Original Article

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Detecting coronary artery disease among the individuals with left-sided dominant coronary circulation

Abstract

Background: Investigating the importance of exercise tolerance test (ETT) in the diagnosis of coronary artery disease (CAD) among people with left-sided dominant coronary circulation is very important.

Methods: This retrospective study aimed to explore the relevance of ETT in CAD diagnosis by analyzing medical records of 2084 patients who underwent ETT and coronary angiography in Urmia's educational therapeutic hospitals between 2018 and 2019. SPSS Version 16 was used for data analysis.

Results: The study included 5.58% males and 5.41% females. The prevalence of co-dominancy was 10.2%, right coronary dominance (RD) was 65%, and left coronary dominance (LD) was 24.8%. There were no significant differences between gender, age, smoking, blood pressure, diabetes mellitus (DM), the prevalence of hyperlipidemia (HLP), family history (FH) and left ventricular ejection fraction (LVEF). The frequency of non-significant CAD was higher in women than in men. Additionally, the frequency of women with LD was significantly higher than that of men. The results of angiography in normal cases, it was observed that the highest frequency was related to female patients with a history of DM. The sensitivity of the ETT was 94%, and the accuracy and diagnostic power of the exercise test for the presence of CAD in individuals with LD were 53% (p = 0.03).

Conclusion: The study highlights the potential for false-positive exercise tests in diabetic individuals with left coronary dominance, providing valuable insights into the nuanced interplay of gender, cardiovascular health, and coronary circulation patterns in CAD risk.

Keywords: Exercise tolerance test, Coronary artery syndrome, Coronary artery involvement severity, Left coronary blood circulation dominance.

Coronary Artery Disease (CAD) stands as a leading global health concern, contributing significantly to morbidity and mortality (1). This multifaceted condition arises from the progressive accumulation of atherosclerotic plaques within the coronary arteries, impeding blood flow to the heart muscle and potentially leading to a spectrum of clinical manifestations (2). It stands as a primary cause of cardiovascular morbidity and mortality, claiming countless lives and imposing a substantial burden on healthcare systems (3). CAD often precipitates severe complications such as myocardial infarction(MI), angina pectoris, and heart failure (HF), further exacerbating its clinical repercussions (4). According to the World Health Organization(WHO), an estimated 17.9 million people died from cardiovascular diseases (CVDs) in 2019, representing about 32% of all global deaths (5). A review published states that CAD accounts for 15.5% of total deaths globally and has risen in epidemic proportion in India. In India, CAD accounted for 26.9% of medically (6).

The prevalence of CAD in Iran is significant, with CAD being a leading cause of mortality, morbidity, and disability in the Iranian population. A study conducted in 2022 estimated the prevalence of CVD, which includes CAD, to be 9.2% in a specific region of Iran (7). The global prevalence of CAD is on the rise, driven by a confluence of factors such as sedentary lifestyles, unhealthy dietary habits, smoking, and an aging population (5). Moreover, the increasing prevalence of risk factors like diabetes and hypertension (HTN) contributes to the escalating incidence of CAD, making it an urgent public health concern (6).

The intricacies of coronary circulation have long been recognized as a key factor influencing the manifestation and progression of CAD (3). In individuals with left-sided dominant coronary circulation, where the left coronary artery (LCA) supplies a majority of the myocardium, the diagnostic landscape may present unique challenges and opportunities (8). Patients with left-sided dominant coronary circulation present a distinct anatomical scenario where the LCA predominantly supplies the myocardium (9). This unique cardiac vasculature may influence the manifestation and progression of CAD in a manner distinct from individuals with other coronary artery dominance patterns. Precise and timely diagnosis is crucial for effective management and improved outcomes (10). Among the myriad diagnostic modalities available, ETT has emerged as a valuable tool, offering insights into cardiac function and potential ischemic events. ETT, encompassing various forms such as treadmill or bicycle ergometry, stress echocardiogram(stress echo), or nuclear imaging, holds promise in detecting coronary insufficiencies by assessing the heart's response to increased physiological demands (11). Conducting comprehensive and cohort studies in Iran to investigate the diagnostic significance of ETT in individuals with left-sided dominant coronary circulation is a rare endeavor, yet one that holds immense potential for advancing cardiovascular research in the country. This study aimed to examine the significance of exercise testing in detecting CAD among individuals with left-sided dominant coronary circulation.

