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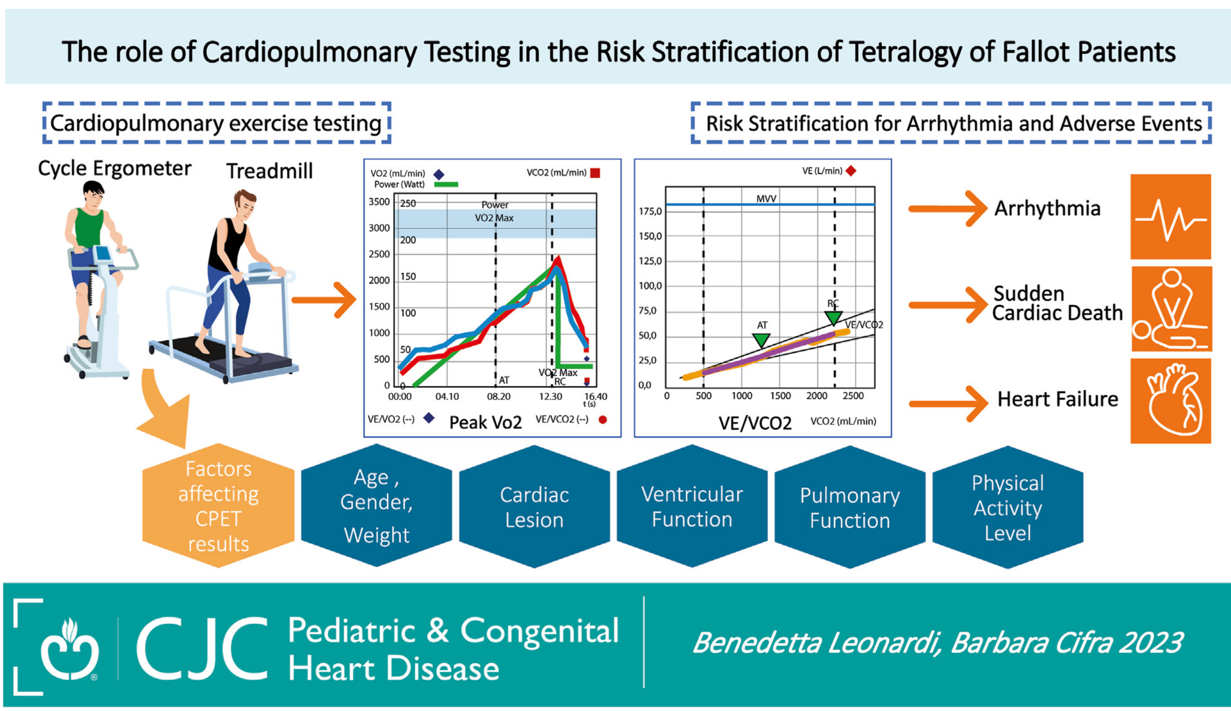
Review

The Role of Cardiopulmonary Testing to Risk Stratify Tetralogy of Fallot Patients

Benedetta Leonardi, MD,[a] and Barbara Cifra, MD[b]

[a] *Department of Pediatric Cardiology, Cardiac Surgery and Heart Lung Transplantation, Bambino Gesù Hospital, IRCCS, Rome, Italy*

[b] *Division of Cardiology, Labatt Family Heart Centre, the Hospital for Sick Children, Toronto, Ontario, Canada*



ABSTRACT

Neonatal repair has completely changed the clinical history of patients with tetralogy of Fallot (ToF); however, these patients carry a significant risk of severe arrhythmias and sudden cardiac death in the long term. The exact mechanism for late sudden cardiac death is multifactorial and still not well defined, and the risk stratification for primary prophylaxis in these patients remains challenging. Cardiopulmonary exercise testing (CPET) is a well-established and safe method to assess cardiopulmonary function in children and adults with congenital heart disease. Several parameters obtained with CPET have been identified

RÉSUMÉ

La chirurgie réparatrice néonatale a complètement changé le parcours clinique des patients nés avec une tétralogie de Fallot (TF). Ces patients demeurent toutefois exposés à un risque important d'arythmie sévère et de mort cardiaque subite (MCS) à long terme. Le mécanisme causal exact de la MCS tardive est multifactoriel et demeure mal défini, ce qui complique la stratification du risque pour le traitement préventif primaire chez ces patients. L'épreuve d'effort cardiorespiratoire (EECR) est une méthode sécuritaire et bien établie pour évaluer la fonction cardiopulmonaire des enfants et des adultes atteints de cardiopathie

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as potential prognostic of major adverse cardiovascular events in congenital heart disease. CPET is routinely used to assess functional capacity also in patients with ToF, and there is some evidence showing its usefulness in predicting the cardiac adverse events in patients with repaired ToF. Current guidelines recognize the importance of CPET in the evaluation and management of patients with ToF, but there is no clear consensus on which the CPET parameter or level of exercise intolerance, as measured by CPET, is truly predictive of an increased risk of arrhythmia and major adverse cardiovascular events in this population. Therefore, the aim of this narrative review is to describe the current evidence on the potential use of CPET in the risk stratification of patients with repaired ToF.

