International Journal of Cardiology 296 (2019) 157–163

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

False-positive stress echocardiograms: Predictors and prognostic relevance

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ARTICLE INFO

Article history:
Received 1 April 2019
Received in revised form
26 July 2019
Accepted 14 August 2019

Keywords:
Stress echocardiography
Cardiac catheterization
Coronary artery disease

ABSTRACT

Background: Recent studies indicate that the pretest likelihood of significant coronary artery disease (CAD) (≥50% luminal stenosis) is over-estimated and that the frequency and severity of positive stress tests have been decreasing. This suggests an increased prevalence of false-positive (FP) stress tests. The aims of this retrospective study were to investigate the predictors of FP stress echocardiography (SE) and to compare the outcomes of patients with FP results to those with true-positive (TP) results.

Methods: Patients who underwent SE between 2013 and 2017 in a tertiary-care center were reviewed. Included were patients aged ≥40 years who had cardiac catheterization (CC) within 1 year of the index stress test. SE was considered FP if a new or worsening wall motion abnormality was present in the absence of significant corresponding CAD.

Results: Of the 5100 patients with SE, 1069 satisfied inclusion criteria. A total of 305 patients had positive SE results; of which 162 (53%) were FP. Logistic regression revealed that female gender ($p = 0.009$), the absence of diabetes ($p = 0.03$), the absence of a personal history of CAD ($p = 0.004$), and lower stress WMSI ($p = 0.03$) were independently associated with FP results. Patients with FP results on SE had similar all-cause mortality to those with TP results.

Conclusions: Accounting for predictors of FP findings on SE could improve the interpretation of SE results and limit the use of unnecessary CC. Furthermore, patients with FP results on SE could benefit from aggressive risk factor control and careful clinical follow-up.

1. Background

Stress echocardiography (SE) is a validated non-invasive diagnostic modality for the detection and risk-stratification of patients with coronary artery disease (CAD). The sensitivity and specificity of SE for the detection of significant CAD (defined as coronary artery stenosis ≥50%) have been reported to be of 85% and 75% when used with exercise, and 80% and 86% when used with dobutamine, respectively [1–3]. As with any diagnostic test, SE has its limitations. These include false-positive (FP) results with clinical implications of unnecessary cardiac catheterization (CC) and false-negative results leading to potentially missing significant CAD. Recent studies indicate that the pretest likelihood of significant CAD is overestimated and that the frequency and severity of positive stress tests have been decreasing [3,4]. This suggests an increased prevalence of FP stress tests. The aims of this study were (1) to identify the clinical and echocardiographic predictors of FP SE and (2) to compare the outcomes of patients with FP results to those with true-positive (TP) results.

2. Methods

2.1. Patient selection

The records of 5100 patients aged ≥40 years who underwent SE between January 1, 2013, and December 31, 2017, at Indiana University Health Methodist Hospital (Indianapolis, IN) were reviewed. Patients who had a CC within 1 year after the index stress test were included. In the event a patient had more than one stress test during the study period, only the first stress test was selected for

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https://doi.org/10.1016/j.ijcard.2019.08.037
0167-5273/

analysis. A total of 1069 patients satisfied the inclusion criteria and constituted our study population. Data collected included patient demographics, medical history, SE findings, CC findings, and mortality. The study was approved by the institutional review board and informed consent was waived due to the retrospective nature of the study.

2.2. Stress echocardiography

Patients underwent clinically-indicated exercise (bicycle or treadmill) or dobutamine SE. Stress testing was performed using previously described methods and endpoints, as published in the 2007 American Society of Echocardiography (ASE) guidelines [5]. Medications that could interact with the outcome of the study (e.g., β-blockers) were discontinued prior to stress testing if instructed by the referring physician or health care provider.

Heart rate and electrocardiogram readings were continuously monitored. Blood pressure was measured at rest and at the end of each stage. The test was considered diagnostic if at least 85% of age-predicted maximal heart rate was achieved. The test was terminated if the patient reached the maximal heart rate (i.e., 100% of age-predicted maximal heart rate), experienced severe angina; or if hemodynamically significant arrhythmia, significant hypertension (defined as systolic blood pressure $\geq$ 210 mmHg in men or $\geq$ 190 mmHg in women or diastolic blood pressure $\geq$ 110 mmHg in men or women), significant hypotension (defined by a systolic blood pressure decrease of >20 mmHg) or ST-segment elevation developed.

