

Original Article

Does ischemic burden on stress testing influence patient survival in subjects with known severe multi-vessel CAD?

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Abstract: Background: Ischemic burden observed during stress testing has been postulated to predict prognosis irrespective of anatomic atherosclerotic burden observed on angiography. However, it is not known if the stress test result influences the long-term prognosis of subjects with diffuse coronary artery disease. We sought to determine the prognostic importance of stress test false negativity amongst patients with severe multi-vessel coronary artery disease (CAD) undergoing stress testing in the previous decade. Methods: We selected subjects from the dates of 1/1/2000 to 12/31/2005 who underwent a nuclear stress test (MPI) or stress echocardiogram (SE) within six months of a coronary angiogram demonstrating severe, multi-vessel CAD. We excluded those with a prior MI, PCI, CABG, resting wall motion abnormality, or perfusion defect at rest. Determination of patient death during the follow-up period was performed using the U.S. social security index. Results: 139 subjects (MPI 81, SE 58) were studied; stress tests were positive for ischemia in 80%. Rates of death were similar at 1 year (MPI 9%, SE 5%, *p*-value 0.44), 5 years (MPI 20%, SE 14%, *p*-value 0.36) and 10 years (MPI 30%, SE 26%, *p*-value 0.63). Using multivariate analysis, mortality at each time period was not affected by stress test positivity. Conclusion: Amongst subjects with diffuse and severe atherosclerosis with preserved ventricular function, ischemic burden on stress testing did not influence short or long-term survival.

Keywords: Three vessel disease, noninvasive imaging, stress testing

Introduction

Coronary artery disease (CAD), the primary cause of death in the United States, afflicts 17.6 million Americans [1]. Multi-vessel involvement represents a more serious facet of CAD, having a one-year mortality nearly twice that of single-vessel disease [2]. Functional imaging is one of the primary methods by which individuals with CAD are recognized and risk stratified for treatment. The published sensitivity of stress testing is reported to be 87% for myocardial perfusion imaging (MPI) and 81% for stress echocardiography (SE) in heterogeneous cohorts referred for a broad variety of indications, and paradoxically may be even lower in patients with multi-vessel disease [3, 4]. There is even evidence that in the diagnosis of left main and triple vessel disease, SE may in fact outperform MPI [5-7].

Several mechanisms have been postulated to account for false negative stress testing results. MPI relies upon differences in perfusion between coronary territories; thus, a false negative result may occur when there is reduced perfusion in all three territories [8]. This phenomenon has been referred to as balanced ischemia. SE may also be susceptible to false negative results when multi-vessel disease is present. Studies have indicated that the presence of collateral circulation distal to the stenosis may be associated with decreased sensitivity [9].

Burden of ischemia on functional imaging has been shown to correlate with CAD prognosis in some samples consisting of mainly regional CAD [10, 11]. We hypothesized that absence of ischemia on SE and MPI in subjects known to have severe diffuse “3-vessel” CAD (i.e. false

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Table 1. Subject characteristics

	Stress nuclear (N = 81)	Stress echo (N = 58)	P- value
Sex			
Female	52 (64)	23 (40)	0.004
Male	29 (36)	35 (60)	
Age (years)	66 ± 11	63 ± 13	0.19
Obese*	31 (38)	25 (43)	0.57
Race			
White	20 (25)	19 (33)	0.30
African-American	26 (32)	15 (26)	0.43
Asian	4 (5)	3 (5)	0.95
Hispanic	13 (16)	6 (10)	0.34
Smoker	20 (32)	15 (30)	0.84
Type II DM	48 (66)	29 (52)	0.11
HTN	66 (93)	48 (87)	0.28
Median zip code income (thousands)	45 [IR: 35, 65]	51 [IR: 39, 65]	0.22

*BMI greater than or equal to 30.

reports were reviewed for presence of ischemia-induced wall motion abnormalities, exercise duration, achieved heart rate, blood pressure, symptoms, mode of stress, and complications. SE positivity was defined as presence of wall motion abnormalities in multiple vessel distributions. Catheterization reports were reviewed for the presence of severe CAD. Coronary stenosis was considered to be severe if greater than 70% in the three major coronary branches. Left main stenosis was considered to be severe if greater than 50%.

negative tests) would also have improved prognosis compared to those who had multivessel CAD and demonstrable ischemia on functional imaging.