congénitale (CC). Plusieurs paramètres obtenus lors d'une EECR ont été décrits comme des marqueurs pronostiques potentiels d'événements cardiovasculaires indésirables majeurs (ECIM) en contexte de CC. L'EECR est couramment utilisée pour évaluer la capacité fonctionnelle des patients atteints de TF et des données probantes démontrent son utilité pour prédire les manifestations cardiaques défavorables chez les patients opérés d'une TF. Les lignes directrices en vigueur conviennent de l'importance de l'EECR dans l'évaluation et la prise en charge des patients opérés d'une TF, mais il n'existe aucun consensus clair sur le paramètre ou le seuil d'intolérance à l'effort mesuré par l'EECR qui possède une réelle valeur prédictive d'un risque élevé d'arythmie et d'ECIM dans cette population. L'objectif de la présente synthèse narrative est de décrire les données probantes actuelles sur l'utilisation potentielle de l'EECR dans la stratification du risque chez les patients opérés d'une TF.

The Use of Cardiopulmonary Exercise Testing in Congenital Heart Disease

Cardiopulmonary exercise testing (CPET) has been widely used in the management of patients with congenital heart disease (CHD).[1–16] The test provides data on a patient's functional capacity, which predicts the onset of clinical deterioration. CPET combines the integrated analysis of ventilation (VE), oxygen consumption (VO_2), and carbon dioxide production (VCO_2) with parameters commonly evaluated during incremental exercise tests, such as heart rate, arterial blood pressure, and continuous electrocardiogram monitoring. Therefore, compared with the traditional stress test, CPET allows us to obtain more information on the patient's cardiorespiratory system, providing a global view of the mechanisms involved in the transport and use of oxygen (O_2) during physical exercise in both children and adults with CHD.[5,17] Das et al.[18] showed that the peak oxygen uptake (peak VO_2) correlates with the New York Heart Association functional classification in adults with CHD. In addition, Diller et al.[5] showed that the reduced exercise capacity measured by CPET correlates with the risk for hospitalization or death in adults with CHD. Furthermore, evidence on the utility of CPET in predicting mortality and morbidity in patients with CHD[5,8,19–21] is increasingly emerging. A recent systematic review including 48 studies, of which 34 were meta-analysis, has documented the associations between CPET parameters and major adverse cardiovascular events (MACE) in adult patients with CHD.[8] In specific, a higher value of peak VO_2 and a lower value of the minute VE/VCO_2 slope seemed to be significantly associated with reduced risk of MACE in patients with CHD.[8] The possibility to use the additional CPET parameters obtained at the anaerobic threshold, such as VE/VCO_2, beside peak VO_2, is of paramount importance in the prediction of mortality and morbidity in patients with CHD, considering that some patients are unable to complete a maximal CPET. A similar association between a reduced peak VO_2 and increased morbidity and mortality in children and adolescent with CHD was shown by Villaseca-Rojas et al.[13] A reduced cardiorespiratory fitness has been previously associated with MACE in people with Fontan circulation,[22] and a >3% yearly decrease in peak VO_2 as a percentage of predicted has been shown to be a predictor for death or cardiac surgery in univentricular heart.[23] CPET has also been used for the indication of cardiac transplantation or mechanical support circulation in CHD[11,24] and in the evaluation of reversible myocardial ischemia in the context of heart failure.[25,26] Moreover, few studies have highlighted the slow progressive decline of exercise capacity in patients with CHD regardless of the lesion.[14,27,28] The fact that some of the parameters derived from a CPET are of predictive value for long-term mortality and morbidity in patients with CHD[5,20,21] is not surprising if we consider that the level of functional capacity is strictly correlated to the severity of cardiac dysfunction, lung function, degree of fibrosis, and sequelae from the surgery. The challenge to a more consistent use of CPET in CHD relies not only on the multiple data obtained by the test but also on the heterogeneity of factors that contribute to the final result of a CPET, some not related to the specific CHD (age, gender, weight, and physical activity level) and others related to the specific patient's clinical status (type of CHD, presence of chronotropic incompetence, ventricular function, and pulmonary function) (Fig. 1). Therefore, a high level of expertise is required for the correct interpretation of single CPET results, especially for the most complex CHD, as well as for the interpretation of results from serial CPET tests in their relation to the clinical status of each patient.

Importance of Risk Stratification in Tetralogy of Fallot: Physiopathology of Arrhythmias in Patients With Tetralogy of Fallot

Chronic pulmonary insufficiency represents the main sequelae of tetralogy of Fallot (ToF) repair,[29,30] leading to progressive dilatation and/or dysfunction of the right ventricle (RV) and potentially fatal ventricular arrhythmias over

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Corresponding author: Dr Barbara Cifra, Division of Cardiology, Labatt Family Heart Centre, the Hospital for Sick Children, 555 University Ave, Toronto, Ontario M5G1X8, Canada. Tel.: +1-416-813-7326; fax: +1-416-813-7547.

