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Don't Stress Out: Using Cardiopulmonary Exercise Testing for Diagnosis, Risk Stratification and Promotion of Exercise

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Disclosures

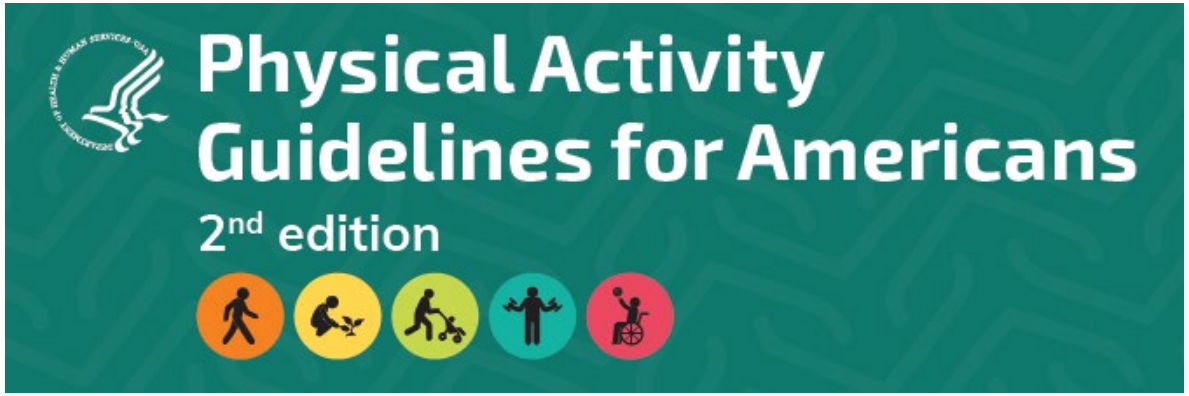
- None

Objectives

- Understand the basic physiologic principles of cardiopulmonary exercise testing (CPET) and its clinical use in the pediatric and congenital heart disease (CHD) population
- Highlight how data from CPET can help determine prognosis and risk of morbidity/mortality in CHD
- Discuss the use of CPET to improve outcomes and quality of life
- Empower primary care providers to encourage and promote exercise

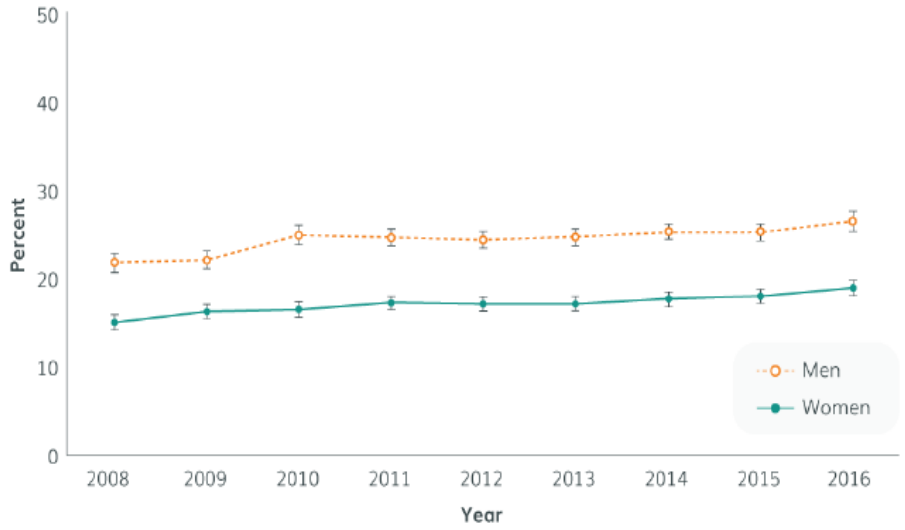
Physical Activity Guidelines

- Children: 60 minutes daily of moderate intensity aerobic exercise, including muscle and bone strengthening exercises 3x/week
- Adults: 2.5-5 hours per week of moderate intensity exercise or 1.25-2.5 hours per week of vigorous intensity; including muscle strengthening exercise 2x/week



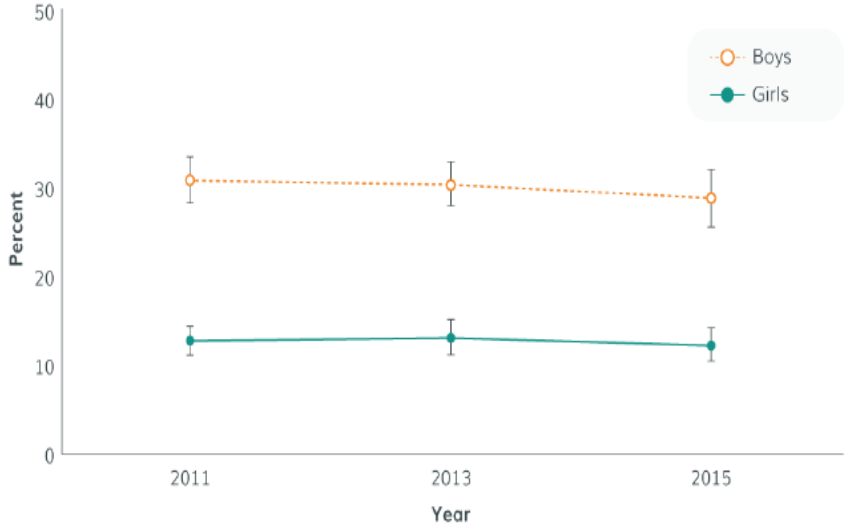
Physical Activity Adherence

Figure 1-1. Percentage of U.S. Adults Ages 18 Years or Older Who Met the Aerobic and Muscle-Strengthening Guidelines, 2008–2016



Source: Centers for Disease Control and Prevention, National Center for Health Statistics, National Health Interview Survey (NHIS).

Figure 1-2. Percentage of U.S. High School Students Who Met the Aerobic Physical Activity and Muscle-Strengthening Guidelines, 2011–2015



Source: Centers for Disease Control and Prevention, Youth Risk Behavior Surveillance System.

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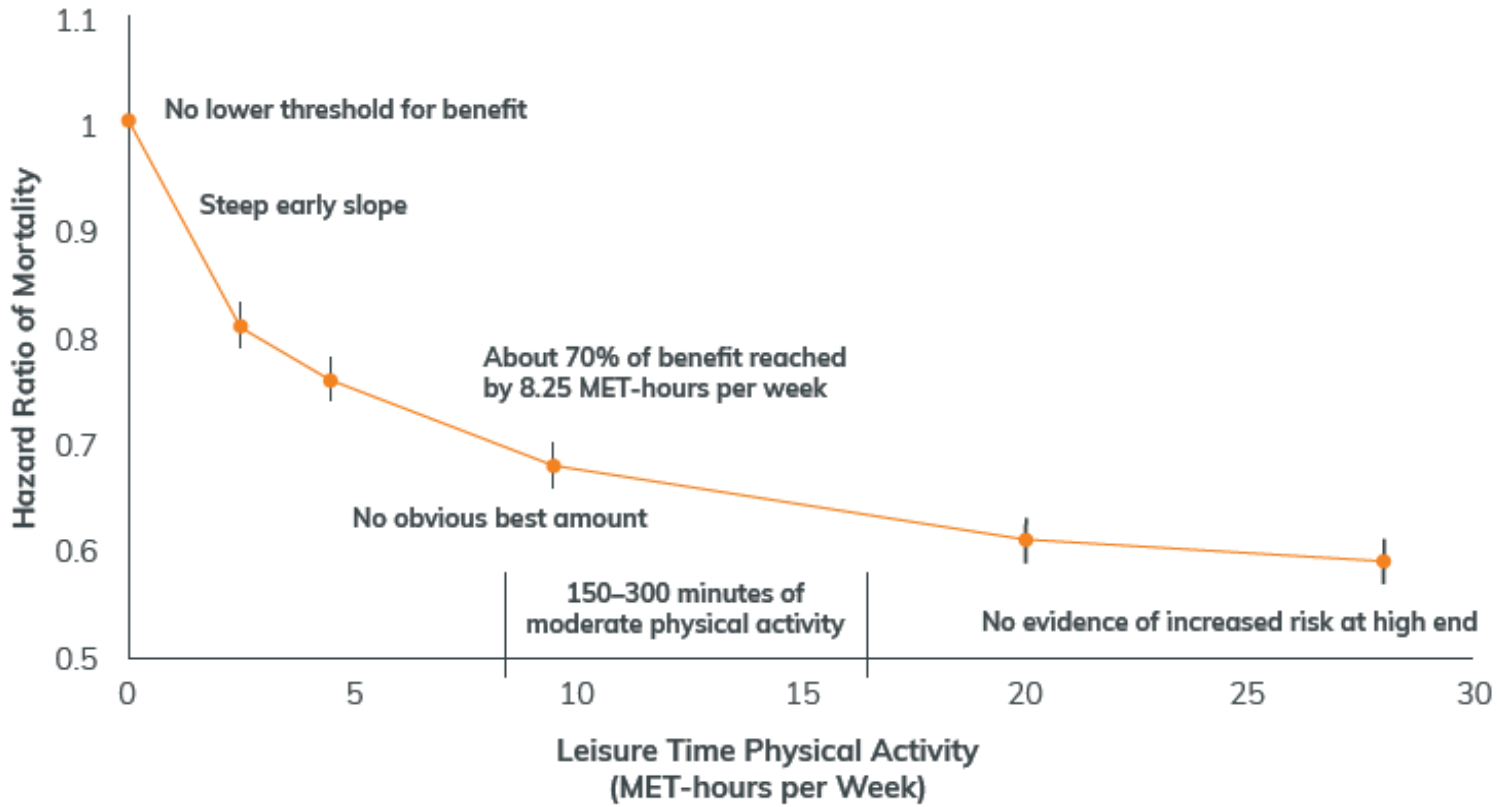
Figure 2-1. Relationship of Moderate-to-Vigorous Physical Activity to All-Cause Mortality



Source: Adapted from data found in Moore SC, Patel AV, Matthews CE. Leisure time physical activity of moderate to vigorous intensity and mortality: a large pooled cohort analysis. PLoS Med. 2012;9(11):e1001335. doi:10.1371/journal.pmed.1001335.

Table 2-1. Health Benefits Associated With Regular Physical Activity

Children and Adolescents
▪ Improved bone health (ages 3 through 17 years) ▪ Improved weight status (ages 3 through 17 years) ▪ Improved cardiorespiratory and muscular fitness (ages 6 through 17 years) ▪ Improved cardiometabolic health (ages 6 through 17 years) ▪ Improved cognition (ages 6 to 13 years)* ▪ Reduced risk of depression (ages 6 to 13 years)
Adults and Older Adults
▪ Lower risk of all-cause mortality ▪ Lower risk of cardiovascular disease mortality ▪ Lower risk of cardiovascular disease (including heart disease and stroke) ▪ Lower risk of hypertension ▪ Lower risk of type 2 diabetes ▪ Lower risk of adverse blood lipid profile ▪ Lower risk of cancers of the bladder, breast, colon, endometrium, esophagus, kidney, lung, and stomach ▪ Improved cognition* ▪ Reduced risk of dementia (including Alzheimer's disease) ▪ Improved quality of life ▪ Reduced anxiety ▪ Reduced risk of depression ▪ Improved sleep ▪ Slowed or reduced weight gain ▪ Weight loss, particularly when combined with reduced calorie intake ▪ Prevention of weight regain following initial weight loss ▪ Improved bone health ▪ Improved physical function ▪ Lower risk of falls (older adults) ▪ Lower risk of fall-related injuries (older adults)

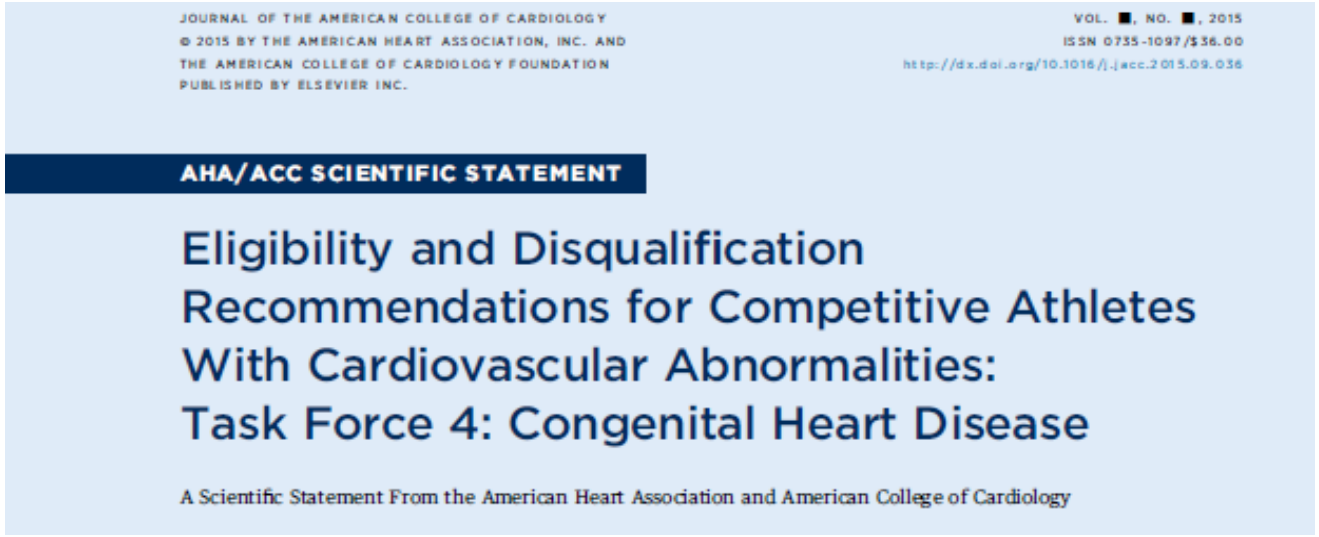
Note: The Advisory Committee rated the evidence of health benefits of physical activity as strong, moderate, limited, or grade not assignable. Only outcomes with strong or moderate evidence of effect are included in this table.

