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ORIGINAL ARTICLE

# Correlation of Echocardiogram and Exercise Test Data in Children with Aortic Stenosis

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**Abstract**

Previous pediatric exercise test criteria for aortic stenosis severity were based on cardiac catheterization assessment, whereas current criteria are based on echocardiographic valve gradients. We sought to correlate exercise test criteria with echocardiographic assessment of severity. We report 65 studies, 51 patients (mean age of 13 ± 4 years; 75% males), with aortic stenosis (AS) who had a maximal exercise test between 2005 and 2016. We defined three groups based on resting mean Doppler gradient across their aortic valve: severe AS ($n=10$; gradient of ≥ 40 mmHg), moderate AS ($n=20$; gradient 25–39 mmHg), and mild AS ($n=35$; gradient ≤ 24 mmHg). We studied symptoms (chest pain) during exercise, resting electrocardiogram changes (left ventricular hypertrophy [LVH]), complex arrhythmias during exercise, change in exercise systolic blood pressure (SBP; delta SBP = peak SBP-resting SBP), exercise duration, work, echocardiogram parameters (LVH), and ST–T wave changes with exercise. Additionally, we compared work and delta SBP during exercise with 117 control males and females without heart disease. Severe AS patients have statistically significant differences when compared with mild AS in ST–T wave depression during exercise, LVH on resting electrocardiogram, and echocardiogram. There was a significant difference in delta SBP between severe AS and normal controls (delta SBP 21.6 vs. 46.2 mmHg), and between moderate AS and normal controls (delta SBP 32 vs. 46.2 mmHg). There were no significant complications during maximal exercise testing. Children with echocardiographic severe and moderate AS have exercise testing abnormalities. Exercise test criteria for severity of AS were validated for echocardiographic criteria for AS severity.

**Keywords** Echocardiogram · Cardiopulmonary exercise testing · Aortic stenosis · Ischemia

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## Introduction

The second natural history study of congenital heart defects showed that patients with aortic stenosis (AS) often progress to needing intervention [1]. Also, patients with congenital AS may be at increased risk of sudden unexpected death [2]. Literature has shown that as AS progresses, duration of exercise decreases, delta systolic blood pressure (SBP) decreases, and more ST–T segment changes occur [3–5]. In 2005, AS management guidelines were updated using echocardiography to determine the severity of AS [6]. Previously, these recommendations were based on data obtained from pediatric patients who underwent cardiac catheterization and used peak-to-peak gradient at catheterization combined with non-invasive data derived from exercise testing and electrocardiograms (ECG) [7, 8]. Exercise data (duration, blood pressure response, ischemia, and arrhythmias) along with the presence of symptoms, ECG presence of left ventricular hypertrophy (LVH) with strain, and echocardiographic evidence of LVH, help determine severity in patients with AS [9].

There have been no empirical studies that have compared exercise stress testing results with different degrees of severity of congenital AS determined by echocardiogram, as delineated in the current American Heart Association/American College of Cardiology (AHA/ACC) guidelines. The purpose of this study was to report empirical exercise testing results in pediatric patients with varying severity of AS (mild, moderate, and severe) as determined by echocardiogram to see if the findings correlate with AS severity.

## Methods

We obtained Institutional Review Board approval through our institution; this research complied with the 1964 Declaration of Helsinki and its later amendments. The electronic medical record was used to perform the initial data review. The data query used International Classification of Disease (ICD)-9 and/or ICD-10 codes between the years 2005 and 2016, searching for patients with the medical diagnosis of AS and who also had the Current Procedure Terminology code for an exercise stress test. The ICD codes for diagnoses included congenital stenosis of aortic valve, congenital insufficiency of aortic valve, congenital subaortic stenosis, supravalvular aortic stenosis, non-rheumatic aortic valve disorder, non-rheumatic aortic valve insufficiency, aortic stenosis, aortic valve disorder, aortic valvular stenosis, and bicuspid aortic stenosis. The initial data review search provided 458 patients. With each patient, a chart review was performed and data were obtained from echocardiogram reports and exercise test reports. Each echocardiogram that was added to the data set was within 12 months of the exercise test.