E-mail: barbara.cifra@sickkids.ca

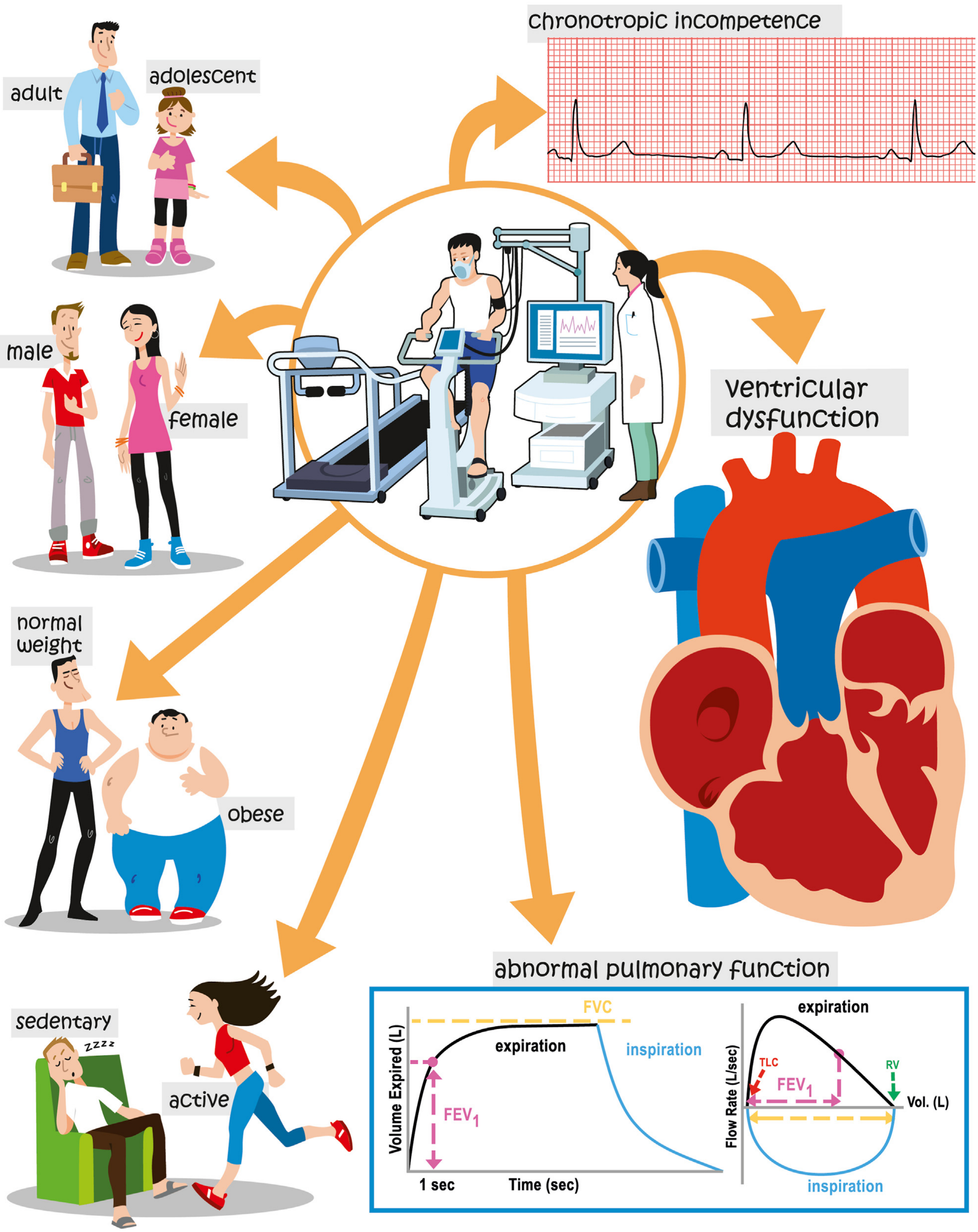

Figure 1. Factors affecting cardiopulmonary exercise testing results. FEV_1, forced expiratory volume in 1 second; FVC, force vital capacity; TLC, total lung capacity.

time.[31–35] Pulmonary valve replacement (PVR) is performed in patients with ToF to protect the RV from the negative effects of chronic volume overload.[36,37] However, despite ongoing research efforts, the timing of PVR in asymptomatic young patients with ToF remains a fundamental question without a definite answer. The controversy on PVR timing is related to the genesis of arrhythmias in patients with ToF, which is not only consequent to volume overload but also to the fibrotic tissue from the surgery. Atrial and ventricular arrhythmias in ToF are both linked to the anatomy of the lesion and the timing and type of surgical repair.[38] Therefore, the rationale for performing PVR is to mitigate the progressive atrial and ventricular remodeling due to pressure or volume overload, which can predispose patients with a higher-risk anatomic substrate to develop severe clinical arrhythmias.[38] Nonetheless, PVR alone cannot reduce significantly the risk of monomorphic ventricular tachycardia (VT) and adverse events in patients with ToF.[37,39–41] Furthermore, PVR is not a definite repair because the prosthetic valve will require additional surgery over time.[42] Finally, although sudden cardiac death (SCD) remains an important cause of death for adults with ToF, the annual risk of SCD in these patients is estimated at 0.2%,[43,44] making it difficult to justify invasive risk stratification screening or implantable cardioverter-defibrillator implantation for all patients with ToF. In this optic, identifying noninvasive prognostic tests for SCD in patients with ToF would radically change their clinical management, given that despite well-documented risk factors associated with ventricular arrhythmia,[45] there is not still a universally accepted risk stratification algorithm. This is even more concerning for the patients with ToF who experience few or no symptoms before a fatal event.[5,46] The lack of reported symptoms in patients with ToF is mainly related to their inability to identify their symptoms during their daily life, as most of them are sedentary or are insufficiently physically active.[47–49] It has also been reported that in a subgroup of well-trained patients with ToF, the lack of symptoms could be related to favourable RV adaptation to volume overload, although this hypothesis is still under investigation.[46,50,51] In addition, up to date, it remains unclear what degree of left ventricular (LV) or RV dysfunction represents a substantial risk for VT in patients with ToF.[38] Limited data exist on the predictive value of noninvasive ambulatory electrocardiography monitoring for patients with ToF at risk for sustained ventricular arrhythmias, and the prognostic value of asymptomatic not sustained VT on Holter monitoring has not been demonstrated.[52] Therefore, in asymptomatic patients with ToF, a noninvasive test such as the CPET could provide additional information on the risk of developing arrhythmias during activity besides providing information on exercise tolerance[53] and potentially help to elicit a possible worsening of their clinical status.

