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WHITE PAPER

The Society of Thoracic Surgeons (STS)/World Society for Pediatric and Congenital Heart Surgery (WSPCHS)/European Congenital Heart Surgeons Association (ECHSA) Expert Opinion on the Role of Exercise Testing in Determining Optimal Timing of Pulmonary Valve Replacement in Tetralogy of Fallot

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ABSTRACT

BACKGROUND Optimal timing of pulmonary valve replacement (PVR) after surgical repair of tetralogy of Fallot remains uncertain. Cardiopulmonary exercise testing (CPET) has been proposed as a tool in determining timing, but clear guidelines are lacking.

METHODS The Society of Thoracic Surgeons (STS) Workforce on Evidence-Based Surgery, in collaboration with the World Society for Pediatric and Congenital Heart Surgery and European Congenital Heart Surgeons Association, convened a writing committee to review available literature and compile expert opinions on the role of CPET in the timing of PVR.

RESULTS After the committee reviewed and extracted data from 17 articles, expert opinions were agreed upon, including the following: (1) CPET is a useful tool in assessing patients' cardiorespiratory system in a dynamic state but requires knowledge and experience to perform and interpret the results; (2) CPET provides prognostic information for patients with tetralogy of Fallot, but optimal use in the timing of PVR remains unclear and varies based on specific patient scenarios; and (3) further research is needed to define optimal CPET variables and thresholds for action.

The Supplemental Tables can be viewed in the online version of this article [https://doi.org/10.1016/j.athoracsur.2026.05.010] on https://www.annalsthoracicsurgery.org.

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CONCLUSIONS CPET is an important adjunct in evaluating patients after surgical repair of tetralogy of Fallot, but optimal use requires further research.

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Although there have been advances in the management of tetralogy of Fallot (ToF), residual lesions after ToF repair have been of significant longitudinal concern, the most common of which is pulmonary regurgitation. Severe pulmonary regurgitation can be well tolerated for many years, but over time leads to right ventricular (RV) dilation, RV systolic dysfunction, progressive tricuspid valve disease, and atrial and ventricular arrhythmias. Because pulmonary regurgitation is well tolerated, pulmonary valve replacement (PVR) done too early increases the lifetime number of procedures that a patient undergoes and increases risk for potential complications associated with those procedures.

With the advent of percutaneous PVR, there is renewed interest in earlier PVR because secondary downstream procedures may be associated with lower risk, although this remains controversial because downstream surgical procedures may also be associated with higher risk. Optimal timing of PVR in ToF remains elusive.

Because symptoms and exercise capacity can be important to the timing of PVR, but details regarding cardiopulmonary exercise testing (CPET) are limited in the current guidelines, we first formulated key clinical questions using a Population, Intervention, Comparison, Outcomes (PICO) framework and completed a comprehensive review of the literature regarding these questions. Owing to limitations in available research, we then broadened the scope of the project to provide an expert opinion guidance document. Our goal output was 4-fold:

1. Define the appropriate objective CPET variables.
2. Elaborate on the use of exercise testing in both symptomatic and asymptomatic patients.
3. Evaluate the utility of exercise testing in specific populations, such as pediatric patients, elderly patients, and patients with obesity and sedentary lifestyles, highly trained athletes, and patients with very limited exercise capacity.
4. Highlight potential directions for future research to optimize the utility of exercise testing in the management of pulmonary regurgitation and timing of PVR.

METHODS

In 2022, the Society of Thoracic Surgeons (STS) Workforce on Evidence-Based Surgery, in collaboration with representatives from the World Society for Pediatric and Congenital Heart Surgery, convened a writing committee to develop expert guidance on exercise in patients undergoing PVR after repaired ToF. The committee included experienced clinicians and researchers from leading global institutions, each bringing significant expertise in pediatric and congenital heart surgery. All members provided detailed disclosures of any potential conflicts of interest.

The writing committee initially conducted a comprehensive review of the available literature, focusing on the timing and indications for PVR in repaired ToF, with specific emphasis on exercise and PVR as part of a broader clinical practice guideline. Owing to the limited body of evidence, the scope was narrowed, leading to the development of this expert opinion document. In addition, the committee formulated key clinical question(s) using the PICO framework, with a focus on:

1. Which exercise variables are associated with adverse outcomes in patients undergoing PVR for repaired ToF?
   a. Is there rationale for using peak oxygen consumption ($\dot{V}O_2$), predicted peak $\dot{V}O_2$, and/or expired volume per minute ($\dot{V}e$)/volume of carbon dioxide production (V_{CO_2})?
2. Can preoperative exercise metrics predict improved postoperative exercise metrics?

