Original Article

Normal Angiogram of ETT Positive Female Patients in Bangladesh

***Sardar Zahid Hossain[1], Md. Iktier Hasan Khan[2], Nazmun Nahar Rosy[3], Md. Ahsanul Kabir[4], Md. Aktaruzzaman[5], Md. Salman Hossain[6]**

Abstract

Background: Coronary artery disease (CAD) is a major global health concern, causing over 17 million deaths annually, significantly impacting low- and middle-income countries, like Bangladesh, where it contributes to the rising prevalence of non-communicable diseases. The electrocardiographic exercise test (ETT) is widely used to assess cardiovascular health, but its specificity and positive predictive value (PPV) are influenced by metabolic conditions, structural heart diseases, and demographic factors, particularly showing lower PPV in women. The study aimed to access the correlation between coronary angiographic results and positive ETT results in female patients. **Methods:** This study was conducted at Cardiology Department in Khulna Specialized Hospital, Khulna, Bangladesh, involving 102 female patients aged between 30 and 45 years, who tested positive for ETT. Angiogram was performed in the patients. Demographic data, including age, occupation, accommodation, and BMI, were collected, and informed consent was obtained. The study was approved by the institution's Ethical Review Committee. Data were analyzed using SPSS version 26.0, with significance set at $p<0.05$. **Results:** The study reveals normal angiograms (69.61%), single vessel coronary artery disease (SVCAD) (13.73%), double vessel coronary artery disease (DVCAD) (5.88%), and triple vessel coronary artery disease (TVCAD) (10.78%) in ETT positive study subjects underscoring false-positivity probably due to hormonal differences and microvascular dysfunction. **Conclusion:** In spite of positive ETT findings, angiogram was normal in most cases in this study. The findings emphasize developing diagnostic strategies and additional tools to better manage cardiovascular risk in women.

Keywords: Coronary Artery Disease, Electrocardiographic Exercise Test, and Angiography.

1. Assistant Professor, Dept. of Cardiology, Addin Akij medical college, Khulna, Bangladesh
2. Assistant Professor, Dept. of Cardiology, Shadid Sheikh Abu Naser Specialized Hospital, Khulna, Bangladesh
3. Associate Professor, Dept. of Forensic Medicine, Sir Salimullah Medical College, Dhaka, Bangladesh
4. Junior Consultant, Dept. of Cardiology, Satkhira Medical College Hospital, Satkhira, Bangladesh
5. Junior Consultant, Dept. of Cardiology, Satkhira Medical College Hospital, Satkhira, Bangladesh
6. Residential Medical Officer, Satkhira Medical College Hospital, Satkhira, Bangladesh.

***Address of Correspondence:** Dr. Sardar Zahid Hossain, Assistant Professor, Department of Cardiology, Addin Akij Medical College, Khulna, Bangladesh. Email: drszahid@yahoo.com.

Introduction

Coronary artery disease (CAD), also called coronary heart disease (CHD), or ischemic heart disease (IHD), is a type of heart disease involving the reduction of blood flow to the cardiac muscle due to a build-up of atheromatous plaque in the arteries of the heart [1, 2]. CAD is the most common of the cardiovascular diseases [3] that can cause stable angina, unstable angina, myocardial ischemia [4], and myocardial infarction [5]. Cardiovascular diseases (CVDs) account for >17 million deaths globally each year (30% of all deaths), 80% of which occur in low-income and middle-income countries, and this figure is expected to grow to 23.6 million by 2030 [6, 7]. Globally, there has been a significant rise in the proportion of women suffering from CAD over the last few decades. South Asia bears the largest overall burden of CAD partly because of its large pop-

ulation and the early onset of CAD in this region [8]. The causes of this evolutionary change may be genetic or environmental factors [9].

Bangladesh has been experiencing epidemiological transition from communicable disease to non- communicable disease (NCD) for more than thirty years. The overall mortality rate has decreased significantly over the last couple of decades. But deaths due to chronic diseases, specially the 'fatal four' i.e., cardiovascular disease (CVD), cancer, chronic respiratory disease and diabetes, are increasing at an alarming rate. CAD is an important contributor to one of the four i.e., CVDs [10]. In Bangladesh, noncommunicable diseases (NCDs) contribute to 67% of all deaths, with CVDs accounting for 30% of total fatalities [11]. CAD is recognized as a leading cause of morbidity and mortality particularly among middle-aged adults [12]. Age is a significant predictor of CAD in both women and men, with prevalence increasing sharply in women in their 70s [13].