Methods

Study design

Patients who had undergone MPI or SE between 1/1/2000 and 12/31/2005 were included if they also had a coronary angiogram demonstrating severe, multi-vessel CAD (in all three major territories or in the left main) within six months. This enrollment period was chosen as we had previously reported the prevalence of false negative stress testing in this group, and now sought to determine the rate of cardiac events for this cohort [12]. Subjects excluded were those with prior MI, CABG, PCI, resting wall motion abnormalities on SE, or myocardial perfusion defects at rest. The Institutional Review Board at Montefiore Medical Center re-reviewed and re-approved the study protocol. The primary outcomes of the study were short-term, moderate-term, and long-term mortality.

Stress testing and catheterization data

SE and cardiac catheterization reports were obtained from our institutional Heart Center database (Apollo, Lumedx, Oakland CA) at Montefiore Medical Center. Echocardiogram

MPI reports were identified using an existing nuclear cardiology quality assurance database within the Nuclear Medicine department at our institution. Data collected included MPI interpretation, summed rest and stress scores, and presence of transient ischemic dilatation. MPI positivity was defined as presence of perfusion defects in multiple distributions not attributed to attenuation or artifact.

Clinical data

Clinical data for each study subject was extracted from the Montefiore Medical Center electronic health record. Additional clinical information was extracted from Montefiore Medical Center's Clinical Looking Glass (Emerging Health Information Technology, Yonkers, NY). This database integrates clinical data from all inpatient visits at three hospital facilities and outpatient encounters at twenty ambulatory sites, home care and community service programs within the Montefiore system. Information extracted included comorbidities, race and ethnicity. CLG also captures all dates of death from a National Death Index and from the hospital's inpatient record. Vital status was determined as of February 1, 2014 for survival analysis. Median income figures were obtained from an existing national database [13].

Data analysis

Data analysis in this study was carried out with STATA v.11 (College Station, TX). Normally dis-

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Table 2. Stress test outcomes

	Stress nuclear (N = 81)	Stress echo (N = 58)	P-value
<i>Stress test parameters</i>			
Positive stress test	69 (85)	42 (72)	0.03
Reduced EF*	13 (16)	5 (9)	0.20
Negative test**	1 (20)	0 (0)	0.10
Pharmacologic stress	66 (81)	15 (16)	<0.001
Negative test	9 (12)	3 (33)	0.07
Exercise stress	14 (17)	45 (78)	<0.001
Negative test	0 (0)	11 (24)	0.04
CABG	44 (54)	29 (50)	0.61
Negative test	5 (12)	6 (21)	0.30
PCI	19 (23)	15 (26)	0.75
Negative test	2 (11)	6 (43)	0.03
<i>Follow-up and outcomes</i>			
Median follow-up (years)			
Survivors	10.2 [IR: 9.1, 11.6]	10.4 [IR: 9.5, 11.2]	0.77
Deceased	3.0 [IR: 0.8, 6.1]	4.6 [IR: 3.2, 6.8]	0.31
Deaths			
1 year	7 (9)	3 (5)	0.44
Negative test	1 (14)	0 (0)	0.49
5 years	16 (20)	8 (14)	0.36
Negative test	3 (19)	2 (25)	0.72
10 years	24 (30)	15 (26)	0.63
Negative test	3 (13)	3 (20)	0.53
Odds of death, unadjusted, with a falsely negative stress test			
1 year	1.3 [CI: 0.0, 13.3 p. 1.00]	°	
5 years	2.4 [CI: 0.5, 10.9 p. 0.26]	0.9 [CI: 0.2, 5.2 p. 0.93]	
10 years	1.3 [CI: 0.3, 5.8 p. 0.72]	0.6 [CI: 0.2, 2.6 p. 0.52]	
Odds of death, adjusted***, with a falsely negative stress test			
1 year	1.4 [CI: 0.0, 20.1 p. 1.00]	°	
5 year	1.9 [CI: 0.1, 17.2 p. 0.82]	1.3 [CI: 0.2, 10.1 p. 0.77]	
10 year	0.9 [CI: 0.1, 6.8 p. 1.00]	0.9 [CI: 0.2, 4.3 p. 0.85]	

*Ejection Fraction less than 50%. **Negative non-invasive test result. ***Adjusted for sex, presence of diabetes, mode of stress, and revascularization. °No deaths in the SE group at 1 year with a FN test.

tributed data were presented as the mean ± standard deviation (SD). Non-normal data were presented as the median [interquartile range (IR)]. Comparison of means was performed using the two-sample t-test. Comparison of categorical data was performed using the Chi-squared test. Comparison of medians was performed using the Mann-Whitney or Kruskal-Wallis tests as appropriate. P-values were considered significant if <0.05. Multivariate regression analysis was performed with selected variables with p-value less than or equal to 0.2 or those posited to significantly interact with our outcome; logistic regression was em-

ployed to calculate odds of death at chosen intervals of 1, 5, and 10 years.