In collaboration with the writing committee, a medical librarian developed a comprehensive search strategy for PubMed and Embase databases. Details of the search strategy are provided in Supplemental Table 1. The search was restricted to studies involving human participants, published

Abbreviations and Acronyms

BMI = body mass index
CHD = congenital heart disease
CO_2 = carbon dioxide
CPET = cardiopulmonary exercise testing
HR = heart rate
O_2 = oxygen
O_2 pulse = oxygen pulse (Volume of oxygen delivered per heartbeat)
PICO = Population, Intervention, Comparison, Outcomes
PVR = pulmonary valve replacement
RV = right ventricle, right ventricular
STS = Society of Thoracic Surgeons
ToF = tetralogy of Fallot
$\dot{V}O_2$ = oxygen consumption
$\dot{V}O_2$ max = maximal oxygen consumption
$\dot{V}E$ = expired volume per minute
$\dot{V}E/VCO_2$ = ventilatory efficiency ratio (expired volume per minute/carbon dioxide production)

in English, with no limits on the publication date (from inception through October 2023) or study design but excluded gray literature. Hand searches of other databases and bibliographies of selected articles were also performed to supplement the initial results.

The primary search yielded 113 potentially relevant articles after duplicates were removed. The writing committee used a 2-stage screening process using Covidence, a collaborative online platform. The first stage involved screening titles and abstracts, followed by a full-text review for inclusion in the second stage. Disagreements were harmonized through comprehensive discussion. A total of 17 articles were identified as potentially relevant. Data were extracted for all the included studies using a customized Microsoft Excel Data Extraction Form, which was piloted, revised, and standardized before data extraction by the writing committee (Supplemental Table 2).

The manuscript was developed through review of these 17 studies, and supported by additional relevant literature and the clinical expertise of the writing committee.

Because the available evidence was insufficient to support development of a formal clinical practice guideline, this manuscript was developed as an expert opinion document in accordance with the methodology described by Milojevic and colleagues.[1] All included studies were observational (retrospective or prospective) and varied in patient populations and reported outcomes. Given the limited and heterogeneous nature of the evidence, formal quality appraisal or risk-of-bias assessment was not performed, consistent with the methodologic approach for expert opinion documents.[1]

The final draft of the manuscript was reviewed and approved by the STS Workforce on Evidence-Based Surgery, the Council on Quality, Research & Patient Safety, and the STS Executive Committee. It was also subjected to a 2-week public comment period and endorsed by the European Congenital Heart Surgeons Association and World Society for Pediatric and Congenital Heart Surgery, with members from these societies actively participating in developing of this manuscript as coauthors.

RESULTS

Systematic review of literature yielded 17 relevant studies published from 2003 to 2021 from multiple regions around the world. Among these studies, 16 were retrospective[2-16] and 1 was prospective.[17] Two of the studies were limited to pediatric patients,[3,8] 3 were limited to adults,[3,4,9] and the remaining 12 were mixed.[2,5-7,10-17] The sample size of patients undergoing PVR ranged from 24 to 221. Most of the studies (11) were specific for ToF,[2,4,7,9-16] but 6 included other diagnoses.[3,5,6,8,17] Most of the studies (10) were specific for surgical PVR,[2,4,8,9,11,13-16] with 6 limited to percutaneous[3,5,6,12,17] and 1 was mixed surgical and percutaneous.[7]

Only 1 study addressed the first PICO question regarding which exercise vaciables are associated with adverse outcomes in patients undergoing PVR for ToF. A peak $\dot{V}O_2$ of <20 mL/min/kg was associated with a higher surgical risk after PVR, including early mortality.[4] The second PICO question pertained to preoperative exercise metrics predicting postoperative exercise metrics. Exercise indicators before and after PVR were reported to evaluate potential changes in cardiopulmonary function after the procedure. Overall results across the studies suggest that $\dot{V}O_2$ and peak $\dot{V}O_2$ remained stable or slightly improved after PVR. Additionally, $\dot{V}e$, measured by $\dot{V}e/Vco_2$ either remained unchanged or showed a slight decrease; however, $\dot{V}O_2$ at the anaerobic threshold remained stable. These findings suggest that PVR does not seem to negatively impact exercise tolerance and may provide modest benefits in certain patients. Detailed results are summarized in Supplemental Table 2.

No preoperative metric predicted a postoperative metric. CPET may not significantly improve after PVR, despite favorable remodeling on imaging, and therefore, CPET should not be used as the sole measure of procedural "success" or the only trigger for timing decisions.