CPET and Risk Stratification in ToF

A reduced exercise capacity expressed as peak VO_2 during CPET has been associated with an increased risk of MACE in patients with ToF.[5,19,54–56] Considering that the arrhythmic events occur starting from the second decade of life, the majority of the available evidence is derived from studies including mainly adult patients with ToF, limiting their application to the paediatric patients with ToF (Table 1).

The study by Diller et al.[5] was the first one documenting that a reduced exercise capacity expressed as peak VO_2 during CPET was associated with an increased risk of MACE in adult patients with CHD also including patients with repaired ToF. Consequently, a great effort has been made to try to identify the cutoff value of peak VO_2 as well as other CPET parameters, like VE/VCO_2, that could help identifying patients with ToF at an increased risk of MACE.[19,54–56] Shafer et al.[55] demonstrated an important link between peak VO_2 and VE/VCO_2 slope, showing how a decrease in the peak VO_2 value and an increase in the VE/VCO_2 slope, as measured during CPET, increase the rate of mortality or risk of VT in adult patients with repaired ToF. The study by Müller et al.,[54] on a cohort of 875 adult patients with repaired ToF (average age of 25.5 $\pm$ 11.7 years), showed that patients with a peak VO_2 value of $\leq$65% of a predicted and resting QRS $\geq$170 ms had a 11.4-fold increased risk of death or sustained VT. In addition, in the same study, a VE/VCO_2 slope of $\geq$31.0, a peak VO_2 value of $\leq$65%, and a QRS of $\geq$170 ms were identified as cutoff points with the best sensitivity and specificity to detect unfavourable outcomes in this population. von Sanden et al.[19] found that older age and a low peak VO_2 are independent risk factors for severe arrhythmia during a 3-year follow-up of 1194 patients with CHD, including 469 adult patients with ToF. In this study, a peak VO_2 value of <24.9 mL/min/kg was shown to be a predictor of arrhythmias in older patients with ToF. Babu-Narayan et al.[6] identified a peak VO_2 of <20 mL/min/kg as the cutoff value correlated with a higher surgical risk in 221 adult patients with repaired ToF who underwent PVR. In the same study, the PVR preoperative peak VO_2 was predictive of early mortality, and for every reduction of 2 mL/min/kg in preoperative peak VO_2, there was an increase of approximately 30% in early mortality.[6] Although in this study, peak VO_2 emerged as the strongest predictor on multivariable analysis, VE/VCO_2 was also identified as a useful parameter to predicting early mortality in patients with ToF who underwent PVR. Interestingly, another study also reported that an increment of VE/VCO_2 predicted the necessity for reintervention and the risk of death in the long-term follow-up of 118 adults with ToF.[20] In this same study, patients with peak VO_2 <36% of predicted value and those with VE/VCO_2 slope >39% were at greater risk for cardiac-related death.[20] Tsai et al.,[56] in one of the very few studies on paediatric patients with repaired ToF, reported that a peak VO_2 of 74% of age prediction represents an important predictor of cardiac-related hospitalization in patients younger than 12 years. The same authors also suggested that the oxygen uptake efficiency slope parameter could be a useful predictor of cardiac-related hospitalization in paediatric patients with ToF. Unfortunately, the above-mentioned study is the only one evaluating the usefulness of CPET parameters in the risk stratification of paediatric patients with repaired ToF. The other before-mentioned studies include paediatric patients in a much larger cohort of patients with ToF including adults.[6,19,20,54] It is well known that peak VO_2 tends to decrease with age in healthy individuals as well as patients with CHD including patients with ToF;[14,28] therefore, any findings should account for the age factor, as in the study by Eshuis et al,[2] which evaluated the difference in

Table 1. CPET parameters and values considered to risk stratification MACE in patients with ToF, and studies evaluating the utility of CPET in the risk stratification process of patients with ToF