2.3. Echocardiogram image acquisition and analysis

Two-dimensional echocardiography images of patients undergoing either exercise or dobutamine stress tests were obtained by highly-trained echocardiography technicians, according to standardized protocols [5]. Echocardiographic images were acquired in the left lateral decubitus position using the apical (two- and four-chambers) and parasternal (short- and long-axis) views of the heart. Level II or III trained echocardiography-certified cardiologists reviewed and analyzed SE images. Left ventricular ejection fraction was determined by the Simpson method or by visual assessment.

A 17-segment model of the left ventricle was used according to the recommendations of the ASE. Wall motion of each segment was graded both at rest and peak stress as normal, hypokinetic, akinetic or dyskinetic and was assigned the score of 1, 2, 3 or 4, respectively. Left ventricular wall motion score index (WMSI) was calculated by adding the score of each segment and dividing the total sum by the number of visualized segments. Image quality was classified as excellent, good, fair and poor subjectively by the interpreting cardiologist. Echocardiographic contrast was used to augment endocardial definition when two or more contiguous segments were not adequately visualized at rest per the discretion of the sonographer.

SE was considered positive for ischemia in the presence of new regional wall motion abnormalities (WMA) or worsening of pre-existing resting WMA, after chemical or exercise-induced stress. FP results were defined in the absence of $\geq$50% coronary artery lesion in any major artery on subsequent angiography that explains the SE result. Severe WMA at rest and peak stress was defined by akinesis or dyskinesis in at least one of $\geq$2 contiguous abnormal segments in a coronary territory.

2.4. Coronary angiography

All patients in this study underwent clinically indicated CC with coronary angiography within 1 year after SE. Coronary angiography was performed and interpreted by highly trained interventional cardiologists. A threshold of $\geq$50% luminal stenosis in $\geq$1 of the epicardial coronary arteries or major branches was used to define significant CAD. Angiographic lesions with <50% luminal stenosis were considered to be angiographically non-obstructive.

2.5. Mortality data

Mortality data were obtained by reviewing hospital databases, medical records, and newspaper obituaries. All-cause mortality was used for analysis.

2.6. Statistical analysis

Categorical data were presented as percentages and continuous data as mean values ± standard deviation. Clinical and echocardiographic characteristics were compared between the FP and TP groups using Fisher's exact test or chi-square analysis for categorical variables and two-sample *t*-test or Kruskal-Wallis test for continuous variables. Univariate analysis was performed to determine the relationship between clinical and echocardiographic variables and FP SE. Stepwise, multivariate regression was performed using variables with $p < 0.20$ on univariate analysis. Kaplan-Meier survival analysis was used to compare event-free survival in patients with FP and TP SE results. The log-rank test was used to test for significant differences in survival. Statistical significance was set at $p < 0.05$. Statistical testing was performed using Stata version 13 (StataCorp, College Station, TX, USA).

3. Results

3.1. Clinical characteristics of the study population

Patient clinical characteristics are summarized in Table 1. Common clinical indications for SE included: preoperative evaluation (603 patients, all pre-solid organ transplant candidates including 588 liver transplant candidates, 57%), chest pain (227 patients, 21%) and dyspnea (100 patients, 10%). Among patients with a positive stress test, the most common reasons for the test were similarly preoperative evaluation (79 patients, 26%), chest pain (100 patients, 33%) and dyspnea (61 patients, 20%).

The FP group had a significant predominance of the female gender as compared to the TP group (56% vs. 31%, $p < 0.001$). Patients with FP results had a higher body mass index (31 kg/m^2 vs. 30 kg/m^2, $p = 0.009$). Personal history of CAD (69% vs. 35%, $p < 0.001$), presence of diabetes (59% vs. 40%, $p = 0.001$), hypertension (82% vs. 70%, $p = 0.001$) and hyperlipidemia (83% vs. 56%, $p < 0.001$) were more commonly associated with a TP result. No significant differences between the two groups were detected for age, race, history of smoking or family history of CAD.

3.2. Echocardiographic characteristics of the study population

Echocardiographic characteristics at rest and peak stress are summarized in Table 1. Among the 1069 included patients, 305 had positive SE results, of which 162 were FP (53% of all positive, 15% of patients who underwent heart catheterization). The mean time to angiography was 1.6 ± 2.6 months.

