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# Assessment of Carotid Plaque Enhancement on Contrast-Enhanced Ultrasound as a Predictor for Severe Coronary Artery Disease

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## Abstract

**Background and Aim** Contrast-enhanced ultrasound (CEUS) can reliably identify vulnerable plaques. As atherosclerosis is a systemic disease, we evaluated whether contrast enhancement of carotid plaque (CECP) can predict severe coronary artery disease (CAD) by comparing CECP in patients who have had acute coronary syndromes (ACS) recently with asymptomatic individuals.

**Settings and Design** This case–control study was done at a tertiary care center during 2022.

**Materials and Methods** Fourteen participants were recruited in each group, after screening in-patients for carotid plaques and inclusion and exclusion criteria. Those who had history of ACS were enrolled as cases, while those who did not were enrolled as controls. All these patients underwent grayscale, Doppler, and CEUS examination for characterization of the carotid plaque. For cases, findings on CEUS were also compared with the severity of CAD on catheter coronary angiography.

**Statistical Analysis** Diagnostic parameters including sensitivity, specificity, and diagnostic accuracy were calculated and proportions were compared by using Fisher's exact test.

**Results** Eight out of 28 patients showed CECP. CECP and CAD were positively associated with $p$-Value of 0.033. Eighty-three percent patients with triple vessel disease and 50% patients with double vessel disease on coronary angiography showed CECP. Sensitivity and specificity of CECP for prediction of CAD were 50 and 92.9%, respectively.

**Conclusion** CECP on CEUS can predict CAD and is a more reliable indicator of severe CAD than plaque characteristics on grayscale and Doppler imaging; making it useful for screening of patients at risk of having CAD.

**Keywords**
- coronary artery disease
- contrast-enhanced ultrasound
- intraplaque neovascularization
- contrast enhancement of carotid plaque

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## Introduction

Coronary artery disease (CAD) is a leading cause of morbidity and mortality due to noncommunicable disease, contributing to 17.8% of total deaths and 8.7% of total disability-adjusted life years in India in 2016.[1] According to the National Family Health Survey 5 data, among a total of 14,571 individuals aged 15 to 49 living in Uttarakhand, 12.7% reported having cardiovascular disease. This is alarming as it indicates CAD is affecting the younger population as well.[2] Most cases of CAD are diagnosed after onset of symptoms, which may be acute or chronic. Early diagnosis in the latent period of disease is desirable to prevent complications. This can be achieved by timely identification and management of the people who have multiple risk factors for the disease, in this case including family history, dyslipidemia, hypertension, diabetes mellitus, cigarette smoking, and physical inactivity.[3,4] In India, 40% of the adults aged 18 to 69 years had three or more risk factors for development of cardiovascular disease and in the population aged 40 to 69 years the 10-year cardiovascular disease risk was $>$ 30% for 12.8% of individuals. The data highlights the need for early recognition of patients at risk for timely management and to decrease the morbidity and mortality in this population related to CAD.[5]

Carotid intima media thickness is being utilized as predictor for significant atherosclerotic disease involving the carotid as well as coronary vasculature.[6] Further research has revealed that it is not the plaque thickness, and rather the plaque characteristics that determine whether the plaque is "vulnerable," that is, it has a higher propensity to cause acute coronary syndromes (ACS).[7,8]

Contrast-enhanced ultrasound (CEUS) of carotid plaques has proven to be a reliable technique for plaque characterization and correlates well with the findings on histopathological examination.[9–11] The second generation ultrasound contrast agents are composed of microbubbles with phospholipid monolayer covering. As the contrast used in CEUS is a purely intravascular contrast agent, it can detect intraplaque neovascularization (IPN) that is seen in the vulnerable plaques. Other features such as thin fibrous cap and lipid-rich necrotic core (LRNC), plaque thickness, and surface morphology can also be assessed.[12,13] Furthermore, this procedure is easily repeatable as there is no associated risk of radiation exposure or contrast-induced nephropathy.[14]

Previous studies conducted on this matter have compared contrast enhancement of carotid plaque (CECP) in patients having CAD to gauge its association with disease severity as well as whether it can accurately predict risk of future ACS in these patients.[15,16] In this study, we have compared symptomatic with asymptomatic individuals to evaluate whether CECP can predict disease status as well. Also, no similar research has been conducted on the Indian population

## Materials and Methods

### Study Population

The study was conducted in a referral center and academic institution in North India, located in a suburban area during 2021 to 2022 as a pilot study. This case–control study enrolled 28 consecutive patients, 14 cases and 14 controls, who were admitted to the cardiology ward. The sample size was calculated for a two-sample proportions test with study parameters: delta = –0.5080 (difference), p1 = 0.8050, p2 = 0.2970.[16] Power was set at 80%, confidence interval 95%, and $\alpha$ 0.05.