Exercise acts as a physiological stressor that can reveal the underlying cardiovascular disease that may not be evident at rest. The electrocardiographic exercise test (EET), also known as the exercise tolerance test (ETT), is one of the most commonly used non-invasive methods to assess cardiovascular health [14]. ETT is employed to evaluate physical fitness, diagnose heart or lung pathologies, induce angina, and assess the stability of the cardiopulmonary system [15]. While sensitivity and specificity are often used to measure the validity and reliability of diagnostic test, physicians are more focused on detecting the disease in patients they suspect of having it. This is reflected in the positive predictive value (PPV) of the test [16].

The PPV of a diagnostic test is critical, as it indicates the likelihood that a positive result corresponds to true disease presence. A high PPV reduces unnecessary hospitalizations, alleviates financial costs, and minimizes patients' anxiety [17]. Although ETT is sensitive and helpful in detecting CAD, its specificity is influenced by several parameters, that can lead to false-positive results [18]. Reduced specificity has been observed in individuals with metabolic conditions such as anemia, glucose load, hyperventilation, and hypokalemia. Structural heart diseases, including severe aortic stenosis, mitral valve prolapse, significant regurgitation, cardiomyopathies, and left ventricular hypertrophy, can also affect test accuracy. Other factors that can affect its accuracy include marked resting ST segment depression, intraventricular conduction disturbances, pre- excitation syndromes, severe hypertension, severe hypoxia, sudden intense exercise, supraventricular arrhythmias, or digitalis therapy [19].

Previous studies have demonstrated a low PPV of ETT in women, particularly in young premenopausal subjects [20]. Currently, ETT serves as a gatekeeper for coronary angiography, with only patients who test positive undergoing further investigation. This approach reduces the number of true-negative results, increasing the test sensitivity while lowering its specificity, a phenomenon known as post-referral bias [21]. However, few studies in developing countries have assessed the PPV of ETT. This study aims to evaluate the variability in coronary angiographic findings among patients with positive ETT results.

Methods

This prospective observational study was conducted at the Department of Cardiology in Khulna Specialized Hospital, Khulna, Bangladesh from the month of May to November of 2024, Bangladesh. A total of 102 female patients aged between 30 and 45 years were considered in this study. All the patients had positive ETT results during the study period

and underwent angiography. Data were recorded using a predefined proforma, and informed consent was obtained from all participants. Patients with coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), ischemic heart disease, aberrant angiography results, contraindications to angiography, and valve replacement surgery were not included. Wolf- Parkinson-White (WPW) syndrome, congenital cardiac disease, aortic stenosis, and anomalies of the ECG (left bundle branch block) were also excluded. Demographic data, including age, occupation, accommodation, and body mass index (BMI), were obtained prior to ETT. Informed consent was obtained from all participants, and confidentiality was ensured. The institution's Ethical Review Committee granted the institution's approval for the study.

Baseline demographic characteristics were compared between true-positive and false-positive ETT results. Significant CAD identified via angiography indicated a “true positive” result, while the absence of significant CAD indicated a “false positive” result. Data were compiled using Microsoft Excel, reviewed for accuracy, and analyzed by using the Statistical Package for Social Sciences (SPSS) version 26.0 for Windows. Descriptive data were presented in tables and graphs and associations between categorical variables were evaluated using the chi-square test. A p-value of less than 0.05 was considered statistically significant.

Results

The sociodemographic profile of 102 ETT-positive female patients with normal angiograms revealed that 70.59% were aged between 30 and 37 years, and 50.98% were housewives. A majority of patients (57.84%) resided in rural areas, and 86.27% had a BMI below 30 kg/m², while 13.73% were classified as obese (Table 1). More than 35% of the female patients had diabetes, 31.37% were hypertensive, and

Table I. Sociodemographic profile of the patients performed ETT (n = 102).

