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Review

Exercise stress testing: A valuable tool to predict risk and prognosis

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ABSTRACT

Exercise stress testing (EST) assesses patient's cardiovascular response to exercise by estimating cardiac output through measurement of the maximal oxygen consumption (VO2), maximal heart rate and oxygen pulse, a surrogate of stroke volume. For children with cardiovascular disease, EST is a valuable diagnostic tool that can be used to evaluate exercise intolerance, assess disease severity, and better understand the etiology of symptoms. This article will review the important role that EST has in children with acquired and congenital cardiac disease, and its utility in assessing clinical status, determining risk and prognosis, and guiding future therapies.

1. Introduction

Regular physical activity in children has many beneficial effects including preventing acquired cardiovascular disease, combating obesity, improving skeletal and vascular health and maximizing psychological function and cognitive processing [1–4]. Children with cardiovascular disease often participate in lower levels of physical activity compared to their healthy peers due to a variety of factors including actual or perceived activity limitations. Restriction to mild exertion and low-intensity sports has been associated with higher BMI in children with congenital heart disease [5]. Exercise stress testing (EST) can help guide clinicians to offer safe and appropriate exercise recommendations through risk stratification. It also assists in the assessing of potential outcomes in certain cardiac conditions. This review will discuss how formal EST can provide helpful information for the clinician managing various types of cardiac disorders in young patients, including congenital defects, acquired cardiac disorders including cardiomyopathies and pulmonary hypertension, and cardiac dysrhythmias.

2. General concepts of exercise testing

To understand how exercise testing can guide recommendations for physical activity, a general review of the cardiopulmonary responses to exercise is helpful (Table 1). Exercise performance depends on an interaction of several physiologic systems, including cardiovascular, pulmonary, musculoskeletal, hematologic and nervous systems [6]. In healthy children, cardiac output increases up to fivefold during exercise. Early exercise cardiac output is augmented by both increasing stroke volume and heart rate, while in late exercise cardiac output is predominately augmented by increasing heart rate. Increased cardiac output in turn provides adequate oxygen delivery, carbon dioxide removal, thermoregulation, and energy substrate delivery to the exercising tissue by shunting systemic blood flow to the skeletal muscle, heart and skin through a local vasodilatory response. Local metabolites from exercising muscles (lactate, carbon dioxide, adenosine) and heat from working muscles result in the rightward shift of the oxyhemoglobin dissociation curve, and allow for oxygen unloading to the exercising muscle groups. Normal pulmonary function is also fundamental for exercise performance, by promoting adequate oxygen delivery and carbon dioxide elimination during exercise. Additionally, any musculoskeletal or neurological impairment will impact exercise performance.

Thus, EST can help evaluate a patient's complex physiologic response to exercise and determine why exercise limitations may occur, as well as risk stratify patients [7,8]. Modern exercise laboratories typically measure maximal oxygen consumption (VO2), carbon dioxide production (VCO2), heart rate and calculate oxygen pulse (VO2/HR), the latter surrogate of stroke volume. Systemic vascular resistance is determined by measuring blood pressure response to exercise. Pulmonary function is assessed at baseline as well as during exercise through measurement of minute ventilation and ventilator equivalents for both oxygen (VE/VO2) and carbon dioxide (VE/VCO2). The latter is

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Table 1
Normative values for aerobic capacity in children and adolescents (cycle ergometry).[a]

	Boys ≤ 13 years	Boys > 13 years	Girls ≤ 11 years	Girls > 11 years
Maximal VO2 (mL/kg/min)	42 ± 6	50 ± 8	38 ± 7	34 ± 4
VO2 at AT (mL/kg/min)	26 ± 5	27 ± 6	23 ± 4	19 ± 3
VO2 at AT/max VO2 (%)	54 ± 6	55 ± 10	61 ± 7	58 ± 8
Work rate (watt/kg)	3.5	3.5	3	3

[a] Cooper DM, Weiler-Ravell D, Whipp BJ, Wasserman K. "Aerobic parameters of exercise as a function of body size during growth in children." *J Appl Physiol Respir Environ Exerc Physiol.* 1984;56(3):628–34.

Table 2
Exercise testing in children with congenital heart disease.