Methods

The present study was conducted retrospectively and in a cross-sectional manner (descriptive-analytical). The research community included all patients with CAD who underwent angiography in the educational and medical centers of Ayatollah Taleghani and Seyed al-Shohada from the beginning of September 2018 to September 2019. After approval of the proposal by the university's research and ethics committee by the Urmia University of Medical Sciences (IR.UMSU.RIC.1398.410).

A total of 5155 patient files were examined. The study focused on patients who had undergone coronary angiography during the mentioned time frame. Patients with advanced age (over 75 years), those with high body mass index (BMI) and weight (over 100 kilograms) who had not undergone ETT, and individuals with negative ETT results were excluded from the study. Additionally, the majority of patients with other reasons, including those with emergency visits who had not undergone ETT, were also excluded from our study. In the end, a total of 2084 participants were included in the study. Demographic information, including age, gender, and BMI, as well as the presence of cardiac risk factors such as high blood pressure, diabetes mellitus (DM), smoking, dyslipidemia, and family history (FH) of coronary heart disease (CHD), were recorded based on the medical records of the patients. BMI was calculated using the recorded height and weight in the patient's file, with the weight (in kilograms) divided by the square of the height (in meters).

To determine the left ventricular ejection fraction (LVEF) and the status of coronary arteries, information from echocardiography and the final report of angiography performed by the attending physician was documented. Coronary artery stenosis was categorized into two groups: normal and abnormal. The normal group included patients whose angiography results were normal, indicating no significant lesions (minimal CAD). The abnormal group included patients with angiography results showing significant lesions, with coronary artery lesions above 50%, and these individuals were classified into the CAD group. This information was obtained from the coronary angiography report.

Exercise testing: All of the patients underwent routine, clinically referred, symptom-limited treadmill stress testing using the standard Bruce protocol. In accordance with clinical guidelines, treadmill testing was terminated at the discretion of the supervising clinician for reasons that included substantial arrhythmias; abnormal hemodynamic responses; diagnostic ST-segment changes; exercise-limiting symptoms, such as chest pain (CP) or shortness of breath; or if the patient was unwilling or unable to continue. Resting heart rate (HR) and BP were measured before stress testing by clinical personnel.

Medical history: A medical history, including age, sex, indication for stress testing, risk factor burden, active medication use, and history of medical conditions, was obtained by nurses or exercise physiologists immediately before the stress test. Medication use and medical history

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were supplemented and verified by an administrative database, and pharmacy claims files from enrollees in the integrated health plan. Current smoking was defined as self-reported active smoking at the time of testing. DM, HLP and HTN were defined by self-report, previous diagnosis, database-verified diagnosis, or use of medications for the respective medical conditions.

Determining sensitivity, specificity, and predictive values: Sensitivity and specificity, with 95% confidence intervals, were calculated for each index test by constructing 2×2 tables for "TP" (=" true positives"), "TN" (= "true negatives", "FP" (=" false positives") and "FN" (= "false negatives") rates. Other assessments of test accuracy that provide additional information for practitioners were also calculated, including positive predictive validity (PPV), negative predictive validity (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR−). PPVs, NPVs, LR+ and LR− values were estimated from TP, TN, FP and FN data.

Statistical analysis: To assess the difference between qualitative variables, the Kruskal-Wallis test was initially employed to determine whether to use parametric or non-parametric tests. Based on the normality test results, either the parametric analysis of variance (ANOVA) or the non-parametric Kruskal-Wallis test was selected. For examining the differences between group means, the choice between parametric and non-parametric tests was determined by the Kolmogorov-Smirnov test. Data analysis was conducted using SPSS Version 16.