The FP group had a higher mean resting left ventricular ejection fraction (60% vs. 57%, $p = 0.005$), higher peak heart rate (141 beats/min vs. 132 beats/min, $p = 0.02$) and a higher percentage of patients who achieved at least 85% of target heart rate (72% vs. 59%, $p = 0.02$) as compared to the TP group. Patients with TP results had a higher rest (1.2 vs. 1.1, $p < 0.001$) and stress WMSI (1.3 vs. 1.2, $p < 0.001$). Furthermore, patients in the TP group had a higher

Table 1
Descriptive statistics of demographic, risk factor and stress test variables.

Variable	Total (n = 1069)	False-positive SE (n = 162)	True-positive SE (n = 143)	p-value
Age (years)	60 ± 9	60 ± 10	62 ± 10	0.295
Gender				
Male	633 (59%)	71 (44%)	98 (69%)	<0.001
Female	436 (41%)	91 (56%)	45 (31%)	
Body mass index (kg/m^2)	30 ± 6	31 ± 8	30 ± 6	0.009
Race				
White	902 (84%)	128 (79%)	112 (78%)	0.183
Black	149 (14%)	33 (20%)	26 (18%)	
Other ethnicities	18 (2%)	1 (1%)	5 (4%)	
Diabetes mellitus	507 (47%)	65 (40%)	85 (59%)	0.001
Hypertension	756 (71%)	113 (70%)	118 (82%)	0.009
Hyperlipidemia	503 (47%)	91 (56%)	119 (83%)	<0.001
Prior or current smoking	582 (54%)	73 (45%)	72 (50%)	0.356
Family history of CAD	91 (9%)	14 (9%)	18 (13%)	0.262
Personal history of CAD	406 (38%)	57 (35%)	98 (69%)	<0.001
SE type				
Dobutamine	699 (65%)	83 (51%)	70 (49%)	0.691
Exercise	370 (35%)	79 (49%)	73 (51%)	
Rest variables				
EF (%)	61 ± 8	60 ± 8	57 ± 9	0.005
WMSI	1.1 ± 0.2	1.1 ± 0.1	1.2 ± 0.2	<0.001
WMA	193 (18%)	75 (46%)	76 (53%)	0.232
Severe WMA [§]	72 (7%)	33 (20%)	39 (27%)	0.104
LV diastolic diameter base (cm)	4.6 ± 0.6	4.6 ± 0.6	4.6 ± 0.6	0.138
IVS diastolic thickness (cm)	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	0.346
Stress variables				
WMSI	1.3 ± 0.2	1.2 ± 0.2	1.3 ± 0.3	<0.001
Severe WMA [§]	168 (16%)	76 (47%)	92 (64%)	0.002
N(%) with achieved target heart rate [‡]	763 (72%)	116 (72%)	85 (59%)	0.02
Peak heart rate (beats/min)	138 ± 17	141 ± 17	132 ± 21	0.02
Peak systolic blood pressure (mmHg)	164 ± 32	169 ± 32	179 ± 30	0.312
Peak diastolic blood pressure (mmHg)	79 ± 15	81 ± 15	84 ± 15	0.695
Presence of chest pain	112 (11%)	16 (10%)	24 (17%)	0.077
Technical quality				
Good	197 (19%)	20 (13%)	9 (6%)	0.07
Fair	649 (62%)	102 (64%)	97 (69%)	
Poor	208 (19%)	37 (23%)	35 (25%)	
Age (years)	60 ± 9	60 ± 10	62 ± 10	0.295
Gender				
Male	633 (59%)	71 (44%)	98 (69%)	<0.001
Female	436 (41%)	91 (56%)	45 (31%)	
Body mass index (kg/m^2)	30 ± 6	31 ± 8	30 ± 6	0.009
Race				
White	902 (84%)	128 (79%)	112 (78%)	0.183
Black	149 (14%)	33 (20%)	26 (18%)	
Other ethnicities	18 (2%)	1 (1%)	5 (4%)	
Diabetes mellitus	507 (47%)	65 (40%)	85 (59%)	0.001
Hypertension	756 (71%)	113 (70%)	118 (82%)	0.009
Hyperlipidemia	503 (47%)	91 (56%)	119 (83%)	<0.001
Prior or current smoking	582 (54%)	73 (45%)	72 (50%)	0.356
Family history of CAD	91 (9%)	14 (9%)	18 (13%)	0.262
Personal history of CAD	406 (38%)	57 (35%)	98 (69%)	<0.001

