

Challenges in Pediatric Drug Trials

- Rapid growth and development in children
 - Impacts pharmacokinetics and pharmacodynamics
- Need for surrogate study endpoints
 - Long life expectancy makes endpoints difficult to define
 - Different endpoints may be needed at different ages
- Rare diseases/Small patient populations
 - Single center studies can not provide adequate sample size
 - Limited market/revenue for pharmaceutical industry
- Ethical considerations for clinical research in children

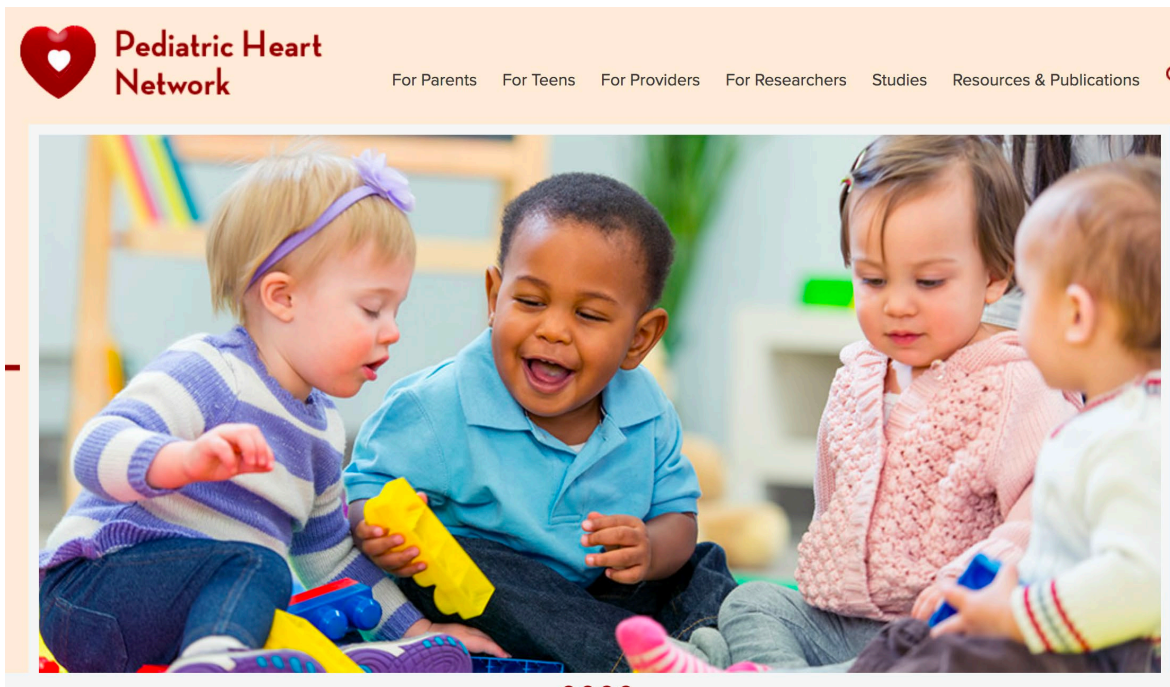


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2017 ACC/AAP/AHA Health Policy Statement in Collaboration with FDA

Pediatric Heart Network



Trial	Primary Endpoint
Single Ventricle Reconstruction Blalock-Taussig vs. Sano Shunt	Survival
Infant Single Ventricle Enalapril vs. Placebo	Somatic Growth
Kawasaki Disease Methylprednisolone vs. Placebo	Coronary Artery Z score
Marfan Losartan vs. Atenolol	Aortic Root Z score



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FUEL: Primary Results

- Udenafil at 87.5 mg twice daily was well tolerated and showed clinical improvement in exercise capacity in adolescents with Fontan
- Most pronounced at VAT with significant improvement in:
 - VO_2 at VAT
 - VE/VCO_2 at VAT
 - Work rate at VAT
- The reasons for these findings are due to the unique response to exercise in the Fontan physiology



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Fontan Exercise Capacity and Study Results

- Max VO_2 has been a generally accepted marker of hospitalization and death
- Max VO_2 may not be an ideal efficacy measure in SV
- Limited ability to increase CO to meet exercise need
 - Lack of a sub-pulmonary pumping ventricle.
 - Baseline CVP rises significantly during exercise
 - Limits ability to increase pre-load and thus CO
- Unique physiologic ceiling for max VO_2 in the Fontan