Results

The results indicated that 59% (1219 individuals) were males, and 41% (865 individuals) were females. Additionally, the chi-square test showed no significant relationship between LD patients and gender (P = 0.56), age (P = 0.27), BMI (P = 0.37), smoking (P = 0.25), history of HTN (P = 0.23), DM (P = 0.27), Smokey (P = 0.32), HLP (P = 0.45), FH (P= 0.38) and LVEF (P= 0.54). No significant relationship was observed between LD patients and other examined laboratory parameters. Furthermore, the chi-square test revealed a significant association between Dominancy and the findings of angiography (= P = 0.01). In the LD group, the frequency of no significant CAD in angiography results was higher compared to RD and CD. Additionally, the frequency of RD group in terms of the severity of vessel involvement was higher compared to other dominancy types. The frequency of patients with involvement of one vessel (1VD) was higher in the overall study sample (table 1).

Table1. Baseline demographic and clinical characteristics of the study cohort stratified by coronary dominancy

Characteristic		Dominancy			P- Value
		Co dominant	Right dominant	Left dominant	
Gender, N (%)	Male	173 (8.2)	916 (44)	130 (6.23)	0.56
	Female	38 (2)	439 (21)	388 (18.57)	
Age (years), Mean±SD		54.75±2.2	60.44±1.2	51.43±4.42	0.27
BMI, Mean±SD		26.38±1.00	26.63±2.01	25.40±1.59	0.37
HTN, N (%)	YES	80 (3.8)	833 (40)	207 (9.95)	0.23
	NO	131 (6.3)	522 (25.0)	311(14.9)	
DM, N (%)	YES	72 (3.5)	615 (29.5)	274 (13.1)	0.27
	NO	139 (6.6)	740 (35.5)	244 (11.7)	
FH, N (%)	YES	107 (5.1)	683 (32.8)	204 (9.8)	0.38
	NO	104 (5)	672 (32.3)	314 (15.1)	
HLP, N (%)	YES	96 (4.6)	779 (37.4)	194 (9.3)	0.45
	NO	115 (5.5)	576 (27.6)	324 (15.5)	
Smoker (%)	YES	94 (4.5)	694 (33.3)	120 (5.7)	0.32
	NO	117 (5.6)	661 (31.7)	398 (19.13)	
Chol, Mean±SD		174.59±6.6	178.94±5.6	168.88±7.1	0.001
TG, Mean±SD		144.07±3.4	149.55±4.5	137.77±4.4	0.001

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Characteristic	Dominancy			P- Value
	Co dominant	Right dominant	Left dominant	
LDL, Mean±SD	109.57±3.1	110.8±3.5	108.34±4.1	0.14
HDL, Mean±SD	37.86±2.6	37.68±4.4	38.07±3.4	0.017
Cratenin, Mean±SD	1.09±0.5	1.14±0.6	1.07±0.5	0.001
Angiography N (%) — Normal	81(3.8)	168 (8.7)	329(15.8)	0.001
Angiography N (%) — 1 VD	70 (3.3)	473(22.7)	113 (5.4)	
Angiography N (%) — 2VD	27 (1.2)	320 (15.4)	33 (1.6)	
Angiography N (%) — 3VD	22 (1.05)	225 (10.8)	22 (1.05)	
Angiography N (%) — Left main	11 (0.52)	165 (8)	21 (1.0)	

BMI: Body mass index, HTN: Hypertension, DM: Diabetes mellitus, FH: Family history, HLP: Hyperlipidemia, Chol: Cholesterol, TG: Triglycerides, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, 1 VD: One-vessel coronary artery disease. 2 VD: Two-Vessel Disease. 3 VD: Triple Vessel Disease.

Table 2 indicates that the frequency of non-significant CAD in women is higher than in men, and the frequency of men with significant CAD is higher compared to women. By comparing angiography results based on coronary dominance by gender, the frequency of women with LD is significantly higher than that of men. Examining normal angiography results reveals that the highest frequency is observed in patients (women) with a history of DMs. It can be inferred that diabetic patients with LD lead to false-positive ETT.

By comparing the results of single-vessel involvement in angiography with risk factors and coronary blood flow, it can be concluded that vessel involvement in men with RD is higher. Among the risk factors, smoking and then high blood pressure among male patients have a higher prevalence compared to other examined risk factors. Comparing the angiography results of patients with two-vessel (2VD) involvement shows that the prevalence of 2VD involvement is still higher in men than in women. Smoking, HLPa, and high blood pressure are the prevalent risk factors among these patients. In patients with three-vessel (3VD) involvement and left main, the prevalence is higher in men than in women. By comparing risk factors, it can be concluded that the higher the prevalence of DM, high blood pressure, HLP, smoking, and positive FH history, the greater the severity of vessel involvement.