Data are presented as the mean value ± SD or number (%) of patients.
SE, Stress echocardiogram; *CAD*, Coronary artery disease; *EF*, Ejection fraction; *WMSI*, Wall motion score index; *WMA*, Wall motion abnormality; *LV*, Left ventricle; *IVS*, Interventricular septum.
[§] Defined by akinesis or dyskinesis of ≥2 contiguous segments.
[‡] Defined as ≥85% of predicted maximal heart rate (220 minus age in years).

percentage of severe stress WMA (64% vs. 47%, $p = 0.002$). Data regarding image quality were missing in 15 patients, of whom 2 had TP and 3 had FP results. Of the 300 patients with a positive stress test and reported image quality, 72 (24%) had a poor image quality; 39 (54%) of whom received echocardiographic contrast.

3.3. Analysis of patients with false-positive stress echocardiographic results

The clinical and echocardiographic characteristics associated with FP SE findings on univariate analysis are shown in Table 2. Patients who were females ($p < 0.001$), non-diabetic ($p = 0.001$), non-hypertensive ($p = 0.01$), non-hyperlipidemic ($p < 0.001$) or without a personal history of CAD ($p < 0.001$) were more likely to have FP results. Regarding echocardiographic variables, stress echocardiograms with higher resting left ventricular ejection fraction ($p = 0.011$), lower rest WMSI ($p = 0.004$), lower stress WMSI ($p < 0.001$), higher peak heart rate ($p < 0.001$) or higher peak systolic blood pressure ($p = 0.005$) were also more likely to be FP.

Multivariate analysis revealed the following independent predictors of FP results on stress testing: female gender ($p = 0.009$), the absence of diabetes ($p = 0.027$), the absence of a personal history of CAD ($p = 0.004$), and lower stress WMSI ($p = 0.029$) (Table 3).

3.4. Mortality analysis

All-cause mortality was obtained on 295 patients (97%) with positive SE over an average follow-up period of 2.6 ± 1.4 years. Kaplan-Meier analysis was stratified according to coronary angiography results. A total of 216 patients (21%) died during that period, among whom 22 had a TP stress test (10%) and 20 had a FP stress test (9%) ($p = 0.001$). Patients with FP results had 1-year and 3-year survival rates of 94% and 87%, respectively; while patients

with TP results had 1-year and 3-year survival rates of 92% and 87%, respectively ($p = 0.63$, vs. FP results) (Fig. 1).

4. Discussion

SE is an important tool for evaluating patients with suspected CAD. However, FP results often lead to unnecessary invasive procedures. In our study, of 1069 patients who underwent CC, we identified 162 patients (15%) who had a FP result. This percentage was similar to those previously reported for dobutamine (11%) and exercise SE (13%) [6,7]. Among the 305 patients who had positive stress echocardiograms and subsequent angiography, 162 patients (53%) had a FP result. Similar results were previously reported by Patel et al. with only 41% of patients with a positive non-invasive test having obstructive CAD on elective CC [8].

4.1. Clinical characteristics and predicting FP SE results

Female gender has been associated with a higher rate of FP SE results [7,9,10]. This could be explained by the fact that females have a lower prevalence of CAD [11]. Similarly, non-diabetic patients have been found less likely to have significant CAD than diabetics and would be expected to have a higher FP rate [12]. The absence of a personal history of CAD was also previously identified as an independent predictor of FP SE results [10]. These observations were consistent with our findings. Morbidly obese patients have been previously reported to have a lower prevalence of significant CAD and to be associated with FP non-invasive tests [13]. In our study, body mass index was found to be predictive of FP results, but the association did not remain statistically significant on multivariate analysis. From et al. found non-hypertensive patients to have a higher FP rate on stress testing [10]. While the absence of hypertension was significantly associated with FP results in our study on univariate analysis, this factor also lost statistical significance after accounting for potential confounders.

Table 2
Demographic, risk factor and stress test variables associated with false-positive stress echocardiograms on univariate analysis.