Fontan Exercise Capacity and Study Results

- VO_2 at VAT, which measures sub-maximal exercise, is more relevant for the Fontan circulation.
- At submaximal exercise, patients with Fontan do not reach the point of an unsustainably high CVP
- VAT occurs at about 70% of max VO_2 in Fontan circulation (vs. 55% in 2V Physiology)
 - Max VO_2 ceiling is lower



FUEL Results: Impact on Practice

- In adults with congenital heart disease, maximal VO_2 of approximately 45 to 50% of predicted is threshold value for increased risk of heart failure and death.
- A medication that addresses the central deficiencies of Fontan physiology and results in improved exercise performance may allow for a longer period of symptom free survival

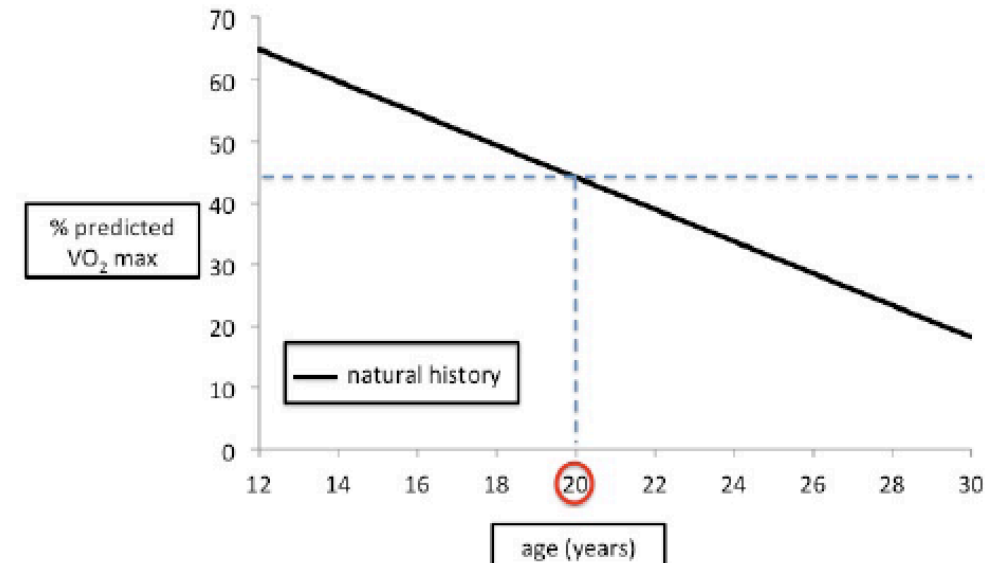


Figure 2. Projected decline in percent predicted maximal VO_2 versus age in years from the PHN Fontan population based on a 2.6% decline per year. Note that the threshold value of 45% is reached by 20 years of age (horizontal dotted line)



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FUEL Results: Press Release

“Landmark pediatric drug trial finds certain exercise benefits in teens with complex single ventricle congenital heart disease with Fontan physiology.”

Drug therapy aims to delay decline in the Fontan teens’ well-being



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The screenshot shows the MEZZION website with the following content:

- MEZZION logo: Discovering • Developing • Delivering Hope
- Navigation: Visit our Korean site >, SVHD, Trials, Access program, About us
- Section: ABOUT SVHD, Single Ventricle Heart Disease explained
- Sub-sections: What is SVHD?, Treatments
- Text under "What is SVHD?":

SVHD stands for Single Ventricle Heart Disease. This means that a person is born with a heart where one of the two lower chambers (ventricle) does not develop properly. In a normal heart, each ventricle does a separate job; the right ventricle pumps blood without oxygen (blue blood) to the lungs and the left ventricle pumps blood with oxygen (red blood) around the body.¹

People with SVHD are left with just one ventricle large enough to pump all the blood and do its job. Because of this, the blue blood and red blood (which are supposed to stay separate) mix together. This means there is a smaller amount of blood with oxygen getting to the rest of the body causing the person's skin to appear blue (cyanosis).¹
- Diagram: A heart with SVHD. Labels include: Superior Vena Cava, Inferior Vena Cava, RA (Right Atrium), RV (Right Ventricle), LA (Left Atrium), LV (Left Ventricle), Aorta, Pulmonary Artery, Pulmonary Vein, Tricuspid Valve, Mitral Valve, Aortic Valve.

