Clinical significance and prognostic value of ST segment depression on ECG during exercise treadmill test in asymptomatic patients with moderate or severe aortic stenosis

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ABSTRACT

Objectives. In patients with asymptomatic moderate or severe aortic stenosis (AS), exercise testing is used for evaluating the need for aortic valve intervention. Expert opinions about the clinical significance and prognostic value of ST segment depression on electrocardiography (ECG) during exercise testing in AS is conflicting and there are no large studies exploring this issue. We aimed to explore the association of ST segment depression > 5 mm during exercise treadmill test (ETT) with all-cause mortality, aortic valve replacement (AVR) or cardiac-related hospitalization. Design. We performed a retrospective analysis of prospectively collected data of a total of 315 patients (mean age 65 ± 12 years, 67% men) with asymptomatic moderate (n = 209; 66%) or severe (n = 106; 34%) AS. All patients underwent clinical evaluation, echocardiography and ETT. Results. During a mean follow-up of 34.9 ± 34.6 months, 29 (9%) patients died and 235 (74%) underwent AVR. The prevalence of ST segment depression (> 5 mm) was 13% (n = 41) in the total study population and was comparable in patients with revealed symptoms (17.6%, n = 16) versus without revealed symptoms (11.3%, n = 25; p = .132). ST segment depression on ETT was strongly associated with aortic valve area. In univariate Cox regression analysis, ST segment depression was not associated with cardiac related hospitalization (HR 1.65; 95% CI 0.89–3.10, p = .113), all-cause mortality (HR 1.37; 95% CI 0.47–3.98, p = .564) or AVR (HR 1.30; 95% CI 0.89–1.91, p = .170). Conclusion. In patients with moderate or severe AS, ST segment depression during ETT is non-specific, carries no prognostic risk and should be used with caution in the clinical interpretation of exercise test.

Introduction

In aortic stenosis (AS), the development of symptoms or systolic left ventricular (LV) dysfunction (ejection fraction < 50%) are currently class I indications for aortic valve intervention, either by surgery or transcatheter implantation (TAVI) [1–2]. Symptoms can occur spontaneously or may be revealed by an exercise test, which is safe and well tolerated [3]. Traditionally, a positive exercise treadmill test (ETT) is defined as the development of symptoms (significant dyspnea, chest tightness, fatigue, dizziness, syncope), progressive ventricular ectopy > 3 beats, new atrial fibrillation, a blunted blood pressure (BP) response (a sustained fall in systolic BP > 20 mmHg from the previous stage or a failure to rise from the baseline level) [3]. An early rapid rise in heart rate, defined as achieving at least 85% of target heart rate or > 50% increase from baseline within the first 6 min, or poor functional capacity may also be of prognostic value [4–5]. However, expert opinions about the clinical significance and prognostic value of ST segment depression on electrocardiography (ECG) during exercise testing in AS is conflicting. Most studies [6–18] have used > 2 mm ST segment depression as a criteria of positive ETT while others used > 5 mm [19–22]. We reasoned that ST depression > 5 mm was likely to have the highest sensitivity for predicting adverse events. We therefore aimed to explore the association of ST segment depression > 5 mm during ETT with all-cause mortality, aortic valve replacement (AVR) or cardiac-related hospitalization in apparently asymptomatic patients with moderate or severe AS.

Design

In the EXTAS (exercise testing in aortic stenosis) database [3], a total of 651 patients with moderate or severe AS were assessed in a heart valve clinic at Guy’s and St Thomas’ Hospitals between January 2000 and May 2017. Clinical, echocardiographic and exercise treadmill test (ETT) data were prospectively collected. Patients with symptoms (n = 283) at presentation were excluded. A further 52 patients were excluded due to either coexistent moderate or
severe mitral valve disease or aortic regurgitation, inability to exercise, peripheral vascular disease, chronic obstructive pulmonary disease and severe anemia, and one patient in whom ST segment changes were not recorded, leaving 315 patients eligible for inclusion in the present analysis.