*See Table 2-3 for additional components of cognition and brain health.

Physical Activity in CHD Patients

- Conflicting data; some reports suggest lower PA levels and others are consistent with overall poor PA activity based on age
- Multifactorial etiologies for poor PA in general:
  - Intrapersonal: motivation
  - Sociocultural: support, social norms
  - Environmental: access
  - In CHD: may also include fear/anxiety, discomfort, fatigue, and parental/teacher/primary caregiver concerns that will limit PA

Eligibility Recommendations for Athletes with CHD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AHA/ACC SCIENTIFIC STATEMENT

Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities: Task Force 4: Congenital Heart Disease

A Scientific Statement From the American Heart Association and American College of Cardiology

The level of sports participation recommended includes consideration of both the training and the competitive aspects of the activity but must be individualized to the particular patient, taking into account the patient's functional status and history of surgery. Noninvasive testing, such as formal exercise testing, Holter monitoring, echocardiography, and cardiac magnetic resonance imaging studies, is also often useful.

Eligibility Recommendations and EST

- Fontan/Single V: Class IB
- D-TGA s/p atrial switch: Class IB
- L-TGA: Class IB
- TOF: Class IB
- Coarctation of the aorta: Class IC
- AS/AI: Class IIaC/IC
- D-TGA s/p ASO: Class IIbC
- Anomalous RCA from the L sinus: Class IIaC

Clinical Value of CPET

- Why does someone stop (or never start) exercising?
- Symptoms with exercise – is it the heart, lungs, fitness?
- Can we predict who may need further testing, procedures, surgery?
- Changes over time and response to and effectiveness of interventions
- Rehab/improve fitness
- Activity restriction guidelines – is there risk? Can we clear them?
- Reducing anxiety about exercise in the CHD population
- Potential long-term improvement in morbidity/mortality

Indications for CPET

Table 1: Indications for exercise testing in children.

(1) Assesses physical capacity for recreational, athletic and occupational recommendations
(2) Evaluates specific pathophysiologic characteristics
(a) provides indications for surgery, therapy, or additional tests
(b) evaluates functional postoperative success
(c) diagnoses disease
(3) Assesses adequacy of therapy
(4) Assesses risk for future complications in existing disease
(5) Instills confidence in child and parents
(6) Motivates child for further exercise or weight loss

Modified after Bar-Or [11].

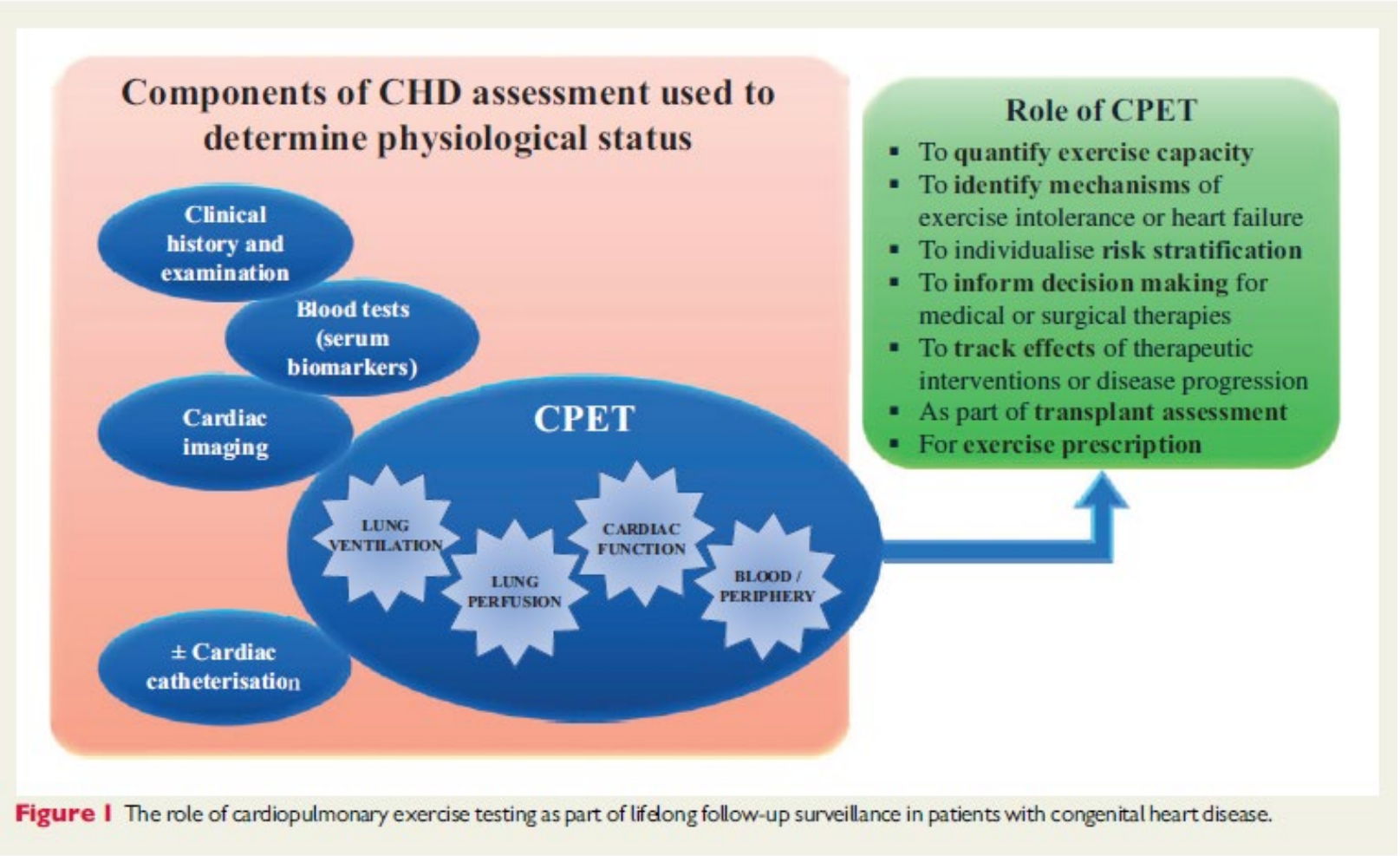

Figure 1 The role of cardiopulmonary exercise testing as part of lifelong follow-up surveillance in patients with congenital heart disease.

Constatine et al, EJPC 2021

Exercise Basics

- Hydrolysis of ATP
- Needs to be constantly replenished through metabolism of fuels, primarily carbohydrates and fat
- Aerobic metabolism: each carbon atom reacts with O2 to form 6 molecules of ATP; glucose (6 carbon = 36 ATP)
- Anaerobic metabolism: No O2; quicker, less ATP, produces lactate
    - Allows body to make ATP when insufficient O2 available
    - Need a way to eliminate the lactate (buffered into CO2)

Oxygen Delivery

Fick Equation

- VO_2 = Cardiac Output x Oxygen extraction

  = [Heart rate x Stroke volume] x [CaO_2 – CvO_2]

  = [HR x SV] x [(1.36xHgb) x (SaO_2 – SvO_2)

Each of these variables is altered during exercise to maximize O_2 delivery.

Heart Rate

- HR increases ~ 3-fold with exercise in normal individuals
    - Peak HR is age dependent
- Many patients with CHD have chronotropic incompetence or are on medications that blunt the HR response
- Pacemakers are usually programmed for a max HR of 160-180 bpm

Stroke Volume

SV increases rapidly and then plateaus to about 1.5-2x baseline early in exercise

- Later increases in CO are due to increases in HR
- Mediated by:
  - Increased contractility
  - Decreased afterload (decreased SVR and PVR)
  - Enhanced ventricular filling (pumping function of skeletal muscles)
  - Improved lusitropic (diastolic) function
- Usually at least 5x increase in CO at peak exercise
- CHD can be associated with reduction/problems in all the above

O_2 Extraction

Arterial O_2 sat is usually about 100% and mixed venous sat 70%

- At peak exercise, greater extraction of O_2 in the exercising muscles, so mixed venous sat may fall to 30% (flux) = doubling of O_2 extraction
  - Recruitment and vasodilation of capillary beds
  - Partial pressure of O_2 within the muscles declines; increased O_2 tension gradient facilitates flow of O_2 from blood to muscles
  - Lactate accumulation facilitates release of O_2 from Hgb (Bohr effect), aka rightward shift of Hgb/O_2 dissociation curve in acidic environments
- Desaturations from R to L shunts, lung disease or decrease in Hgb will affect this
- Combination of increased O_2 extraction with cardiac output results in ~ 10-fold increase of VO_2 from rest to peak exercise in normal patients

CO_2 Elimination (pulmonary part of the CPET)

- CO2 production increases with exercise
- Excreted via respiration
  - Increase in tidal volume
  - Increase in respiratory rate
  - Decrease in physiologic dead space
  - Improved V/Q matching
- Factors that affect lungs will impact exercise

CPET Equipment

- Treadmill or cycle ergometer
- EKG monitoring
- Metabolic cart
  - Breath by breath volume
  - CO2/O2 concentrations
  - ETCO2 and ETO2
- BP cuff
- Pulse oximeter
- Safety equipment

Patient Instructions

AHA Scientific Statement

Clinical Stress Testing in the Pediatric Age Group

A Statement From the American Heart Association Council on Cardiovascular Disease in the Young, Committee on Atherosclerosis, Hypertension, and Obesity in Youth

Stephen M. Paridon, MD; Bruce S. Alpert, MD, FAHA; Steven R. Boas, MD; Marco E. Cabrera, PhD; Laura L. Caldarera, MA; Stephen R. Daniels, MD, PhD, FAHA; Thomas R. Kimball, MD; Timothy K. Knilans, MD; Patricia A. Nixon, PhD; Jonathan Rhodes, MD; Angela T. Yetman, MD

Exercise Test Information

A Metabolic Exercise Test helps your doctor find out how well your child's heart, lungs, and muscles work during exercise. The test can also show if there is a lack of blood supply to the heart as your child does work, and helps the doctor know the kind and level of activity that's right for your child.

During the test, your child will be hooked up to equipment to monitor his or her heart and blood pressure, and may also be asked to breathe into a mouthpiece before, during, and after exercise. Your child will walk slowly in place on the treadmill. Every few minutes, the speed of the treadmill will get faster and the treadmill will tilt so it will feel like your child is walking up a hill. Your child can stop the test at any time if he/she needs to. Most children walk for 10 to 15 minutes; however, there is no set time limit for the test. Your child will *only* be asked to work to the best of his/her abilities.

As your child walks on the treadmill, several things will be monitored and recorded for the physician. These include:

- Heart rate and heart rhythm
- Blood pressure
- Breathing
- How tired your child feels

For the test, your child should wear comfortable clothing that he/she can exercise in. Shorts or sweatpants and a T-shirt are recommended. Athletic shoes should be worn (no open-toed shoes or sandals, please). Your child can eat a light meal or snack before the test.

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Pediatric Considerations

- Proper size equipment – BP cuffs, face masks, handrails
- Emotional/developmental – cooperation, anxiety, understanding directions
- Children are not "small adults"
  - Varying peak VO_2
  - Higher submaximal HR at relative workloads
  - Lower stroke volumes


Heart rate and oxygen
in the blood are analysed
every minute

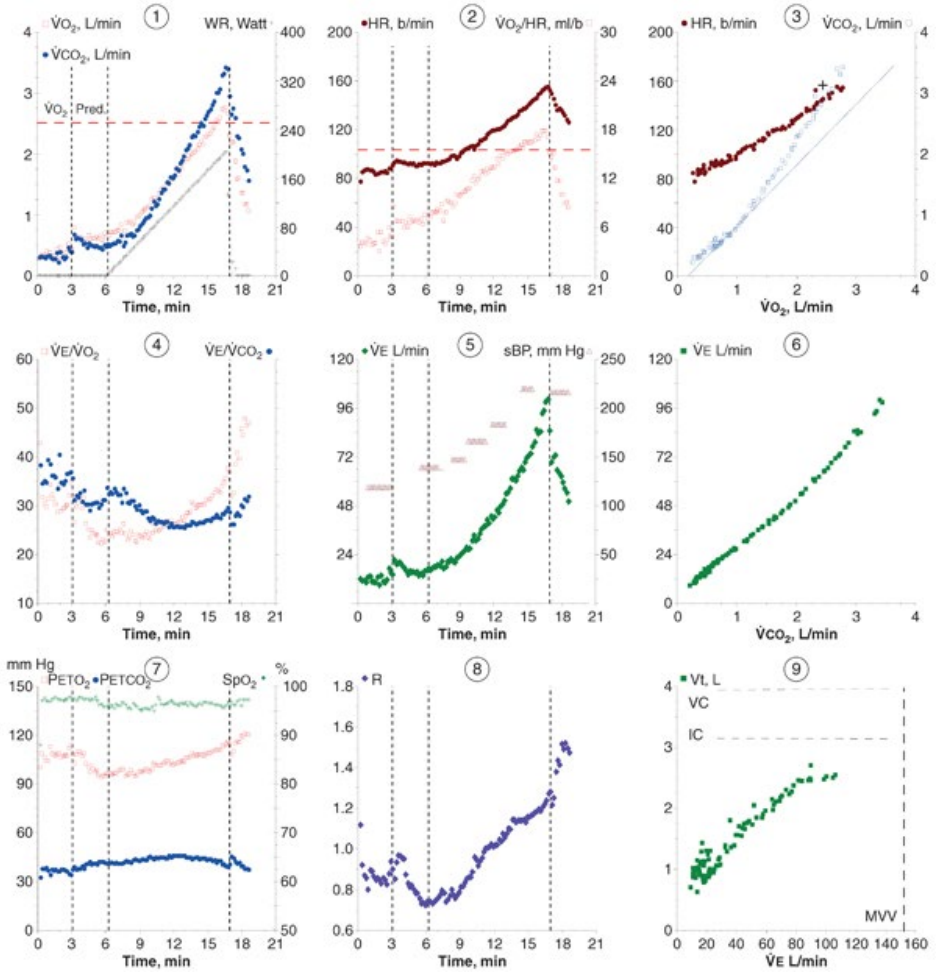
CPET Protocols

- Dependent on purpose of test and patient characteristics (e.g. Bruce protocol)
- Treadmill vs Cycle
  - TM will result in higher VO2, not height dependent*, is often more familiar
  - Cycle has more stability (no falls and stress echo is easier), less EKG artifact, can quantify work
- Designed to have patient reach peak VO2 in 10+/-2 minutes
  - Peak HR alone may not accurately reflect a maximal effort
  - Self reported symptoms may be too subjective in children
  - Most younger children will want to stop before maximal (not used to pushing themselves; they usually stop/start)

CPET Peak Exercise Values

- Peak VO2 = highest VO2 achieved
- Max VO2 = VO2 does not increase with increasing work
- "Normal VO2":
  - Increases/peaks in adolescence/early adulthood and then declines ~7%/decade
  - Differs between males/females
  - Larger body size leads to greater VO2; however, adipose tissue consumes very little O2, so normalizing VO2 for body mass may be misleading in obese patients
  - Prediction equations (height, weight, age)
- % predicted values

CPET 9-Plot Graph



Reproduced from: Wasserman & Whipp's: Principles of Exercise Testing; Sietsema K et al.

