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Cardiopulmonary exercise test as a tool in surveillance after Fontan operation

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Abstract

Fontan patients have significantly decreased exercise tolerance secondary to several factors, most notably, a lack of a subpulmonary pump to augment systemic venous return to the heart and to overcome the pulmonary vascular resistance. Cardiopulmonary exercise testing is an important inexpensive non-invasive tool to monitor for subclinical changes and functional data over time that may portend the need for earlier intervention.

Keywords: Fontan, cardiopulmonary exercise test, fontan outcomes, oxygen consumption, oxygen uptake efficiency slope, anaerobic threshold

INTRODUCTION

The Fontan operation was first performed in the early 1970s to palliate functionally single ventricle patients[1]. It has gone through many iterations and has been fraught with complications such as liver fibrosis, plastic bronchitis, protein-losing enteropathy, and arrhythmia[2]. Subsequent surgical technique modifications and closer monitoring have improved outcomes; however, surveillance of complications continues to be highly variable between institutions.

Patients with Fontan circuits have significantly decreased exercise tolerance secondary to several factors. The absence of a subpulmonary ventricle causes a lack of negative pressure pulling blood back into the heart and driving pressure to overcome the pulmonary vascular resistance with progressive exercise. In addition, these patients have decreased muscle mass, diminished vascular function, and abnormal autonomic regulation that can impede oxygen delivery to the muscles, thereby further decreasing the ability to exercise efficiently[3]. Factors such as depression, deconditioning, chronic illnesses, and arrhythmia further complicate the picture[4,5].

Cardiopulmonary exercise testing (CPET) is an important non-invasive tool to monitor functional measures of the Fontan circuit and serves as adjunct information to guide timing and need for interventions. It is a relatively inexpensive modality to evaluate the Fontan circuit for any significant desaturations, arrhythmia, oxygen delivery and monitor for any decreased function over time.

In this paper, we will discuss the physiology of exercise in the Fontan circulation and the various CPET measures that can be used to follow Fontan function as well as guide intervention in the Fontan patient.

PHYSIOLOGY OF EXERCISE IN THE FONTAN POPULATION

Preload dependency

During exercise in a normal biventricular system, the pulsatile flow of the blood through the pulmonary vasculature stimulates the release of nitric oxide, thereby decreasing pulmonary artery pressures[6-8]. The subpulmonary ventricle produces a negative pressure to augment the systemic venous return to the heart and generates increasing pressure to drive blood through the pulmonary vasculature, thereby increasing cardiac output to allow adequate oxygen delivery with increasing amounts of exertion.

Fontan circuits lack this subpulmonary pump and depend on the negative pressure of inspiration in order to overcome pulmonary artery pressures. Stroke volume is limited by the inability to increasingly drive the blood through the pulmonary vasculature, even in the setting of normal ventricular function and end-diastolic pressure[9]. In addition, there is some energy loss in the Fontan circuit due to the total cavopulmonary connection.

Because of multiple sternotomies, Fontan patients have intrathoracic fibrous adhesions that can decrease chest wall compliance; therefore, they have decreased forced vital capacity (FVC), which also negatively affects their ability to increase preload back to the heart during inspiration[8]. These factors contribute to the relatively decreased cardiac output with increasing exertion compared to biventricular physiology, which contributes to exercise intolerance in Fontan patients at high exertion.

Ventricular compliance and atrioventricular valve regurgitation

Fontan circulation is well tolerated in younger patients; however, as the patient ages, the ventricular compliance decreases secondary to myocardial fibrosis. This then affects ventricular filling and decreases cardiac output and is most evident at higher heart rates because of the decreased filling time of the ventricle. Significant atrioventricular (AV) valve regurgitation further decreases forward flow that can affect cardiac output negatively in a Fontan patient.

Chronotropic incompetence and arrhythmias

Peak heart rate decreases as patients age. Chronotropic incompetence and arrhythmias are well-known complications in the Fontan population. These patients have compromised cardiac output compared to biventricular patients when chronotropic incompetence is present. Arrhythmias, such as atrial tachycardias,

are relatively common secondary to previous incisions in the atria creating a substrate for arrhythmias during exercise.

Peripheral vascular dysfunction

Patients with Fontan physiology have reduced endothelial function and autonomic dysregulation, which is deleterious to the aerobic function[10]. The etiology of this is multifactorial. A lifetime of activity restriction and fear of adverse events from exercise leads to decreased muscle mass and poor conditioning. Low skeletal muscle mass causes decreased oxygen extraction and poor conditioning leading to poor oxygen utilization efficiency, thereby further contributing to decreased exercise performance.

