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Use of Supine Bicycle Stress Echocardiography in Quantitating Right Ventricular Reserve and Exercise Capacity in Adults with Repaired Tetralogy of Fallot

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Abstract

Objective: This study aimed to examine exercise hemodynamic parameters and exercise capacity in adults with repaired tetralogy of Fallot (rTOF) obtained during supine bicycle echocardiography.

Background: In addition to volumetric MRI parameters, exercise capacity in adults with rTOF is often used to determine timing for pulmonic valve replacement (PVR). Supine bicycle echocardiography is useful in measuring right ventricular (RV) hemodynamic parameters and quantifying exercise capacity and myocardial workload.

Methods: Supine bicycle echocardiograms performed since 2002 were retrospectively reviewed among 33 adults with rTOF followed at a single adult congenital heart disease center. Echocardiographic and hemodynamic parameters were measured before and at peak exercise.

Results: Mean age was 36 ± 12 yrs and severe pulmonic regurgitation (PR) was present in 56%. Mean exercise duration was 15 ± 5 minutes and peak double product was 24,461 ± 6779 units. There was no correlation between resting right ventricular volumetric measurements or tricuspid regurgitant velocity with exercise duration or peak double product. Symptomatic patients in this study had significantly shorter exercise times (17.1 ± 4 vs 12.1 ± 4 minutes, p=0.01) and a trend toward a significantly lower change in the mean pulmonary gradient with exercise (13 ± 8 mmHg vs. 7 ± 2 mmHg, p=0.07). After multivariable linear regression analysis adjusting for age, sex, and severity of PR, a 7 mmHg increase in the ΔPVG_p was independently associated with an additional minute of exercise duration (p=0.01).

Conclusion: Obtaining exercise right heart hemodynamics with supine bicycle echocardiography is feasible among adult patients with rTOF. Change in transpulmonary valvular gradient with exercise, may reflect RV contractile reserve and provide a physiologic correlate to symptoms and exercise capacity in patients with rTOF.

Keywords: Exercise echocardiography; Tetralogy of fallot; Pulmonic valve replacement; Congenital heart disease

Abbreviations: rTOF: Repaired Tetralogy of Fallot; PR: Pulmonic Regurgitation; PVR: Pulmonic valve Replacement; RV: Right Ventricular; ΔPVG_p : Change in Peak Pulmonic Valve Gradient; ΔPVG_m: Change in Mean Pulmonic Valve Gradient

Background

Tetralogy of Fallot is one of the most common cyanotic congenital heart defects with a prevalence of 0.26-0.8/1000 live births [1]. Definitive surgical correction during early childhood has significantly improved outcomes in this population, but survival is still diminished relative to an age-matched population because of increased risk of sudden death in adulthood [2]. A strong determinant of sudden death is severe pulmonary regurgitation (PR), a potentially reversible etiology [3]. However, identifying the optimal timing for Pulmonary valve replacement (PVR) in this high risk cohort can be challenging.

Current surgical decision-making is primarily driven by anatomic assessment of the right ventricle using Magnetic Resonance Imaging (MRI). Right ventricular (RV) volumes as measured by MRI are closely associated with outcomes and predict surgical success [4,5]. Cardiac MRI however is expensive and limited expertise in congenital imaging makes MRI much less available in the community setting. Supine bicycle echocardiography is more widely available and more cost effective as a mechanism to assess exercise capacity and right ventricular hemodynamics. There is incomplete understanding of the relationship between RV contractile reserve and exercise capacity—another strong predictor of increased mortality in this patient population [6].

The goal of this study was to correlate quantitative echocardiographic parameters during supine bike stress testing with exercise tolerance in patients with repaired tetralogy of Fallof. By capturing dynamic changes in RV with exercise, we hope to contribute to the understanding of the hemodynamic underpinnings of exercise intolerance in patients with rTOF with severe PR.

Methods

Supine bicycle echocardiograms of 33 adults with rTOF who were being followed at an adult congenital heart disease center from 2002 to 2009 were reviewed. This study was approved by the Institutional Review