Table2. Prevalence of risk factors stratified by angiography findings and coronary dominancy

Sex	Dominancy	Angiography	DM	HTN	FH	HLP	Smoker
Male	CD	Normal	9 (12.3%)	17 (23%)	32 (43%)	10 (13.7%)	34 (46%)
Male	RD	Normal	15 (11%)	38 (27%)	39 (28%)	3 (2%)	67 (47%)
Male	LD	Normal	18 (39%)	10 (23%)	15 (32%)	13 (35%)	25 (54%)
Female	CD	Normal	5 (62%)	3 (37/5%)	4 (50%)	0	2 (25%)
Female	RD	Normal	11 (36%)	8 (26%)	8 (26%)	2 (6%)	4 (14%)
Female	LD	Normal	180 (64%)	89 (31%)	85 (30%)	5 1(18%)	14 (4.5%)
Male	CD	1VD	16 (30.2%)	20 (37%)	23 (43%)	28 (53%)	24 (46%)
Male	RD	1VD	102 (36%)	170 (60%)	153 (54%)	111 (39%)	194 (68%)
Male	LD	1VD	22 (50%)	17 (40%)	19 (45%)	26 (62%)	29 (69%)
Female	CD	1VD	9 (52%)	7 (41%)	12 (70%)	7 (41%)	2 (5%)
Female	RD	1VD	73 (37%)	117 (60%)	86 (45%)	79 (42%)	21 (11%)
Female	LD	1VD	40 (59%)	37 (52%)	36 (50%)	34 (48%)	4 (5%)
Male	CD	2VD	8 (40%)	10 (45%)	15 (75%)	15 (75%)	13 (65%)

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Sex	Dominancy	Angiography	DM	HTN	FH	HLP	Smoker
	RD		121 (54.3%)	147 (65%)	120 (53%)	155 (69%)	158 (71%)
	LD		13 (59%)	17 (77%)	17 (77%)	16 (72%)	18 (80%)
	CD		6 (85%)	6 (85%)	2 (28%)	7 (100%)	1 (14%)
Female	RD		53 (54%)	71 (73%)	54 (55%)	72 (47%)	1 8 (18%)
	LD		8 (70%)	8 (70%)	7 (63%)	8 (72%)	2 (18%)
	CD		10 (58.8%)	11 (64%)	11 (64%)	16 (94%)	12 (70%)
Male	RD		92 (62.2%)	107 (73%)	88 (59%)	125 (84%)	112 (75%)
	LD	3VD	9 (69%)	9 (69%)	9 (69%)	13 (100%)	10 (76%)
	CD		4 (80%)	3 (60%)	3 (60%)	4 (80%)	0
Female	RD		45 (58%)	51 (66%)	34 (44%)	71 (92%)	16 (21%)
	LD		7 (70%)	4 (33%)	5 (55%)	9 (100%)	2 (22%)
	CD		5 (50%)	4 (40%)	4 (40 %)	9 (90%)	7 (70%)
Male	RD		76 (61.3%)	90 (72%)	79 (63%)	118 (95%)	95 (76%)
	LD	Left Main	7 (100%)	7 (100%)	4 (57%)	6 (85%)	4 (58%)
	CD		1 (100%)	1 (100%)	1 (100%)	1 (100%)	0
Female	RD		29 (64%)	36 (80%)	23 (51%)	45 (100%)	10 (22%)
	LD		10 (72%)	9 (64%)	10 (71%)	14 (100%)	2 (14%)

DM: Diabetes mellitus, HTN: Hypertension, FH: Family history, HLP: Hyperlipidemia, 1VD: One-vessel disease, 2VD: Two-vessel disease, 3VD: Three-vessel disease, RD: Right coronary dominance: LD: Left coronary dominance, CD: Coronary dominance.