Abnormal ventilatory function

Patients with Fontan palliation have abnormal ventilation at both rest and with exercise. The exact cause is not entirely clear; however, it is more than likely due to several factors. Fontan patients have multiple median sternotomies, resulting in decreased chest wall compliance secondary to multiple adhesions. Patients with Fontan circulation also hyperventilate compared to normal two ventricle physiology patients because of systemic cyanosis and increased dead space to tidal volume ratio[11,12].

In the presence of a Fontan fenestration, there is increasing right to left shunt with progressive exercise, thereby exacerbating the Ventilation/Flow (V/Q) mismatch, further compromising the oxygen delivery to muscle and producing decreased exercise capacity.

CARDIOPULMONARY EXERCISE MEASURES

VO_2 peak

VO_2 peak is the rate at which the patient consumes oxygen at peak exercise and represents the efficiency with which the patient utilizes oxygen. It is a measure of aerobic capacity that has been shown to have prognostic values in adult heart failure patients[13]. Fontan patients have a multitude of reasons for VO_2 peak to be decreased, such as decreased preload from a lack of a subpulmonary pump, obstruction of the Fontan circuit, significant AV valve insufficiency, left ventricular outflow obstruction, chronotropic insufficiency, arrhythmias, decreased peripheral vascular function and abnormal ventilatory function.

Numerous studies in Fontan patients have shown decreased VO_2 peak of ~50%-60% of expected[14-17]. It has also been shown that VO_2 peak declines with age and is also dependent on the morphology of the systemic ventricle, a single right ventricle having decreased VO_2 peak over time compared to a single left ventricle[18,19]. A recent metaanalysis by Udholm *et al.*[20] reports that in the seven studies analyzed, there was universal exercise impairment in Fontan patients with a VO_2 peak range of 21.2-27.1 mL/kg/min; however, it was noted that there was no clear consensus of whether VO_2 peak itself portends greater risk of hospitalization or cardiac adverse event.

Several studies that analyzed the peak VO_2 in Fontan patients as it relates to outcome indicate that decreasing VO_2 peak correlates with cardiac adverse events, i.e., death or cardiac surgery[21-23]. An absolute cut-off value remains elusive, however, decreased peak VO_2 does correlate with cardiac symptoms and worsening functioning class[24]. Egbe *et al.*[23] noted that a decline in ≥ 3% per year was the only predictor of a 5-year risk of death or surgery. VO_2 peak over time can be a helpful measure to survey for possible functional derangements.

Submaximal measures

Aerobic metabolism is the primary source of energy to sustain exercise during the early phase. With progressive intensity, metabolism shifts from aerobic to anaerobic metabolism. Patients with a Fontan

circulation have problems exercising with anaerobic metabolism. It is difficult to sustain high intensity exercise in a Fontan circulation, as there is decreased flow through the pulmonary vasculature due to lack of subpulmonary pump and increased pulmonary vascular resistance, thus diminishing cardiac output with progressive exercise. For these reasons, submaximal measures can also be used to monitor Fontan function over time.

VO_2 at anaerobic threshold

Anaerobic threshold (AT) is the point during exercise at which the patient changes from aerobic to anaerobic metabolism. AT is decreased in patients with poor aerobic fitness as well as heart failure patients. While VO_2 peaks in Fontan patients are generally decreased, VO_2 at the anaerobic threshold is less impaired and is generally ~75% expected as opposed to 65% expected[25].

There is no data to suggest a clear cut-off for significantly increased risk for mortality; however, the lower the AT, the more risk of morbidity and mortality. Fernandes *et al.*[26] suggested that a cut-off of 9 mL/kg/min was associated with a significantly increased risk of mortality, while Diller *et al.*[22] showed a correlation between a lower VO_2 at AT and hospitalization.

Interestingly, some interventions such as pulmonary vasodilators and strength training have shown improvement in the VO_2 at AT[3,27]. Therefore, despite a lack of clear cut-off, VO_2 at AT is a measure that can be trended over time to assess a Fontan's function and aerobic fitness in Fontan patients.

Oxygen uptake efficiency slope

Oxygen uptake efficiency slope (OUES) is a submaximal relationship of oxygen consumption and minute ventilation, is calculated from submaximal data, and does not depend on intra/inter observer variability[28,29]. It is calculated using a logarithmic curve using the equation: $VO_2 = A \log 10\ VE + B$, where "A" is the OUES, VE is minute ventilation, and it has been well validated in healthy adults and patients with heart failure[28].