Lesion	Expected peak VO2[a] compared to normative values	Lesion-specific diagnostic features of testing
Simple two ventricle lesion		
ASD	100%	• Impaired exercise performance due to RV dilation or RV dysfunction (unrepaired)
VSD	100%	• Impaired exercise performance due to LV dilation or LV dysfunction (unrepaired) • Ventricular arrhythmia
Coarctation	100%	• Hypertensive response to exercise or residual upper-lower extremity gradient
Aortic Stenosis	100%	• Subendocardial ischemia • Blunted BP response to exercise
Complex two ventricle lesion		
TGA	85–100%	• Chronotropic impairment (atrial switch) • Atrial arrhythmias (atrial switch) • Myocardial ischemia (arterial switch)
TOF	80–85%	• Ventricular arrhythmia • Impaired exercise performance due to free PI, RV dilation or RV dysfunction • Abnormal pulmonary functions at rest and exercise(restrictive or obstructive)
AV Canal	80–85%	• Ventricular arrhythmia
Single ventricle (Fontan physiology)	65–80% (Anaerobic threshold is better preserved)	• Impaired exercise performance and physical working capacity due to Fontan physiology • Desaturation with exercise • Chronotropic impairment • Abnormal pulmonary function (restrictive)

[a] There are no defined reference exercise values for pediatric congenital heart disease and significant variation exists within each disease cohort.

a measure of overall pulmonary efficiency and is helpful to assess for intrinsic lung disease, V/Q mismatch, systemic acidosis, desaturation with exercise, increased pulmonary vascular resistance and increased systemic ventricular filling pressure. Musculoskeletal function is evaluated by assessing physical working capacity as well as the efficiency of oxygen utilization during exercise (Table 2).

3. Congenital heart disease

EST in patients with congenital heart disease can help with risk stratification for exercise participation, as well as decision-making for surgical or transcatheter interventions. In adults with congenital heart disease (CHD), depressed exercise capacity is common, with peak VO2 predicting both hospitalization and death [9]. There are ample data for the use of EST as a clinical guide for a number of forms of CHD.

3.1. Tetralogy of Fallot

In repaired tetralogy of Fallot (TOF), EST can help risk-stratify patients for adverse events. Impaired exercise performance in repaired TOF is common, and tends to worsen over time [10,11]. Chronotropic response is a key predictor of exercise performance in those with repaired TOF, and impaired chronotropic response is associated with a higher risk of mortality in adults [12,13]. Adult patients with abnormal exercise capacity, defined as VO2 ≤ 65% peak predicted, and those with a prolonged QRS duration ≥ 170 ms are at significantly higher risk for death, sustained ventricular tachycardia or cardiac-related hospitalizations [10,14]. Abnormal ventilatory efficiency (VE/VCO2 slope ≥ 31) is also an independent predictor for mortality and need for reintervention and decreased breathing reserve during maximal exercise further contributes to exercise limitation [15,16]. Additionally, EST may help identify patients with asymptomatic ventricular dysfunction due to significant pulmonary valve insufficiency in the setting of a transannular patch or right-ventricle to pulmonary conduit and therefore help guide the evaluation for pulmonary valve replacement [17]. However, more study is needed in this area to determine how to best use EST as a predictive tool for interventional planning. Pathologic arrhythmias may also be detected during maximal EST, which can help guide pharmacologic therapy.

3.2. Transposition of the great arteries

Two major types of surgical interventions have historically been performed for transposition of the great arteries (TGA): the early era employed the atrial switch operation (Mustard or Senning) in the 1960s and 1970s while in the current era beyond the 1980s, the arterial switch operation has become the primary procedure. The earlier atrial switch operation is associated with significant atrial arrhythmias, diminished right ventricular function, chronotropic impairment and impaired exercise performance, while patients with arterial switch repair have been shown to have normal or near normal exercise capacity [18,19]. In patients after atrial switch, abnormal ventilatory efficiency (VE/VCO2 slope) ≥ 35.4 and lower peak VO2 ≤ 52% of peak predicted were associated with increased four-year risk of death or emergent cardiac-related hospitalization [20]. After the arterial switch operation, which involves coronary artery translocation, significant exercise induced ST depression or abnormalities in exercise associated myocardial perfusion imaging may be seen in up to 10% of patients, further supporting the role for routine EST prior to vigorous sport participation [19].

