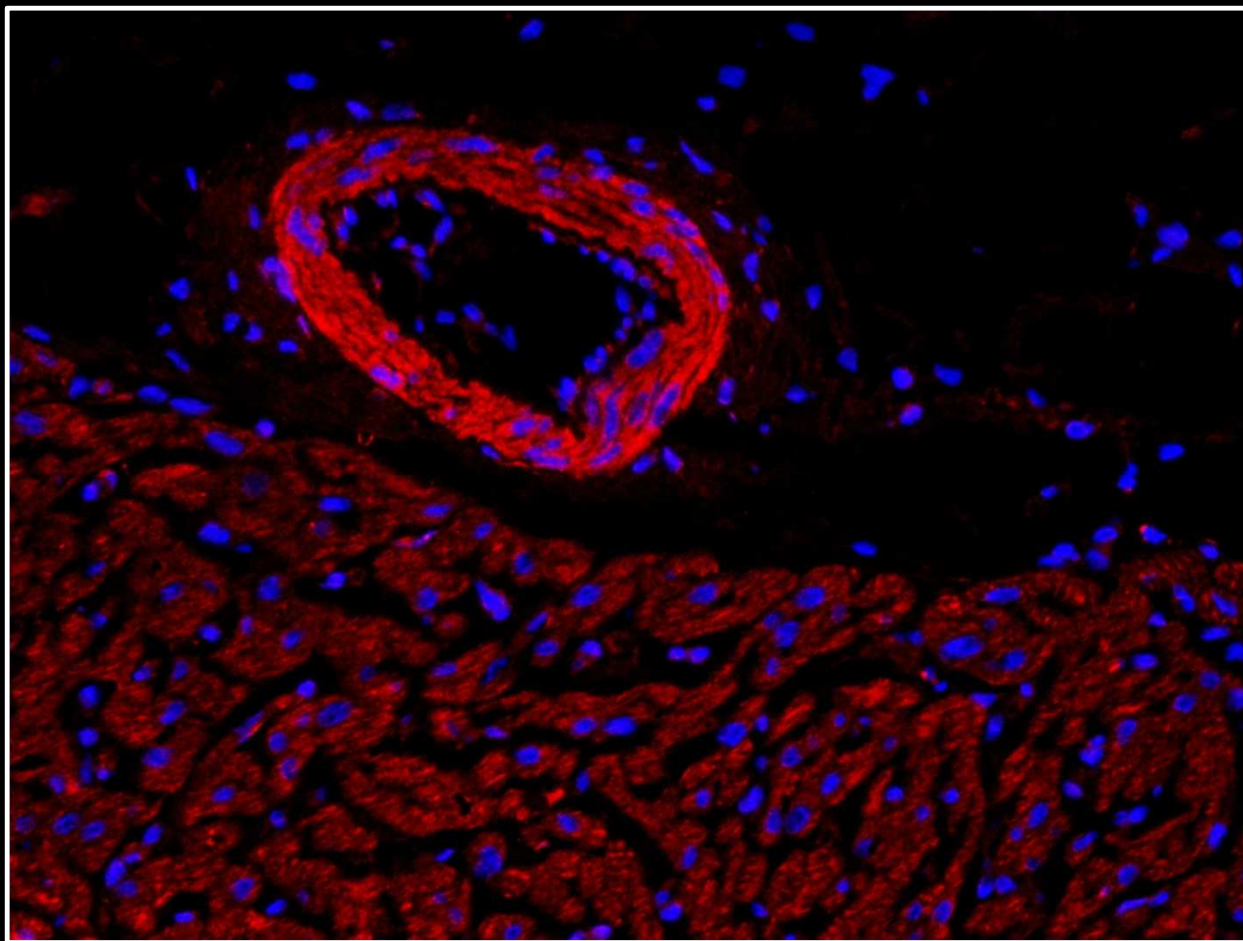
- Improved filling?
- Direct myocardial effect of PDE5 inhibition?

## PRE-CLINICAL RESEARCH

### **Sildenafil Stops Progressive Chamber, Cellular, and Molecular Remodeling and Improves Calcium Handling and Function in Hearts With Pre-Existing Advanced Hypertrophy Caused by Pressure Overload**

Takahiro Nagayama, PhD,\* Steven Hsu, BA,\* Manling Zhang, MD, PhD,\*  
Norimichi Koitabashi, MD, PhD,\* Djahida Bedja, MS,† Kathleen L. Gabrielson, PhD,†  
Eiki Takimoto, MD, PhD,\* David A. Kass, MD\*

*Baltimore, Maryland*



3 year-old Fontan  
Single right ventricle  
Transplanted for  
systolic dysfunction

Brian Snarr, MD  
Preliminary Data

## Summary

- Growing pool of short- and mid-term data suggesting a role for pulmonary vasodilators
- PDE5 inhibitors may be uniquely suited given their efficacy and safety profile
  - May have an additional direct myocardial benefit
- FUEL / FUEL OLE / FUEL FALD Trials will provide data on long(er)-term efficacy, safety, potential impact on the liver



# Thank You!