Variables		Frequency n (%)
Age (year)	30-37	72 (70.59)
	38-45	30 (29.41)
Occupation	Service	42 (41.18)
	Housewives	52 (50.98)
	Others	8 (7.84)
Locality	Rural	59 (57.84)
	Urban	43 (42.16)
BMI (kg/m²)	<30	88 (86.27)
	>30	14 (13.73)

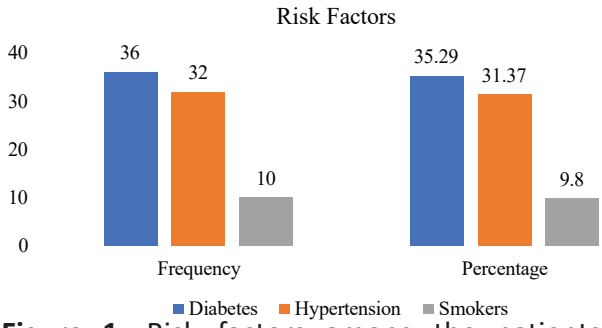


Figure 1: Risk factors among the patients (n=102).

Most women (69.61%) had normal angiograms. Among those with coronary artery disease, 13.73% were diagnosed with single-vessel coronary artery disease (SVCAD), 5.88% with double- vessel coronary artery disease (DVCAD), and 10.78% with triple-vessel coronary artery disease (TVCAD) (Figure 2).

Table 2 indicates no significant difference in diabetes prevalence between true-positive (35.48%) and false-positive (35.21%) ETT results. However, significant differences were observed in smoking and hypertension, with a higher proportion of smokers in the true-posi-

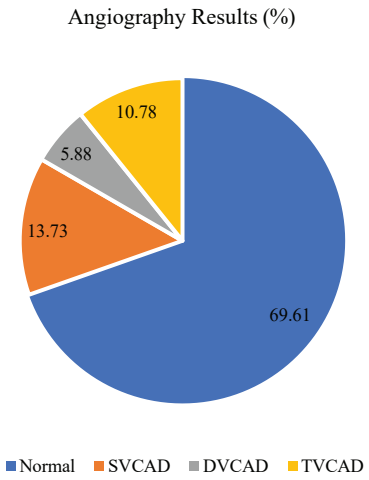


Figure 2: Angiography results among the patients (N=102). SVCAD, DVCAD, and TVCAD denote single vessel coronary artery disease, double vessel coronary artery disease, and triple vessel coronary artery disease, respectively.

tive group (12.90%) and more hypertensive patients in the false-positive group (35.21%). True-positives results were more frequently observed in earlier stages of ETT, whereas false-positive results were more common in stage 3 (47.89%), though this difference was not statistically significant (Table 2).

Table II. Comparison between true-positives and false-positives of ETT patients.

Parameters		True Positive n (%)	False Positive n (%)	*p* value
Diabetics		11 (35.48)	25 (35.21)	NS
Non-diabetics		20 (64.52)	46 (64.79)	
Smoker		4 (12.9)	6 (8.45)	S
Non-smoker		27 (87.1)	65 (91.55)	
Hypertensive		7 (22.58)	25 (35.21)	S
Non-hypertensive		24 (77.42)	46 (64.79)	
Stage of ETT	Stage 1	10 (32.26)	12 (16.9)	NS
	Stage 2	12 (38.71)	25 (35.21)	
	Stage 3	9 (29.03)	34 (47.89)	

Discussion

The exercise tolerance test (ETT) is a widely used, non-invasive diagnostic tool for evaluating patients with suspected CAD. A positive ETT result typically indicates myocardial ischemia, suggesting the presence of obstructive coronary lesions. However, some patients, particularly females, may have a positive ETT result but exhibit normal coronary angiogram, a condition known as false-positive ETT. This phenomenon is more prevalent in women due to several factors, including hormonal differences, microvascular dysfunction, and the inherent limitations of standard diagnostic protocols [17,20].

In Bangladesh, where cardiovascular disease represents a growing public health concern, the frequent observation of normal angiograms in ETT-positive females raises critical questions regarding the diagnostic approach to CAD in female patients. Understanding the implications of false-positive ETT results in women is essential for improving diagnostic accuracy and ensuring appropriate management of cardiovascular risks in this population. Our study included 102 patients, of whom 57% were employed in the service sector. The majority, 72 (71%), were under 37 years of age, and 59 patients (57%) resided in the rural areas. Additionally, 12 patients (13%) were classified as obese. This sociodemographic profile aligns with the findings of a Bangladeshi study conducted by Islam and Majumder [10] and is consistent with the work of Ikbal et al. [21].