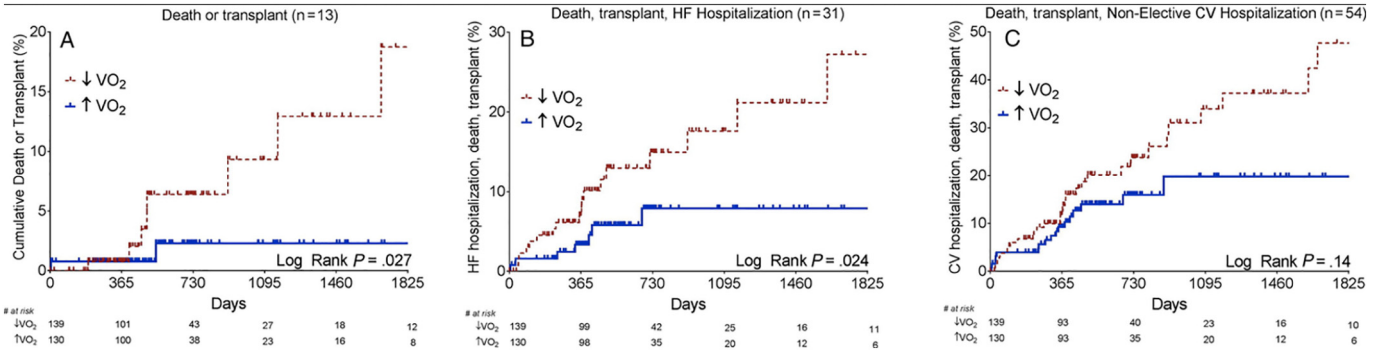

Fig. 1. Cumulative incidence plots for death, transplant heart failure hospitalization or non-elective cardiovascular hospitalization stratified by change in peak oxygen consumption in adult Fontan patients.

3.3. Fontan physiology

In single ventricle Fontan physiology, systemic cardiac output relies on passive pulmonary blood flow from the central venous circulation into a low resistance vascular bed. Patients who have undergone Fontan repair have diminished aerobic and physical working capacity for multiple reasons, including chronotropic impairment, inability to maintain stroke volume at higher heart rates, abnormal pulmonary mechanics, right to left shunting and elevated pulmonary vascular resistance either at rest or during exercise [21]. Interestingly, submaximal exercise performance is better preserved, likely related to the limited ability of the Fontan circulation to maintain pulmonary blood flow at higher work rates and thus maintain systemic ventricular preload [21–23]. In adults with the Fontan physiology, EST identifies patients at increased risk for morbidity and mortality based on low VO2 < 16.6 mL/kg/min or peak HR < 122.5 bpm [24,25]. Additionally, worsening VO2 over time predicted poorer outcomes including death, transplant and unscheduled cardiac-related re-hospitalization [24,26,27] (Fig. 1) The oxygen saturation response to exercise can also be used to inform the safety of referral of patients with Fontan physiology and symptomatic cyanosis for delayed transcatheter fenestration closure.

4. Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most common form of inherited cardiomyopathy with an incidence of 0.47 per 100,000 children and a wide variety of etiologies and phenotypes [28–30]. While the majority of patients with HCM have a relatively benign course, it is also an important cause of cardiac death [31]. Multiple studies have shown that an abnormal blood pressure response during exercise is associated with sudden cardiac death [32,33], as the inability to mount a normal blood pressure response likely correlates with impaired coronary perfusion and arrhythmia. More recent studies in adults have also shown that measures of gas exchange, including peak V02 and ventilatory inefficiency are associated with reduced survival [34–37] (Fig. 2) and may be more sensitive markers of impaired cardiac output. There are fewer studies in the pediatric population, however there are data that shows that a failure in the ability to augment blood pressure response during exercise is a risk factor for cardiac death in children, as well as adults [38].

The management of pediatric patients with HCM can be incredibly challenging. Often these patients are well appearing and asymptomatic at the time of diagnosis. This is increasingly the case with the evolution of genetic screening. Counseling families with respect to disease evolution and participation in sports has critical implications in terms of both risk stratification and quality of life. The current evidence shows that EST is an integral part of this process. Further studies with a pediatric focus are tremendously important.