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VO_2

- Independent predictor of death and/or hospitalization in:
  - TOF
  - D-TGA s/p atrial switch
  - Fontan
  - PAH
  - CHF
  - Awaiting heart transplant
- Comparing trends over time may help elucidate new issues, allow for improved training/conditioning

Heart Rate

- HR increases linearly in proportion with VO2
- 5-10% lower peak HR on cycle
- Chronotropic incompetence will show depressed HR:VO2 curve
- Impaired SV will show higher HR:VO2 due to more rapid increase in HR to compensate
- Heart rate reserve = Peak HR – resting HR (vs. pred peak HR – peak HR)
- Chronotropic index = [(100 x HRR)/(predicted Peak HR – resting HR)]

O2 Pulse

- VO2/HR
  - Surrogate for stroke volume, e.g. effective amount of oxygenated blood ejected with each heartbeat
  - Also includes O2 extraction (at peak exercise, this will often but not always be normal)
  - Helpful particularly with chronotropic incompetence; if no other issues, O2 pulse should be higher than predicted
- Limited if anemia or significant arterial desaturation
- Overestimate with polycythemia (e.g. increased arterial O2 content)
- Rare cases of poor O2 extraction (e.g. mitochondrial or metabolic disorders)

O2 Pulse

- Rapid increase early in exercise due to increase in stroke volume
- Later gradual increase due to increased O2 extraction
- Low with reduced SV such as systolic or diastolic dysfunction, outflow obstruction, severe valvular regurgitation
  - Due to decreases in SVR and PVR, AI and PI may not affect O2P as much unless severe
- Fontan patients can not increase preload well (if at all)
- Should never go down during exercise
  - CAD/MI
  - Cardiomyopathy
  - Severe outflow tract obstruction

Respiratory Exchange Ratio (RER)

- RER = VCO_2/VO_2
- Measured via exhaled CO_2
  - Aerobic metabolism
    - Carbs: 1 mole of CO_2 produced for 1 mole of O_2 consumed
    - Fats: 1 mole of CO_2 for 1.5 moles of O_2 consumed
  - At rest, RER ~ 0.85
  - As exercise increases past AT, VCO_2 rises out of proportion to VO_2
- RER > 1.09 is considered to be compatible with a good effort
  - < 1.09 would be considered submaximal, most commonly due to suboptimal effort

BP and O2

- BP increases by at least 20%, up to about 200 mmHg
  - Excessive rise in BP from residual arch obstruction
  - Never should see a drop in BP with exercise; poor prognostic feature in HCM
- In R to L shunts
  - Magnitude of shunt may increase with exercise
  - Mixed venous O2 sat declines, so shunt will continually have lower sat

Pulmonary Assessment

- Spirometry/flow volume loops
  - Pre- and post-exercise maximal expiratory and inspiratory measurements
- Obstructive/EIB if FEV1 decreases 10-15% from baseline
- Clinical symptoms
- A note on EIB…

Respiratory Measures

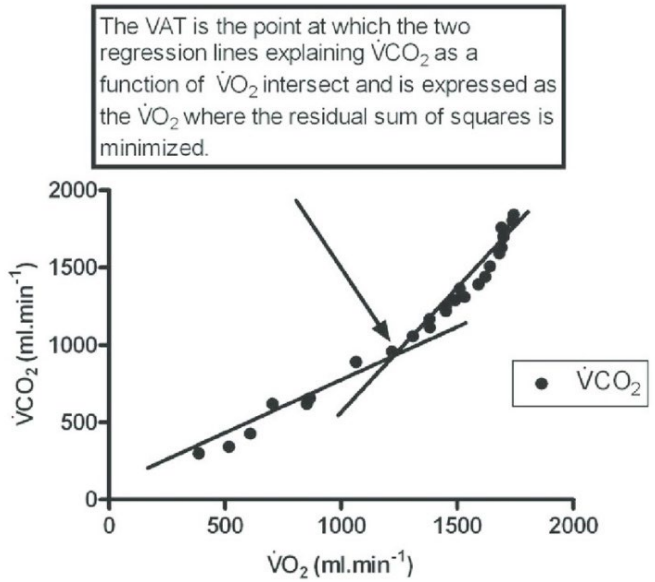
- MVV = maximal voluntary ventilation
  - Maximal amount of air someone can breathe in and out in a minute
  - Breathe in/out as rapidly and deeply as possible x 12 seconds; multiply by 5
  - Estimate MVV = FEV1 x 40 (more easily attained)
- Breathing reserve
  - Most people utilize about 65% of the MVV at peak exercise; therefore, reserve is ~ 35%
  - Essentially this means that most people don't stop exercising typically due to breathing problems

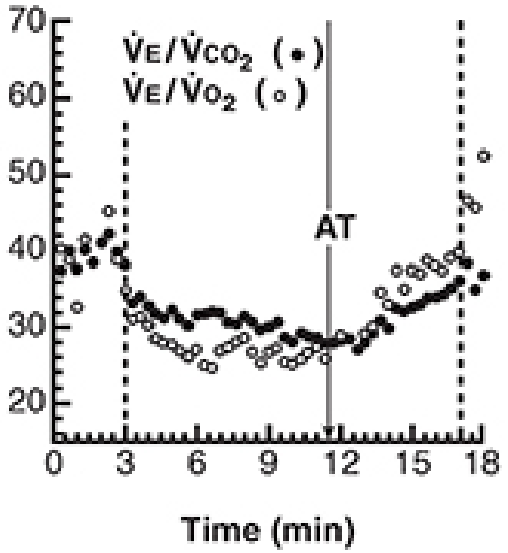
Anaerobic Threshold and Respiratory Compensation Point

- During progressive exercise, VCO_2 will eventually increase out of proportion to O_2 consumption
  - Due to lactate increase from switch to anaerobic metabolism
  - Point of increase is the AT
- As exercise continues and lactate accumulates, a metabolic acidosis develops
  - To maintain a normal pH, need compensatory respiratory alkalosis (increased ventilation); the point at which this happens is the RC

AT

- How to measure:
  - The point where VCO2 rises out of proportion to VO2
  - VE/VO2 increases while VE/VCO2 is flat/declining
    - VE increases in proportion with VCO2; however, VO2 does not rise as rapidly as VCO2 after AT so therefore VE/VO2 ratio increases
    - This method can distinguish between hyperventilation from anxiety (both are rising) vs. the true VAT





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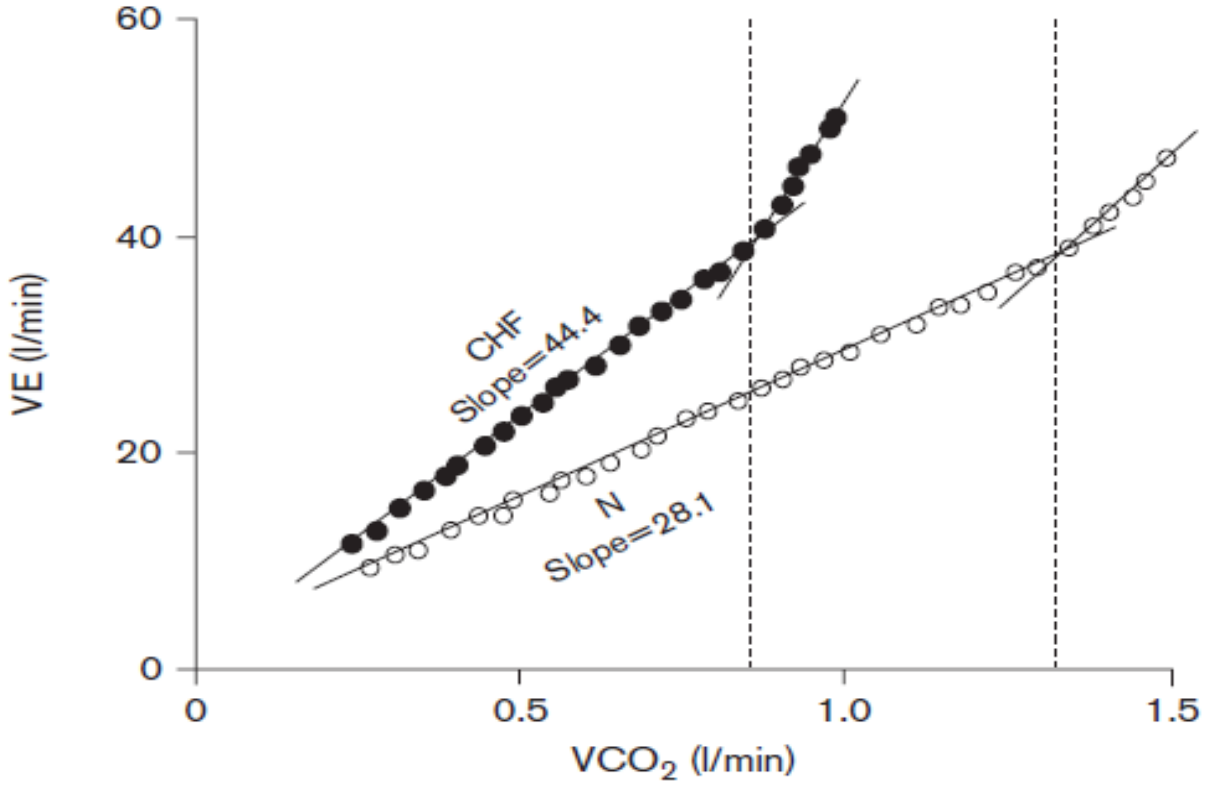
Submaximal Measurements

- VO_2 @ AT = ventilatory anaerobic threshold (VAT)
  - CO_2 production increases due to anaerobic metabolism with no further consumption of O_2
  - Reflects the level of O_2 delivery beyond which the circulatory system can no longer fulfill the metabolic needs ["aerobic max"]
  - Physiologic and not effort dependent; however not as helpful if maximal test performed
  - Typically around 50-60% of predicted peak VO_2
    - Below 40% is abnormal and associated with conditions that impair ability to increase CO or O_2 delivery
    - Potentially helpful in patients that can't increase stroke volume (but can compensate with greater HR, eg. Fontan)

VE/VCO_2 Slope

- VE rises proportionally with VCO_2 until a point after AT and then increases rapidly
- The slope/linear portion of the curve – e.g. how much additional liters of air needs to be exhaled to eliminate one additional liter of CO_2
- The point where slope is no longer linear (when PCO_2 declines due to compensatory resp alkalosis) = respiratory compensation point
- Age dependent, but normal is generally < 28; worsens as gas exchange becomes more inefficient
- Conditions that cause maldistribution of PBF and V/Q mismatch will worsen this, e.g. TOF with residual obstructions, CHF, PAH
- Higher values may be associated with poor prognosis

VE/VCO2



Mezzini et al. Standards for use of CPET in cardiac patients. EJCPR 2009.

CPET in non-CHD Patients

- Exertional CP and SOB – Low sensitivity/specificity in standard EST
- Addition of metabolic data may help with determining etiology and treatment, e.g. pulmonary problem or conditioning issue
- Syncope (exertional and post-exertional)
- Athletic training/fitness program

CPET in CHD

- Peak VO_2 reduction somewhat across the board
  - May be a first sign of changes in cardiac function or other issues
- Increased VE/VCO_2 slope, especially in cyanotic CHD
- Lower VAT
- Decreased lung function (can be both obstructive and restrictive)
- Lower peak HR, HR recovery, and HR reserve

Peak VO2 in CHD

- Peak VO2 ~ 50% predicted on average
- Worst in ccTGA, single V/Fontan, and Eisenmenger's
- Peak VO2 < 15.5 ml/kg/min predicted hospitalization (HR 2.9) and death (HR 5.6)
- NYHA class did not fully estimate the degree of exercise limitation

Exercise Intolerance in Adult Congenital Heart Disease: Comparative Severity, Correlates, and Prognostic Implication

Gerhard-Paul Diller, Konstantinos Dimopoulos, Darlington Okonko, Wei Li, Sonya V. Babu-Narayan, Craig S. Broberg, Bengt Johansson, Beatriz Bouzas, Michael J. Mullen, Philip A. Poole-Wilson, Darrel P. Francis and Michael A. Gatzoulis

Circulation 2005;112:828-835; originally published online Aug 1, 2005;
DOI: 10.1161/CIRCULATIONAHA.104.529800