Table 3 demonstrates that the highest sensitivity of the exercise test is observed in patients of the RD group. In patients with LD coronary anatomy, the sensitivity of the test is 94%. This implies that 94% of patients who undergo the ETT will have a true positive result, and the rest will be false negatives. The specificity of the test, meaning its ability to correctly identify everyone who is not a patient, is higher for patients in the RD group. The specificity of ETT in LD patients is 42%, indicating that 42% of healthy individuals screened will have a true negative result, and the rest will be false positives. The PPV indicates the probability that an individual with a positive test result is actually diseased. In LD patients, the PPV is 36%, suggesting a 36% probability of having CAD. The (NPV indicates the probability that an individual with a negative test result is truly healthy. In LD patients, the NPV is 71%, indicating a 71% probability of being healthy with a negative test result. The accuracy and diagnostic power of the exercise test for the presence of CAD in individuals with LD circulation are 53%.

Table 3. Accuracy, sensitivity, and specificity of the exercise test based on coronary dominancy

	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Accuracy
RD (%)	98.18	60	87	48	2.1	1.2	89
LD (%)	94	42	36	71	1.01	10.45	53
CD (%)	86.66	39	62	70	2.26	2.1	70
Total (%)	92	47	62	63	1.7	4.5	70

RD: Right coronary dominance, LD: Left coronary dominance, CD: Coronary dominance.

Discussion

The present study was conducted to determine the diagnostic value of the ETT in detecting CAD in patients with LD circulation. The results of angiography were examined based on CD minance, and it was observed that the frequency of normal angiography results in the LD group is significantly higher than in the RD and CD groups. By examining the results of normal angiography in the LD

group, it is observed that the majority of female patients with LD anatomy have non-significant CAD in angiography results. Upon investigating the risk factors in this patient group, the highest prevalence is related to DM. In fact, in this study, the prevalence of LD is higher among women in the age group between 40 to 56.

However, the ETT's sensitivity and specificity is lower in women than men, so the dominance of female gender in this study is a confounding variable and the final result that claims more false positive results in LD group, can simply be due to female gender predominancy and not due to LD.

The presence of DM and LD contribute to false-positive results in exercise testing, particularly in women, acting as confounding variables. By examining the samples in our study, it is observed that single-vessel involvement has the highest prevalence in all three dominance groups. In men, the severity of vessel involvement is also higher than in women. Additionally, the prevalence of the examined risk factors is higher in the male group compared to the female group. The prevalence of the smoking risk factor is also higher in men than in women. One of the findings of our study is that with increasing age, the prevalence of RD also increases. The findings of our study, including the frequency of male gender, the average age of patients, and also the average age of RD patients, are consistent with the study by Max Knaapen in 2012. However, in our study, the prevalence of LD is higher, which contradicts with this study (12). Furthermore, the prevalence of dominancy in our study contradicts with the Brownwald textbook of cardiovascular medicine. According to Brownwald's book, approximately 85% of people are right-dominant, 15% are left-dominant, and the remaining 5% exhibit co-dominance or balanced dominance (13). However, in our study, the prevalence is RD=65%, LD=25%, CD=10%. This study indicates that in Iranians (specifically in the West Azerbaijan region), the prevalence of left dominance is higher than the reference, aligning with the findings of Vashaghani Farahani et al. (14).