5. Pulmonary arterial hypertension

Pediatric pulmonary arterial hypertension (PAH) is a rare disease, affecting 2.1–3.7 children per million [39–41]. Affected individuals experience symptoms including dyspnea and fatigue, and have markedly reduced lifespans, with a 5 year mortality of 25%–35% [42,43]. Given the severity of the disease, metrics that can accurately determine disease severity and prognosis are useful in guiding treatment, and can be used as an endpoint in clinical trials. The 6-minute walk test (6MWT) has minimal cost, is representative of activities of daily living, and can be performed by patients in comparatively poor clinical condition [44]. It has been shown to be an independent predictor of prognosis, with decreased median distance covered correlating with increased mortality [45] (Fig. 3). Similarly, EST has shown a statistically significant difference in survival rates in patients with high compared to those with low peak V02 [46] (Fig. 4). EST, while more resource intensive than a 6MWT, has the additional capabilities of characterizing the mechanisms for exercise-related symptoms and is a non-invasive way to assess hemodynamics because EST testing has been correlated with pulmonary artery pressure, pulmonary vascular resistance and cardiac

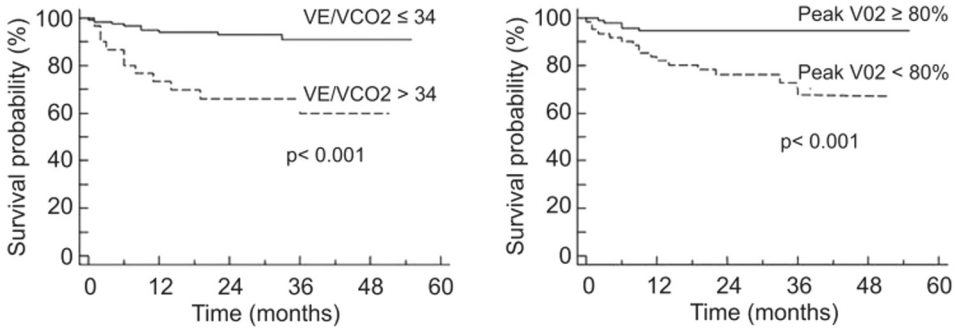

Fig. 2. There is worse long term survival in those patients with HCM and either VE/VC02 > 34 or peak V02 ≤ 80%.

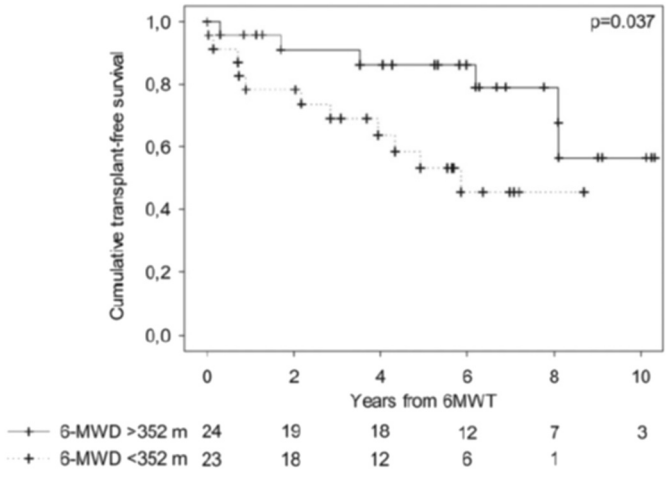

Fig. 3. In patients with PAH, transplant free survival is lower in patients with a 6 MW distance of < 352 m.

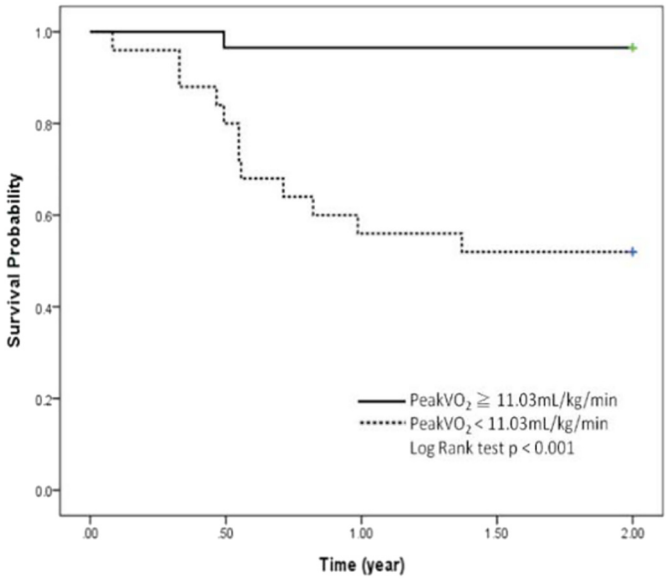

Fig. 4. Impaired peak V02 on EST is predictive of death in patients with PAH.

