

Hypertensive retinopathy as a predictor of coronary artery disease in elderly hypertensive patients with angina pectoris: A comparative study

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ABSTRACT

Background: In exploring novel avenues to assess cardiac health, this study investigates the potential of retinal vascular signs (RVS) as an effective tool for predicting coronary artery disease (CAD) in elderly hypertensive patients who present with angina pectoris. Considering the rising prevalence of cardiac disorders, there is an increasing interest in using noninvasive imaging modalities for early cardiovascular disease detection. This study conducts a comprehensive analysis to establish a direct correlation between retinal microvascular alterations and the development of heart disease in hypertensive patients. **Methods:** A total of 70 elderly hypertensive patients with acute angina underwent coronary angiograms and were divided into two groups (case and control). Each patient underwent ultrasound of the carotid artery and pulsed Doppler flow of the ophthalmic artery (OA). The severity of coronary artery stenosis was determined using the Gensini score (GS). Significant CAD was defined as the confirmed obstruction of more than 75% of one's main coronary arteries. **Results:** The mean systolic velocity/mean diastolic velocity (MSV/MDV), pulsatile index, and resistance index in the Doppler flow of the OA were found to have significant and independent correlations with carotid intima-media thickness (c-IMT). Additionally, MSV/MDV was found to have a significant and independent correlation with the GS, and retinopathy was significantly associated with coronary artery disease ($p = 0.05$). **Conclusions:** Changes in retinal blood vessels caused by hypertension are confirmed as excellent predictors of coronary artery disease and a useful screening tool for the same, particularly in primary healthcare centers.

Keywords: coronary arteries, retinal vessels, ophthalmic artery, hypertensive retinopathy

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DOI: <https://doi.org/10.37319/inqjm.6.2.1>

Received: 12 OCT 2023

Accepted: 26 DEC 2023

Published online: 15 JUL 2024

INTRODUCTION

Despite remarkable advancements in the understanding, prevention, and treatment of cardiovascular diseases (CVDs) over recent decades, they remain the leading cause of mortality both globally and in the United States

of America (USA).^{1,2} Developing nations particularly experience a significant burden, with over 4.5 million deaths attributed to CVD annually in developing nations.³ While the risk factors for heart disease are well

defined, the escalating prevalence of this condition has spurred interest in innovative approaches aimed at its early detection and risk assessment. Noninvasive imaging methods for assessing coronary microcirculation have gained prominence since their emergence at the beginning of the current century, with coronary computed tomography (CT) at the forefront of these techniques.^{4,5}

The notion that retinal vasculature mirrors coronary circulation has persisted for years, substantiated by several factors: 1) The transparent nature of the ophthalmic medium facilitates easy visualization of retinal vessels; 2) Retinal vessel size is comparable to coronary microvasculature; and 3) Observations of retinal microvascular sclerosis in hypertensive patients have shown concordance with changes in coronary microcirculation over the past decades.^{6,7} Consequently, a growing body of expert-evaluated research suggesting an association between retinal microvascular signs and cardiovascular disorders has emerged. To date, however, concomitant studies have only explored the relationship between retinal blood vessel diameter and various cardiovascular and systemic conditions.^{8,9}

Considering the above context, this study aimed to investigate whether a correlation exists between hypertensive retinopathy and coronary diseases. To this end, it examined alterations in retinal vessels among elderly hypertensive patients with angina. By evaluating changes in retinal vasculature, this research sought to contribute to the existing understanding of the potential relationship between retinal microvascular manifestations and cardiovascular health, specifically about patients with hypertension and angina pectoris.

MATERIALS AND METHODS

Study site and duration: This study was conducted at Elsadar Teaching Hospital between 2022 and 2023. It obtained the approval of the hospital's institutional review board before initiation.

Study design and participant selection: Employing a comparative study design, this study enrolled 70 senior citizens who were at least 60 years old at the time of its commencement. The participants were divided into two groups based on the presence or absence of coronary artery disease (CAD): CAD and non-CAD groups, as shown in Figure 1.

Clinical history interview: Each participant underwent a comprehensive clinical history interview. This interview encompassed several crucial factors:

1. Hypertension: Defined as blood pressure exceeding 140/90 mmHg.¹⁰
2. Diabetes: Defined as fasting glucose levels exceeding 126 mg/dL, indicating the requirement of oral antidiabetic medications.¹¹
3. Smoking: Explained as previous history or current status of smoking.
4. Hyperlipidemia: Defined as LDL cholesterol levels surpassing 130 mg/dL and requiring the use of statins.¹²

Diagnosis of Coronary Artery Disease (CAD): Coronary angiograms (CA) were employed for the diagnosis of CAD. Knowledgeable medical professionals visually evaluated coronary stenosis severity using multiple-view CA projections.