	CPET parameter	Number of patients	Age (y)	Cutoff value	Author	Year
Adults	Peak VO_2	221	(range: 16-64)	<20 mL/kg/min	Babu-Narayan et al.[6]	2014
		469	Adults	24.9 (IQR 17.4-34.6) mL/kg/min	von Sanden et al.[19]	2022
		163	24.5 ± 10.2	<27 mL/kg/min	Rashid et al.[46]	2020
	Peak VO_2 predicted	875	25.5 ± 11.7 (range: 7-75)	≤65%	Müller et al.[54]	2015
		118	24 ± 8	<36%	Giardini et al.[20]	2007
	VE/VCO_2 slope	875	25.5 ± 11.7 (range: 7-75)	≥31	Müller et al.[54]	2015
		118	24 ± 8	>39	Giardini et al.[20]	2007
Children	Peak VO_2	40	9.0 ± 1.8	<74%	Tsai et al.[56]	2016
	OUES/BSA	40	9.0 ± 1.8	<1.029	Tsai et al.[56]	2016

BSA, body surface area; CPET, cardiopulmonary exercise testing; IQR, interquartile range; MACE, major adverse cardiovascular events; OUES, oxygen uptake efficiency slope; Peak VO_2, peak oxygen uptake; VE/VCO_2 slope, minute ventilation/carbon dioxide production.

peak VO_2 in repaired ToF across different age groups ranging from 6 to 63 years. Furthermore, Rashid et al.[46] showed that RV function also correlates with peak VO_2 in adult patients with ToF, and that both values are independent predictors of MACE in patients with ToF. Specifically, in this study, it was demonstrated that a peak VO_2 threshold of <27 mL/kg/min is associated with a consistent probability of having a right ventricular ejection fraction of less than 40%. Therefore, to identify the correct peak VO_2 cutoff related to MACE in this population, peak VO_2 future studies should aim to explore how to adequately account for the patient's age and RV function when interpreting peak VO_2 values.

Challenges Related to CPET Implementation

Despite being an informative test, CPET interpretation requires dedicated training, given that its multiple parameters are influenced by various factors, such as chronological age,[57] anthropometric measurements (height, weight, and body surface area), type of CHD, and the patient's collaboration (attitude and motivation), in addition to the degree of training of the specific patient. Furthermore, to date, the equations for the prediction of peak VO_2 based on age and gender refer to a healthy population and do not account for the specific CHD.[58] The age at the time of the CPET assumes a lot of importance given that aging is associated with a decline in oxygen consumption in the general population as well as in CHD, including patients with ToF.[9,58,59] Overweight/obesity also affects the reported measurements with no established correction equation for ideal body weight, as well as pulmonary lung function and lean muscle mass. In the paediatric setting, it is also essential to select the appropriate CPET protocol based on a child's compliance and symptoms, and also considering their physical fitness. Thus, even in the scenario of a general consensus on a specific peak VO_2 cutoff value at which patients with ToF present with a significant increase risk of MACE, it is clinically difficult to measure it properly. Furthermore, the result of the different CPET parameters is dependent on the used protocol and CPET methodology (treadmill vs cycle ergometer). Therefore, based on current data, it is reasonable to assume that a determined reduced peak VO_2 has a different importance if reported in an adolescent compared with an adult patient with ToF and/or in a male instead of a female. Another limiting factor to the implementation of CPET for the risk stratification of patients with ToF is that published data are mostly from single-centre studies with a limited number of patients, and when a larger number of patients are reported, CPET parameters are not correlated with parameters of cardiac function such as RV dilatation or RV/LV dysfunction. This is of considerable importance because in studies in which CPET data are correlated with magnetic resonance imaging parameters, such as the one of Meadows et al.,[60] right ventricular ejection fraction appeared to be the only cardiac magnetic resonance imaging predictor of percent-predicted peak VO_2, ventilatory anaerobic threshold, and oxygen pulse. However, this study only enrolled 37 patients with ToF. Finally, it is well known that peak VO_2 is higher in patients with repaired ToF who exercise regularly.[61–63] Avila et al.[63] even demonstrated that exercise training, in addition to improving exercise capacity, has a beneficial effect on VT in adults with repaired ToF with no history of severe RV outflow obstruction or sustained VT.

Key Points

- CPET can offer useful information for the risk stratification of ToF patients. However, many of the studies are performed on the adult population.
- Peak VO_2 is the maximal parameter of CPET useful in ToF risk stratification, but its value is affected by many factors
- VE/VCO_2 and OUES are the main submaximal parameters obtained using CPET, that can be used to risk stratify ToF patients, who are unable to achieve a maximal effort
- Serial CPET should be part of ToF long term follow-up management to predict clinical deterioration.

Figure 2. Key points. CPET, cardiopulmonary exercise testing; OUES, oxygen uptake efficiency slope; Peak VO_2, peak oxygen uptake; ToF, tetralogy of Fallot; VE/VCO_2, minute ventilation/carbon dioxide production.

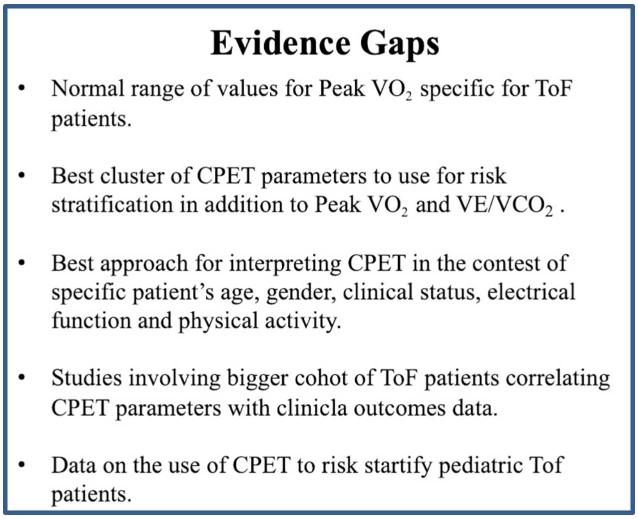

Figure 3. Evidence gap in the use of CPET for risk stratification of patients with ToF. CPET, cardiopulmonary exercise testing; OUES, oxygen uptake efficiency slope; Peak VO_2, peak oxygen uptake; ToF, tetralogy of Fallot; VE/VCO_2, minute ventilation/carbon dioxide production.