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Board and the requirement for informed consent was waived due to the retrospective nature of the analysis. Patients underwent a symptom limited supine bicycle exercise test after a six hour fast. Echocardiography was performed using the Siemens Sequoia system (Acuson, Mountain View CA). Baseline rest imaging included standard echocardiographic views from the parasternal and apical windows to evaluate right and left ventricular size and function, color Doppler to assess tricuspid and PR and spectral Doppler imaging to measure the tricuspid regurgitant jet velocity and transpulmonic valve gradients. Right ventricular volumes were measured using the single plane method of discs. Severe PR was defined by standard echocardiographic definitions as at least one of the following: a wide color Doppler jet occupying more than 2/3 of the RV outflow tract, steep and dense continuous wave Doppler jet reaching baseline prior to the end of diastole, or holodiastolic flow reversal within the main pulmonary artery. The standard supine bicycle protocol began with three minutes of exercise at 10 Watt resistance and continued at the same speed (60 rpm) as the resistance increased by 30 Watts every 3 minutes. Patients exercised until they were limited by general fatigue, shortness of breath, leg fatigue or chest discomfort. A 12-lead electrocardiogram and oxygen saturation by finger oximetery were monitored throughout exercise. Blood pressure was measured by auscultation by a registered nurse at baseline and in the final minute of each exercise stage. Symptoms were measured during exertion using a standard scale rating of perceived exertion adapted from Borg and Linderholm. Exercise was terminated by the examiner in the following situations: 1.) significant atrial or ventricular arrhythmia, 2.) decrease in overall blood pressure with exercise or hypotension (<90 mmHg for ± 2 minutes) or severe hypertension (systolic blood pressure >220, diastolic blood pressure >120) 3.) ST depressions ≥ 2 mm and 4.) Chest pain or dyspnea. Repeat echocardiographic images were obtained at 85% of the maximal predicted heart rate, and during the recovery phase. There was minimal lag for capture of the images. Exercise duration was recorded. Total myocardial workload was estimated using peak double product a measure of biventricular augmentation with exercise (calculated as the product of systolic blood pressure and maximal heart rate at peak exercise) [7].

Measurements of the following variables were obtained at baseline and at peak exercise: right ventricular body end-systolic and end-diastolic volumes in the apical 4-chamber view, peak transtricuspid valve gradient, and peak and mean transpulmonic gradients. Right ventricular body volumes or fractional area changes were measured by a single echocardiographer (DDY) in the apical four chamber view at baseline and at peak exercise using a single plane method of discs algorithm. All echocardiograms were interpreted by one of five attending echocardiographers at the University of California San Francisco Medical Center.

Medical charts were retrospectively reviewed for baseline information, timing of initial repair and functional capacity. New York Heart Association (NYHA) functional class was determined based on the clinical visit notes immediately prior to the date of the exercise stress study.

All continuous variables are reported as mean ± standard deviation. Paired t-tests were used to detect differences between rest and peak exercise among echocardiographic and clinical parameters (Table 1). Pairwise associations between echocardiographic parameters and exercise duration as well as peak double product were assessed using Pearson correlation coefficients. Multiple linear regression was performed to assess independent echocardiographic predictors of exercise duration and peak double product after adjustment for age, sex, NYHA class and severity of pulmonic valve regurgitation. Regression diagnostics were performed to ensure that the assumption of linearity was appropriate, errors were normally distributed, and the model was robust to influential points. A value of p less than 0.05 was accepted as indicative of statistical significance. All statistical calculations were performed using STATA (Stata Corp. 2008. Stata Statistical Software: Release 12, College Station, TX: StataCorp LP).

	Baseline	Peak exercise	p value
Heart rate (bpm)	70 ± 9	149 ± 21	<0.001
Percent of Max predicted heart rate (%)	38 ±5	81 ± 10	<0.001
Systolic blood pressure (mmHg)	118 ± 16	169 ± 24	<0.001
Right ventricular end diastolic volume (ml)	83 ± 57	85 ± 48	0.88
Right ventricular end systolic volume (ml)	41 ± 29	37 ± 27	0.56
Right ventricular ejection fraction (%)	50 ± 17	58 ± 17	0.06
Peak transtricuspid gradient (mmHg)	35 ± 14	64 ± 26	0.33
Peak transpulmonary valve gradient (mmHg)	21 ± 15	42 ± 25	<0.001

Table 1: Hemodynamic and right ventricular volumetric data pre and at peak exercise. Tricuspid gradients were available for 27 patients at rest and 28 patients at peak exercise.

Results

Thirty three patients were enrolled in this study. Mean age at the time of stress test was 36 +/- 12 years and 56% were female. The mean age of initial TOF repair was 7.6 ± 10 years, and 8 patients (25%) had subsequently undergone a second operation, PVR with pulmonary homograft, prior to their stress echocardiogram. Exercise right heart hemodynamic data was obtained in 100% of patients evaluated and all studies were terminated due to shortness of breath or fatigue. Patients with prior PVRs had similar exercise durations (p=0.63) and peak double products (p=0.89) compared to those that did not undergo valve replacement. Of 27 patients with functional class documentation available at the time of the supine bicycle study, 17 were NYHA functional class I (63%), 9 were NYHA functional class II (33%), and one patient was functional class III (4%). No patients were functional class IV. Severe PR was present in 18 patients (56%), and 2 of these patients had recurrent PR following PVR. Moderate PR was present in 2 patients (6%), mild PR in 4 patients (13%), and less than mild PR in 7 (21%). Importantly, no patient had severe RV outflow obstruction (peak transpulmonic valve gradient >50 mmHg).