COMMENT AND RECOMMENDATIONS

BACKGROUND ON CPET. CPET is a comprehensive assessment of the cardiorespiratory system in a dynamic state, providing a global view of the mechanisms involved in the transport and use of oxygen during physical exercise and an individual's overall functional status.[18] In addition to the standard exercise variables of heart rate (HR), blood pressure, pulse oximetry, and electrocardiogram changes, breath-by-breath gas exchange analysis, including oxygen uptake ($\dot{V}O_2$) and carbon dioxide production (VCO_2), is also obtained. Variables from a CPET can be used to understand an individual's cardiac, respiratory, and metabolic response to maximal and submaximal exercise.[19,20]

Absolute and relative contraindications to CPET exist and vary slightly depending on specific guidelines and institutional practices. Criteria have also shifted over the last 2 decades, now with many higher-risk patients routinely undergoing CPET. Absolute contraindications include uncontrolled/unstable cardiovascular or respiratory conditions such as unstable angina, uncontrolled arrhythmias, and severe untreated arterial or pulmonary hypertension. Other relative contraindications include conditions such as moderate to severe aortic stenosis, thyrotoxicosis, acute bleeding, electrolyte abnormalities, and advanced or complicated pregnancy.[20]

VARIATIONS/TESTING PROTOCOLS. Although CPET provides valuable data, multiple factors can influence various CPET variables (age, sex, body size, physical activity level, patient cooperation, clinical diagnosis/es, patient familiarity), and thus, results should be interpreted carefully by individuals who understand these nuances.

The 2 primary methods for CPET are stationary cycle ergometer and treadmill, both of which have advantages and disadvantages.[19] Cycle ergometer allows more convenient intratest monitoring of electrocardiogram, pulse oximetry, and blood pressure. Treadmill induces more stimulation of the heart and lungs and activates more muscle groups, producing a higher HR, blood pressure, and peak $\dot{V}O_2$. Patient preference and center experience also factor into choice of exercise method.

For both cycle ergometry and treadmill, there are specific exercise protocols and variations. On a cycle ergometer, there is typically a resting phase, an unloaded phase, an incremental exercise phase, and a recovery phase. During the incremental exercise phase, the workload is increased every minute. The amount of work increases from 5 to 30 W/min based on age and baseline level of fitness. For the treadmill, the standard Bruce protocol, with increases in both speed and incline every 3 minutes, is often used. A ramp Bruce or modified Bruce can be used for patients with lower levels of fitness. With both cycle ergometry and treadmill, the goal is for the individual to reach maximal exercise within 10 to 12 minutes. Reports of exercise test results should include protocol details and effort indices to allow future comparison.

ABNORMAL THRESHOLDS. Maximal peak $\dot{V}O_2$ is often used to determine aerobic capacity in clinical practice and research studies. It normally declines with age but can be improved with training. However, consensus is lacking on the most appropriate indicators and/or cutoffs to use in clinical studies or in patient care. The minimum report set for CPET should include peak $\dot{V}O_2$, predicted peak $\dot{V}O_2$ percentage, workload/workload percentage, $\dot{V}O_2$ at anaerobic threshold, $\dot{V}E/VCO_2$, O_2 pulse, and respiratory exchange ratio. Consistent reporting across centers will support comparability and future meta-analyses. Table 1 lists the most used indicators and their commonly used abnormal values.

PROGNOSTIC VALUE OF CPET. CPET is an important tool to assess clinical deterioration, provide prognostic information, and help risk-stratify patients with repaired ToF for intervention. A recent multicenter study in 300 patients, ages 6 to 63 years, showed reduced peak $\dot{V}O_2$ in all ages.[21] Different measures of exercise capacity and ventilatory efficiency have been associated in both children and adults to outcomes such as death, event-free survival, and cardiac-related hospitalization (refer to Table 2).[4,22-24] Peak $\dot{V}O_2$ and peak $\dot{V}O_2$ predicted were the most common variables studied.

ROLE OF SERIAL TESTING. Serial testing is beneficial to monitor for change. The 2020 European Society of Cardiology Guidelines for the Management of Adult Congenital Heart Disease and the 2025 American College of Cardiology guidelines both recommend PVR when a decrease occurs in objective exercise