Conclusions

CPET represents a valid noninvasive method that should be used to identify patients with repaired ToF at risk of MACE, but it must be complemented by additional clinical-instrumental data for each patient (Fig. 2). Without the latter, a peak VO_2 value alone cannot be used for patient risk stratification, even when the CPET is performed in the best way. A major limitation of CPET studies performed on patients with ToF until now is the lack of correlation of the CPET results with the level of patients' physical training. Therefore, multicentre studies are needed to know what value represents a "normal" peak VO_2 value for a specific-ToF patient stratified by age group, clinical status (New York Heart Association class), cardiac function (degree of RV dilatation and/or dysfunction, LV dysfunction, and RV hypertrophy), electrical function (QRS duration or fragmentation), and physical activity level. Further studies should also evaluate the potential use of additional CPET parameters, such as VE/VCO_2 slope, to identify a cluster of parameters and their "real threshold" below which there is an increase in the risk of SCD in the population of patients with ToF. Finally, a single peak VO_2 value is not predictive of adverse events in patients with ToF, but at least 2 peak oxygen values must be evaluated over time (Fig. 3). Improving current evidence on the use of CPET for risk stratification of patients with ToF is crucial to help reduce the occurrence of MACE in these patients' population.

Ethics Statement

The research reported has adhered to the relevant ethical guidelines.

Patient Consent

The authors confirm that patient consent is not applicable to this article. This is a narrative review; therefore, it did not require consent from the patient.

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Disclosures

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References

1. Yang MC, Chen CA, Chiu HH, et al. Assessing late cardiopulmonary function in patients with repaired tetralogy of Fallot using exercise cardiopulmonary function test and cardiac magnetic resonance. *Acta Cardiol Sin*. 2015;31:478–484.
2. Eshuis G, Hock J, Marchie du Sarvaas G, et al. Exercise capacity in patients with repaired tetralogy of Fallot aged 6 to 63 years. *Heart*. 2022;108:186–193.
3. Kim W, Kwak JG, Kwon HW, et al. Pulmonary valve replacement may not restore ventricular volume and functional status in patients with pulmonary regurgitation after late tetralogy of Fallot repair. *Eur J Cardiothorac Surg*. 2021;61:64–72.
4. Stout KK, Daniels CJ, Aboulhosn JA, et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *Circulation*. 2019;139:e637–e697.
5. Diller GP, Dimopoulos K, Okonko D, et al. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. *Circulation*. 2005;112:828–835.
6. Babu-Narayan SV, Diller GP, Gheta RR, et al. Clinical outcomes of surgical pulmonary valve replacement after repair of tetralogy of Fallot and potential prognostic value of preoperative cardiopulmonary exercise testing. *Circulation*. 2014;129:18–27.
7. Zaqout M, Vandekerckhove K, De Wolf D, et al. Determinants of physical fitness in children with repaired congenital heart disease. *Pediatr Cardiol*. 2021;42:857–865.
8. Wadey CA, Weston ME, Dorobantu DM, et al. The role of cardiopulmonary exercise testing in predicting mortality and morbidity in people with congenital heart disease: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2022;29:513–533.
9. van Genuchten WJ, Helbing WA, Ten Harkel ADJ, et al. Exercise capacity in a cohort of children with congenital heart disease. *Eur J Pediatr*. 2023;182:295–306.
10. Hock J, Hacker AL, Reiner B, et al. Functional outcome in contemporary children and young adults with tetralogy of Fallot after repair. *Arch Dis Child*. 2019;104:129–133.
11. Das BB. A systematic approach for the interpretation of cardiopulmonary exercise testing in children with focus on cardiovascular diseases. *J Cardiovasc Dev Dis*. 2023;10:178.
12. Ferri K, Gich I, Guerra-Balic M, et al. Aerobic capacity in adults with congenital heart disease: more than VO(2peak), a follow-up study. *Life (Basel)*. 2022;12:2118.
13. Villaseca-Rojas Y, Varela-Melo J, Torres-Castro R, et al. Exercise capacity in children and adolescents with congenital heart disease: a systematic review and meta-analysis. *Front Cardiovasc Med*. 2022;9:874700.
14. Muller J, Ewert P, Hager A. Only slow decline in exercise capacity in the natural history of patients with congenital heart disease: a longitudinal study in 522 patients. *Eur J Prev Cardiol*. 2015;22:113–118.

15. Buys R, Cornelissen V, Van De Bruaene A, et al. Measures of exercise capacity in adults with congenital heart disease. *Int J Cardiol*. 2011;153:26−30.