In terms of risk factors, 36 patients (35.29%) had diabetes (DM), 32 (31.37%) suffered from hypertension, and 10 (9.8%) were smokers. These results align with previous research, which identified diabetes and hypertension as the common risk factors for ischemic heart disease (IHD). Smoking and lifestyle were also noted as significant contributors to IHD [15].

In our study, 69.61% of ETT-positive patients had normal angiography. The finding contrasts with other studies reporting a positive predictive value (PPV) of ETT between 75% and 85% [14,21]. Additionally, no statistically significant difference was observed in the prevalence of diabetes between the true-positive group (35.48%) and the false-positive group (35.21%) ($p>0.05$). While diabetes is a known risk factor for CAD, it may contribute to false-positive results due to microvascular dysfunction or autonomic neuropathy, which can affect the sensitivity of ETT

without revealing significant stenosis on angiography [22]. Previous studies have reported PPV among people with diabetes to be hovering at 77% [23].

Smoking showed a significant association ($p<0.05$) between the two groups, with a higher percentage of smokers in the true-positive group (12.90%) compared to the false-positive group (8.45%). This finding suggests that smokers are more likely to have true-positive ETT results. However, the low prevalence of smoking among women in Bangladesh may have limited the overall impact of this factor in the study. Nonetheless, research indicates that chronic smokers, both male and female, tend to have higher PPV than non-smokers [23]. Identification of diabetes and chronic tobacco smoking as established risk factors for the development of complex CAD may explain the higher PPV in these subsets of patients [23].

Hypertension was significantly more prevalent in the false-positive group (35.21%) than in the true-positive group (22.58%) ($p<0.05$). This finding is consistent with the notion that hypertensive females are more prone to false-positive ETT results, potentially due to increased vascular resistance and impaired endothelial function [21]. In hypertensive patients, microvascular ischemia or exaggerated blood pressure responses during exercise may lead to abnormal ETT results without corresponding coronary artery stenosis on angiography. Other studies also report a higher number of false positives among hypertensive individuals, with PPVs for hypertensives found to be lower (50%) compared to normotensives (88.2%) [22]. Impaired subendocardial perfusion in hypertensives may contribute to these discrepancies, leading to increased false- positive results [23].

In this study, true-positive patients showed positive ETT results earlier, with 32.26% in stage 1 and 38.71% in stage 2, compared to 16.90% and 35.21% for false-positive patients, respectively. A larger proportion of false positives (47.89%) reached stage 3 before testing positive, compared to 29.03% of true positives. Though the differences were not statistically significant, the trend suggests that true positives are more likely to exhibit ischemic changes earlier, while false positives tend to occur after prolonged exertion. These findings are consistent with the findings of Khan et al. [17]. Due to the limited specificity of ETT in detecting inducible angina, there has been an increased reliance on advanced technologies, such as myocardial perfusion scans (MPS) and cardiac magnetic resonance imaging (CMR), for more accurate diagnosis. Nevertheless, ETT remains a valuable tool for assessing the functional capacity of the heart during exercise and stress, especially in cases with a normal resting ECG [20].

Limitations of the study

This study contains several limitations. First of all, the sample size is relatively small and restricted to a specific demographic (female patients aged 30 to 45 years) in a single medical institution, which may limit the generalizability of the findings. Furthermore, the exclusion of male patients and those with a history of ischemic heart disease or significant medical interventions may influence the results. Addi-

tionally, the reliance on self-reported data for risk factors such as smoking and hypertension could introduce potential bias.

Conclusion & Recommendations

The study highlights the high prevalence of normal angiograms in female patients with positive ETT results in Khulna, with 69.61% of the cases showing no significant CAD. This finding underscores the challenge of false-positive ETT results in women likely to be influenced by factors such as hormonal differences and microvascular dysfunction. The higher prevalence of hypertension and smoking among true-positive cases suggests the need for more refined diagnostic strategies. These insights emphasize the importance of considering additional diagnostic tools alongside ETT to enhance accuracy and ensure effective management of cardiovascular risk in women, ultimately improving clinical outcomes in this community.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee.