TABLE 1 Exercise Variables and Commonly Used Abnormal Values

Variable	Variable Description	Abnormal Value
Peak $\dot{V}O_2$	Aerobic capacity	Varies based on age, sex, weight, fitness level, and disease.
Predicted peak $\dot{V}O_2$ percentage	An individual's peak $\dot{V}O_2$ is compared to a predicted or calculated peak $\dot{V}O_2$ using normative data.	<80% (mild), <60% (moderate), <40% (severe)
Workload percentage	Maximal watts achieved represent peak workload on cycle ergometer. It can be reported as watts, compared with a predicted watts, expressed as a percentage, or divided by weight and expressed as watts/kg.	
$\dot{V}O_2$ at AT	Level of oxygen uptake when metabolism changes from aerobic to anaerobic. Generally, it occurs at 50%–65% peak $\dot{V}O_2$ (55%–65% in children).	<40% (mild), <30% (moderate), <25% (severe) Rarely falls to <40% in absence of disease
$\dot{V}e/VCO_2$ slope	Reflects ventilatory efficiency. Minute ventilation ($\dot{V}e$) rises linearly in proportion to VCO_2 in progressive exercise until above AT. It is an index of gas exchange during exercise—equivalent to liters of air exhaled to eliminate 1 liter of CO_2. Measured at AT given terminal hyperventilation with exercise.	>30; >28 in pediatrics
O_2-pulse	Volume of oxygen delivered per heartbeat. It represents stroke volume, assuming no anemia, hypoxia, and normal tissue extraction.	<80% predicted during peak exercise
Respiratory exchange ratio	Ratio of CO_2 produced to O_2 consumed.	< 1.05 (pediatrics) or 1.1 (adults) suggests insufficient patient effort

AT, anaerobic threshold; CO_2, carbon dioxide; CV, cardiovascular; O_2, oxygen; $\dot{V}e$, expired volume per minute; VCO_2, carbon dioxide production; $\dot{V}O_2$, oxygen consumption.

capacity.[25,26] There are no evidence-based recommendations on testing intervals or what constitutes a clinically meaningful decline. For patients with low baseline activity level and/or RV dilation/dysfunction that are on the cusp of needing PVR, annual testing is indicated. For patients with excellent functional status and minimal RV dilation, testing every 3 years may be more appropriate.

CPET variables have an overall low coefficient of variation, suggesting a meaningful change is at least 10% to 20%, taking into consideration patient-specific variables such as changes in weight, fitness level, and overall health.[27,28] A recent study showed the $\dot{V}e/VCO_2$ slope at anaerobic threshold is the only CPET variable that was similar between testing methods (treadmill vs cycle ergometer), reinforcing the importance of using the same testing method on serial studies to guide clinical care.[29]

SPECIFIC SCENARIOS

SYMPTOMATIC PATIENT WITH AN ABNORMAL STRESS TEST RESULT. Current guidelines have a Class I indication for PVR in the setting of dyspnea, chest pain, and/or exercise intolerance, if the symptoms are attributable to pulmonary regurgitation.[30] An exercise test can provide a more objective measure than symptoms and better define whether cardiac physiology is contributing to symptoms.[19] Findings on an exercise test that may suggest cardiac etiology include elevated $\dot{V}e/VCO_2$ slope, flat O_2 pulse, electrocardiogram changes, and inadequate blood pressure response. The Figure presents a recommended strategy for integrating CPET into clinical decision-making.

A common clinical scenario is when a patient with repaired ToF presents with new symptoms, but there are extenuating circumstances, such as weight gain or a change in baseline exercise routine. It can be difficult to know whether the valve disease is indeed causing the symptoms and may in fact be the underlying etiology for the change in exercise/weight gain, or whether the cardiac function is stable and the symptoms are unrelated. A CPET is helpful in this situation, particularly if there are no other compelling indications for PVR.

CPET is also helpful in symptomatic patients when there is significant heart failure and/or

TABLE 2 Measures of Exercise Capacity and Ventilatory Efficiency and Associated Outcomes

Study	No.	Study Design	Age (y)	Outcome	Comments
Peak $\dot{V}O_2$					
Babu-Narayan,[4] 2014	220	Retrospective	Median 32 (range 16-64)	Death after PVR	Lowest quartile ≤16.9 mL/kg/min had worst mortality; Peak $\dot{V}O_2$ was strongest predictor on multivariable analysis
Peak $\dot{V}O_2$ predicted					
Müller,[22] 2015	875	Multicenter retrospective	25.5 (11.7)	Death or sustained VT; event-free survival	Peak $\dot{V}O_2$ ≤62.6% had 82% sensitivity for death/VT; ≤62.6% had 73% sensitivity for event-free survival
Giardini,[23] 2007	118	Retrospective	24 (8)	Death or hospitalization	Peak $\dot{V}O_2$ ≤36% at greater risk for cardiac-related death
Tsai,[24] 2016	40	Retrospective	9.0 (1.8)	Cardiac hospitalization	Peak $\dot{V}O_2$ <74% had HR 20.074 on multivariate analysis
$\dot{V}E/VCO_2$ slope					
Müller,[22] 2015	875	Multicenter retrospective	25.5 (11.7)	Event-free survival	$\dot{V}E/VCO_2$ slope ≥31.0 had 64% sensitivity, 67% specificity
Giardini,[23] 2007	118	Retrospective	24 (8)	Death or hospitalization	$\dot{V}E/VCO_2$ >39 at greater risk for cardiac-related death