Inclusion criteria were the following: patients with bicuspid aortic valve (BCAV), BCAV with AS, BCAV status post balloon aortic valvuloplasty, BCAV with AS with mild or less than mild aortic regurgitation, and BCAV with AS status post aortic valve replacement and subaortic stenosis. Exclusion criteria were any patients with status post coarctation repair, status post Ross procedure, idiopathic hypertrophic subaortic stenosis, idiopathic hypertrophic cardiomyopathy, apical ventricle to aorta conduits, greater than mild aortic regurgitation (defined as diastolic flow reversal in descending aorta) genetic disorders (e.g., Williams syndrome), other cardiac heart defects such as transposition of the great arteries, and hypoplastic left heart syndrome. If the data query resulted in a patient who did not have a documented aortic mean Doppler gradient, these data points were then excluded. The cohort was narrowed to 65 echocardiographic studies in 51 patients. Two patients had a prosthetic aortic valve, one had subaortic stenosis, and the other 62 had BCAV at time of exercise testing.

Patients were classified as having severe, moderate, or mild AS based on resting echocardiographic data, specifically the mean Doppler gradient, which coincides with the most current AHA/ACC guidelines eligibility criteria for athletes with cardiovascular abnormalities [9]. We defined severe AS as a resting mean Doppler gradient of greater than or equal to 40 mmHg. Moderate AS was defined as a resting mean Doppler gradient of 25–39 mmHg. Mild AS was determined by having a resting mean gradient across the aortic valve by Doppler of less than or equal to 24 mmHg.

Echocardiograms were performed within 14 months of the exercise study. Ninety-one percent of exercise tests were within 3 months of the most recent echocardiogram. Echocardiogram variables that were gathered were mean and peak Doppler gradient across the aortic valve, left ventricular function (shortening fraction), interventricular septal thickness at end-diastole and left ventricular posterior wall dimension, and left ventricular mass. Presence of LVH and left ventricular function were obtained from the echocardiogram report. Left ventricular hypertrophy by echocardiogram was defined as interventricular septal thickness at end-diastole or left ventricular posterior wall dimension that was greater than two standard deviations (SD; based on Boston Children's Hospital *z* score values).

Variables aggregated from the exercise stress test included blood pressure and heart rate response during rest and peak exercise, exercise duration, amount of work, ECG at rest, and ECG ST–T segment changes during exercise.

An ECG was obtained before exercise and a rhythm strip was monitored throughout the test. Left ventricular hypertrophy on ECG was defined using the voltage criteria for LVH as outlined by Park and Guntheroth [10].

## Exercise Protocol

The exercise test took place with an electronically braked cycle ergometer (Sensormedics, VIAsprint 150P, Yorba Linda, CA) or on the treadmill (Series 2000 Treadmill, GE Marquette Medical Systems, Milwaukee, WI). We used a non-steady state ramp protocol on the bike increasing the workload at 0.3–0.35 Watt/kg/min. Patients who were not able to use the cycle ergometer (usually due to small stature) exercised on the treadmill using the Bruce protocol [11]. Predicted values of exercise duration and normal blood pressure ranges on the bike ergometer were derived from 117 (51% male) individuals without structural heart disease based on age and sex from our laboratory using the same bike protocol (workload increased at 0.3–0.35 Watt/kg/min) [12]. Duration on the bike ergometer was divided as time of exercise test that was within ± 1 SD and ± 2 SD of normal duration based on age and sex. Abnormal exercise duration on the bike ergometer was defined as an exercise duration < 2 SD or more below the normal average for our lab. Predicted values of exercise duration for the Bruce treadmill test endurance were based on a prior study [11]. Patients were exercised until maximal volitional fatigue in all studies. Respiratory gases were collected by mouthpiece and analyzed by a metabolic cart (Vmax 29C, Sensormedics, Yorba Linda, CA). Metabolic measurements during exercise were obtained by breath-by-breath analysis throughout the study.