To quantitatively assess the degree of coronary artery stenosis, the Gensini score (GS) was utilized.¹³ Each patient's coronary artery was divided into 14 segments, and the degree of stenosis in each segment was evaluated. The GS was derived from these stenosis assessments, assigned based on the degree of stenosis (ranging from 1% to complete occlusion). Thereafter, weighting factors corresponding to the lesion significance were applied to the scores.

Gensini score calculation: Gensini scores were assigned as follows:

- Stenosis 1–25%: 1
- Stenosis 26–50%: 2
- Stenosis 51–75%: 4
- Stenosis 76–90%: 8
- Stenosis 91–99%: 16
- Complete occlusion: 32

Moreover, lesions in specific segments were assigned different weighting factors based on their significance. Subsequently, these Gensini scores were multiplied by certain weighting factors that corresponded to the significance of the lesion in each section. A weighting factor of 5 was given to a lesion that was found in the left main artery, whereas a factor of 2.5 was given to a lesion that was found in the proximal left anterior descending (LAD) or the left circumflex (LCX). A lesion in the distal LAD, LCX, first diagonal branch, first obtuse marginal branch, right coronary artery, posterior descending artery, or septal artery was assigned a factor of 1. On the other hand, lesions found in the second diagonal or obtuse marginal branches were given a factor of 0.5 in the scoring system.

Total GS was computed by adding the products of the scores and weighting factors from all 14 artery segments of each patient. Severe CAD was defined as > 75% blockage of the main coronary arteries.

Using this comprehensive research strategy, this study aimed to investigate the relationship between hypertensive retinopathy and coronary heart disease by analyzing changes in retinal vessels among elderly hypertensive patients with angina.

Conditions for inclusion:

1. Age: Participants were at least 60 years old or older.
2. Hypertension categories: Participants with different stages of hypertension were included based on the categorization system used by the Joint National Committee (JNC) VI. Hence, this study included patients with prehypertension, Stage I hypertension, and Stage II hypertension.
3. Angiography schedule: Participants had undergone an angiography procedure scheduled for assessment.
4. Informed consent: All participants provided their informed consent to participate in the study. Additionally, the approval of the relevant hospital's ethics committee was obtained before the study's commencement.

Conditions for exclusion:

1. Metabolic syndrome: Participants with metabolic syndrome were not included in the study.
2. Visible nephropathy: Individuals with visible nephropathy, indicated by a creatinine level of 1.5 mg/dL or above, were excluded.
3. Current coronary artery disease treatment: Individuals currently undergoing treatment for coronary artery disease were excluded from the study.
4. Prior revascularization: Individuals with a history of prior revascularization procedures were excluded.
5. Acute myocardial infarction: Participants with a history of acute myocardial infarction were excluded.
6. Atrial fibrillation: Individuals presenting with atrial fibrillation were excluded.
7. Retinal detachment: Participants with a history of retinal detachment were excluded.
8. Uncontrolled glaucoma: Individuals with uncontrolled glaucoma were excluded.

The above exclusion criteria were used to ensure that the study's participant pool adequately represented the specific patient group under investigation and that the

potential confounding factors that could impact the study's findings were eliminated to the greatest possible extent.

Ophthalmic artery evaluation with doppler:

Operator Consistency: Doppler imaging of the ophthalmic artery (OA) of all patients was performed by the same operator. This operator intentionally minimized the potential bias in the assessment process.¹⁴

Ultrasound Measurements: Noninvasive ultrasound measurements of the ophthalmic artery (OA) were conducted using an M3S-D transducer with a frequency range of 1.5–4.0 MHz (Vivid 7, General Electric Medical Systems, Wallingford, Connecticut, USA). These measurements were obtained using an ultrasound probe.

Preparation and patient positioning: Before the test commenced, the participants were instructed to lay in a supine position for 10 minutes. This preparatory step was aimed at enhancing the accuracy of readings, possibly by allowing participants to relax and achieve a stable baseline before the measurements were taken.

Ultrasound Probe Placement: Following the application of a sterile ophthalmic lubricating pad on the closed eyelid, the ultrasonic probe was positioned over the eye of each patient. This placement was executed with simplicity and minimal effort.