Age reported as mean (SD) unless otherwise indicated. Peak $\dot{V}O_2$ expressed as mL/kg/min or percentage predicted, as reported. HR, hazard ratio; PVR, pulmonary valve replacement; $\dot{V}E/VCO_2$, expired volume per minute/carbon dioxide production; $\dot{V}O_2$ oxygen consumption; VT, ventricular tachycardia.

volume overload. It is often clear that pulmonary regurgitation has a causal link to the symptoms, but an exercise test can still offer prognostic information. As noted previously, patients with an extremely low peak $\dot{V}O_2$ are at increased operative risk and may benefit from a transplant evaluation or other optimization.[4] In symptomatic repaired ToF patients with extremely low $\dot{V}O_2$, without

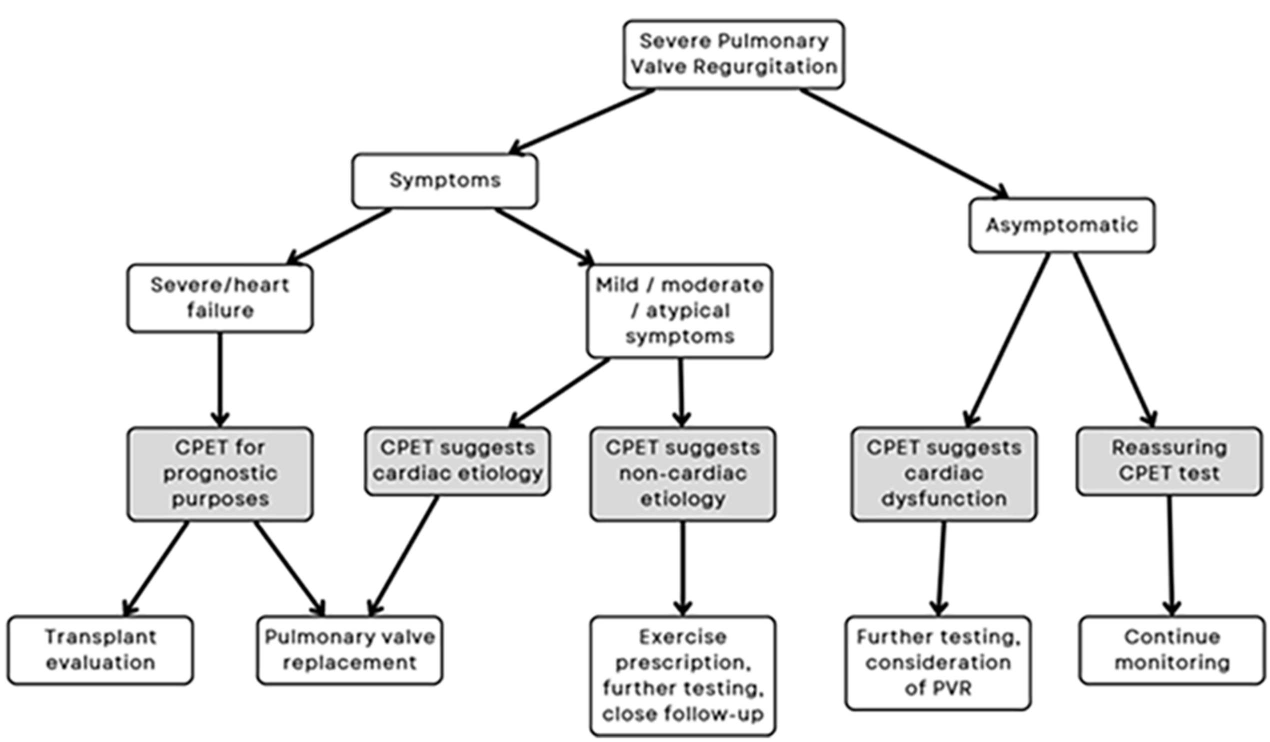

FIGURE Recommended strategy for integrating cardiopulmonary exercise testing (CPET) into clinical decision-making in this population. (PVR, pulmonary valve replacement.)

surreptitious assessments and irreversible causes, where the etiology is attributed to unrecoverable myocardium, a right-sided durable ventricular assist device or orthotopic heart transplant evaluation should become considerations.

SYMPTOMATIC PATIENT WITH A STRESS TEST RESULT WITHIN NORMAL LIMITS. When patients present with symptoms but their exercise test shows normal indicators, further evaluation may be necessary. Although clinicians may declare the symptoms are noncardiac, it is possible the patient has had a decline in exercise variables but still falls within the normal range. Reviewing any prior stress test results can help identify a downward trend. In the absence of prior stress tests, a history of athleticism could also support a history of an above-average exercise test result. Further testing may include imaging, biomarkers, such as brain natriuretic peptide, and rhythm monitoring, any of which may suggest cardiac stress and a potential indication for intervention.