Variable	False-positive stress echocardiogram	
	OR (95% CI)	*p*-value
Age	0.98 (0.96–1.00)	0.258
Male gender	0.36 (0.22–0.57)	<0.001
Body mass index	1.01 (0.99–1.04)	0.757
Black patients (vs, non-black patients)	1.15 (0.65–2.04)	0.483
Diabetes mellitus	0.45 (0.29–0.72)	0.001
Hypertension	0.49 (0.28–0.84)	0.01
Hyperlipidemia	0.26 (0.15–0.44)	<0.001
Smoking history [*]	0.81 (0.51–1.27)	0.356
Family history of CAD	0.66 (0.31–1.37)	0.264
Personal history of CAD	0.25 (0.15–0.40)	<0.001
Study type		
Exercise SE (vs. dobutamine SE)	0.91 (0.58–1.43)	0.691
Rest variables		
EF	1.04 (1.01–1.06)	0.011
WMSI	0.15 (0.04–0.54)	0.004
WMA	0.76 (0.48–1.19)	0.233
Severe WMA [§]	0.64 (0.38–1.10)	0.106
LV diastolic diameter base	0.94 (0.66–1.32)	0.712
IVS diastolic thickness	0.45 (0.15–1.34)	0.154
Stress variables		
WMSI	0.10 (0.03–0.34)	<0.001
Severe WMA [§]	0.45 (0.27–0.75)	0.002
N(%) with achieved target heart rate [‡]	1.75 (1.09–2.84)	0.021
Peak heart rate	1.02 (1.01–1.03)	<0.001
Peak systolic blood pressure	0.99 (0.98–1.00)	0.005
Peak diastolic blood pressure	0.99 (0.97–1.00)	0.088
Presence of chest pain	0.54 (0.28–1.08)	0.08
Technical quality		
Good (vs. not good [Δ])	2.11 (0.93–4.80)	0.075

OR, Odds ratio; *CAD*, Coronary artery disease; *SE*, Stress echocardiography; *EF*, Ejection fraction; *WMSI*, Wall motion score index; *WMA*, Wall motion abnormality; *LV*, Left ventricle; *IVS*, Interventricular septum.
[*] Prior or current smoking.
[§] Defined by akinesis or dyskinesis of ≥2 contiguous segments.
[‡] Defined as ≥85% of predicted maximal heart rate (220 minus age in years).
[Δ] Defined as fair or poor.

Table 3
Demographic, risk factor and stress test variables associated with false-positive stress echocardiograms on multivariate analysis.

Variable	False-positive stress echocardiogram	
	OR (95% CI)	*p*-value
Male gender	0.48 (0.28–0.83)	0.009
Diabetes mellitus	0.54 (0.31–0.93)	0.027
Personal history of CAD	0.41 (0.22–0.75)	0.004
Stress WMSI	0.26 (0.07–0.87)	0.029

OR, Odds ratio; *CAD*, Coronary artery disease; *WMSI*, Wall motion score index.

4.2. Echocardiographic characteristics, stress test performance and predicting FP SE results

Our study demonstrated that lower stress WMSI was more likely to be associated with FP SE results. Shin et al. identified lower peak stress WMSI as an independent predictor of FP outcome on SE [7]. WMSI is a visual semi-quantitative method for the evaluation of regional wall motion and thickening and is subject to intraobserver and interobserver variability. Patients with lower stress WMSI exhibit a lower degree of segmental endocardial excursion and systolic wall thickening on SE in any given coronary territory. As such, it could be difficult to distinguish between normal segments and those with mild hypokinesia contributing to an increase in FP results [14–16]. Furthermore, mild hypokinesia has been described as a normal variant under stress conditions and widely overlaps between normal and diseased patients [17]. More than half of the patients in the FP group of our study had mild WMA on SE, which possibly contributed to increased FP results.