Blood pressure measurements (Tango Stress blood pressure machine, SunTech Medical, Morrisville, NC) were recorded at rest, every 3 min, at peak exercise, and during recovery. The peak exercise SBP minus the resting SBP was calculated and termed the delta SBP.

A resting ECG was obtained (GE Case System, GT Marquette Medical Systems, Milwaukee, WI). Throughout the stress test, the ECG strip was monitored. The ST–T wave depression was defined as a greater than 1 mm depression for more than 60 ms below a baseline that connects the PQ junction of 3–5 consecutive P–QRS–T complexes in any lead during exercise [13].

### Statistical Analysis

Comparisons between groups were made using one-way analysis of variance, then subsequent pairwise comparisons between groups were made using t-tests. Distributions of quantitative variables were summarized using means and SD. Distributions of categorical variables were summarized using counts and proportions. Two-sample unpaired Student's t-test was used to compare the distribution of ST–T segment depression between groups. Nested multiple regression models and Wilcoxon rank-sum test were used to detect differences in delta SBP between groups, accounting for the effect of age and sex. All analyses were two-tailed with the level of significance at 5%. All statistical analysis was performed using R Statistical Software, version 3.3.1 [14].

## Results

We analyzed 65 exercise studies (51 patients) for our cohort (see Table 1). Of these studies, 71% were done on the bike ergometer and 29% on the treadmill. The 65 studies in the final cohort were classified into three groups: severe AS ($n = 10$), moderate AS ($n = 20$), and mild AS ($n = 35$) based on mean Doppler gradient.

## Symptoms with Exercise

In the severe AS group, 10% (1/10) of studies had chest pain, none of the moderate AS studies admitted to chest pain, and 6% (2/35) of studies with mild AS had chest pain. In those patients with mild AS who reported chest pain with exercise, there were no ECG changes, no evidence of LVH on echocardiogram, and the chest pain was described as non-crushing. Given these findings, they were not felt to have ischemic chest pain from AS. There was one patient in the severe AS group who had chest pain associated with exercise ECG ST–T segment depression.

## ECG, Resting, and Exercise

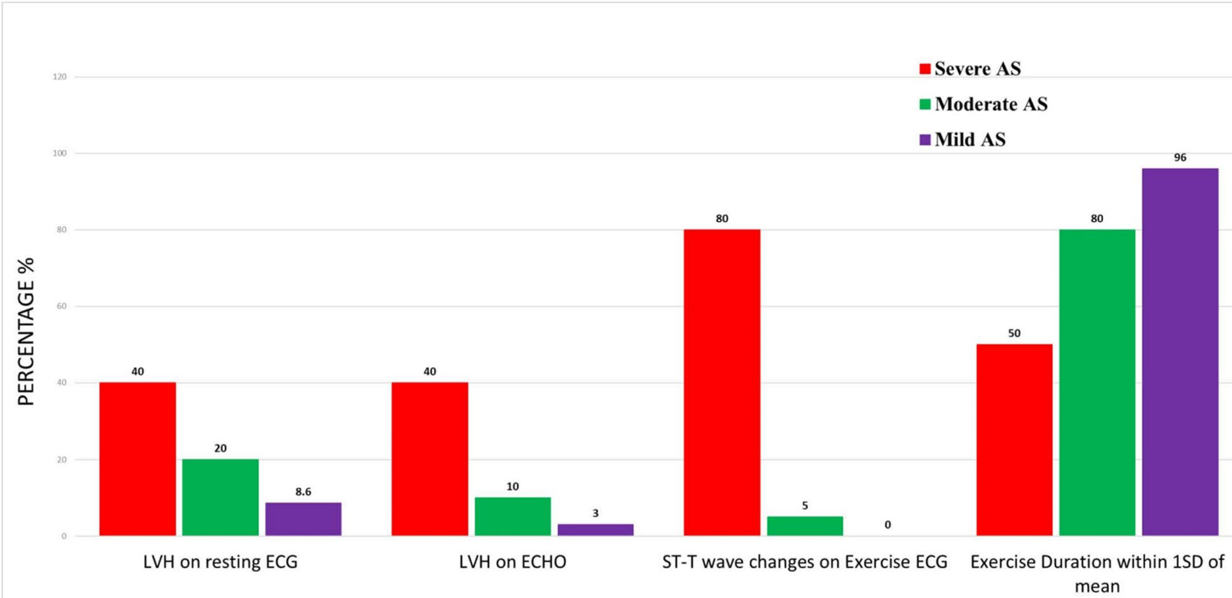
The severe AS group had LVH in 40% (4/10) of studies; the moderate AS group had LVH in 20% (4/20) of studies; and the mild AS group had LVH in 8.6% (3/35) of studies (severe AS group vs. mild AS group; $p = 0.03$). No other comparisons were significant; see Fig. 1.