References

1. Bhatia SK (2010). Biomaterials for clinical applications (Online-Ausg. ed.). New York: Springer. p. 23. ISBN 978-1-4419-6920-0. Archived from the original on 10 January 2017.
2. Ischemic Heart Disease. National Heart, Lung, and Blood Institute (NHLBI). Retrieved 2 February 2019.
3. Murray CJ (January 2015). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013". Lancet. 385 (9963): 117–71. doi:10.1016/S0140-6736(14)61682-4. PMC 4340604. PMID 25530442.
4. Myocardial ischemia – Symptoms and causes. Mayo Clinic. Retrieved 5 February 2022.
5. Wong ND (May 2014). "Epidemiological studies of CHD and the evolution of preventive cardiology". Nature Reviews. Cardiology. 11 (5): 276–89. doi:10.1038/nrcardio.2014.26. PMID 24663092. S2CID 9327889.
6. George, S. (2017) Angiographic Profile and Treadmill Test Relationship of Women with Chest Pain Suggestive of Coronary Artery Disease. World Journal of Cardiovascular Diseases, 7, 225- 232.
7. Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, Abbastabar H, Abd-Allah F, Abdela J, Abdelalim A, Abdollahpour I. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. The lancet. 2018 Nov 10;392(10159):1736-88.
8. Moran A, Vedanthan R. Cardiovascular disease prevention in South Asia gathering the evidence. Global heart. 2013 Jun;8(2):139.
9. Mendis, S., Puska, P. & Norrving, B. (Eds) Global Atlas on Cardiovascular Disease Prevention and Control (WHO, 2011).
10. Islam AK, Majumder AA. Coronary artery disease in Bangladesh: a review. Indian Heart J. 2013 Jul-Aug;65(4):424-35. doi: 10.1016/j.ihj.2013.06.004. Epub 2013 Jul 10. PMID: 23993003; PMCID: PMC3861019.
11. World Health Organization. Noncommunicable diseases progress monitor 2020. World Health Organization; 2020 Mar 23.
12. Khan KA, Aziz S, Saif M, Kamran J, Rauf A, Khalid W, Mazhar MW. Pattern of coronary artery disease in asymptomatic serving soldiers having abnormal screening ETT. Pakistan Armed Forces Medical Journal. 2019 Nov 29; 69(Suppl-3):S354-58.
13. Levisman JM, Aspry K, Amsterdam EA. Improving the positive predictive value of exercise testing in women for coronary artery disease. The American journal of cardiology. 2012 Dec 1;110(11):1619-22.
14. Attar A, Mehrzadeh A, Foulad M, Aldavood D, Fallahzadeh MA, Rad MA, Khosropanah S. Accuracy of exercise tolerance test in the diagnosis of coronary artery disease in patients with left dominant coronary circulation. Indian heart journal. 2017 Sep 1;69(5):624-7.
15. Sarma S, Levine BD. Beyond the Bruce Protocol: Advanced Exercise Testing for the Sports Cardiologist. Cardiology clinics. 2016 Aug 27;34(4):603-8.
16. Pais P. Treadmill stress tests should not be part of "routine health check package". Indian Heart Journal. 2018
Nov 1;70(6):934-6.
17. Khan I, Hasan M, Hasan J, Dhillon AI, Khan M, Kaneez M. Gauging the positive predictive value of exercise tolerance test using angiographic evaluation: a cross-sectional analysis from a developing country. Cureus. 2020 Dec;12(12).
18. Habeeb QS. Reliability and accuracy of exercise tolerance test in the diagnosis of coronary heart disease. Duhok Medical Journal. 2007; 1(1).
19. Chaitman B. Exercise stress testing. Heart disease. 1992:161-79.
20. Chrysohoou C, Aggeli C, Avgeropoulou C, Aroni M, Bonou M, Boutsikou M, Brili S, Chamodraka E, Dagre A, Flevari P, Fountoulaki A. Cardiovascular disease in women: Executive summary of the expert panel statement of women in cardiology of the hellenic cardiological society. Hellenic Journal of Cardiology. 2020 Nov 1;61(6):362-77.
21. Ikbal AT, Ayub M, Salehuddin M, Biswas RS. Coronary angiographic findings of exercise tolerance test (ETT) positive cases.
22. Esteghamati A, Abbasi M, Nakhjavani M, Yousefizadeh A, Basa AP, Afshar H. Prevalence of diabetes and other cardiovascular risk factors in an Iranian population with acute coronary syndrome. Cardiovascular Diabetology. 2006 Dec;5:1-6.
23. Lau GT, Wei H, Wickham J, To AC. The significance of equivocal exercise treadmill ECG for intermediate risk chest pain assessment–Insight from coronary CT angiography data. Heart, Lung and Circulation. 2018.