Prior studies have identified SE-related predictors of FP results. Resting WMA have been reported to be associated with FP SE

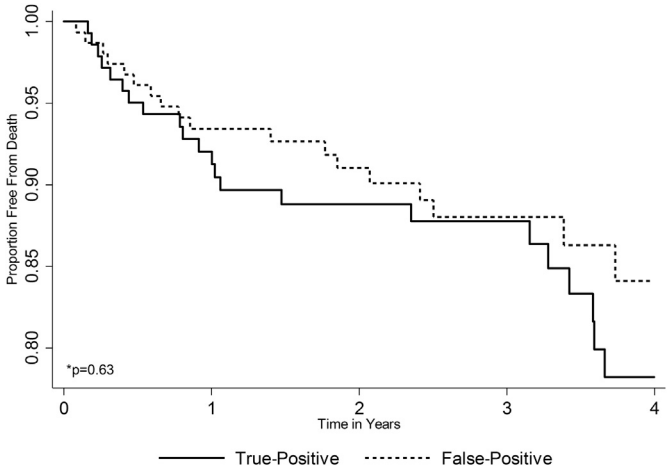

Fig. 1. Mortality of patients with false-positive and true-positive results on stress echocardiography.

results. Heinicke et al. studied 69 patients undergoing SE. Authors found 12 of the 69 stress tests to be FP, with 45% having resting WMA. This was assumed to be related to hypercontractility of neighboring segments as compared to hypo- or akinetic segment(s) [18]. In our study, the presence of resting WMA was not significantly associated with a FP result. A possible explanation could be that patients with resting WMA have a higher likelihood of residual significant CAD and subsequent TP SE result. It was previously reported that reduced image quality and subsequent poor visualization of the endocardium are associated with a higher incidence of FP SE. This was particularly true in regions with thinner myocardium (i.e., inferior wall, inferoposterior wall, and apex) that could be falsely interpreted as hypokinetic [6]. While we did not find a significant association between image quality and FP results, we note a relatively high number of poor-quality studies (72 of 300, 24%) in patients with positive SE. Therefore, it is quite likely that reduced image quality contributed to inaccurate or FP test results. Furthermore, the evaluation of WMA in SE can be difficult at high heart rates (needed for test sensitivity), mostly because of image quality degradation [19]. In our study, higher peak heart rate was significantly associated with FP results on univariate analysis but lost significance after adjusting for potential confounders. Higher systolic blood pressure response to stress has been associated with a greater likelihood of new or worsening WMA with exercise, even in the absence of significant CAD [7,20]. The latter finding was not consistent with our results and warrants further study. It is possible that chest pain or discomfort from underlying CAD leads to higher systolic blood pressure in some cases. As such, caution should be taken not to assume a FP result in cases of exaggerated systolic blood pressure response to stress (i.e., systolic blood pressure $\geq$ 210 mmHg in men or $\geq$ 190 mmHg in women).

4.3. Explanation for FP SE results

Our study found that approximately half of the patients with a positive SE result did not have angiographically significant CAD. Possible explanations for ischemia detected on SE in the absence of significant CAD, traditionally defined as $\geq$50%, include the presence of microvascular abnormalities, endothelial dysfunction, coronary vasospasm, vasomotor changes, and small-vessel CAD [21,22]. These observations have been supported by a previous study of 118 patients using single-photon emission computed tomography that showed myocardial perfusion abnormalities in 59% of patients without obstructive CAD on CC performed 3 months apart [23]. Previous studies suggested that the assessment of coronary flow reserve is a sensitive method to detect vascular abnormalities prior to the development of angiographically identifiable lesions [24,25]. Bortone et al. studied the coronary vasomotion and flow reserve in patients with normal coronary arteries who had ischemic symptoms on stress testing. The authors identified a subset of patients who had a nonsignificant increase in blood flow in the intramyocardial resistance vessels in response to dipyridamole and paradoxical exercise-induced vasoconstriction of the distal coronary arteries. Abnormal neurohormonal regulation of the coronary vascular bed was hypothesized to account for the reported findings [25]. Cox et al. demonstrated an impaired vasodilatory reaction in response to increased blood flow in coronary arteries with mild atherosclerosis on CC [26]. While the presence of microvascular changes has been proposed to account for perfusion abnormalities, it is possible that abnormalities of the microvascular circulation may similarly be associated with WMA leading to apparently FP SE results.

While coronary angiography was used as a gold standard for the detection of significant CAD, it has several limitations when compared to intracoronary imaging modalities [27]. In one study of 20 patients with chest pain, angiographically normal coronary arteries and perfusion abnormalities, intravascular ultrasound with Doppler velocimetry revealed undetected atherosclerotic changes in 19 patients (95%) [28]. Therefore, it was possible that some cases of apparent FP stress tests may actually be due to CAD that was not detected on coronary angiography.