It is also important to evaluate for potential modifiable noncardiac etiologies of symptoms, such as a change in baseline exercise activity, recent change in weight, change in lifestyle or stress levels, recent illnesses (anemia, thyroid, liver/kidney disease), or change in mental health such as depression, anxiety, or health anxiety. Some features, such as low peak HR and normal $\dot{V}e/\dot{V}co_2$ on an exercise test may suggest deconditioning as an underlying etiology that may improve with physical conditioning. Even when a noncardiac etiology is discovered, it does not rule out a true cardiac factor. It is suggested these noncardiac factors be addressed and followed up with repeat evaluation.

In the absence of other compelling indications, management of symptomatic patients with a stress test result within normal limits requires shared decision-making and multidisciplinary counselling to guide optimal management. Considerations favoring PVR include possibly improving quality of life and potentially preventing myocardial damage.[31] With exercise indicators within normal limits, however, continued monitoring remains an acceptable treatment option.

ASYMPTOMATIC PATIENT WITH AN ABNORMAL STRESS TEST RESULT. Although not explicitly stated, the rationale for recommending PVR in symptomatic patients is likely 2-fold. It is partly to improve symptoms but also to acknowledge that symptoms imply a degree of myocardial dysfunction. It is not uncommon for a patient to deny cardiac symptoms but have an abnormal CPET result. As in other scenarios, looking beyond just the peak $\dot{V}o_2$ is important.[19,32,33] If there are factors in the patient's history and the CPET that suggest deconditioning, pursuing increased physical activity and repeat evaluation to see whether the $\dot{V}o_2$ improves is reasonable. Comparing the current result against prior results can also suggest cardiac involvement. A decline in peak $\dot{V}o_2$, percentage peak $\dot{V}o_2$, and an increase in the $\dot{V}e/\dot{V}co_2$ are all concerning findings. In the absence of other causes, cardiac etiology becomes more likely and may prompt a discussion about PVR surgery.

Some features of a CPET are more concerning for serious cardiac etiology, including severe abnormalities in $\dot{V}o_2$ and $\dot{V}e/\dot{V}co_2$, arrhythmias, and a decline in blood pressure.[19,32,33] Even when patients deny symptoms in these situations, consideration for further evaluation, closer follow-up, or even pulmonary valve intervention may be warranted to prevent progressive or irreversible myocardial dysfunction.[19,32,33]

SPECIFIC POPULATIONS

CHILDREN AND ADOLESCENTS. There is no absolute lower age limit for CPET testing.[34] Having appropriately sized equipment, including pediatric-sized cycle ergometry and facemasks is essential. Treadmill protocols have been designed for pediatric populations, with normative data for patients as young as 4 years old.[35,36] Specially trained personnel are also crucial. Patients must understand the purpose of the testing and be provided encouragement throughout the process. Interpretation of the results also requires expertise in understanding the nuanced differences in pediatric patients.

Limited data exist on PVR in pediatric patients having previously undergone ToF repair, and fewer data are available on CPET and outcomes. The study by Warner and colleagues[16] of 36 ToF patients who underwent PVR at a mean age of 15 years included CPET data, with 6 patients having CPET testing data before and after. This study demonstrated both symptomatic improvement and objective improvement in exercise capacity.

Similarly, Gauthier and colleagues[8] studied 86 pediatric patients undergoing PVR with preoperative exercise testing and found that those with a peak $\dot{V}o_2$ of at least 70% had a shorter hospital stay than those at <70%.[8] Borik and colleagues[6] examined a cohort of 51 ToF patients undergoing transcatheter PVR who were a mean age of 20 (SD, 10) years. They found that younger age at implantation had improved max $\dot{V}O_2$, improved biventricular ejection fraction, and decreased RV end-diastolic dimension.

Clearly, with such limited data, further work is required to understand the utility of CPET in the pediatric population. Although some data exist that suggest improved functional outcomes at a younger age, this does not take into consideration the repeated interventions and risk that earlier interventions would incur on a young patient over the course of their lifetime. As is well documented, the younger the patient, the less durable the valve.

ELDERLY POPULATIONS. There are scant data on exercising older adults with ToF, but many of the same principles apply. Elderly patients often benefit from a modified Bruce and/or ramp protocol on the treadmill. They may need more coaching and practice on the cycle ergometer compared with their younger counterparts. It is important to note that many older patients with ToF have risk factors for atherosclerotic cardiovascular disease.[37] Although assessing the ST segments is not typically useful in the timing of PVR, it is useful in evaluating for cardiac ischemia, which may be an alternative etiology for symptoms. ST depressions, especially flat or down sloping in the inferior and lateral leads, may warrant further evaluation for coronary artery disease.