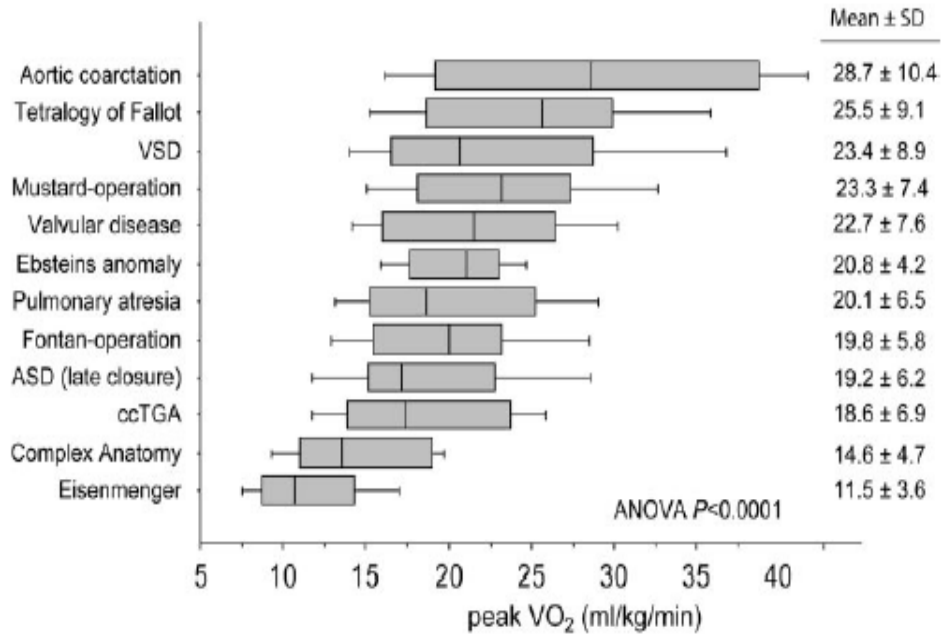
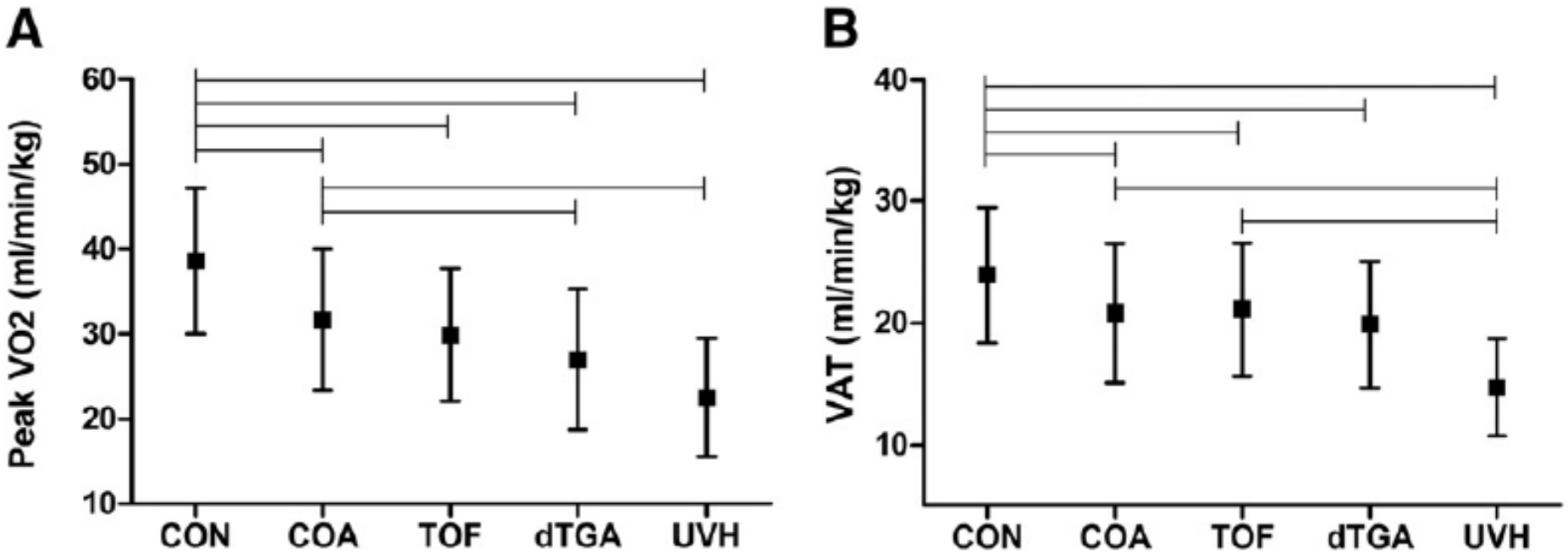
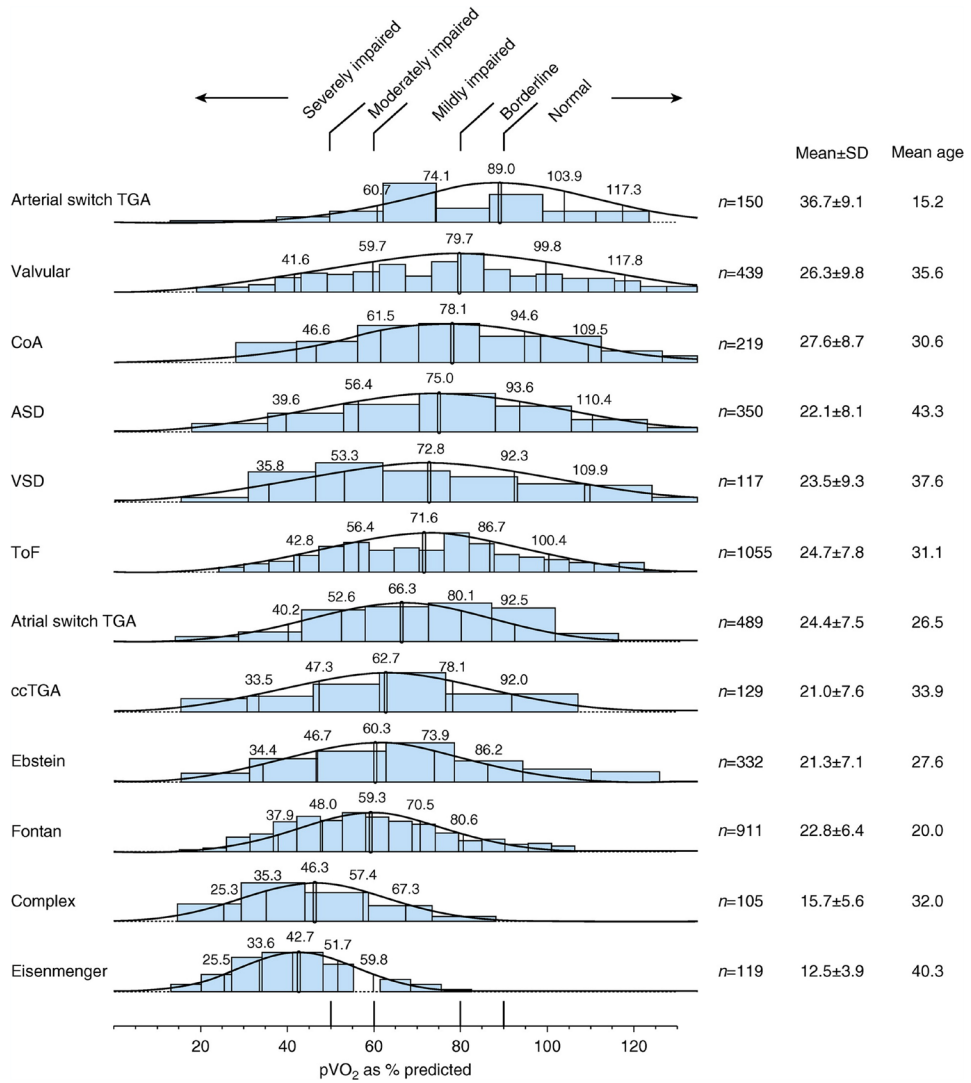


Figure 1. Distribution of peak $\dot{V}O_2$ (peak VO_2) in different diagnostic groups. ccTGA indicates congenitally corrected TGA; VSD, ventricular septal defect.



Buys et al, Measures of exercise capacity in adults with CHD, IJC 2010

Peak VO2 in CHD



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VO2 Requirements for Various Activities

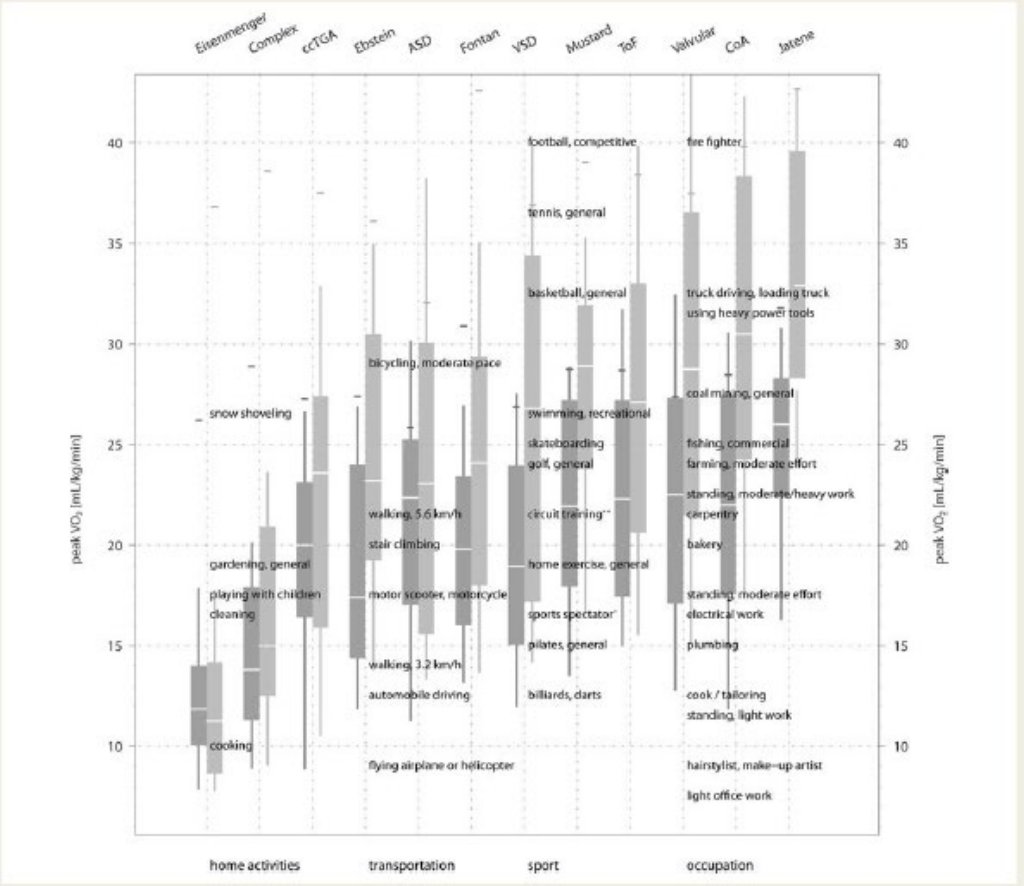

Figure 2 Peak oxygen consumption (peak VO_2) for various diagnostic groups stratified by gender and compared with oxygen consumption derived from estimated average energy expenditure for different types of activities based on values provided in the literature.[5] It should be noted that these are point estimates and differences depending on gender and anthropometric measures as well as dexterity or mechanical efficiency in performing an activity are likely to exist. For details see text. Each box and whiskers graph represents (from bottom to top) the 10, 25, 50, 75, and 90th quantile. Dark grey—female, light grey—male. The short horizontal lines plotted outside the boxes indicate 100% of the predicted peak VO_2 value. (*), sports spectator, very excited, emotional; (**), moderate effort.

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Peak VO2 and M/M

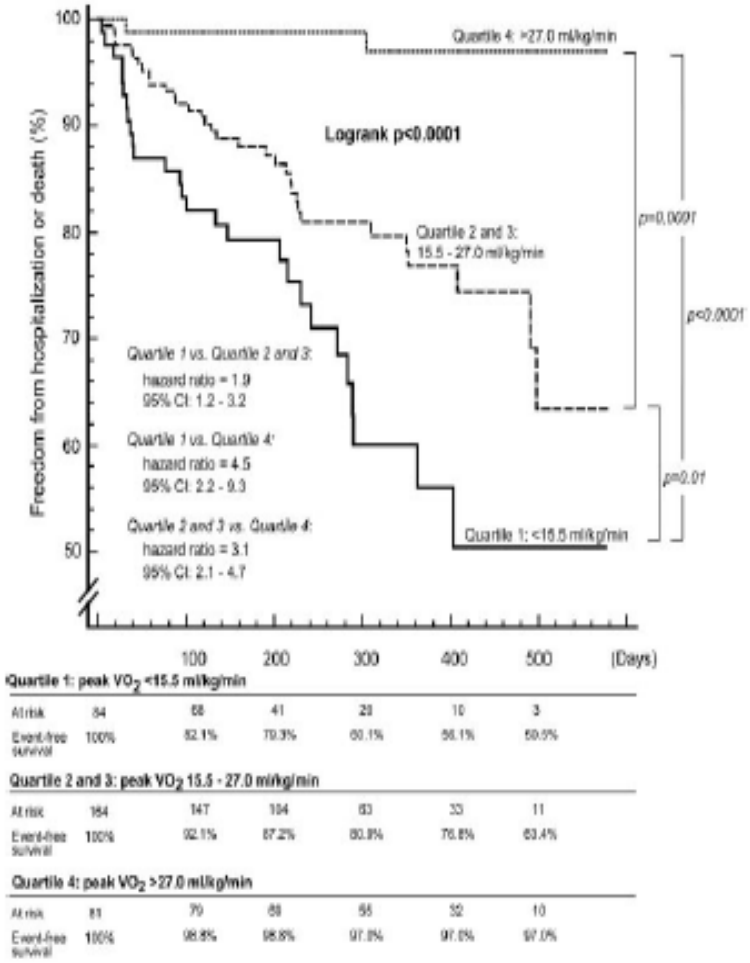

Figure 4. Kaplan-Meier plots for combined end point of hospitalization or death (event-free survival). Patients were classified into increasing quartiles (1 through 4) of peak $\dot{V}o_2$ (peak VO_2), and hazard ratios, 95% CIs, and log-rank probability values for comparisons between quartiles are shown.