Cardiovascular risk factors

Hypertension was defined as previously-known hypertension, use of antihypertensive medications or a BP at the baseline clinic visit >140/90 mmHg [23]. Hypercholesterolemia was defined by the use of lipid-lowering drugs. Clinic BP was measured in the sitting position with a semiautomatic device after 5–10 min of resting. All patients underwent conventional coronary angiography as a part of pre-AVR work-up. Coronary artery disease was defined as previous myocardial infarction, coronary artery bypass grafting or percutaneous coronary intervention, or evidence of coronary artery disease on angiography.

Exercise treadmill test protocol

A detailed method for ETT is published previously [3,24]. Briefly, a modified Bruce protocol was used for ETT [25–26]. The exercise test was stopped prematurely if the patients developed symptoms (breathlessness, chest constriction or dizziness), progressive ventricular ectopy >3 beats, new atrial fibrillation, a sustained fall in systolic BP >20 mmHg from the previous stage or more than 5 mm ST segment depression. Exercise time (minutes), exercise capacity in metabolic equivalents (METs), peak heart rate, peak BP and maximum fall from peak BP, and ST segment depression were recorded. METs were calculated from the speed and gradient of the treadmill using the formula \( \text{METs} = \frac{(\text{speed} \times 0.1) + (\text{gradient}/100 \times 1.8 \times \text{speed}) + 3.5}{3.5} \), where speed is measured in m/s and gradient as a percentage. One MET is defined as the amount of energy spent at rest which is equal to a body oxygen consumption of nearly 3.5 mL per kilogram of body weight [27]. Blunted BP response was defined as a sustained fall in systolic BP >20 mmHg below the previous stage or a failure to rise from the baseline level [3,24]. An exaggerated BP response was defined as a peak systolic BP ≥ 190 mmHg during ETT [24,28].

Transthoracic echocardiography

A number of commercial ultrasound machines (Vingmed system 5, 7, 9 GE Medical, Milwaukee, Wisconsin, USA and a Philips ‘Epiq 7’) were used. Moderate AS was defined by an aortic valve area (AVA) 1.0–1.5 cm² and severe by AVA <1.0 cm² [1–2]. LV wall thicknesses, chamber dimensions, stroke volume and ejection fraction were measured according to standard guidelines [29], and standardized retrospectively. LV hypertrophy was defined as LV mass >46.7 g/m² in women and 49.2 g/m² in men, respectively, and relative wall thickness as LV posterior wall thickness/LV internal radius at end-diastole, and considered increased if ≥0.43.

Study endpoints

Endpoints of interest were (all-cause mortality, AVR and cardiac related hospitalization) ascertained by reviewing the electronic patient record or the NHS Care Record Service. Follow-up time was calculated from the baseline ETT until death or censoring on 19 Sept 2017.

Statistical analyses

SPSS version 26.0 (IBM corporation, Armonk, New York, USA) was used for statistical analyses. Continuous variables were tested for normality of distribution and presented as mean ± standard deviation. Student t test and chi-square test were used for comparison of groups, as appropriate. The predictors of ST-segment depression ≥5 mm was identified in univariate and multivariate logistic regression analyses. Cumulative event rates were examined in Kaplan–Meier plots, and the difference between groups was tested using a log-rank test. Cox proportional Hazard models were used to assess the association between ST segment depression and all-cause mortality. A p-value <.05 was considered to be statistically significant.

Results

The study population included 315 patients with moderate (n = 209; 66%) or severe (n = 106; 34%) AS. The mean age was 65 ± 12 years and 67% were men. Baseline characteristics of patients according to ST segment depression during ETT is presented in Table 1. Aortic valve was bicuspid in 96 (30.5%) patients (mean age 56 ± 12 years) and tricuspid in 211 (67%) patients (mean age 70 ± 9 years). In eight (2.5%) patients the number of aortic cusps could not be determined. The incidence of ST segment depression (≥5 mm) was 13% (n = 41) in the total study population, 9.1% (n = 19) in moderate and 20.8% (n = 22) in severe AS (p = .004) (Table 1). However, ST segment depression was the reason for stopping in only 3 (1%) patients and the incidence of ST segment depression ≥5 mm was similar in patients with revealed symptoms (17.6%, n = 16) and those who remained symptom-free (11.3%, n = 25; p = .132). There was no difference in the incidence of ST segment depression in patients with a bicuspid versus tricuspid aortic valve (12.5 versus 13.2%, p = .864).