Mean duration of exercise was 15 minutes and 6 seconds +/- 5 minutes and mean peak double product was 24,461 ± 6,779 units. Heart rate increased on average from 70 ± 9 minutes to 149 ± 21 minutes at peak exercise (mean of 81% max predicted heart rate). Peak transpulmonic valve gradient was a mean of 21 ± 15 mmHg at baseline and 42 ± 25 mmHg at peak exercise (p<0.001). Mean transpulmonic gradient was a mean of 10 ± 7 mmHg at baseline and 22 ± 15 mmHg at peak exercise (p<0.001). There was no significant change in transtricuspid gradients or RV volumetric or functional parameters from baseline to peak exercise (Table 1). There were no significant differences in tricuspid or pulmonary valve gradients between symptomatic and asymptomatic patients (Table 2A). Additionally, there were no significant differences between patients with severe PR and those with less than severe PR (Table 2B). However, when compared to asymptomatic (NYHA Class I) subjects, those patients that were symptomatic (NYHA Class II or greater) did have significantly lower exercise times (17.1 ± 4 vs. 12.1 ± 4 minutes, p=0.01) and a trend toward a significantly lower change in the mean pulmonary gradient with exercise (13 ± 8 mmHg in asymptomatic patients versus 7 ± 6 mmHg in symptomatic patients, p=0.07). Interestingly, the peak double product was not significantly

	NYHA Class I	NYHA Class II or greater	p value
Baseline			
Peak Transtricuspid Gradient (mmHg)	32 ± 11	40 ± 16	0.17
Peak Transpulmonary Gradient (mmHg)	23 ± 17	21 ± 13	0.75
Mean Transpulmonary Gradient (mmHg)	11 ± 7	12 ± 8	0.87
Post Exercise			
Peak Transtricuspid Gradient (mmHg)	62 ± 24	63 ± 20	0.94
Peak Transpulmonary Gradient (mmHg)	45 ± 25	37 ± 23	0.39
Mean Transpulmonary Gradient (mmHg)	24 ± 15	17 ± 11	0.27
Change with Exercise			
Peak Transtricuspid Gradient (mmHg)	37 ± 20	24 ± 17	0.13
Peak Transpulmonary Gradient (mmHg)	23 ± 18	16 ± 13	0.25
Mean Transpulmonary Gradient (mmHg)	13 ± 8	7 ± 6	0.07

Table 2A: Trans-tricuspid and trans-pulmonary gradients at baseline and peak exercise among patients with and without symptoms.

	Less than severe PR	Severe PR	p value
Baseline			
Peak Transtricuspid Gradient (mmHg)	40 ± 15	31± 9	0.07
Peak Transpulmonary Gradient (mmHg)	18 ± 12	23 ± 17	0.44
Mean Transpulmonary Gradient (mmHg)	9 ± 7	11± 8	0.44
Post Exercise			
Peak Transtricuspid Gradient (mmHg)	68 ± 28	61 ± 20	0.39
Peak Transpulmonary Gradient (mmHg)	45 ± 27	39 ± 24	0.56
Mean Transpulmonary Gradient (mmHg)	21 ± 16	22 ± 14	0.77
Change with Exercise			
Peak Transtricuspid Gradient (mmHg)	28 ± 23	34 ± 21	0.48
Peak Transpulmonary Gradient (mmHg)	28 ± 24	17 ± 13	0.12
Mean Transpulmonary Gradient (mmHg)	13 ± 14	11 ± 8	0.73

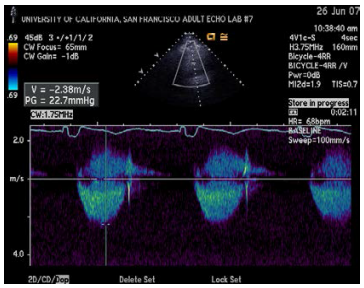
Table 2B: Trans-tricuspid and trans-pulmonary gradients at baseline and peak exercise among patients with and without severe pulmonary regurgitation.