TABLE 5. Significant Predictors of Hospitalization or Death on Cox Proportional-Hazards Analysis

	P	Hazard Ratio	95% CI for Hazard Ratio
Single-variable analysis			
NYHA class	<0.001	2.556	1.790–3.652
Peak $\dot{V}o_2$	<0.001	0.908	0.873–0.943
Diagnosis	0.04	...	...
Peak heart rate	<0.001	0.985	0.976–0.991
Age at surgery	0.04	1.018	1.000–1.036
Multivariable analysis			
NYHA class	0.002	2.150	1.317–3.486
Peak $\dot{V}o_2$	0.01	0.937	0.890–0.986

Hazard ratio refers to unit increase in NYHA class, peak $\dot{V}o_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$), heart rate (bpm), and age at surgery (years).

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VE/VCO2 in CHD

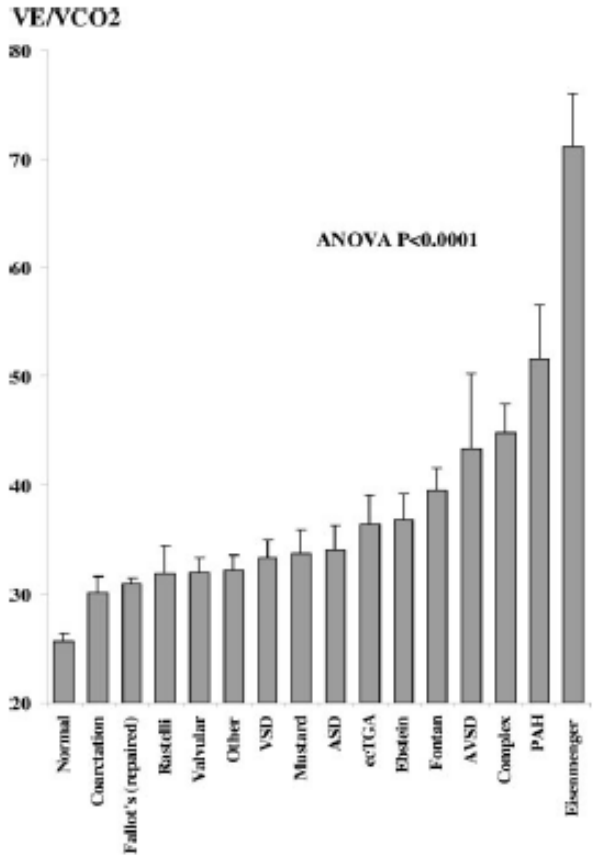
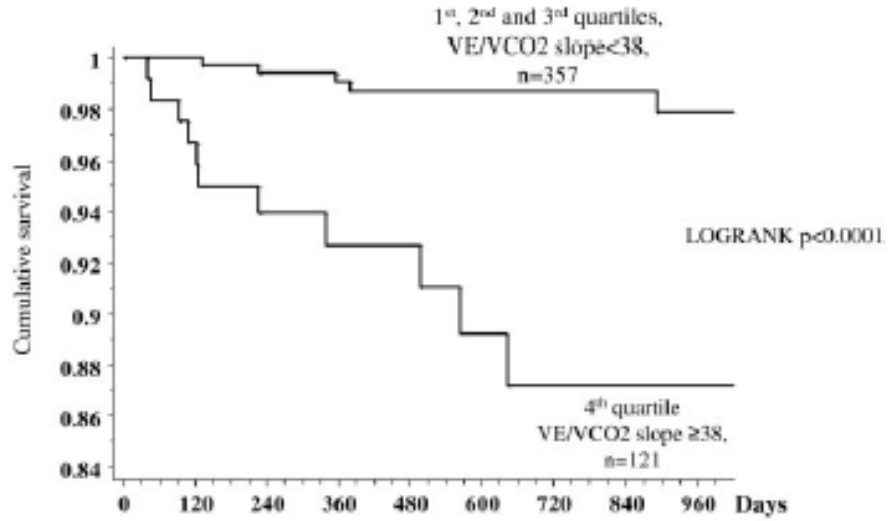


Figure 1. Distribution of the $\dot{V}_E/\dot{V}_{CO_2}$ slope across the different ACHD diagnostic groups and in normal controls (mean and SE). ASD indicates atrial septal defect; AVSD, atrioventricular septal defect; ccTGA, congenitally corrected (L-) transposition of great arteries; PAH, pulmonary arterial disease; and VSD, ventricular septal defect.

Abnormal Ventilatory Response to Exercise in Adults With Congenital Heart Disease Relates to Cyanosis and Predicts Survival

Konstantinos Dimopoulos, Darlington O. Okonko, Gerhard-Paul Diller, Craig S. Broberg, Tushar V. Salukhe, Sonya V. Babu-Narayan, Wei Li, Anselm Uebing, Stephanie Bayne, Roland Wensel, Massimo F. Piepoli, Philip A. Poole-Wilson, Darrel P. Francis and Michael A. Gatzoulis

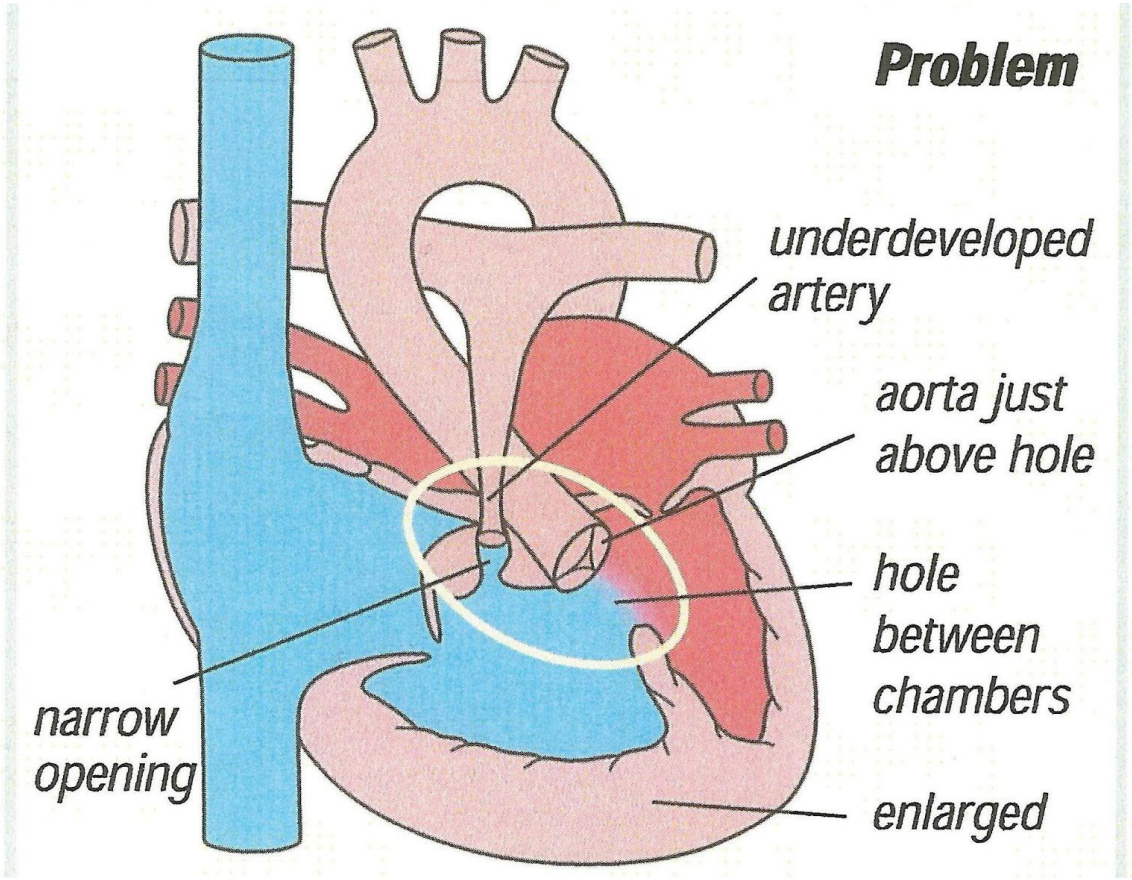
Circulation 2006;113:2796-2802; originally published online Jun 12, 2006;

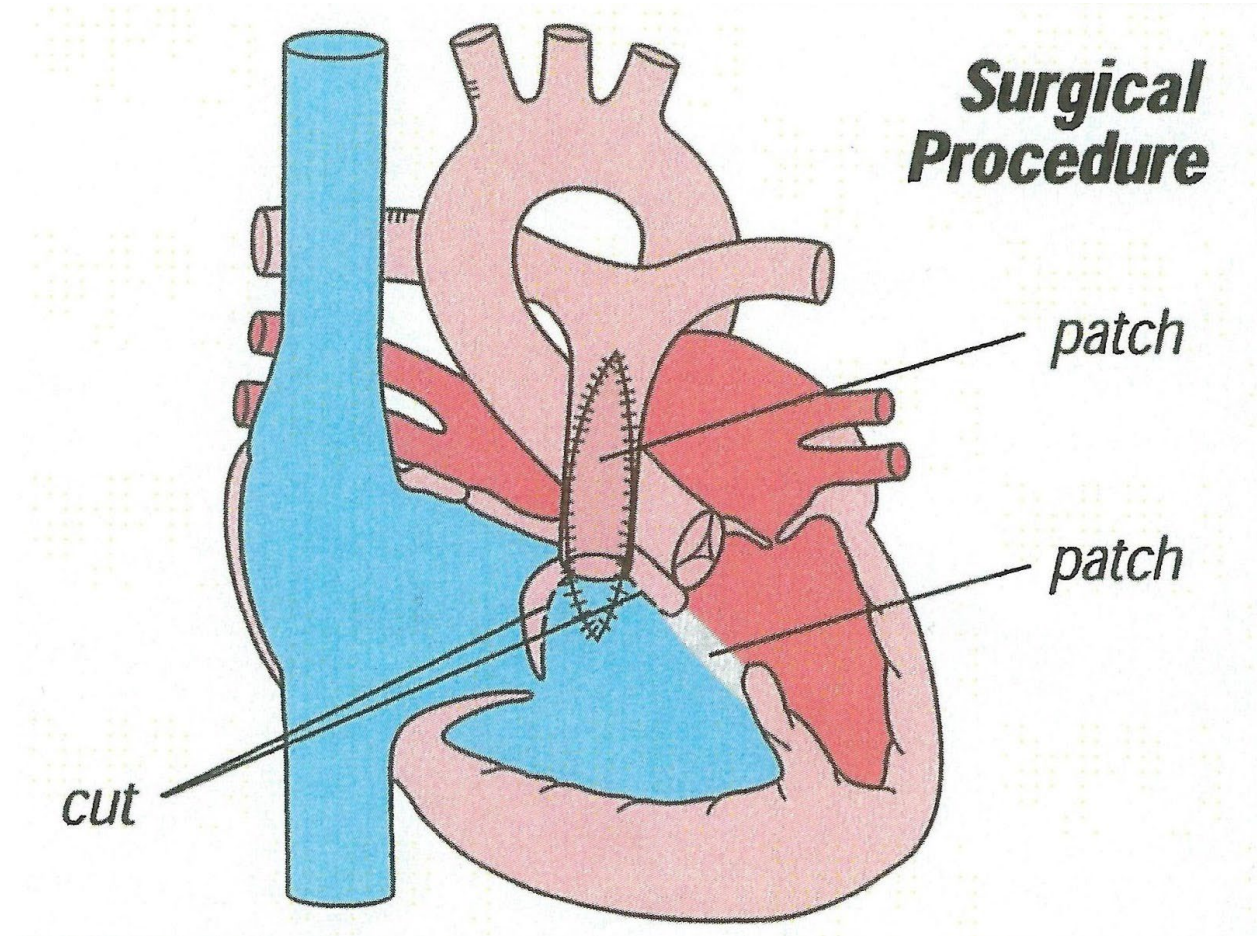


1st, 2nd and 3rd quartile	At risk	357	323	245	167	100
	Events	-	2	4	4	5
	%Cum Survival	100	99.4	98.7	98.7	97.9
4th quartile	At risk	121	90	63	37	22
	Events	-	7	8	11	11
	%Cum Survival	100	94	92.7	87.2	87.2

Figure 2. Kaplan-Meier survival chart of first, second, and third quartiles of $\dot{V}_E/\dot{V}_{CO_2}$ slope in the noncyanotic population versus the fourth quartile ($\dot{V}_E/\dot{V}_{CO_2}$ slope ≥38). %Cum indicates percent cumulative.

Tetralogy of Fallot





TOF

- Adults (mean age 36):
  - Diller et al, JACC 2006: mean peak VO_2 56% predicted
  - Inuzuka et al, Circulation 2012: median peak VO_2 71% predicted; only 25% had a peak VO_2 > 85% predicted
- Children/adolescents (mean age 12.5):
  - Mahle et al, Ped Card 2002: Peak VO_2 averaged 95% predicted

TOF

- Age related decrease in VO2
- Hemodynamic issues that worsen with time
  - Incompetent PV/PI
  - Residual stenoses
  - Ventricular function
    - RV function: MRI RVEF correlated with VO2
    - RV/LV interaction due to significant RV enlargement (stroke volume)

TOF

- VE/VCO2 elevation and decreased VO2 correlate with PBF maldistribution (V/Q mismatch)
- Amount of PI may not be the primary factor: since PVR decreases with exercise therefore less PI
- Increased gradient across residual stenoses with exercise
- Improvement (post-cath) in PA stenoses showed improved VE/VCO2 and VO2

CPET in TOF

Table 3
Significant univariate and multivariate predictors of death and hospitalization

Variable	p Value	Hazard Ratio	95% CI
Univariate analysis			
NYHA functional class	<0.001	2.286	1.789–3.324
Peak heart rate (beats/min)	<0.001	0.982	0.966–0.998
Right ventricular systolic pressure (mm Hg)	0.002	1.021	1.014–1.036
Peak oxygen uptake (% of predicted)	<0.001	0.962	0.934–0.992
VE/VCO_2 slope	<0.001	1.098	1.046–1.148
Pulmonary regurgitation	<0.001	1.762	1.256–1.987
Right ventricular systolic function	<0.001	1.934	1.623–2.134
Multivariate analysis			
NYHA functional class	0.001	2.118	1.344–3.542
Peak oxygen uptake (% of predicted)	0.01	0.974	0.950–0.994
VE/VCO_2 slope	0.002	1.076	1.038–1.115

Hazard ratios refer to unit increases in NYHA functional class, peak oxygen uptake (percent of predicted), VE/VCO_2 slope, heart rate (beats/min), and right ventricular systolic pressure (mm Hg).