The higher OUES or the steeper the slope, the more efficient the oxygen uptake. It has been shown to strongly predict peak VO_2 in Fontan patients and is significantly lower in Fontan patients compared to healthy subjects and other congenital heart disease patients, such as Tetralogy of Fallot[30]. Multiple studies have shown OUES as an excellent predictor of adverse cardiac events in Tetralogy of Fallot patients.

OUES has been validated as an excellent predictor of VO_2 peak in Fontan patients. However, Bongers *et al.*[30] and Giardini *et al.*[31] noted that in Fontan patients with baseline cyanosis, OUES taken during the first half of exercise did not correlate with peak OUES, this was not the finding in noncyanotic Fontan patients. A study from Taiwan showed an OUES ≤ 45% predicted 2-year cardiac morbidity and hospitalization with a sensitivity of 64% and specificity of 93%[32].

OUES is a promising independent predictor of outcomes in Fontan patients, and further studies need to be performed to validate the usefulness of this measure.

Exercise oscillatory ventilation

Exercise oscillatory ventilation (EOV) is a common measure in adult heart failure patients and has long been established as a poor prognostic indicator in adult heart failure[33-35]. In a study from Japan, it was noted that 58% of their young Fontan patients displayed EOV[36].

However, Muneuchi *et al.*[36] found that their patients with EOV were typically smaller, younger and had a higher VO_2 peak, which they attributed EOV to be a compensatory mechanism to overcome the pulmonary artery pressure. Nathan *et al.*[24] found that EOV during a CPET for Fontan was a strong independent predictor for non-elective hospitalization, death or cardiac transplant. There was no correlation between VO_2 peak and EOV, mostly likely because patients in this study were larger and older. EOV still is a promising submaximal measure to follow in older Fontan patients, although more studies need to be performed.

O_2 pulse

O_2 pulse is the VO_2 at peak divided by heart rate and is a marker of stroke volume. O_2 pulse in patients with Fontan's is lower than biventricular counterparts, largely because of decreased peak VO_2[25]. Although higher O_2 pulse at peak exercise was associated with higher peak VO_2[37], few studies that have reported O_2 pulse and have shown no significant correlation with risk of morbidity or mortality[23,26]. Despite these findings, patients in both studies were relatively midterm in their course after their Fontan's; therefore, it would be difficult to conclude whether changes over a longer period of time would portend a different outcome.

Respiratory efficiency and spirometry

Patients who have undergone staged Fontan have had at least two to three median sternotomies, therefore, have the presence of adhesions in the chest cavity. These adhesions can decrease chest wall compliance and restrict excursion of the chest during inspiration. This negatively affects preload given preload is directly affected by the negative inspiratory pressure and lack of subpulmonary pump. FVC correlates with Fontan mortality[38].

VE/VCO_2 is a marker of respiratory insufficiency and can be decreased in Fontan patients. Chen *et al.*[32] showed that a VE/VCO_2 slope ≥ 37 conferred a hazard ratio of 10.77 (p0.023) on univariate analysis for 2-year cardiac morbidity. Studies have shown that this is less predictive than FVC for mortality in Fontan. More than likely, this is secondary to cyanosis that is associated with progressive exercise in Fontan patients.

Heart rate reserve and chronotropic index

Sinus node dysfunction and chronotropic incompetence commonly occur as patients with Fontan circulation age due to incisions at the SVC/RA junction and progressive fibrosis. The peak heart rates on average in a large study in Fontan patients were ~155-165 bpm[25], which is likely because of other physiologic factors of the Fontan circulation, rather than chronotropic incompetence. Metabolic acidosis and cyanosis with progressive exercise in a Fontan patient limit the length and intensity of exercise, thus keeping the patient from achieving a higher heart rate. There are mixed findings on whether HRR and Chronotropic index confers poor outcomes and is likely age-dependent.

CONCLUSION

CPET is an important tool in the surveillance of the Fontan circulation to detect trends in the function that would necessitate intervention. Preload and overcoming pulmonary vascular resistance seem to be the most important determinant of exercise intolerance in the Fontan population. Metabolic measures including VO_2 peak, VO_2 at anaerobic threshold, oxygen pulse and oxygen uptake efficiency slope and ventilatory efficiency can be followed over time to monitor for subclinical changes and be paired with catheterization, imaging and clinical data to determine need and timing for intervention.

DECLARATIONS

Authors' contributions

Writing of the manuscript: Wang-Giuffre EW, Doshi UH

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Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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