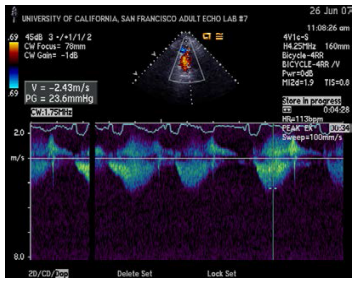
different among the two groups (26352 ± 4400 vs. 24043 ± 6090, p=0.27).

There was a significant association between the change in perk transpulmonic valve gradient Δpvgp and exercise duration (8.3 ± 2.4 mmHg change per additional minute of exercise, p=0.002). After multivariable linear regression analysis adjusting for age, sex, and severity of PR, a 7 mmHg increase in the ΔPVG_p was independently associated with an additional minute of exercise duration (5.6 ± 2.4 mmHg, 95% CI 3.44-13.23, p=0.01, correlation coefficient 0.56) (Figure 1). The presence of moderate or severe PR was not associated with either peak double product (OR 1.00, 95% CI 0.99-1.00, p=0.44) or exercise duration (OR 0.99, 95% CI 0.99-1.00, p=0.44). Interestingly, there was no significant association between 2-dimensional derived RV volumetric measurements in diastole or systole with exercise duration or peak double products.

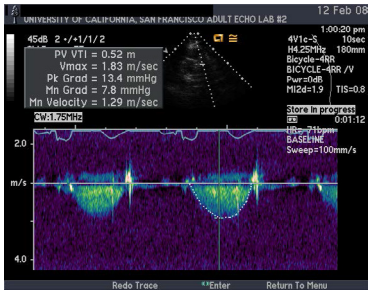
Discussion

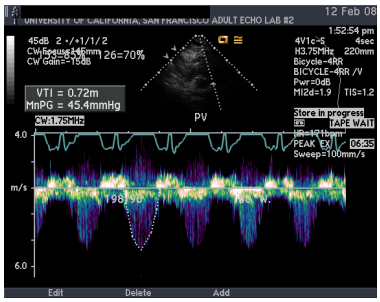
Cardiac MRI has proven to be the gold standard in assessment of RV volumes and function, however MRI is expensive and expertise in adult congenital MRI interpretation is not widely available outside of large academic centers. Other modalities such as exercise echocardiography as less expensive and more widely available however exercise RV hemodynamics have no been studied in the adult rTOF population. This is the first study to evaluate exercise capacity and hemodynamic parameters as measured by supine bicycle exercise echocardiography in adults with rTOF, and right heart hemodynamic assessment was obtained in all patients evaluated. Our analysis suggests an association between the change in the transpulmonic gradients with exercise and exercise duration in patients with rTOF who have pulmonary valve regurgitation. This association persisted after adjustment for clinical and demographic factors. Importantly, the relationship also persisted after accounting for the severity of PR in multivariate analysis, which can be a powerful determinant of the transpulmonary gradient. Finally,





A: Patient 1: Poor exercise capacity





B. Patient 2: Excellent exercise capacity

Figure 1: A) Exercise duration of 9min18sec, peak double product of 16,330. Peak pulmonic valve gradient of 23 mmHg at baseline. No significant change in peak transpulmonic gradient with exercise. B) Exercise duration of 21min 3sec, peak double product of 34,600. Peak pulmonic valve gradient of 13 mmHg at baseline. Change in peak transpulmonary valve gradient with exercise of 73 mmHg.

though not significant, there was a trend towards a lower change in transpulmonic gradient in patients with worse functional status as measured by NYHA Class.

In addition to cardiac MRI RV volumetrics, the determination of symptoms or reduced exercise capacity is useful when evaluating patients with rTOF and severe PR for PVR, as a reduced exercise capacity has been linked to escalating morbidity [6]. Although formal cardiopulmonary exercise testing is the preferred method of evaluation of exercise capacity in theses patients, these tools are also not widely available outside of academic centers. As such, simple, widely available modalities are much needed to assess the functional status of the patient as well as the status of the right ventricle to determine the appropriate timing for surgery. If intervention with PVR occurs too late in the disease process after the RV has become dilated and hypocontractile, patients will fail to demonstrate improvement in RV function and exercise capacity post operatively [8]. As a result, timing of PVR should ideally occur just after patients have begun to develop symptoms or have begun to develop early RV dilation or dysfunction, but before significant and irreversible RV dilation or dysfunction occurs.