Usefulness of Cardiopulmonary Exercise to Predict Long-Term Prognosis in Adults With Repaired Tetralogy of Fallot

Alessandro Giardini, MD[a,*], Salvatore Specchia, MD[b], Theresa Ann Tacy, MD[c], Gloria Coutsoumbas, MD[b], Gaetano Gargiulo, MD[a], Andrea Donti, MD[a], Roberto Formigari, MD[a], Marco Bonvicini, MD[a], and Fernando Maria Picchio, MD[a]

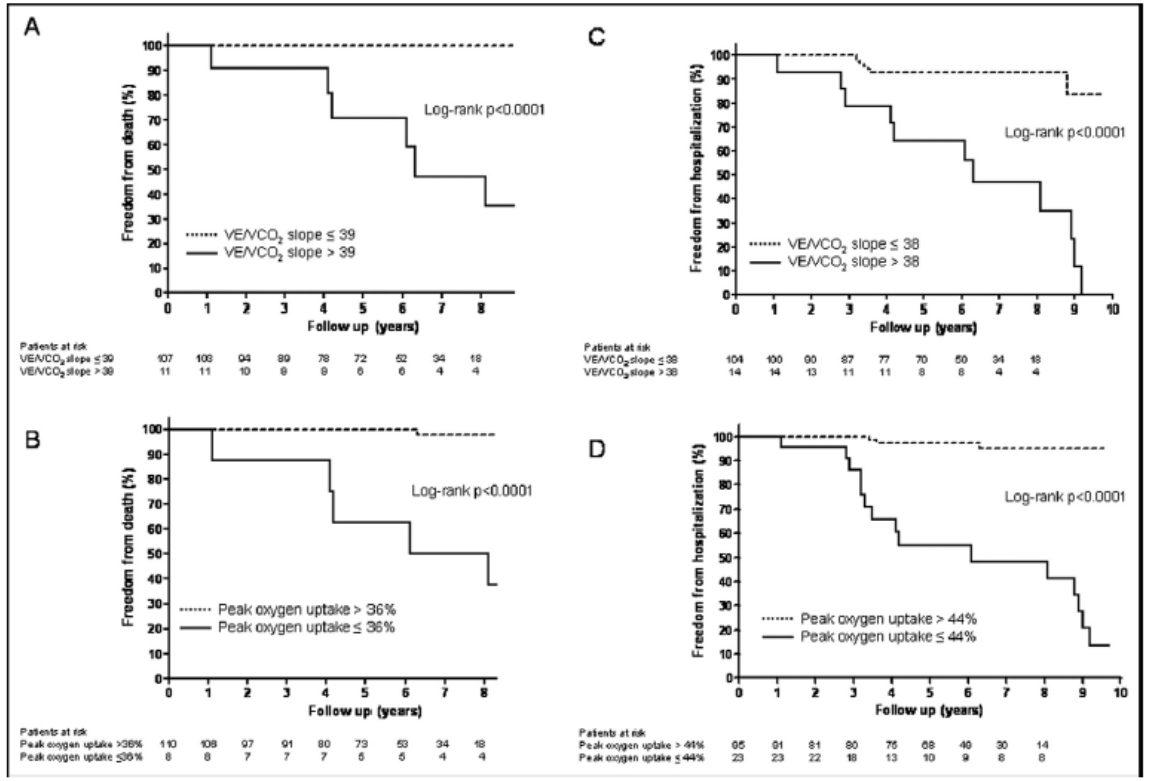


Figure 1. Kaplan-Meier plots for the end points of death *(A, B)* and hospitalization *(C, D)*. Patients were stratified using the cut-off values for peak oxygen uptake and VE/VCO_2 slope provided by receiver-operating characteristic curve analysis.

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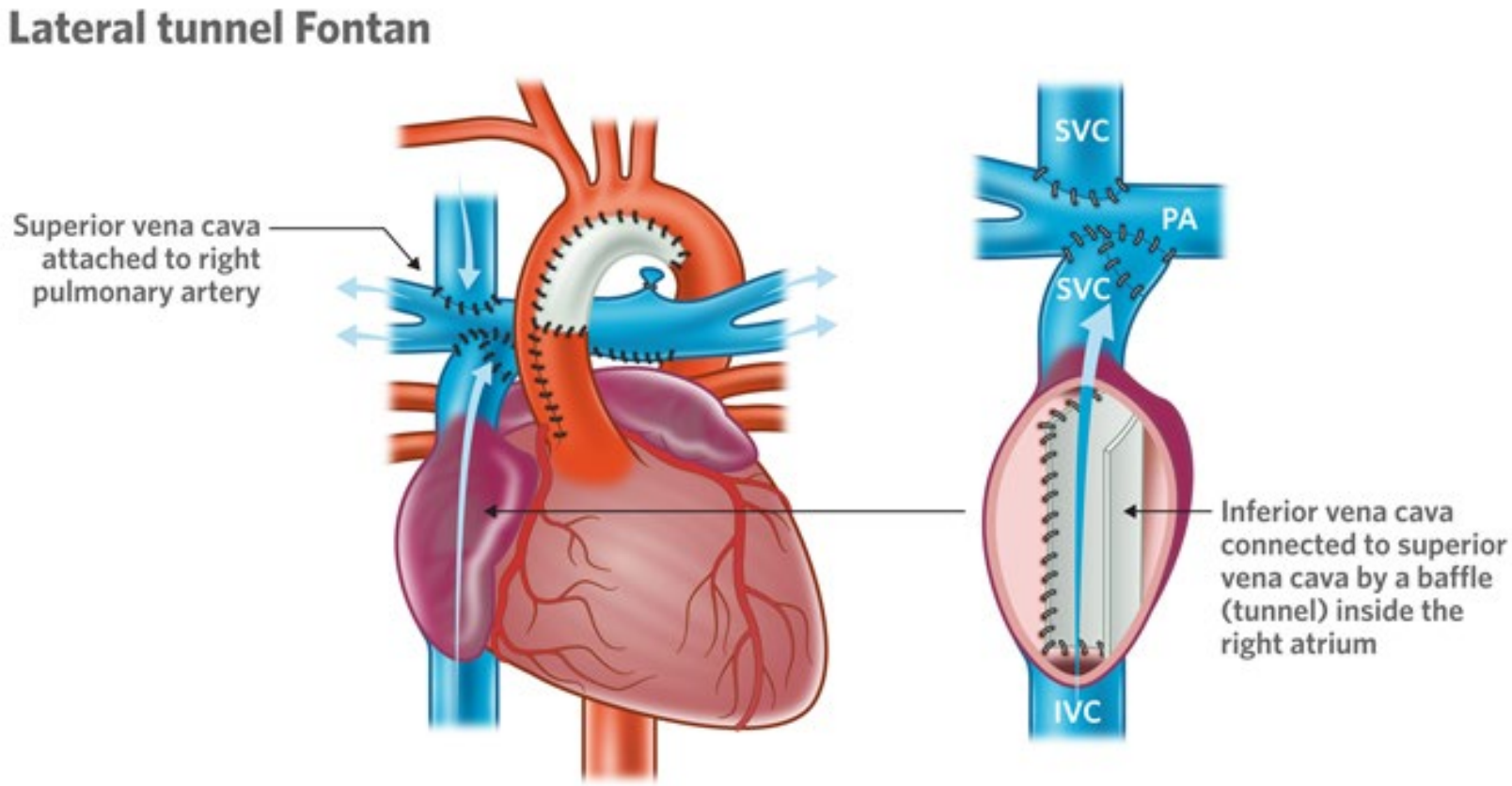
Fontan



Fontan

- Physiologic issues
  - No sub-pulmonary ventricle
  - Passive venous return to lungs with variable muscle pump support
    - Skeletal muscle abnormalities affect preload, afterload, and O2 extraction
  - Lower CO and SV at rest and with exercise
  - Preload dependent
  - Chronotropic incompetence
- Exercise compensation
  - Increased O2 extraction
  - Peak HR may be lower, but HR at a given VO2 is usually higher

Fontan Peak VO2

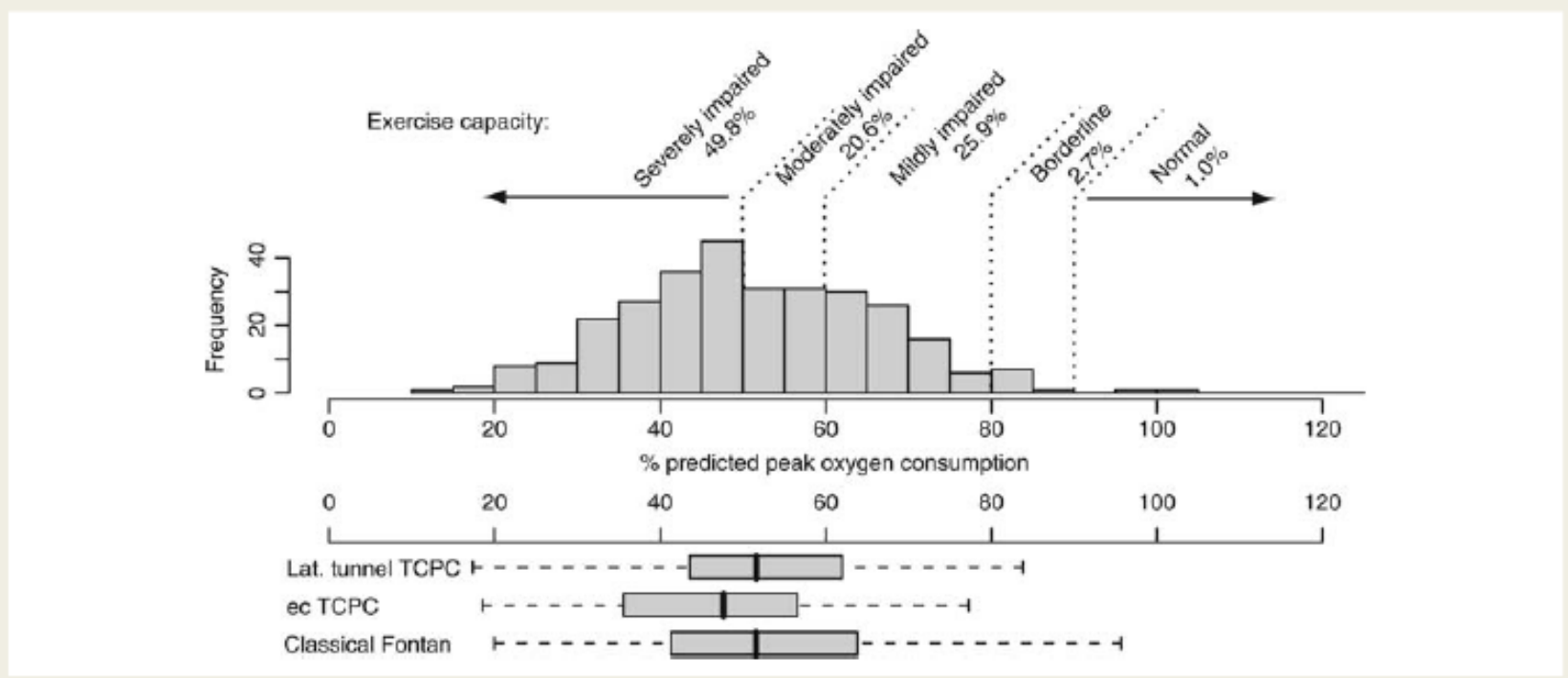


Figure 1 Distribution of % predicted peak oxygen consumption in patients after Fontan operation and its distribution in patients with different types of Fontan surgery.

Diller et al, predictors of morbidity and mortality in Fontan patients, EHJ 2010

CPET Abnormalities

- Median peak VO2 50-60% predicted
- VO2 declines steeply during adolescence
- Inability to increase stroke volume is likely the biggest cause of exercise limitations (not usually due to ventricular systolic functional impairment)
- Muscle pump: resistance training increased leg muscle mass and exercise performance (increased preload); known reduced skeletal muscle mass in the Fontan population

  Cordina et al, Resistance training improves cardiac output…, IJC 2013

  Avitabile et al, Lean leg mass correlates with exercise systemic output… Heart, 2018

- Elevated VE/VCO2
  - V/Q mismatch due to absent pulmonary artery pulsatility
  - R to L shunting
- Lower FVC and FEV1 (usually proportional)

Fontan – Younger Patients

- Harteveld et al, IJC 2021
- Ages 8-18 yrs
- Reduced diastolic function (based on TDI) and increased arterial stiffness
- Peak HR 174 bpm (93% predicted), peak VO2 ~54% predicted, O2 pulse 58% predicted
  - Suggests low SV with preserved chronotropy
- Higher resting HR was associated with lower peak VO2
- No sig differences between single LV vs. RV

CPET Prognostic Value in Fontan

- Fernandes et al, CHD 2011: Peak VO2 < 16.6 ml/kg/min = HR 7.5, peak HR < 123 = HR 10.6; if above those cut-offs and VAT > 9 ml/kg/min, 98% NPV for mortality over a median of ~4 years
- Inuzuka et al, Circ 2012: combination of % predicted VO2 and HRR had greater predictive value for mortality
- Diller et al, EHJ 2010: CPET parameters associated with increased risk of hospitalization, not mortality
- Egbe et al, IJC 2017: decline in % pred VO2 of > 3%/yr strongly predicted ACE
- Cunningham et al, AHJ 2017: 10% decline between CPET 6-30 months apart associated with 2x risk of death or need for transplant (even after adjusting for baseline peak VO2)

FUEL Trial

- Decreasing PVR should allow for greater venous return, more PBF, and therefore higher stroke volume
- Udenafil did not significantly increase peak VO2
- VO2 @ AT was mildly improved
- Future study questions:
  - Greater impact in those with baseline pulmonary vascular issue?
  - Systemic venous (mal)effect with vasodilators?
  - Could improved skeletal muscle mass and function help?