Predictors of ST segment depression ≥5 mm

In univariate logistic regression analysis, smaller AVA was strongly associated with the presence of ST segment depression ≥5 mm on ETT (OR 8.20; 95% CI 1.57–43.48, p = .013), while LV hypertrophy was not a predictor (OR 0.77; 95% CI 0.35–1.71, p = .523). Hypertension (OR 2.59; 95% CI 0.98–6.87, p = .056) and coronary artery disease (OR 1.87; 95% CI 0.96–3.63, p = .064) had a borderline significant association with ST segment depression ≥5 mm. No association was found with blunted BP response which occurred in 37% with ST segment depression ≤5 mm and
>5 mm (p = .981) (Table 1). In a multivariate logistic regression analysis, smaller AVA was a powerful predictor (OR 14.49; 95% CI 2.23–90.90, p = .005) of ST segment depression on ETT independent of non-significant associations with age (p = .907), male gender (p = .059), coronary artery disease (0.084) and hypertension (0.114).

Table 1. Baseline characteristics of patients according to ST segment depression >5 mm during exercise treadmill test (ETT).

| ST segment >5 mm depression during ETT | Yes (n = 41) | No (n = 274) | p  |
|--------------------------------------|-------------|--------------|----|
| Age (years)                          | 68 ± 10     | 65 ± 12      | .214|
| Body mass index (kg/m²)              | 27.6 ± 4.0  | 27.7 ± 4.5   | .861|
| Smokers (%)                          | 47          | 47           | .998|
| Coronary artery disease (%)          | 56          | 41           | .061|
| Diabetes mellitus (%)                | 11          | 14           | .654|
| Hypertension (%)                     | 87          | 72           | .049|
| Atrial fibrillation (%)              | 13          | 15           | .815|
| Antihypertensive treatment (%)       | 62          | 51           | .178|
| LV ejection fraction (%)             | 60 ± 8      | 61 ± 7       | .337|
| Aortic valve area (cm²)              | 0.85 ± 0.21 | 0.95 ± 0.22  | .010|
| Mean pressure gradient (mmHg)        | 40 ± 12     | 34 ± 13      | .008|
| Doppler stroke volume index (ml/m²)  | 39 ± 10     | 44 ± 14      | .104|
| LV mass index (g/m²)                | 55 ± 21     | 51 ± 17      | .387|
| Pre ETT systolic BP (mmHg)           | 144 ± 21    | 141 ± 18     | .353|
| Pre ETT diastolic BP (mmHg)          | 86 ± 11     | 85 ± 11      | .665|
| Pre ETT heart rate (bpm)             | 78 ± 14     | 77 ± 15      | .808|
| Peak systolic BP (mmHg)              | 169 ± 27    | 166 ± 26     | .435|
| Peak diastolic BP (mmHg)             | 91 ± 18     | 90 ± 16      | .677|
| Blunted BP response (%)              | 37          | 37           | .981|
| Peak heart rate (bpm)                | 138 ± 19    | 133 ± 26     | .228|
| Exercise duration (min)              | 10.3 ± 3.6  | 9.6 ± 4.5    | .326|
| METs                                 | 9.0 ± 4.6   | 8.6 ± 4.5    | .550|
| Revealed symptoms at baseline ETT (%)| 39          | 28           | .132|
| Aortic valve replacement (%)         | 76          | 75           | .874|
| All-cause mortality (n)              | 4           | 25           | .896|

BP: blood pressure; ETT: exercise treadmill test; LV: left ventricular; METs: metabolic equivalents.

Discussion

In the present study, ST segment depression >5 mm during ETT was observed in 13% patients, and was not associated with a higher risk of cardiac-related hospitalization, all-cause mortality, or AVR.

We routinely exercise patients with moderate AS since their outcome is not benign and may be as poor as severe AS [30]. Clearly, the diagnostic cutpoints for differentiating moderate from severe AS are to a degree arbitrary meaning. Furthermore, clinical outcome is likely to be partly related to coexisting coronary or LV disease in addition to AS. We reason that exercise testing is a stressor summating the pathophysiological effects of all these disease processes.