output [47]. Exercise capacity differs in those patients with PAH depending on disease severity, and given the integral role that both 6MWT and EST have in assessing the risk of mortality, both are now recommended by the European Society of Cardiology (ESC) and European Respiratory Society (ERS) as part of a comprehensive prognostic evaluation and risk assessment [48].

6. Arrhythmias

6.1. Wolff-Parkinson-White Syndrome

Wolff-Parkinson-White Syndrome (WPW) is characterized by the presence of an accessory atrioventricular pathway and typically results in either no symptoms at all, or a relatively benign form of orthodromic reciprocating tachycardia. However, WPW can result in sudden cardiac death, a consequence of atrial fibrillation with rapid conduction through the accessory pathway resulting in ventricular fibrillation [49]. Pathways with a relatively short refractory period, which by convention is defined as a cycle length of ≤250 ms, are more likely capable of rapid conduction. Loss of pre-excitation during EST has been shown to be an effective and reliable noninvasive marker of low risk pathways in multiple studies [50–53] and is now part of the accepted management algorithm of children with WPW [54].

6.2. Catecholiminergic polymorphic ventricular tachycardia

Catecholiminergic polymorphic ventricular tachycardia (CPVT) is a rare but potentially life threatening inherited arrhythmia in which an adrenergic surge triggers ventricular tachycardia, and potentially, sudden cardiac death [55]. EST is a critical component when evaluating for this disease, as the catecholamine release during exercise will trigger ventricular arrhythmias in patients with CPVT, and has shown to be a highly predictive, and non-invasive, method of diagnosis. Patients with CPVT typically have a normal EKG at rest, however the adrenergic stimulation of exercise typically results in the onset and worsening of ventricular ectopy as exercise intensifies [56–58]. Not only has EST been showed to be an accurate method by which to diagnose CPVT, but missed or delayed diagnoses have been shown to be attributable to overlooked findings on EST, or to a lack of an exercise testing, further highlighting the importance of the modality [59].

7. Heart failure and transplant assessment

Similar to adults, EST in children with heart failure is useful for the assessment of heart failure severity and for predicting outcome. In children with biventricular circulation and heart failure, a peak VO2 < 50% predicted and VE/VCO2 slope ≥ 34 is associated with higher risk of death or clinical deterioration [60]. Notably, these values are not applicable when evaluating single ventricle or complex congenital heart disease for transplant candidacy due to abnormal baseline parameters and primarily intra-cardiac right to left shunting [60,61]. In children with dilated cardiomyopathy, abnormal or worsening parameters on serial EST, including lower peak heart rate, abnormal blood pressure response to exercise, lower peak oxygen consumption and higher VE/VCO2 slope, were risk factors for worsening heart failure, need for mechanical circulatory support, heart transplant or death [62,63].

8. Exercise stress testing and exercise training

In patients with exercise limitation and physical deconditioning due to congenital or acquired heart disease, appropriate exercise training recommendations can help augment rehabilitation and improve exercise performance. This in turn will help reduce risk for future acquired cardiovascular morbidity as these patients transition into adulthood. EST provides individualized targeted physiologic parameters that are safe for each patient's unique physiology. Specifically tailoring exercise training that targets heart rate from the anaerobic threshold on a maximal EST will provide appropriate guidance for children with congenital or acquired heart disease, including those with heart failure and ventricular assist devices [64,65]. Additionally, EST assists providers when recommending appropriate levels of physical activity, allowing children to participate in self-limited physical activity. Unique to the Fontan population, lower extremity exercise strengthening may have significant potential for improving pulmonary venous return and cardiac output by creating pulsatile pulmonary blood flow and is an area for ongoing study [66] (Fig. 5).