OBESE, SEDENTARY, AND/OR DECONDITIONED PATIENTS. Although CPET provides objective measurements that can be helpful to monitor cardiac impairment to exercise capacity over time, obesity can have an impact on these measurements. For example, peak $\dot{V}O_2$ is commonly measured in mL/min and can be higher in obese patients. The peak $\dot{V}O_2$, however, is commonly indexed to body mass (mL/kg/min), and in obesity, the patient's current weight measured in kg may be significantly higher than their lean body mass. These indexed measurements can therefore overestimate the cardiac limitation related to exercise.

Additionally, deconditioning related to obesity frequently is a contributing factor, and teasing out how much of the limited exercise capacity is cardiac related can be challenging. Currently, no adjustment is made for obesity within CPET measurements. In terms of relevance of obesity to prognosis and outcomes, in adults with heart failure not related to congenital heart disease (CHD) an "obesity paradox" has been documented in which those with higher body mass index (BMI) have better outcomes than patients with heart failure with normal or low BMI.[38] However, at some point when BMI >35 or 40 kg/m^2, better outcomes are no longer seen. Such data have not been documented in detail in the congenital population, but peak $\dot{V}O_2$ was inversely related to BMI in a broad study of adult CHD patients.[39] There are additional data demonstrating that when evaluating RV dimensions in ToF patients having undergone repair, using ideal body surface area is more accurate.[40]

As noted previously, a reduced exercise capacity is associated with an increased risk of cardiovascular events in patients with repaired ToF as well as increased surgical risk at the time of PVR.[22,24,39,41,42] However, peak $\dot{V}O_2$ can be decreased due to many factors, including physical deconditioning or lack of cardiorespiratory fitness, anthropometric measures, chronologic age, as well a true cardiovascular limitation to exercise, and differentiating between these states can be difficult.[18] In patients with CHD, this becomes even more challenging given the heterogeneity of factors contributing to CPET interpretation, including lesion-specific considerations and physiologic status of the patient, making careful evaluation of CPET variables critical for test interpretation and guiding management decisions.

In individuals with low (<80% predicted) peak $\dot{V}O_2$ despite normal cardiovascular, pulmonary, or metabolic variables, deconditioning should be considered as a possible etiology of reduced exercise capacity.[43] Additional features that may help differentiate deconditioning from circulatory impairment include an exaggerated HR response to exercise, low HR recovery, reduced HR reserve, low ventilatory anaerobic threshold (as the percentage of peak $\dot{V}O_2$), and a steep HR increase relative to $\dot{V}O_2$ with a shallow rise in O_2 pulse, all of which can be seen in deconditioning,[19,43,44] although no specific cutoff values are available. In another study, abnormal $\dot{V}E/VCO_2$ slope to peak $\dot{V}O_2$ ratio of $\geq$2.7 was found to be the best gas exchange indicator to discriminate between circulatory impairment and deconditioning, along with a $\Delta\dot{V}O_2/\Delta$work rate < 8.6.[45]

PREGNANCY. Pregnancy in women with repaired ToF is generally well tolerated; however, there is an increased risk of maternal cardiovascular events during pregnancy, predominately arrhythmia development and heart failure.[46-48] Data using CPET in pregnancy are limited, and pregnancy-specific testing guidelines are lacking. CPET can be safely performed during pregnancy, although changes in physiologic responses to exercise are seen even in early pregnancy, with a slower HR recovery and increased ventilatory response to exercise, including increased ventilation-perfusion mismatch and increased dead space ventilation.[49] Although no significant difference in peak $\dot{V}O_2$ between pregnant and nonpregnant women during maximal exercise was seen,[50] a deconditioning effect of pregnancy has been shown, with slightly lower peak $\dot{V}O_2$ values in the early postpartum setting compared with pregnancy.[51]

A study examining CPET indicators in pregnant women with repaired ToF found no significant effect of pregnancy on most exercise variables, including peak $\dot{V}O_2$.[52] However, a blunted HR response to exercise and a low peak $\dot{V}O_2$ of <25 mL/kg/min on a prepregnancy CPET in women with congenital heart disease are known to be associated with adverse maternal cardiac and neonatal events.[53,54] Unfortunately, there are no definitive data suggesting that a prepregnancy PVR could prevent cardiovascular events in women with repaired ToF. Based on the available evidence, prepregnancy PVR should occur in patients who meet established adult CHD guidelines for replacement.