Prognostic effect of ST segment depression >5 mm

During a mean follow-up of 34.9 ± 34.6 months, 29 (9%) patients died and 235 (74%) underwent AVR. In a Kaplan-Meier curve event free survival was comparable in patients with ST segment depression >5 mm versus normal ST segment during ETT (Figure 1). In univariate Cox regression analysis, ST-segment depression was not associated with cardiac related hospitalization (HR 1.65; 95% CI 0.89–3.10, p = .113), all-cause mortality (HR 1.37; 95% CI 0.47–3.98, p = .564) or AVR (HR 1.30; 95% CI 0.89–1.91, p = .170). Combining ST segment depression with a blunted BP response, did not materially change the results; only one death was detected in this composite group versus 28 in the group without any ECG or BP changes (p = .773). Similarly, a composite of ST segment depression and blunted BP response did not predict AVR (HR 1.10; 95% CI 0.58–1.08, p = .762).

Figure 1. Kaplan-Meier curve showing event free survival in patients with ST segment depression >5 mm versus normal ST segment during exercise treadmill test (ETT).
A patient with moderate AS and coexistent coronary disease may develop symptoms on ETT while a patient with severe AS but no coronary disease may remain asymptomatic. The first patient requires coronary angiography and a multidisciplinary meeting (MDT) discussion over whether treatment should involve AVR and coronary bypass grafting or coronary angioplasty alone in the first instance. This study has shown that the presence of ST segment depression >5 mm does not aid this decision. Furthermore, we showed no association between ST depression >5 mm and known coronary artery disease, or LV hypertrophy, and ST segment depression >5 mm was the reason for stopping the ETT in only 1% patients. In patients with moderate or severe AS, ST segment depression during ETT was strongly related to the severity grade of AS, but was non-specific, carried no prognostic risk and should be cautiously used in the clinical interpretation of exercise tests.

There is little previously published data. Only one other study [31] with a small sample size \( n = 31 \) assessed the prognostic value of ST segment depression. The authors concluded that ST segment depression >2 mm had a low positive predictive accuracy (55%) for endpoints (development of spontaneous symptoms requiring AVR and serious complications), and reported a negative predictive accuracy of 73%. This is consistent with the results of our current study.

**Limitations**

First, the incidence of ST segment depression between 2 and 5 mm was not reported. If ST segment depression >2 mm is a cutpoint then our comparison might have been diluted by the inclusion of ST segment depression 2–5 mm in the control group. However, no other studies have shown ST segment depression >2 mm to be prognostically important so this is unlikely. Second, the burden of silent ischemia was not investigated. A recent study of patients with severe AS and normal exercise testing and LV ejection fraction showed that one out of five had a silent significant coronary artery disease despite the absence of inducible ischemia on ETT [32]. However, the true prevalence, clinical significance and prognostic value of silent ischemia in AS is still matter of further investigation. Third, the use of CT calcium score could add prognostic information in AS assessed as moderate by echocardiography. Finally, our study population was relatively young. Most of elderly patients with severe AS might not be able to perform ETT in a satisfactory manner.

**Clinical implications**

Clinicians supervising an exercise test in patients with moderate to severe AS may be inclined to stop an exercise stress test prematurely on the basis of ST segment depression when the BP response has remained appropriate and no symptoms have occurred. The current study shows that even severe ST segment depression >5 mm in the absence of abnormal BP response and revealed symptoms carries no prognostic value and should not be used as a criterion to determine test positivity in AS. Exercise stress testing should be allowed to continue until fatigue, symptoms onset or an inadequate rise in BP.

**Conclusion**

In patients with moderate or severe AS, ST segment depression during ETT is non-specific, carries no prognostic risk and should be cautiously used in the clinical interpretation of exercise test.

**Ethical approval**

The study was approved by the local Institutional Review Board (Study Protocol ID 7461/2017).

**Disclosure statement**

No potential conflict of interest was reported by the author(s).

**Human and animal rights**

No animals/humans were used for studies that are the basis of this research.

**Funding**

We thank the Bergesenstiftelsen for financial support for S.S. to conduct this study.

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**Data availability statement**

All data are included in the present analysis.

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