Our study, with an average age of 57.6 years and a male prevalence of 62.7%, differs from the findings of Vashaghani Farahani. In their study, no significant differences were observed between risk factors and dominancy. In contrast, our study revealed a higher prevalence of 3VD in RD patients, while in our findings, the prevalence of 1 1VD was higher among RD patients, there were no significant association between dominancy and risk factors (gender, age, FH, LVEF, BMI, smoking, BP, DM, and HLP).. Our study is consistent with the study of Attar et al. (15). In our research, the prevalence was RD=83.6%, LD=8.2%, CD=8.2%. The average age of LD patients was 62.3, and the male prevalence was 72.4%. Discrepancies were noted regarding the prevalence of LD, the average age of patients with LD anatomy, and the gender distribution compared to the Alexander Goldberg study. The anatomy of LD can lead to the creation of myocardial ischemia through mechanisms, even in the absence of significant obstructive CAD. In Iranians, the prevalence of LD is higher than the reference, and the prevalence of RD and CD is lower than the reference, which may be due to regional and racial factors. In the study by Hussein Ali Fakhir et al. (2012) (16), which included 675 patients, RD=76.4%, LD=12.6%, and CD=10%. The higher prevalence of LD compared to CD in their study aligns with our findings. According to Fakhir's study and the research by Vashaghani Farahani, RD patients show a tendency toward developing 3VD, while in our study, there is a propensity for 1VD. In the study by Attar et al. (2013), which included 720 patients with positive ETT undergoing angiography, RD=82%, LD=12%, and CD=6%. The ranking of dominance prevalence in their study is consistent with our findings (17). Attar and colleagues did not find a significant difference in age and gender among patients, whereas our study revealed a meaningful association. Overall, 27% of patients in Attar's study with positive exercise test results had no significant (CAD on angiography. In our study, 27% of patients had no CAD, while 73% had CAD, with a higher prevalence of LD. The diagnostic accuracy of the exercise test in patients with LD was reported as 31% accuracy, 80% sensitivity, and 9% specificity. In our study, the diagnostic accuracy of the exercise test in patients with predominantly left-sided coronary circulation was 53% accuracy, 94% sensitivity, and 42% specificity, showing discrepancies with Attar's study. In the study by involving 140 patients, 29 (20.7%) patients had involvement of 1 vessel, 31 (22.1%) individuals had involvement of 2 vessels, and 60 (42.9%) patients had involvementof 3 vessels. Interestingly, the highest prevalence was observed in the severity of involvement of 3 vessels. In contrast, in our study, involvement of 1 vessel had the highest prevalence. Finally, the reported positive predictive value of exercise treadmill testing was 75% in their study, while in our study, the positive predictive value of exercise testing was 62%. It can be concluded that coronary vessel dominance is considered a risk factor because coronary arteries are uniformly exposed to systemic risk factors, while the distribution of atherosclerosis in them is variable and focal. This may be attributed to the nature of coronary arteries, and coronary dominance is one of the factors contributing to the progression of atherosclerotic plaque. According to Braunwald's book, approximately 85% of people are right-

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dominant, 15% are left-dominant, and the remaining 5% exhibit co-dominance or a balanced pattern (13).

In our study, 73% of the examined cases were found to have CAD, indicating that approximately one-third of the study population did not have CAD. This finding suggests a lower diagnostic power of ETT , especially in females, similar to the study by Patel and colleagues (18). This result emphasizes the need for more accurate medical histories, particularly in women, and underscores the importance of focusing on cardiovascular risk factors in the medical history based on the exercise testing guidelines. Additionally, alternative methods such as myocardial perfusion scanning, computed tomography angiography (CTA), which have higher diagnostic accuracy, should be considered in addition to ETT.

Limitations: Our study has some limitations. The study utilized a retrospective design, which relies on preexisting medical records. This type of design is susceptible to limitations such as incomplete or missing data, and the inability to control for confounding variables. The study was conducted in two hospitals, which may limit the generalizability of the findings to a broader population. The results may not be representative of other healthcare settings or regions. The study was conducted in Urmia's educational therapeutic hospitals, which may limit the generalizability of the findings to a broader population. The results may not be representative of other healthcare settings or regions. **Suggestions for future researches:** Conducting a prospective study would allow for better control of variables and the collection of more robust data, enhancing the reliability of the findings. Comparing ETT results with other diagnostic modalities, such as imaging techniques (e.g., cardiac MRI or CT angiography), could provide a more comprehensive evaluation of CAD diagnosis and improve the understanding of the limitations and accuracy of ETT. Conducting long-term follow-up studies to assess the predictive value of ETT in individuals with left coronary dominance and its association with subsequent cardiovascular events would provide valuable insights into the clinical implications of the test.

Our study uncovered a higher frequency of normal angiography results in the LD group, particularly among females, emphasizing the importance of meticulous medical histories and consideration of cardiovascular risk factors in this population. Contrary to conventional prevalence patterns reported in literature, our findings indicated a higher prevalence of LD among Iranians, suggesting potential regional and racial influences. Furthermore, the study underscored the impact of diabetes as a prominent risk factor in LD anatomy, contributing to false-positive ETT

results. These observations advocate for a nuanced approach in diagnostic strategies, with consideration for alternative methods such as myocardial perfusion scanning and CTA alongside ETT, particularly in populations with left-sided coronary dominance.

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