The inclusion criteria were: (1) adult patients, (2) carotid plaque of thickness more than 1.5 mm, and (3) patients who gave consent for the procedure. The exclusion criteria were: (1) ischemia due to nonatherosclerotic disease, (2) extensive plaque calcification, (3) patients who have undergone carotid endarterectomy, (4) history of allergic reaction to sulfa drugs (due to sulfur hexafluoride microbubbles), (5) patients having underlying lung pathology, for example, obstructive airway disease or interstitial lung disease, and (6) any contraindications to the use of contrast agent. Patients who had right to left shunt, severe pulmonary hypertension, acute respiratory distress syndrome, who were receiving dobutamine or were suffering from conditions where dobutamine is contraindicated, and pregnant and lactating women were excluded from the study due to higher incidence of adverse events reported in this population and are relative contraindications for the use of the drug.

Adverse events reported after intravascular use of contrast agent for ultrasound include allergic reactions, vomiting, dizziness, headache, local injection site reactions, and other more severe complications like anaphylactic shock and chest distress as well, seen in patients with preexisting cardiac disease, especially conditions where dobutamine is contraindicated. Incidence of adverse reaction following contrast administration has been reported to be 0.12% and most of these are mild reactions.[17]

All the patients were briefed about the study, a participant information sheet was made available to all patients and written and informed consent was obtained from all patients before enrollment. All procedures performed were in accordance with the ethical standards of the institutional ethics committee and with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from all individual participants included in the study. None of the figures submitted reveal the identity of the participants.

### Imaging Protocol

The patients were evaluated on ESAOTE MYLAB9XP machine with a high-frequency linear probe (L4–15). Patients were made to lie supine with shoulder roll for neck extension and head rotated to the contralateral side for approximately 45 degrees to aid in the visualization of the carotid arteries.

Bilateral common carotid artery (CCA), internal carotid artery (ICA), and external carotid artery (ECA) were evaluated sequentially. The vessels were imaged to the maximum extent possible in cranial and caudal aspects.

- Grayscale imaging for the carotid plaque was done for determining the number of plaques, their location, size, morphology, and modified Gray–Weale classification.[18]

- Doppler imaging was also performed and the following parameters were recorded: peak systolic velocity (PSV) of ICA and CCA, and carotid index was calculated using these values as PSV ICA/PSV CCA.[16]
- Contrast Sonovue was prepared by mixing 25 mg of lyophilized powder in 5 mL of normal saline.
- Contrast was injected at a dose of 0.8 to 1 mL intravenously by one person and at the same time, ultrasound was performed by the radiologist. In the case of multiple plaques, the largest hypoechoic plaque was evaluated while injecting the contrast.
- Patients were observed postprocedure for at least 30 minutes for adverse reactions.

Patients were subjected to history taking and examination. Results of relevant investigations were noted. For patients enrolled in the case group, the findings from the index catheter coronary angiography were retrospectively extracted from the patients' medical records and were used for assessment of the severity of CAD.

### Image Interpretation

#### Grayscale Ultrasound and Doppler Imaging

The size of the carotid plaque (length and maximum thickness), echogenicity, surface morphology, and degree of stenosis were assessed by the radiologist at the time of scanning, and later by a second radiologist as well. The radiologists were blinded to the patient details. For plaque echogenicity, the plaques were classified according to the Gray–Weale classification.[18] The surface of the plaque was categorized as regular and irregular based on their appearance on grayscale images. The degree of stenosis was assessed by calculating the percentage of residual luminal area of the artery under evaluation (ICA, ECA, or CCA). Further, these were evaluated for the presence of any hemodynamic obstruction based on the carotid index.[19]

#### Contrast-Enhanced Ultrasound

Contrast enhancement of the largest plaque was assessed on CEUS for all the patients. The findings were categorized into no enhancement, patchy or peripheral enhancement, and diffuse enhancement. The time of uptake and washout of contrast were also recorded.

Small doses of the reconstituted contrast were found adequate for plaque evaluation. This may decrease the risk of adverse events and it brings down the cost of the investigation. Hence, CEUS may be more feasible than other modality like computed tomography (CT) angiography as a screening tool considering the cost as well as patient safety.

#### Catheter Coronary Angiography

Catheter coronary angiography images of all the 14 cases with history of ACS were extracted and analyzed. The involvement of left main coronary artery (LMCA), left anterior descending artery, left circumflex coronary artery, and right coronary artery was assessed. More than 50% luminal stenosis of a main coronary artery (for a segment > 2.5 mm) was considered as significant involvement.[20] Single vessel disease was defined as significant stenosis of one of the major arteries, and double and triple vessel disease as involvement of two and three vessels, respectively. None of the patients in our study had significant involvement of LMCA.