9. Conclusions

EST in children with congenital heart defects, acquired heart disease, and arrhythmias is useful and necessary for risk stratification, prognostication and guiding therapy. EST provides in depth analysis of the complex cardiopulmonary and musculoskeletal interactions that interplay during exercise and help identify mechanisms for limitations to exercise. Furthermore, EST provides a complementary tool for risk stratification by assessing patient's physical capabilities and physiologic

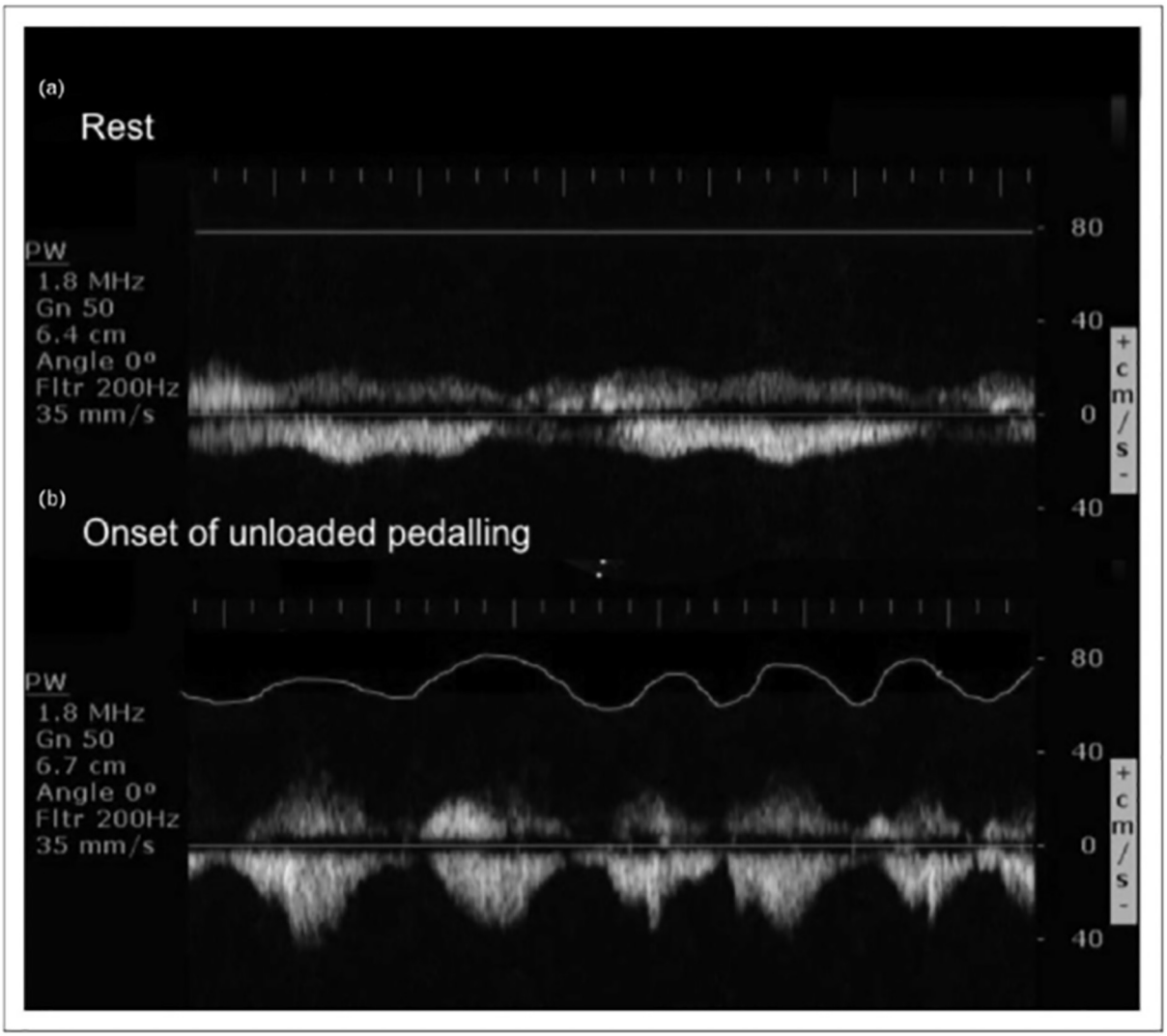

Fig. 5. Cavopulmonary flow at rest and during cycle ergometer.

response during stress and more accurately reflecting patient's physiology during normal daily activities.

Declaration of competing interest

The authors have no relevant disclosures.

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