There was a correlation with the AS gradient and the incidence of ST–T wave changes. In the severe AS group, 80% (8/10) of studies had ST–T segment depression during their exercise ECG versus 5% (1/20) in the moderate AS group, and 0 in the mild AS group (see Fig. 1). Prevalence was significantly different among the severe AS group versus the moderate AS and versus the mild AS group ($p < 0.001$).

**Table 1** Demographics of study cohort

| | Patients (*n*) | Studies (*n*) | Average age in years (SD) | Bike ergometer protocol studies | Bruce treadmill protocol studies |
|---|---|---|---|---|---|
| Male | 38 | 45 | 13 (4) | 31 | 14 |
| Female | 13 | 20 | 13 (3) | 15 | 5 |
| Total | 51 | 65 | 13 (3.5) | 46 (71%) | 19 (29%) |

*SD* standard deviation




| | LVH on resting ECG | LVH on ECHO | ST-T wave changes on Exercise ECG | Exercise Duration within 1SD of mean |
|---|---|---|---|---|
| Severe vs. mild AS | 0.03* | 0.006* | <0.001* | 0.037* |
| Severe vs. moderate AS | NS | NS | <0.001* | NS |
| Moderate vs. mild AS | NS | NS | NS | NS |

**Fig. 1** Exercise stress test and echocardiogram findings in patients with AS. *$p < 0.05$ considered significant. *AS* aortic stenosis, *ECG* electrocardiogram, *ECHO* echocardiogram, *LVH* left ventricular hypertrophy, *NS* not significant

## Echocardiogram

Left ventricular hypertrophy correlated with increasing AS gradient. In 40% (4/10) of the severe AS studies, 10% (2/20) of the moderate AS studies, and 3% (1/35) of the mild AS studies, LVH was present (severe AS vs. mild AS group; $p = 0.006$). There was a trend for hyperdynamic function (increased shortening fraction) in the severe AS group.

## Exercise Duration

As the AS gradient increased, the number of patients with exercise duration below or < 1 SD decreased on the bike ergometer (see Fig. 1). The number of studies in the severe AS group below or < 1SD duration was 50% (2/4), which was significantly different than the mild AS group with duration below or < 1 SD of 96% (26/27; $p = 0.037$).

When looking at the studies performed using the Bruce treadmill protocol, the duration of exercise inversely correlated with degree of AS, as compared with normal controls in our lab. Using the 50th percentile as the average duration, 2% (1/6) of the severe AS group exercised greater than the 50th percentile, 20% (1/5) of the moderate AS group exercised greater than the 50th percentile, and only 38% (3/8) of the mild AS group exercised greater than the 50th percentile for duration. Given the small number of treadmill studies conducted (19/65 or 29%), statistical analysis was not performed.