16. Leonardi B, Gentili F, Perrone MA, et al. Cardiopulmonary exercise testing in repaired tetralogy of Fallot: multiparametric overview and correlation with cardiac magnetic resonance and physical activity level. *J Cardiovasc Dev Dis*. 2022;9:26.

17. Takken T, Bongers BC, van Brussel M, Haapala EA, Hulzebos EHJ. Cardiopulmonary exercise testing in pediatrics. *Ann Am Thorac Soc*. 2017;14(suppl 1):S123−S128.

18. Das BB, Young ML, Niu J, et al. Relation between New York Heart Association functional class and objective measures of cardiopulmonary exercise in adults with congenital heart disease. *Am J Cardiol*. 2019;123:1868−1873.

19. von Sanden F, Ptushkina S, Hock J, et al. Peak oxygen uptake on cardiopulmonary exercise test is a predictor for severe arrhythmic events during three-year follow-up in patients with complex congenital heart disease. *J Cardiovasc Dev Dis*. 2022;9:215.

20. Giardini A, Specchia S, Tacy TA, et al. Usefulness of cardiopulmonary exercise to predict long-term prognosis in adults with repaired tetralogy of Fallot. *Am J Cardiol*. 2007;99:1462−1467.

21. Giardini A, Hager A, Lammers AE, et al. Ventilatory efficiency and aerobic capacity predict event-free survival in adults with atrial repair for complete transposition of the great arteries. *J Am Coll Cardiol*. 2009;53:1548−1555.

22. Udholm S, Aldweib N, Hjortdal VE, Veldtman GR. Prognostic power of cardiopulmonary exercise testing in Fontan patients: a systematic review. *Open Heart*. 2018;5:e000812.

23. Egbe AC, Driscoll DJ, Khan AR, et al. Cardiopulmonary exercise test in adults with prior Fontan operation: the prognostic value of serial testing. *Int J Cardiol*. 2017;235:6−10.

24. Chen CA, Chen SY, Chiu HH, et al. Prognostic value of submaximal exercise data for cardiac morbidity in Fontan patients. *Med Sci Sports Exerc*. 2014;46:10−15.

25. Arena R, Myers J, Aslam SS, Varughese EB, Peberdy MA. Peak VO2 and VE/VCO2 slope in patients with heart failure: a prognostic comparison. *Am Heart J*. 2004;147:354−360.

26. Chen SM, Wu PJ, Wang LY, et al. Optimizing exercise testing-based risk stratification to predict poor prognosis after acute heart failure. *ESC Heart Fail*. 2023;10:895−906.

27. Reybrouck T, Rogers R, Weymans M, et al. Serial cardiorespiratory exercise testing in patients with congenital heart disease. *Eur J Pediatr*. 1995;154:801−806.

28. Kipps AK, Graham DA, Harrild DM, et al. Longitudinal exercise capacity of patients with repaired tetralogy of Fallot. *Am J Cardiol*. 2011;108:99−105.

29. Leonardi B, Calvieri C, Perrone MA, et al. Risk factors of right ventricular dysfunction and adverse cardiac events in patients with repaired tetralogy of Fallot. *Int J Environ Res Public Health*. 2021;18:10549.

30. Krieger EV, Valente AM. Tetralogy of Fallot. *Cardiol Clin*. 2020;38:365−377.

31. Atallah J, Gonzalez Corcia MC, Walsh EP, Participating Members of the Pediatric and Congenital Electrophysiology Society. Ventricular arrhythmia and life-threatening events in patients with repaired tetralogy of Fallot. *Am J Cardiol*. 2020;132:126−132.

32. Khairy P, Dore A, Poirier N, et al. Risk stratification in surgically repaired tetralogy of Fallot. *Expert Rev Cardiovasc Ther*. 2009;7:755−762.

33. Khairy P, Aboulhosn J, Gurvitz MZ, et al. Arrhythmia burden in adults with surgically repaired tetralogy of Fallot: a multi-institutional study. *Circulation*. 2010;122:868−875.

34. Probst J, Diller GP, Reinecke H, et al. Prevention of sudden cardiac death in patients with tetralogy of Fallot: risk assessment and long term outcome. *Int J Cardiol*. 2018;269:91−96.

35. Geva T, Mulder B, Gauvreau K, et al. Preoperative predictors of death and sustained ventricular tachycardia after pulmonary valve replacement in patients with repaired tetralogy of Fallot enrolled in the INDICATOR cohort. *Circulation*. 2018;138:2106−2115.

36. Geva T. Indications for pulmonary valve replacement in repaired tetralogy of Fallot: the quest continues. *Circulation*. 2013;128:1855−1857.

37. Harrild DM, Berul CI, Cecchin F, et al. Pulmonary valve replacement in tetralogy of Fallot: impact on survival and ventricular tachycardia. *Circulation*. 2009;119:445−451.

38. Krieger EV, Zeppenfeld K, DeWitt ES, et al. Arrhythmias in repaired tetralogy of Fallot: a scientific statement from the American Heart Association. *Circ Arrhythm Electrophysiol*. 2022;15:e000084.

39. Bokma JP, Geva T, Sleeper LA, et al. A propensity score-adjusted analysis of clinical outcomes after pulmonary valve replacement in tetralogy of Fallot. *Heart*. 2018;104:738−744.