ATHLETES. Although CPET use in athletes is well described, elite athletes with congenital heart disease are uncommon, and those with repaired ToF are even fewer. As such, CPET data among repaired ToF athletes and how these data inform PVR timing are unknown. Most of these patients are likely asymptomatic, with exercise testing results within normal limits, and therefore, serial CPET assessments to evaluate trends and examine changes relative to baseline over time are likely to be more informative. When evaluating CPET results in athletes with ToF, it is important to know the common differences in overall CPET results in athletes compared with nonathletes, such as higher cardiac output, faster HR recovery, higher peak $\dot{V}O_2$, higher prevalence of exercise-induced arterial hypoxemia, and lower breathing reserve.[55]

PREHABILITATION AND REHABILITATION. CPET testing is also a useful component of prehabilitation and rehabilitation. Prehabilitation is a structured, individualized, multimodal program designed to improve the physical fitness of patients and reduce the risk of planned cardiac interventions.[56] Rehabilitation is similar, but occurs after the procedure with a goal of recovery and return to prior levels of function and promote secondary prevention.[57,58] CPET indices can be used to write exercise prescriptions.

Because many patients with CHD are unable to achieve a predicted HR, it is more appropriate to use the patient's peak HR on a symptom-limited exercise test for HR targets.[58] HR reserve, which uses both peak and resting HR, is likely an even better approach. More work is needed to fully evaluate prehabilitation and rehabilitation in adults with CHD and the role CPET plays in optimizing therapies.

LIMITATIONS, FUTURE RESEARCH, AND CONCLUSION

These recommendations have many limitations. Without available high-quality prospective data, many of the recommendations are based on expert opinion and consensus. As more data are available in the future, these recommendations will inevitably shift and evolve. Recommendations on CPET are also limited by a lack of standardization in protocols. The Bruce protocol for treadmill testing is well known but is not suitable for all populations. Adjusting the choice of protocol, and sometimes even altering available protocols, based on individual patient characteristics, remains common clinical practice.

Similarly, recommending an optimal interval between serial tests is challenging. In some patients, such as stable patients with a good functional ability, establishing a baseline functional level and not retest for several years may be appropriate. In other patients, more frequent testing may be needed to assess for subtle changes that would change decision-making.

Patient selection and optimal timing of PVR after repair of ToF remains unclear. Current recommendations are based on RV volumetric indices and RV-related symptoms. Several studies have assessed the preprocedural and postprocedural impact of CPET on clinical outcome. A cascade of complementary tests has evolved, but they are not deployed strategically. Thus, reliance solely on imaging, functional, and volumetric indicators for decision-making may neglect important CPET determinants of outcome. Careful analysis of the cardiopulmonary response to intense exercise during CPET may help to identify patients with impaired cardiac reserve unable to adequately increase their cardiac output during exercise. Hence, methodologically proper CPET (integrating CPET slopes and variable kinetics) may likely be helpful to improve risk stratification and allow for differentiation of patients with abnormal response to exercise from those without.

Future research is warranted to evaluate the critical effects of age and RV functional capacity and their correlation with peak $\dot{V}O_2$, novel volumetric indices, along with the association of RV-pulmonary artery coupling and uncoupling on adverse outcomes in repaired ToF patients for the proper timing of PVR. In some with poor cardiac reserve, chronotropic insufficiency (HR response) may further contribute to a suboptimal cardiac output during exercise. Thus, this combination of chronotropic insufficiency and abnormal CPET may be used as predictive factor of lower myocardial reserve. As options for surgical and transcatheter interventions continue to evolve, preoperative evaluation, including CPET, nutritional optimization, and cardiopulmonary preconditioning/rehabilitation, merits rigorous prospective evaluation.

Considering the current inconsistency of obtaining preoperative CPET in children, studying systematically performed CPET will enhance our ability to inform reliable decision-making. Adjusting CPET results for body size, age, and sex is critical and can mitigate biases introduced by simple body weight indexation--this will need standardization. Normalized definitions to facilitate accuracy in interpreting data of future meta-analyses or multisite studies are required.

Further research is necessary to (1) assess, whether CPET may be useful to improve risk stratification by identifying those patients or subset incapable of sufficiently augmenting their cardiac output during exercise; (2) explore, whether adequate preconditioning or rehabilitation might be required to achieve improved CPET performance and, hence, suitability for PVR; and (3) determine, whether machine-learning applications can alter the current criteria used for the timing and appropriateness pursuing PVR.[59] The use of customized machine-learning algorithms could unmask combinations of clinical, CPET, and cardiac magnetic resonance-based data predictive of early RV dysfunction in repaired ToF patients and support a vigilant process to identify patients at elevated risk of major adverse cardiac events and improve patient selection for timely PVR.

In conclusion, CPET is an important tool in the management of patients with repaired ToF. It is helpful in both symptomatic and asymptomatic patients. CPET can help distinguish cardiac from noncardiac limitations and identify high risk patients. There are limitations to the optimal use of CPET, making further research crucial to optimizing the care of this complex and varied patient population.

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