## Work

Work (Watts/kg) was evaluated in those patients who used the bike ergometer and was compared with controls. As the severity of AS increased, the amount of work performed decreased. The controls had an average work of $2.95 \pm 0.67$ Watts/kg; the severe AS group had an average of $2.32 \pm 0.92$ Watts/kg ($p = 0.07$ vs. controls), the moderate AS group average was $2.511 \pm 0.73$ Watts/kg ($p = 0.02$ vs. controls), and the mild AS group average was $2.85 \pm 0.73$ Watts/kg ($p = 0.51$ vs. controls).

In all 65 studies and 51 patients, including both the ergometer and the treadmill studies, there were no adverse events that occurred during exercise, including syncope or significant arrhythmias such as ventricular tachycardia.

## Systolic Blood Pressure

There was a significant difference in delta SBP between severe AS and normal controls (delta SBP 21.62 ± 21.5 mmHg vs. 46.2 ± 19.3 mmHg; $p < 0.001$) and between moderate AS and normal controls (delta SBP 32 ± 16.5 mmHg vs. 46.2 ± 19.3 mmHg; $p = 0.002$). There was a significant difference in delta SBP between the severe AS group and the mild AS group (delta SBP 21.6 ± 21.5 vs. 40.7 ± 16.8 mmHg; $p = 0.010$). Mild AS patients did not have a significant difference from controls (delta SBP 40.7 ± 16.8 mmHg vs. 46.2 mmHg; $p = 0.14$ (see Fig. 2). Again, given the small sample size of patients who completed the exercise test using the bike ergometer, we combined all delta SBP values from both the bicycle and treadmill tests for each AS group and compared values to controls.

Adjusting for age and sex, difference in delta SBP between the control and all AS groups remained statistically significant ($p < 0.0006$). Holding age and sex constant, delta SBP continued to be statistically significant when comparing severe AS with the controls ($p = 0.008$), moderate AS compared with controls ($p = 0.005$), and mild AS compared with controls ($p = 0.003$).

## Clinical Follow-Up

If an exercise stress test showed ST–T segment depression, it was considered a positive result and the patient therefore underwent further testing or surgery. There were nine patients who met this criterion. There was one patient in the moderate AS group who had an ST–T segment depression.

Of those nine patients, one patient went straight to surgery for an aortic valve replacement. Another patient had a previous cardiac catheterization a year before that did not qualify him for surgery (peak-to-peak gradient 38), so when the exercise test showed ST–T wave changes, the patient was sent straight to surgery. The last seven patients went to cardiac catheterization: two had balloon angioplasty of the aortic valve with reduction in gradient and one had balloon angioplasty with reduction in gradient but later developed moderate-to-severe aortic regurgitation and needed a Ross procedure. Three had a cardiac catheterization but did not fulfill criteria for intervention and one went to surgery based on the aortic valve that was felt to be blocking the left coronary artery orifice.

## Discussion

We report empirical results of exercise testing in patients with different severities of AS determined by echocardiogram. Children with severe and moderate AS by echocardiogram have exercise testing abnormalities, whereas mild AS patients had normal studies. The findings presented in this study suggest that exercise test outcomes correlated with echocardiographic criteria for AS severity are comparable to findings from the cardiac catheterization era.

Nishimura and associates evaluated 232 patients from the second natural history study of congenital heart defects. They showed that there was a direct relationship between aortic valve echocardiogram mean gradient and left ventricular wall thickness. They also showed that there was an inverse relationship between aortic valve mean gradient and exercise time [15]. Our study confirmed this finding; however, we are unique in showing empirical exercise test results for the mild, moderate, and severe AS groups as determined by echocardiogram and outlined in the current AHA/ACC guidelines [9].