40. Wu MH, Wang JK, Chiu SN, et al. Long-term outcome of repaired tetralogy of Fallot: survival, tachyarrhythmia, and impact of pulmonary valve replacement. *Heart Rhythm*. 2022;19:1856−1863.

41. Bessiere F, Gardey K, Bouzeman A, et al. Impact of pulmonary valve replacement on ventricular arrhythmias in patients with tetralogy of Fallot and implantable cardioverter-defibrillator. *JACC Clin Electrophysiol*. 2021;7:1285−1293.

42. Oechslin EN, Harrison DA, Harris L, et al. Reoperation in adults with repair of tetralogy of Fallot: indications and outcomes. *J Thorac Cardiovasc Surg*. 1999;118:245−251.

43. Diller GP, Kempny A, Alonso-Gonzalez R, et al. Survival prospects and circumstances of death in contemporary adult congenital heart disease patients under follow-up at a large tertiary centre. *Circulation*. 2015;132:2118−2125.

44. Silka MJ, Hardy BG, Menashe VD, Morris CD. A population-based prospective evaluation of risk of sudden cardiac death after operation for common congenital heart defects. *J Am Coll Cardiol*. 1998;32:245−251.

45. Possner M, Tseng SY, Alahdab F, et al. Risk factors for mortality and ventricular tachycardia in patients with repaired tetralogy of Fallot: a systematic review and meta-analysis. *Can J Cardiol*. 2020;36:1815−1825.

46. Rashid I, Mahmood A, Ismail TF, et al. Right ventricular systolic dysfunction but not dilatation correlates with prognostically significant reductions in exercise capacity in repaired tetralogy of Fallot. *Eur Heart J Cardiovasc Imaging*. 2020;21:906−913.

47. Dua JS, Cooper AR, Fox KR, Graham Stuart A. Physical activity levels in adults with congenital heart disease. *Eur J Cardiovasc Prev Rehabil*. 2007;14:287−293.

48. Reybrouck T, Mertens L. Physical performance and physical activity in grown-up congenital heart disease. *Eur J Cardiovasc Prev Rehabil*. 2005;12:498−502.

49. Larsson L, Johansson B, Wadell K, Thilen U, Sandberg C. Adults with congenital heart disease overestimate their physical activity level. *Int J Cardiol Heart Vasc*. 2019;22:13–17.

50. O'Meagher S, Munoz PA, Alison JA, et al. Exercise capacity and stroke volume are preserved late after tetralogy repair, despite severe right ventricular dilatation. *Heart*. 2012;98:1595–1599.

51. O'Meagher S, Munoz PA, Muthurangu V, et al. Mechanisms of maintained exercise capacity in adults with repaired tetralogy of Fallot. *Int J Cardiol*. 2014;177:178–181.

52. Koyak Z, de Groot JR, Bouma BJ, et al. Symptomatic but not asymptomatic non-sustained ventricular tachycardia is associated with appropriate implantable cardioverter therapy in tetralogy of Fallot. *Int J Cardiol*. 2013;167:1532–1535.

53. Gratz A, Hess J, Hager A. Self-estimated physical functioning poorly predicts actual exercise capacity in adolescents and adults with congenital heart disease. *Eur Heart J*. 2009;30:497–504.

54. Müller J, Hager A, Diller GP, et al. Peak oxygen uptake, ventilatory efficiency and QRS-duration predict event free survival in patients late after surgical repair of tetralogy of Fallot. *Int J Cardiol*. 2015;196:158–164.

55. Shafer KM, Opotowsky AR, Rhodes J. Exercise testing and spirometry as predictors of mortality in congenital heart disease: contrasting Fontan physiology with repaired tetralogy of Fallot. *Congenit Heart Dis*. 2018;13:903–910.

56. Tsai YJ, Li MH, Tsai WJ, et al. Oxygen uptake efficiency slope and peak oxygen consumption predict prognosis in children with tetralogy of Fallot. *Eur J Prev Cardiol*. 2016;23:1045–1050.

57. Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis*. 1984;129(Pt 2):S49–S55.

58. Kempny A, Dimopoulos K, Uebing A, et al. Reference values for exercise limitations among adults with congenital heart disease. Relation to activities of daily life—single centre experience and review of published data. *Eur Heart J*. 2012;33:1386–1396.

59. Beaver WL, Lamarra N, Wasserman K. Breath-by-breath measurement of true alveolar gas exchange. *J Appl Physiol Respir Environ Exerc Physiol*. 1981;51:1662–1675.

60. Meadows J, Powell AJ, Geva T, et al. Cardiac magnetic resonance imaging correlates of exercise capacity in patients with surgically repaired tetralogy of Fallot. *Am J Cardiol*. 2007;100:1446–1450.

61. Duppen N, Etnel JR, Spaans L, et al. Does exercise training improve cardiopulmonary fitness and daily physical activity in children and young adults with corrected tetralogy of Fallot or Fontan circulation? A randomized controlled trial. *Am Heart J*. 2015;170:606–614.

62. Schuermans A, Boerma M, Sansoni GA, et al. Exercise in patients with repaired tetralogy of Fallot: a systematic review and meta-analysis. *Heart*. 2023;109:984–991.

63. Avila P, Marcotte F, Dore A, et al. The impact of exercise on ventricular arrhythmias in adults with tetralogy of Fallot. *Int J Cardiol*. 2016;219:218–224.