OA location and sample volume marker: It was noted that the OA is a substantial artery positioned in proximity to the optic nerve. The precise placement of the sample volume marker was determined to be at a distance of 40–50 mm from the top eyelid of each patient.

By ensuring consistent operator involvement, proper patient preparation, and accurate probe placement, this study aimed to obtain reliable and accurate noninvasive ultrasound measurements of each patient's ophthalmic artery for further evaluations, as shown in Figure 2.

Retinal microvascular signs:

The following, defined briefly, are fundus-color-photography-derived signs

Clinical significance:

(I) Central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE), measured as the average diameter of the largest 6 arterioles and 6 venules, respectively;

(II) Arteriolar-to-venular ratio (AVR), defined as the ratio of CRAE to CRVE;

- (III) Simple tortuosity, defined as the ratio of actual path length to the straight-line length of a retinal vessel segment; curvature tortuosity, derived from the integral of the curvature squared along the path of the retinal vessel and normalized by the total path length;
- (IV) Focal narrowing over a constricted area comprising two-thirds (or less) of the widths of proximal and distal vessel segments;
- (V) Fractal dimension (Df), used to quantify the branching architecture of retinal vasculature using the box-counting method;
- (VI) Optimality ratio, a measure of power loss in the blood flow through bifurcations related to endothelial dysfunction; optimality deviation measures the extent to which the optimality ratio deviates from the theoretically predicted optimum;
- (VII) Branching angle, the first angle subtended by two daughter vessels at each vascular bifurcation.

Hypertensive Retinopathy Classification (Keith-Wagner Barker Classification):

The retinopathy changes were interpreted using the Keith-Wagner Barker Classification of hypertensive retinopathy based on fundoscopic examination using indirect ophthalmoscopy or +90 D lens, as outlined below.

Group 1: Mild Retinal Arteriolar Constrictions

Group 2: Group 1 + Retinal Arteriolar Focal Narrowing + AV Nicking

Group 3: Group 2 + Flame-Shaped Hemorrhages + Cotton-Wool Spots + Hard Exudates

Group 4: Group 3 + Swelling of the Optic Disc

Carotid ultrasound evaluation:

In this study, a carotid ultrasound examination was also performed on all patients. The c-IMT was defined as the greatest axial thickness of IMT at the carotid arteries. Carotid plaque was defined as a local thickening of the c-IMT by > 50% compared to the surrounding vessel wall, a c-IMT > 1.5 mm, or a local thickening > 0.5 mm.

Statistical Analysis:

All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) for Windows version 24 (SPSS Inc., Chicago, IL, USA). Quantitative and normally distributed continuous variables were expressed as the standard deviation. Differences in frequencies were analyzed using the chi-square test, while differences in continuous variables

between the two participant groups were examined using the independent t-test. Univariate linear relationships between key variables were tested using Pearson's correlation coefficient. Further, multivariate linear regression analysis was used to evaluate independent factors regarding the c-IMT. A value of $p < 0.05$ was considered statistically significant.

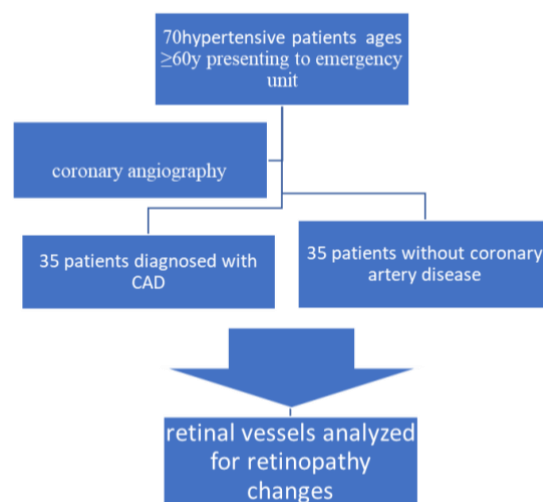


Figure 1: Study design and participant selection

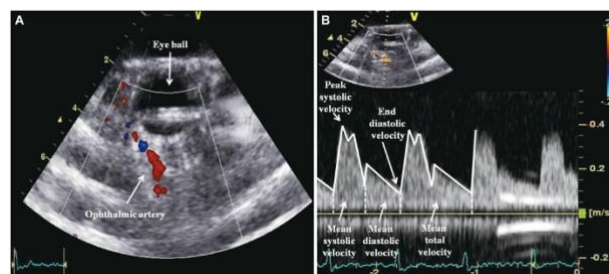


Figure 2: Ultrasonic measurements of ophthalmic artery

RESULTS

Clinical, laboratory, angiography, ultrasonography:

Table 1 shows the clinical and laboratory characteristics relevant to this study. Overall, the participant pool consisted of 42 (60%) men and 28 (40%) women, with a mean age of 64.3 ± 4.5 years. The prevalence of hypertension and diabetes was 50% and 30% for men and women, respectively. Notably, there were no differences in clinical and laboratory characteristics between the CAD group and the non-CAD group. The quantitative coronary angiographic characteristics, in addition to the GS, are shown in Table 2. A total of 10

patients (14.2%) presented with significant CAD (> 75% stenosis). Among them, one-vessel disease was found in 4 patients (40% of the CAD group) and two-vessel disease in 6 patients (60% of the CAD group). In this study, among the 70 patients with CAD, the sum of stenotic segments amounted to 80. Among these 80 segments, 35 (50%) showed significant CAD. The mean value concerning the GS was found to be 26.5.

Additionally, the ultrasonography characteristics of the participant pool are shown in Table 3. According to the echocardiographic characteristics, the left ventricular ejection fraction (LV EF) tended to decrease more in the CAD group than in the non-CAD group. Regarding the carotid ultrasound parameters, both c-IMT and the incidence of carotid plaque were significantly higher in the CAD group than in the non-CAD group. Regarding the Doppler flow of the OA, EDV and MDV were significantly lower in the CAD group than in the non-CAD group. Moreover, MSV/MDV, PI, and RI were significantly higher in the CAD group than in the non-CAD group. The correlations between parameters in the Doppler flow of the OA are shown in Table 4. Importantly, MSV/MDV showed a significantly positive correlation with RI and PI. However, MSV/MDV showed a significantly negative correlation with EDV and MDV.

Correlation between carotid intima-media thickness and clinical, laboratory, and ultrasonographic parameters:

The correlations between c-IMT and clinical, laboratory, and ultrasonographic parameters are shown in Table 5. Regarding the correlation between c-IMT and clinical parameters, c-IMT was significantly positively correlated with age, pulse rate, GS, and the presence of hypertension, diabetes, calcium channel blockers, significant CAD, and carotid plaque. However, c-IMT did not correlate significantly with laboratory parameters. Concerning the correlation between c-IMT and the echocardiographic parameters, as well as the correlation between c-IMT and the Doppler flow of the OA, c-IMT was found to be significantly negatively correlated with EDV and MDV; however, it was significantly positively correlated with MSV/MDV, PI, and RI. The clinical and ultrasonographic parameters that correlated with c-IMT were used in a multivariate logistic linear regression. Among several parameters, MSV/MDV, PI, and RI were identified as significant and independent factors of c-IMT (Table 5).

Correlation between Gensini score and clinical, laboratory, and ultrasonographic parameters:

The correlations between the GS and clinical, laboratory, and ultrasonographic parameters are shown in Table 6. It was found that the GS was significantly positively correlated with c-IMT and the presence of hypertension, diabetes, significant CAD, and carotid plaque. However, the GS was significantly negatively correlated with LV EF. Concerning the correlation between the GS and the Doppler flow of the OA, the former was significantly negatively correlated with EDV and MDV. However, it was significantly positively correlated with MSV/MDV, PI, and RI. The clinical and ultrasonographic parameters that correlated with the GS were used in a multivariate logistic linear regression. Among several parameters, MSV/MDV and the presence of significant CAD were identified as significant and independent factors with regard to the GS (Table 6).

Moreover, this study analyzed the retinal vessel changes and classified hypertensive retinopathy in all its participants. It found that 80% of them had retinopathy, and 54% of the control group had retinopathy changes. These changes significantly correlated with the risk of developing CAD ($p \leq 0.05$; Figure 3).

Further, JNC classification was used to grade the participants' stage of hypertension. This study observed that grade II was the commonest grade of hypertension found in the study and control groups (Figure 4).