Trends Over Time in Fontan Patients

Table 2 Change in peak exercise performance from Fontan I to Fontan III

Characteristic	*N*	Fontan I	Fontan III	Annualized change	*p* value*
Age at exercise testing	95	13.7 ± 2.8	23.1 ± 2.9		< 0.001
Peak VO_2, mL/kg/min	95	28.1 ± 6.2	26.6 ± 7.5	− 0.2 ± 0.7	0.03
% predicted VO_2	95	68.5 ± 14.3	61.4 ± 15.9	− 0.8 ± 1.7	< 0.001
Peak work rate, W	95	101.1 ± 40.2	128.2 ± 39.2	2.9 ± 4.6	< 0.001
% predicted peak work rate	95	68.7 ± 15.4	55.6 ± 15.9	− 1.4 ± 1.6	< 0.001
Maximum respiratory rate	95	52.6 ± 12.3	45.9 ± 10.7	− 0.7 ± 1.2	< 0.001
Peak heart rate	95	161.0 ± 20.5	153.3 ± 23.7	− 0.8 ± 2.1	< 0.001
% predicted peak heart rate	95	78.0 ± 9.8	77.8 ± 11.9	− 0.0 ± 1.0	0.85
Resting O_2 saturation	94	94.1 ± 4.2	93.2 ± 4.4	− 0.1 ± 0.4	0.03
Peak O_2 saturation	89	91.4 ± 5.0	90.7 ± 4.4	− 0.1 ± 0.5	0.13

VO_2 oxygen consumption, *W* Watts, *O_2* oxygen

*Paired Student's *t* test

Table 3 Change in exercise performance at the ventilatory anaerobic threshold from Fontan I to Fontan III

Characteristic	*N*	Fontan 1	Fontan 3	Annualized change	*p* value*
Age at exercise testing	270	12.2 ± 3.2	21.6 ± 3.3		< 0.001
VO_2 at VAT, mL/kg/min	196	19.4 ± 6.5	17.0 ± 5.7	− 0.3 ± 0.6	< 0.001
% predicted VO_2 at VAT	196	80.0 ± 24.7	72.1 ± 24.8	− 0.8 ± 2.6	< 0.001
% predicted FVC	251	76.1 ± 14.9	81.6 ± 16.7	0.6 ± 1.5	< 0.001
% predicted FEV1	247	76.7 ± 15.2	81.1 ± 16.3	0.5 ± 1.6	< 0.001
FEV1/FVC at rest	248	88.8 ± 8.0	85.7 ± 7.8	− 0.3 ± 1.0	< 0.001
VE/VCO_2 at VAT	194	43.4 ± 10.7	33.4 ± 4.6	− 1.1 ± 1.1	< 0.001
Resting O_2 saturation	262	94.2 ± 4.0	93.4 ± 4.6	− 0.1 ± 0.5	0.001

*Paired Student's *t* test

VO_2 oxygen consumption, *VAT* ventilatory anaerobic threshold, *FVC* forced vital capacity, *FEV1* forced expiratory volume in 1 s, *VE/VCO_2* ratio of minute ventilation to carbon dioxide production, *O_2* oxygen

Goldberg et al, Exercise capacity and predictors of performance after Fontan (PHN Fontan 3 study), Ped Card 2021

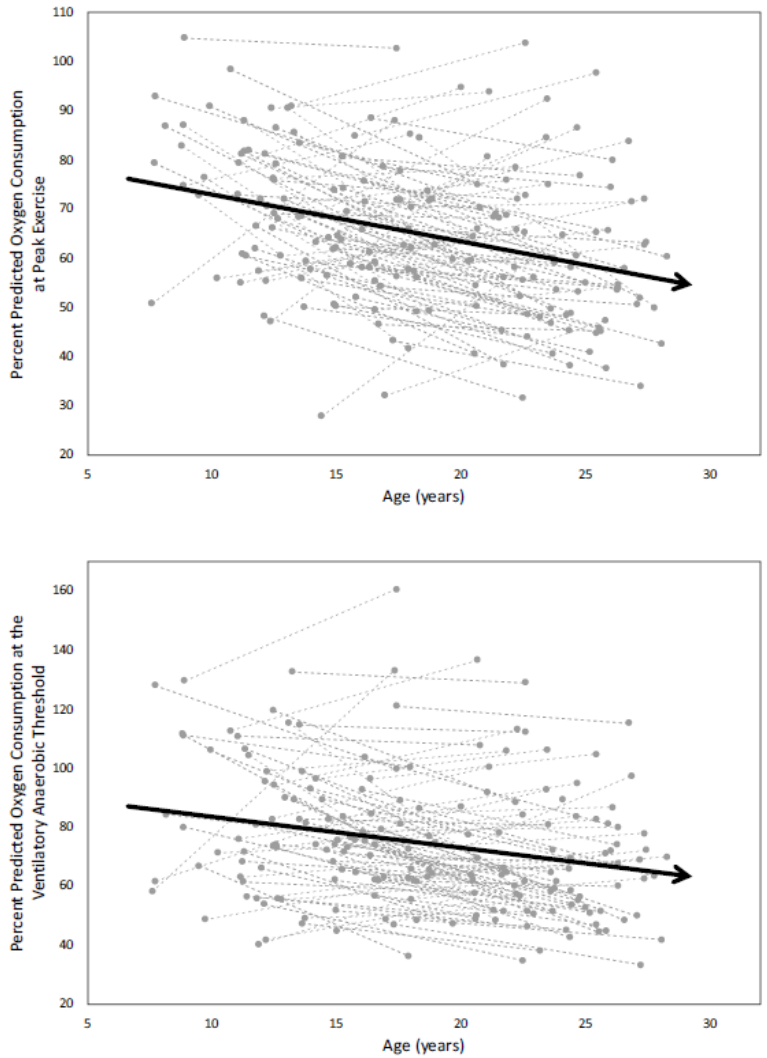


Fig. 2 Longitudinal percent-predicted exercise data for individual subjects with **a** paired maximal tests (VO_2) and **b** paired data at the ventilatory anaerobic threshold (VAT). The dashed lines represent each participant, while the solid lines with arrows represents the trend line for the cohort. Both plots demonstrate a decline in exercise capacity from Fontan 1 to Fontan 3

Table 4 Exercise performance at Fontan III divided into tertiles by percent predicted peak oxygen consumption

Characteristic	Total		Tertile 1		Tertile 2		Tertile 3		*p* value
	N	Mean ± SD or *n* (%)	*N*	Mean ± SD or *n* (%)	*N*	Mean ± SD or *n* (%)	*N*	Mean ± SD or *n* (%)	
Peak VO_2, mL/kg/min	275	26.1 ± 7.3	91	19.5 ± 4.0	92	26.1 ± 4.8	92	32.6 ± 6.1	<0.001*
Percent predicted peak VO_2 (%)	275	60 ± 16	91	43 ± 7	92	59 ± 4	92	78 ± 11	<0.001*
Age at exercise testing, years	275	21.1 ± 3.3	91	21.4 ± 3.6	92	21.7 ± 3.2	92	20.2 ± 3.0	0.007*
Height, cm	275	168.9 ± 9.3	91	169.2 ± 9.7	92	169.0 ± 9.2	92	168.6 ± 9.0	0.89*
Weight, kg	275	67.0 ± 15.7	91	72.3 ± 20.0	92	66.6 ± 13.4	92	62.1 ± 10.9	<0.001*
BMI categories	275		91		92		92		<0.001†
Normal		196 (71%)		52 (57%)		64 (70%)		80 (87%)	
Overweight		51 (19%)		20 (22%)		19 (21%)		12 (13%)	
Obese		28 (10%)		19 (21%)		9 (10%)		0 (0%)	

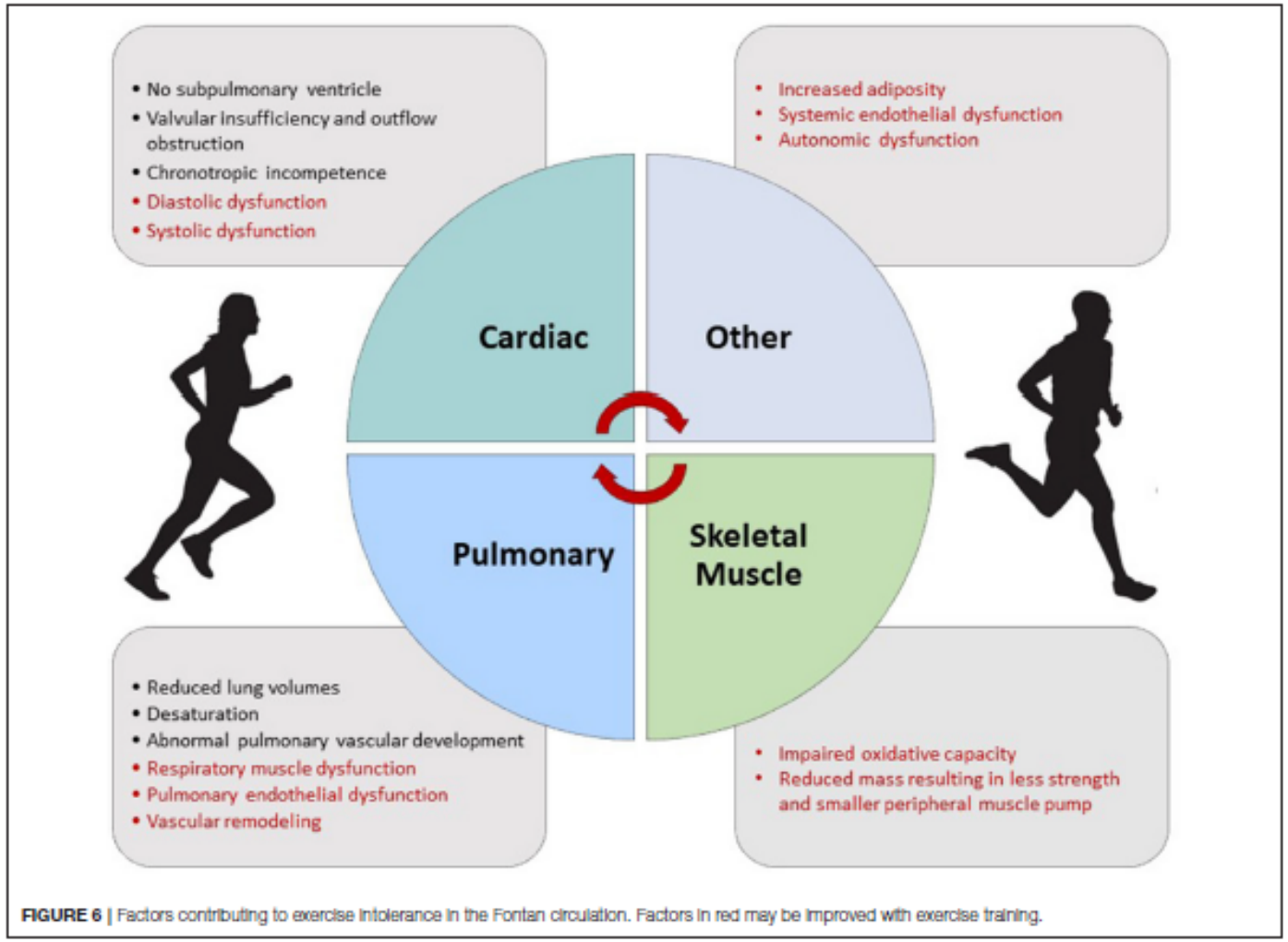


FIGURE 6 | Factors contributing to exercise intolerance in the Fontan circulation. Factors in red may be improved with exercise training.

Tran et al. Exercise Intolerance, Benefits, and Prescription for People Living With a Fontan Circulation: The Fontan Fitness Intervention Trial (F-FIT)—Rationale and Design. Frontiers in Pediatrics, 2022

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“Super” Fontan

Tran et al, The “Super-Fontan” Phenotype: Characterising Factors Associated with High Physical Performance, Frontiers in Pediatrics, 2021

- Compared subset of Fontan patients with peak VO2 > 80% predicted (“super-Fontan) to a Fontan control group
- Average age ~ 29 yrs, 48% male
- Spent 4.3 hrs vs. 2 hrs in weekly sports/physical activity
- Greater reported time in physical activity when younger
- Super-Fontan group more likely had a healthy weight and had a dominant LV

TABLE 1 | Participant demographics.