Results

Table 1 displays the clinical characteristics of the 139 subjects included in the study, as stratified by mode of stress. Women comprised the majority of the MPI group and the minority of the SE group. Otherwise, characteristics between the two cohorts were similar.

In **Table 2**, more individuals undergoing MPI underwent pharmacologic testing and had a positive stress test. Although baseline cardiac

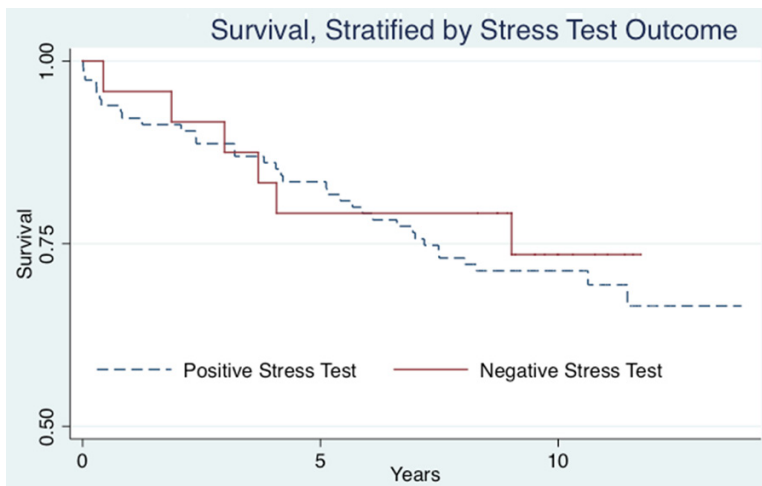


Figure 1. Subject survival as stratified by stress test outcome. Survival for each included subject was determined and plotted as per their individual stress test result. Those with negative stress tests are illustrated in solid red, while those with positive stress tests are indicated in dotted blue.

function and post-test intervention did not significantly with respect to non-invasive test performed, false negativity was more common in those who underwent exercise testing and those who underwent percutaneous coronary intervention (PCI).

The median period of follow-up was similar in both groups. With respect to outcomes, rates of all cause mortality were similar at years 1, 5, and 10. Odds of death with a falsely negative test, when adjusting for sex, presence of diabetes, mode of stress, and baseline cardiac function, were also similar between each group. Odds of death with a false negative MPI as compared to a false negative SE were 3.3 (CI: 0.3, 46.3, *p*-value 0.24) and 2.0 (CI: 0.2, 20.0, *p*-value 0.47) at 5 and 10 years, respectively.

Figure 1 presents survival (Kaplan-Meier) curves in those with positive and negative stress tests.

Discussion

The purpose of this study was to assess the prognosis of individuals with a falsely negative stress test in the setting of severe, multi-vessel CAD. We found that overall mortality was high in our study group and that having a negative stress test in this setting did not affect patient mortality in the short or long term.

There is little published data on the prognostic importance of a negative stress test in those

with significant, multi-vessel CAD. The mortality rate of 25% in our study over 10 years (or 2.5% per year annualized over the course of the study) in those with a falsely negative stress test is similar to prior reported observational studies [10].

This study has several important limitations. Given the size of our sample as well as the observed mortality rate, our study had power of 80% to detect a 10% absolute 5-year mortality difference between those with and without positive stress tests. Therefore, a true difference in mortality between

groups that is <10% may not be detected by our methods. Furthermore, there were notable differences in our cohorts, such as the prevalence of pharmacologic stress testing. One would suspect that those undergoing pharmacologic testing would have comorbidities that increase their risk of death, potentially confounding the results. The characteristics of our study population are unique, given that the majority of our subjects were of ethnic minorities, had high rates of comorbidities, and were of lower socioeconomic classes. This may limit generalizability to other patient samples.

Conclusion

Stress testing does not appear to have an impact on long-term survival amongst individuals with severe, multi-vessel coronary artery disease.

Disclosure of conflict of interest

None.

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