Table1: Clinical and laboratory characteristics

Variable	All subjects (n = 70)
Age (years)	64.3 ± 4.5
Sex	
Male (n, %)	42(60)
Female (n, %)	28(40)
BMI (kg/m ²)	25.4 ± 2.8
Hypertension (n,%)	35(50)
Diabetes (n,%)	21(30)
Hyperlipidemia (n,%)	11(15.7)
Unstable angina (n,%)	25(35.7)
ACE, ARB (n,%)	20(28.5)
Beta-blockers (n,%)	23(32.8)
CCB (n,%)	28(40)
Statin (n,%)	9(12.8)
SBP (mmg)	124.5 ± 14.6
DBP (mmg)	75.5 ± 11.2
PR (bpm)	68.9 ± 11.6
Hg (gm/dl)	12.5 ± 2.5
e GFR (ml/min/1.73m ²)	65.4 ± 20.7
Total cholesterol (mg/dl)	172.6 ± 36.5
Triglyceride (mg/dl)	145.3 ± 64.5
HDL-C (mg/dl)	43.0 ± 13.5
LDL-C (mg/dl)	110.3 ± 35.7

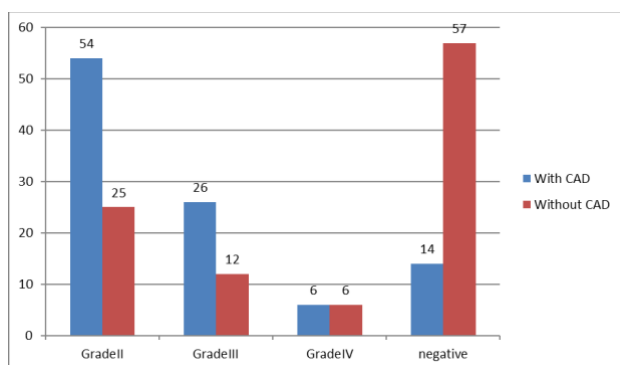


Figure 4: Classification of grades of retinopathy in case and control groups

DISCUSSION

The results of the current study showed that the average age of its participant patients with hypertensive retinopathy was 64.3 years, with a standard deviation of 4.5 years. This finding was consistent with previous research conducted by Hong et al. (2014),¹⁵ who reported an average age of 60.4 ± 9.9 years in the investigated group regarding the presentation of hypertensive retinopathy. Similarly, Balkrashnann et al. (2020) reported an average age of 67 years in the studied group regarding the same condition.¹⁶ This alignment in age-related findings across multiple studies suggests a common trend concerning this condition and provides additional support for the age distribution in the hypertensive retinopathy patient population.

Specifically, the results of Balkrashnann et al. (2020) indicated that both males and females are affected by hypertensive retinopathy; however, they found no significant difference between the sexes in terms of the severity of this condition.¹⁶ However, other studies have presented differing conclusions. Indeed, some investigations have suggested that a narrowing of the retinal arteries is associated with a higher risk of coronary artery disease in females than in males. Such a discrepancy in findings highlights the complexity of the relationship between retinal changes and cardiovascular risk; further research is needed for researchers to fully understand the gender-specific implications of these retinal alterations on coronary artery disease.

Both identification and understanding of the risk factors associated with coronary atherosclerosis are crucial for effective cardiovascular risk assessment and management. Hong et al. (2014),¹⁵ Sarnak et al. (2003),¹⁷ and Cheung et al. (2012)¹⁸ have highlighted well-established risk factors for coronary atherosclerosis,

such as advanced age, hypertension, diabetes, smoking, hyperlipidemia, and chronic kidney disease, among others. Despite the recognition of these factors, there remains an ongoing interest in exploring novel approaches and biomarkers that can further enhance risk stratification for the benefit of patients.

Among these potential markers/approaches, the examination of retinal vessels and the measurement of Doppler flow in the ophthalmic artery (OA) have emerged as promising methods to detect coronary atherosclerosis. In particular, several studies have considered retinal vasculature as a non-invasive and safe surrogate for assessing coronary circulation.^{19,20} While this avenue of research holds promise, the connection between OA Doppler flow and systemic atherosclerosis, encompassing carotid and coronary atherosclerosis, has received comparatively limited attention and urgently requires further investigation. Findings from related studies in this area are not fully conclusive.

As the field of cardiovascular research continues to advance, the exploration of these abovementioned innovative methodologies and possible additional indicators has the potential to refine risk assessment, thus allowing for more personalized and targeted preventive strategies for individuals at risk of coronary artery disease.