Contractile reserve has been well evaluated in the left heart, particularly among patients with aortic stenosis and cardiomyopathy. Contractile reserve of the RV is less well defined. In this study, we proposed a simply measured, objective marker of RV functional capacity transpulmonary valve gradients with exercise. At baseline, flow across the pulmonary valve the primary determinant of transpulmonary gradients is determined by the RV cardiac output, the orifice area of the RV outflow tract and the pulmonary vascular afterload. In the absence of any significant pulmonary valvular obstruction, the transpulmonary gradient at peak exercise (when the pulmonary vasculature is maximally dilated) is primarily driven by the contractility of the RV. If the change from baseline conditions is evaluated, the resulting value ΔPVGp- is plausibly a measure of RV contractile reserve. We have shown that this measure of contractile reserve is potentially associated with functional status and objective measures of exercise capacity two established predictors of morbidity in this population. Put together, this data provides a biologically plausible explanation that decline in RV contractile reserve may be one factor contributing to decline in exercise capacity among adults with rTOF.

Importantly, no patients in this analysis demonstrated significant pulmonary stenosis. In the absence of severe pulmonary stenosis, increases in the transpulmonic valve velocity with exercise could suggest one of two potential physiologic mechanisms. The first is the scenario stated above, where RV functional reserve is able to generate increased contractile force, leading to a greater ΔPVG with exertion. This is akin to low flow low gradient aortic stenosis, where LV contractile reserve in response to dobutamine signifies a healthier left ventricle than one that cannot augment. Another physiologic explanation is that there may be a degree of mild residual pulmonic stenosis, whose gradient is amplified as flow increases with exertion and improved RV contractility. In these cases, pulmonary stenosis may protect from the deleterious effects of PR, including severe RV volume overload.

There are limitations to our analysis. First, RV fractional area change as measured in the apical four chamber view did not correlate with exercise capacity, possibly reflecting the limitations of standard echocardiographic techniques. The unusual geometry of the RV and heavy trabeculation makes accurate measurement of end-systolic and end-diastolic volumes, ejection fraction and stroke volume technically challenging, particularly at peak exercise. Magnetic resonance imaging has shown to be more accurate in ventricular volume assessment than two dimensional echocardiography [9]. However, this modality is limited in their ability to measure changes with exercise. Additionally, there is some heterogeneity among the studied population. This may have resulted in wide confidence intervals around studied measurements increasing the possibility of a type II error among some of our secondary findings. Notable, the key finding in this study, however, was statistically significant.

There are also several methodologic limitations, which are primarily reflective of the retrospective nature of the study. First, RV dimensions were only measured in one view. The addition of other views or 3D echocardiography may have improved volumetric measurements. Second is the lack of additional correlates of overall functional capacity, including left ventricular function and cardiac output. Certainly variations in left sided function could change exercise capacity, although it is unlikely to see significant differences between patients in this younger cohort. Third, the population examined is somewhat heterogenous as there is some variation in the degree of PR and some patients have undergone pulmonary valve replacement. Further, quantitative measurement of PR was not available, nor was PR at peak exercise, limiting the interpretability of the study. Additionally, novel markers of RV function were not obtained including doppler imaging of the Tricuspid Annular Plane Systolic Excursion (TAPSE) before and after exercise. Right ventricular function as assessed with quantitative tissue Doppler imaging has been evaluated in children late after repair of TOF, demonstrating that the magnitude of increase in tricuspid annulus flow during systole was correlated with RV contractile reserve as assessed by RV peak dP/dt [10]. Additionally, impaired contractile reserve can be documented with tissue Doppler imaging of the tricuspid annular motion during dobutamine stress echo and is predicted by tissue Doppler imaging indices at rest [11]. No studies to this date have evaluated tissue Doppler imaging with supine bicycle exercise echocardiography, and this information would certainly add to the assessment of RV performance. Finally, in many patients transtricuspid valve velocities were likely underestimated due to incomplete tricuspid regurgitant jets. One may expect that the transtricuspid gradient may correlate with the transpulmonic valve gradient, however we are unable to demonstrate this relationship with the available data; peak transtricuspid gradients may have been underestimated at peak exercise due to incomplete tricuspid regurgitant jets at high heart rate.

Conclusion

Assessment of right heart hemodynamics with supine bicycle transthoracic echocardiography is feasible and may be useful in quantifying exercise capacity and myocardial workload in adults with rTOF. The magnitude of increase in pulmonic valve gradients (ΔPVG_p) with exercise correlated with peak exercise duration even when accounting for severity of PR. This may reflect better RV contractile reserve and may be useful is assessing prognosis among adults with rTOF as well as timing for PVR. Additional studies are necessary to further define exercise RV hemodynamics in the rTOF population and correlate with outcomes.

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