	All Fontan Participants		“Super-Fontan”		Control		*p*-value
	n		*n*		*n*		
Sex (males), *n* (%)	60	29 (48.3%)	15	5 (33.3%)	45	24 (53.3%)	0.18
Age, years	60	28.7 ± 7.6	15	27.9 ± 5.7	45	28.9 ± 8.2	0.53
BMI, kg/m^2	60	25.9 ± 4.7	15	24.4 ± 2.7	45	26.3 ± 5.1	0.34
Obese, *n* (%)	60	10 (16.7%)	15	0 (0%)	45	10 (22.2%)	**0.046**
Type of Fontan, *n* (%)	60		15		45		0.75[a]
APC		18 (30.0%)		4 (26.7%)		14 (31.1%)	
LT		23 (38.3%)		8 (53.3%)		15 (33.3%)	
ECC		19 (31.7%)		3 (20.0%)		16 (35.6%)	
Dominant ventricle, *n* (%)	60		15		45		**0.043**[b]
Left		37 (61.7%)		13 (86.7%)		24 (53.3%)	
Biventricular		3 (5%)		1 (6.7%)		2 (4.4%)	
Indeterminant		4 (6.7%)		0 (0%)		4 (8.9%)	
Right		16 (26.7%)		1 (6.7%)		15 (33.3%)	
Age at Fontan palliation, years	60	6.4 ± 5.0	15	4.0 ± 2.9	45	7.2 ± 5.3	**0.002**
Patent fenestration, *n* (%)	60	10 (16.7%)	15	1 (6.7%)	45	9 (20%)	0.23
Time since Fontan palliation, years	60	22.2 ± 5.6	15	23.9 ± 4.2	45	21.7 ± 6.0	0.19

APC, atriopulmonary connection; BMI, body mass index; ECC, extra cardiac conduit; LT, lateral tunnel.
[a]*APC vs. total cavopulmonary connection.*
[b]*Dominant left ventricle, biventricular, or indeterminant ventricle vs. dominant right ventricle. Bold values denote statistical significance ($p < 0.05$).*

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“Super” Fontan

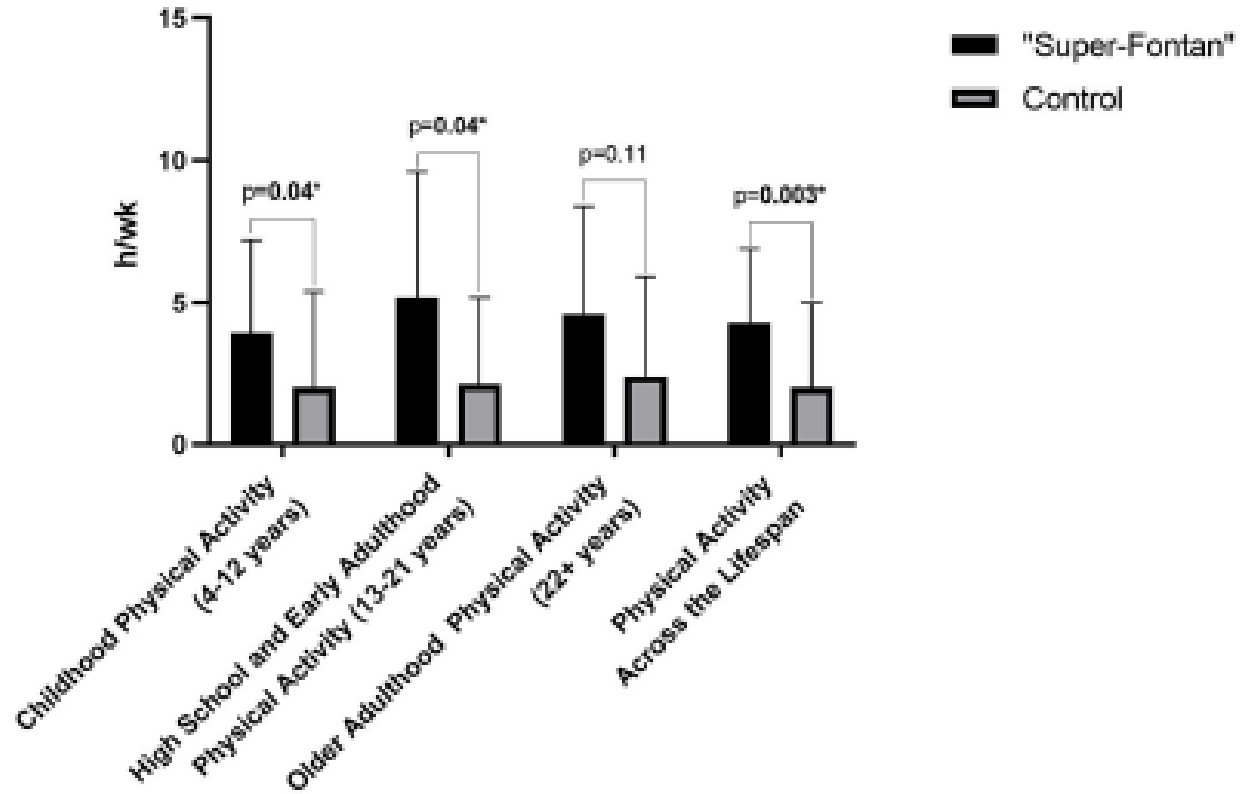

FIGURE 1 | Hours per week (h/wk) spent participating in sports and physical activity.

Exercise Training in Fontan Patients

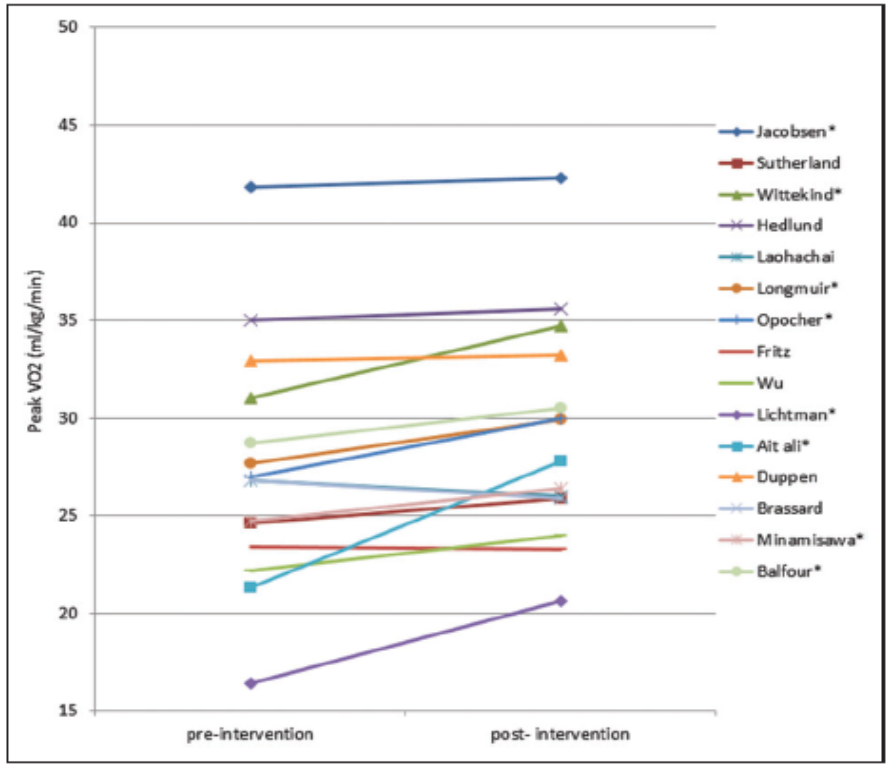

Figure 2. Peak oxygen uptake (VO_2) changes before and after training.
Cordina et al. is not shown, the study only mentioned improvement of peak VO_2 in ml/min and percentage of predicted. *Significant increase.

Sheffers et al, Physical exercise training in patients with a Fontan circulation: A systematic review, EJPC, 2020

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Fontan and Exercise Capacity

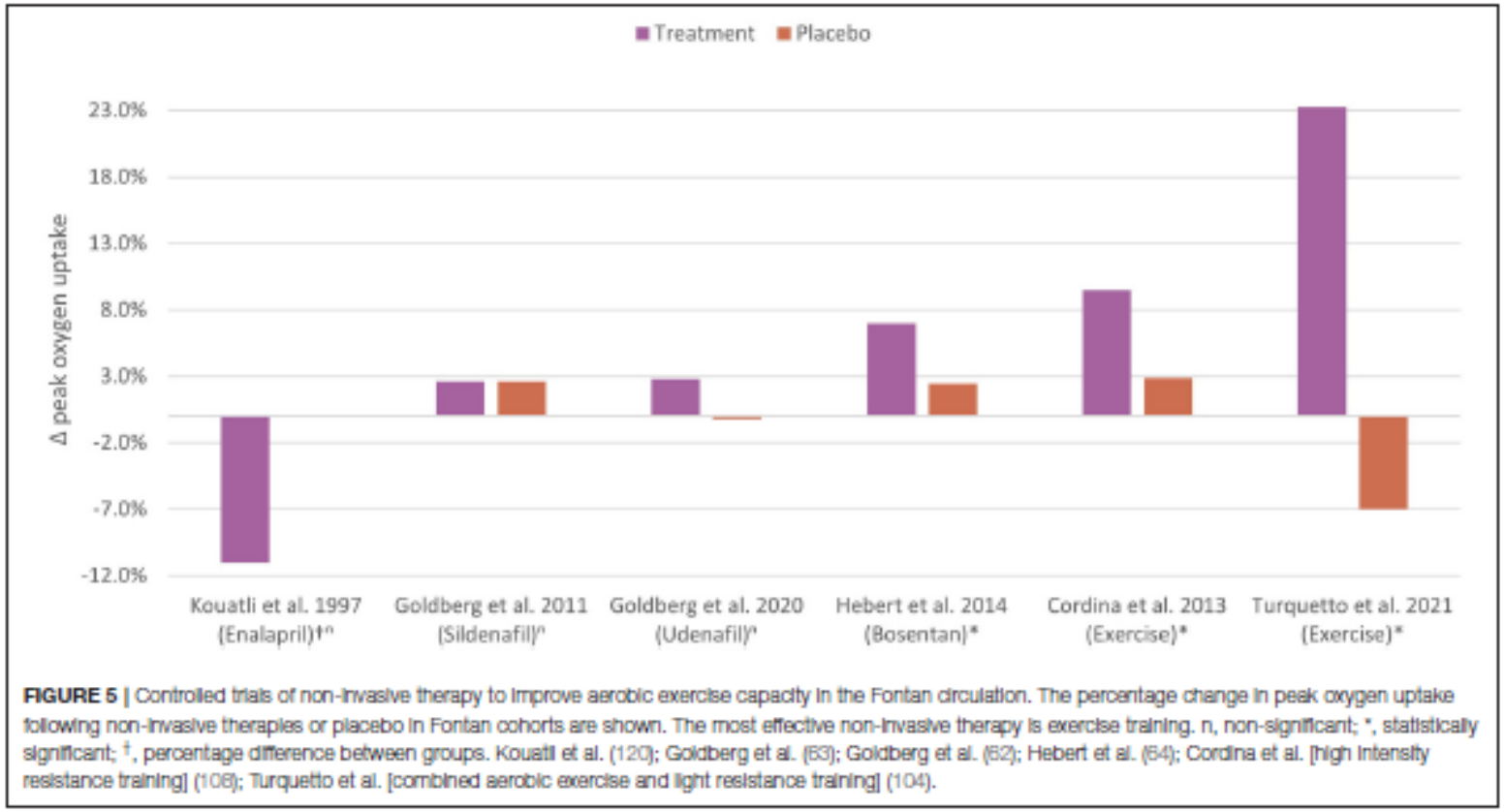

FIGURE 5 | Controlled trials of non-invasive therapy to improve aerobic exercise capacity in the Fontan circulation. The percentage change in peak oxygen uptake following non-invasive therapies or placebo in Fontan cohorts are shown. The most effective non-invasive therapy is exercise training. n, non-significant; *, statistically significant; †, percentage difference between groups. Kouatli et al. (120); Goldberg et al. (63); Goldberg et al. (62); Hebert et al. (64); Cordina et al. [high intensity resistance training] (108); Turquetto et al. [combined aerobic exercise and light resistance training] (104).

Tran et al. Exercise Intolerance, Benefits, and Prescription for People Living With a Fontan Circulation: The Fontan Fitness Intervention Trial (F-FIT)—Rationale and Design. Frontiers in Pediatrics, 2022

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Exercise Training

Amir et al; Exercise training in paediatric CHD: fit for purpose? Arch dis child, 2021

- Review of many (small) studies of exercise prescriptions and formal rehabilitation programs have shown:
  - Increased peak VO2 in many (but not all studies); sometimes increased submaximal measures, e.g. VO2 at AT
  - Increased daily recorded activity level (use of activity trackers or other tech, even in young ages 5-10 yrs)
  - Improved perceived exercise function
  - Positive psychological impacts
  - Very low risk
- Survival/mortality benefits still unknown

Exercise Training and Rehab

Home based CR strategies have also mostly shown some improvement in exercise capacity

Table 2

Cardiac Rehabilitation and Exercise Training in Pediatric Congenital Heart Disease

Reference	Diagnosis	n	Age, yr	Program Training	Outcome
McBride et al (2007)[4]	Heart failure awaiting TX	20	13 ± 3.2	3 sessions/wk aerobic and resistance	Increased work efficiency (*10%*)
Duppen et al (2015)[12]	CHD and acquired heart disease	7	13-19	4-5 sessions/wk aerobic	Increased $\dot{V}O_2$ (*20%*) and TM time (*21%*)
Brassard et al (2006)[8]	Fontan	7	11-26	3 sessions/wk aerobic and resistance (↓ resting SBP 9 mm Hg)	Improved skeletal muscle function
Hedlund et al (2016)[16]	TOF/Fontan	93	10-25	3 sessions/wk aerobic	Improved $\dot{V}O_2$ (*5%*)
Longmuir et al (1991)[11,a]	CHD	129	10-16	2 sessions/wk	Improved $\dot{V}O_2$
Opocher et al (2005)[9]	Fontan	10	7-12	2 sessions/wk home training 2 times/wk	Improved $\dot{V}O_2$ (*15%*) Increased O_2P (*19%*)
Rhodes et al (2005, 2006)[5,6]	CHD	30	8-17	2 sessions/wk aerobic and resistance	Improved $\dot{V}O_2$ (*14%*) Improved work (*12%*) Improved VAT (*18%*)
Avitabile et al (2014)[17] and Kirk et al (2014)[18]	Fontan, DCM	18	8-31	2 sessions/wk aerobic	Improved $\dot{V}O_2$ (*11%*) Increased O_2P (*12%*)

Abbreviations: 6MWT, 6-min walk test; CHD, congenital heart disease; DCM, dilated cardiomyopathy; O_2P, oxygen pulse; SBP, systolic blood pressure; TOF, tetralogy of Fallot; TM, treadmill; TX, transplant; VAT, ventilatory anaerobic threshold; $\dot{V}O_2$, oxygen uptake.

[a]Data unavailable in online text.

McBride et al, Cardiopulmonary Rehabilitation in Pediatric Patients With Congenital and Acquired Heart Disease, JCRP, 2020

So What Can You Do?

- Screen for physical activity levels
- Gauge fears/anxiety of patients and families regarding exercise
- Encourage patients and families to make small changes and add time daily for physical activity
- Encourage a variety of activities, short and longer duration, cardio, strength training, coordination, and flexibility
- Schedule check-ups a few months before the sports season and refer to cardiology for any concerns

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