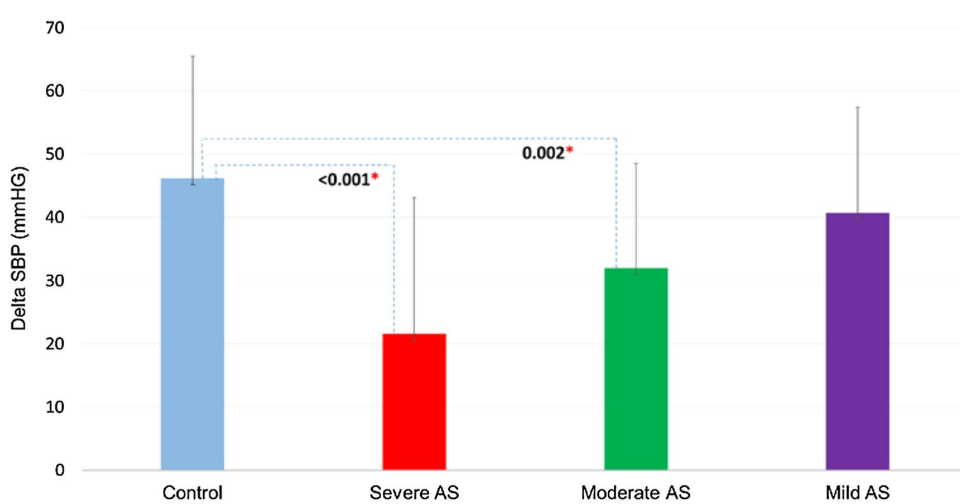



**Fig. 2** Delta SBP in aortic stenosis groups versus control cohort. Control cohort versus AS groups with standard deviation bars. *$p < 0.05$ is considered significant. *AS* aortic stenosis, *SBP* systolic blood pressure

Clinicians face the challenge of how much exercise to recommend for patients with AS. Exercise recommendations for participation and restriction from sports participation for children with AS were created by expert consensus groups. The current AHA/ACC guidelines for determining exercise eligibility in patients with AS are based on the severity of AS as determined by echocardiographic gradients [9]. Previous studies have shown that there is an association between the degree of change in SBP and aortic gradients measured by catheterization peak-to-peak gradient [3, 4]. We confirmed that delta SBP decreases as AS severity increases as measured by echocardiogram. Given these findings, the assessment of blood pressure in combination with ECG changes during exercise could help with clinical management. For instance, a patient with moderate AS who does not have ST–T segment changes on exercise testing, but has borderline delta SBP response with exercise (~34), may need to be followed more closely.

## Limitations

We only looked at patients who had the diagnosis of AS and subaortic stenosis and excluded all other forms of congenital heart disease. Therefore, our results only speak to the recommendations for left ventricular outflow tract obstruction and not specific valvular disease as per the ACC/AHA document [16].

The exercise stress tests performed at our cardiac center were not all performed at the same time as the echocardiograms. In this study, the echocardiogram that was included in the data set was performed within one year of the exercise stress test. Patients were studied using both bicycle and treadmill protocols so results may be not be exactly comparable; furthermore, when analyzing parameters such as duration, these were stratified by protocol versus delta SBP. Delta SBP values for bicycle and treadmill tests were combined before comparing with the control group given the sample size. This was a single-center study.

## Conclusion

Pediatric patients with congenital AS restricted from physical activity do not benefit from consensus recommendations [17]. With empirical evidence, physicians may use resting ECG changes and echocardiographic findings to help decide when to perform exercise testing. Patients with mild AS may not need exercise testing. Patients with moderate-to-severe AS and ST–T changes during exercise may need intervention. Echocardiogram and exercise stress testing are safe and complementary ways to monitor the natural progression of AS in children.

## Compliance with Ethical Standards

**Conflict of interest** Stephanie Santana declares that she has no conflict of interest. Samuel S. Gidding declares that he has no conflict of interest. Sherlly Xie declares that she has no conflict of interest. Tiancong Jiang declares that she has no conflict of interest. Rami Kharouf declares that he has no conflict of interest. Bradley W. Robinson declares that he has no conflict of interest.

**Ethical Approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed Consent** Informed consent was obtained for the exercise tests. Informed consent for the study was NOT obtained, but identifying data (medical record number, date of birth, etc.) were removed as per our Institutional Review Board guidelines to pass muster.

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