Coronary vasospasm can occur in response to stress from exercise or dobutamine. This phenomenon can erroneously lead to interpreting the stress test as positive and has been reported to be an independent predictor of FP results during dobutamine SE [22]. In our study, invasive vasospasm testing was not performed and thus we were unable to determine how often this accounted for FP results in our dataset.

Another explanation may be provided by the observation that the frequency and severity of abnormal stress testing have been decreasing over the past two decades. In addition, the traditional pre-test probability estimates for age, gender and angina typicality appear to overestimate the likelihood of angiographically significant CAD [4,29]. These findings indicate a lower than expected overall prevalence of CAD in patients undergoing non-invasive testing. Therefore, according to the Bayesian principle, FP rate would be predicted to be increased.

4.4. Mortality

Recent studies suggested that patients with abnormal SE results are at higher risk for major cardiovascular events compared to patients with normal results, irrespective of angiographic findings [10,21,30]. Sicari et al. evaluated the prognostic role of dipyridamole SE in patients with angiographically normal coronary arteries over a period of 140 months and found that patients with FP results had a lower survival rate when compared to those with negative results (90% vs. 76%, $p = 0.0018$) [31]. This poses diagnostic and management challenges since guidelines do not directly address this group and these patients have been historically treated as if they had no significant CAD [21,30]. However, this concept has been challenged in a retrospective study where the authors showed that there was no difference in mortality between patients with TP and FP SE results when followed over a 4-year period [10]. Similarly, our results showed that patients with abnormal SE findings had similar all-cause mortality, irrespective of the coronary angiography results.

4.5. Study limitations

This study is a retrospective analysis and is subjected to the limitations of this study design. In our study, only 1069 patients with SE (21% of the initial population) had a subsequent CC. More importantly, only 305 patients with a positive stress test underwent CC in our institution. However, it is likely that some patients who did not meet inclusion criteria had a positive stress test but had a CC outside our medical center or did not undergo a CC because it was decided it was not clinically needed. Furthermore, patients were mostly referred for CC at the discretion of their cardiologist which could lead to test verification bias. We arbitrarily included patients who underwent CC up to 1 year after SE. While the coronary anatomy may change over a 1-year period, we did not want to exclude patients with positive tests not warranting prompt CC for clinical reasons, such as a mildly abnormal stress test or mild symptoms. While we described predictors of FP SE, our study did not investigate the safety of excluding patients who were more likely to have a FP stress test from undergoing a CC. As such, our results are hypothesis-generating but can help identify patients who may benefit from non-invasive coronary angiography (such as by cardiac computed tomography) in order to decide on

reassurance versus initial optimal medical management, as opposed to confirmatory invasive angiography. Our study was not designed to determine the pathophysiologic basis for why patients with FP stress tests experienced similar all-cause mortality to those with TP stress tests. This is an interesting observation that would require further study in order to determine how to best manage patients with FP results. Intracoronary imaging was not performed during the timeframe of our study and could have led to the inaccurate assignment of an abnormal stress test to the FP group. We were also unable to determine how often vasospasm contributed to apparent FP studies in our dataset. Data for exercise and dobutamine SE were combined for this analysis and some differences in test performance and characteristics between the two modalities were not accounted for. We did not account for the presence of ST-segments changes during stress testing in our analysis since our definition of positive SE was solely based on echocardiographic findings. We did not collect data about the effect of echocardiographic contrast on image quality, and therefore were unable to determine the percentage of studies that remain of poor quality despite contrast use. Our study included pre-solid organ transplant patients (accounting for 26% of patients with a positive stress test), which likely contributed to a higher-than-expected mortality rate. The cause of death was only available if the patient died in hospital settings. Therefore, all-cause mortality alone and not cause-specific mortality (cardiac vs. non-cardiac) was analyzed.

5. Conclusion

Current practice guidelines recommend analyzing stress testing results in the context of pretest probability, test performance characteristics, and posttest probability. Our study identified female gender, the absence of diabetes, the absence of a personal history of CAD, and lower stress WMSI as independent predictors of FP SE findings. Accounting for these factors could improve the interpretation of SE results and potentially avoid unnecessary CC. Additionally, patients with FP results had similar outcomes to those with TP results. Therefore, patients with FP results on SE could benefit from aggressive risk factor control and careful clinical follow-up. Future prospective studies to explore the clinical significance of these findings are warranted.

Funding sources

None.

Declaration of competing interest

None declared. All the authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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