Significantly, the utilization of duplex flow measurements of the OA is demonstrably instrumental in gaining an understanding of various vascular disorders.²¹ These measurements contribute to a better comprehension of vascular diseases by providing insights into their hemodynamics. The technical reliability of OA Doppler imaging has been well established, particularly within the field of ophthalmology and among experienced observers.²² In this respect, the unique anatomical advantages of the OA, i.e., its depiction of peripheral arteries, absence of ultrasound-reflective structures like bones, and nearly vertical transducer angle, set it apart from the carotid artery and other vessels.²¹ Hence, hemodynamic imaging of the OA using duplex flow may reveal indications of peripheral vascular resistance and systemic atherosclerosis. Duplex imaging has previously indicated atherosclerotic changes in retinal arteries, supporting the idea that these alterations may serve as indicators of systemic cardiovascular diseases.²²

The association between OA duplex flow and coronary atherosclerosis can be explained by the fact that atherosclerotic changes in retinal arteries may signify

broader systemic cardiovascular issues.¹⁶ This connection helps scholars understand the relationship between the two abovementioned conditions. Furthermore, individuals with CAD exhibit significantly different MSV/MDV ratios compared to healthy individuals. For instance, Maruyoshi et al. (2020) suggested that elevated MSV/MDV levels in the OA duplex flow could potentially serve as a feasible screening tool for severe CAD (stenosis exceeding 75%).²³ This study's findings support such an argument, highlighting a correlation between high MSV/MDV levels and severe coronary atherosclerosis, which is indicative of CAD.

Regarding hypertension, this study identified that the participating individuals with grade II hypertension and a longer duration of diagnosis were at a higher risk of developing CAD. Conversely, those with a shorter duration of hypertension diagnosis had a lower risk of CAD. To categorize elderly hypertensive patients presenting with angina, this study used the classification system proposed by Keith-Wagner and Barker based on the arteriolar narrowing induced by hypertension and its associated changes.^{24, 25}

Additionally, this study found significant correlations between the hypertensive retinopathy of grade II hypertension and left ventricular hypertrophy as well as CAD in hypertensive elderly patients with angina. These findings are consistent with those of Balkrashnann et al. (2020) and Taqueti et al. (2018).^{16, 26}

Further, this study's application of advanced imaging techniques and its exploration of associations between various vascular parameters offer promising avenues for an improved understanding of cardiovascular diseases and the concomitant development of robust and holistic risk assessment strategies.^{27, 28}

CONCLUSIONS

This study highlights the potential value of using the Doppler flow of the OA as a tool for evaluating CAD and systemic atherosclerosis.

The following key conclusions are outlined:

1. Grade II hypertensive retinopathy and CAD: This study finds that grade II hypertensive retinopathy is strongly associated with the development of coronary artery disease.
2. Correlation between hypertensive retinopathy and CAD: This study emphasizes that both hypertensive retinopathy and coronary artery disease are linked to high blood pressure. This suggests a common underlying

mechanism that contributes to the development of both conditions.

3. Use of OA Doppler flow for evaluation: This study suggests that the Doppler flow of OA can be utilized as a robust approach for evaluating CAD and systemic atherosclerosis. This technique has the potential to serve as a screening tool for CAD, particularly in basic healthcare settings.

4. Retinal vascular changes as predictors: In this study, the retinal vascular changes induced by high blood pressure are highlighted as promising predictors of coronary artery disease.

The above conclusions effectively summarize the significance of this study's findings and offer insights into how they can impact clinical practice and future research in cardiovascular diseases.

Limitations:

This study's sample only consisted of 70 participants, with 35 individuals in each of the two participant groups (case and control). Owing to the limited sample size, this study could not determine the presence of any other risk factors for CAD. Moreover, it was a retrospective case-control study; future studies should conduct a prospective study to ascertain any correlation between the two variables used in this study.

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Table 7: List of abbreviations

Abbreviations	Full word
BMI	body mass index
ACEI	angiotensin-converting enzyme inhibitor
ARB	angiotensin receptor blocker
CCB	calcium channel blocker
SBP	systolic blood pressure
DBP	diastolic blood pressure
PR	pulse rate
eGFR	estimated glomerular filtration rate
HDL-C	high-density lipoprotein-cholesterol
LDL-C	low-density lipoprotein-cholesterol
hs-CRP:	high-sensitivity C-reactive protein
CAD	coronary artery disease
LM	left anterior descending coronary artery
LCX	left circumflex coronary artery
RCA	right coronary artery
OM	obtuse marginal coronary artery
LV	left ventricle
EF	ejection fraction
c-IMT	carotid intima-media thickness
PSV	peak systolic velocity
MSV	mean systolic velocity
EDV	end-diastolic volume
MDV	mean diastolic velocity
MTV	mean total velocity
PI	pulsatility index
RI	resistive index
CCB	calcium channel blocker