### Statistical Analysis

Categorical variables were described as frequency and proportion. Continuous variables were described as mean ± standard deviation or median with interquartile range as applicable. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated for CECP and Gray–Weale score. We compared proportions by using chi-square test and Fisher's exact test as and when required. The means in two groups were compared using the Mann–Whitney *U* test.

## Results

### Demographic Details and Risk Factors

The demographic details and clinical characteristics of the patients in the case and control groups are shown in ►**Table 1**. The contrast agent was well tolerated and no adverse effects were reported. The only notable differences between the groups were the mean age and mean high-

**Table 1** Demographic details and frequency distribution/mean value of risk factors including BMI, hypertension, diabetes mellitus, and history of smoking of patients in the case and control groups

| Demographic details and risk factors | Group | |
|---|---|---|
| | Case ($n = 14$) | Control ($n = 14$) |
| Age (y)[a] | 55.00 ± 8.43 | 62.71 ± 10.05 |
| Gender | | |
| Male | 11 (78.6%) | 10 (71.4%) |
| Female | 3 (21.4%) | 4 (28.6%) |
| BMI (kg/m$^2$)[a] | 24.15 ± 3.37 | 22.99 ± 2.55 |
| Hypertension | | |
| Absent | 7 (50.0%) | 3 (21.4%) |
| Controlled | 4 (28.6%) | 8 (57.1%) |
| Uncontrolled | 3 (21.4%) | 3 (21.4%) |
| Diabetes mellitus | | |
| Absent | 10 (71.4%) | 9 (64.3%) |
| Controlled | 0 (0.0%) | 1 (7.1%) |
| Uncontrolled | 4 (28.6%) | 4 (28.6%) |
| HbA1c (%)[a] | 6.54 ± 1.70 | 6.26 ± 1.18 |
| Smoking | | |
| Never | 5 (35.7%) | 5 (35.7%) |
| Occasional | 2 (14.3%) | 1 (7.1%) |
| Reformed | 1 (7.1%) | 2 (14.3%) |
| Chronic | 6 (42.9%) | 6 (42.9%) |

Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1c.
[a]Signifies different test was used to compare the means of these variables (Kruskal-Wallis test was used).

density lipoprotein value. The control group participants were older than the case group which can be explained by the variations observed in plaque histology with age. Redgrave et al found that plaque burden increases and plaque morphology also changes with age with the carotid endarterectomy specimens from the older patients showing a larger LRNC.[21]

### Imaging Findings

The most common location of plaques was in the carotid bulb followed by distal CCA. Few of the plaques in the carotid bulb (6 out of 25) showed extension into the ICA. Of these, three showed evidence of moderate hemodynamic obstruction of ICA on Doppler examination with carotid index > 2. Findings on grayscale as well as Doppler imaging have been summarized in ►**Table 2**.

Of the 28 plaques examined, < 5 plaques had irregular surface/hemodynamically significant luminal stenosis/ concentric shape. No notable difference was found between the case and control groups based on these characteristics.

**Table 2** Frequency distribution of different characteristics of carotid plaques, including the size, shape, surface morphology, degree of stenosis caused by the plaque, Gray–Weale scale score, and presence or absence of contrast enhancement of carotid plaque, observed in the case and the control groups

| Parameters | Group | |
|---|---|---|
| | Case ($n = 14$) | Control ($n = 14$) |
| Length of plaque (mm) | 13.71 ± 5.24 | 11.96 ± 5.32 |
| Thickness of plaque (mm) | 2.60 ± 0.97 | 2.29 ± 0.60 |
| Shape | | |
| Concentric | 3 (21.4%) | 2 (14.3%) |
| Eccentric | 11 (78.6%) | 12 (85.7%) |
| Stenosis | | |
| < 25% | 5 (35.7) | 8 (57.1) |
| 25–50% | 4 (28.6) | 5 (35.7) |
| 50–75% | 4 (28.6) | 1 (7.1) |
| 75–90% | 1 (7.1) | 0 (0.0) |
| Obstruction (present) | 2 (14.3%) | 1 (7.1%) |
| Carotid Index | 0.95 ± 0.53 | 1.06 ± 0.46 |
| Surface | | |
| Regular | 9 (64.3%) | 13 (92.9%) |
| Irregular | 5 (35.7%) | 1 (7.1%) |
| Gray–Weale scale | | |
| Score1/ 2 | 5 (35.7%) | 1 (7.1%) |
| Score 3 | 8 (57.1%) | 8 (57.1%) |
| Score 4 | 1 (7.1%) | 5 (35.7%) |
| Enhancement (present)[a] | 7 (50.0%) | 1 (7.1%) |

[a]Difference in proportions was significant with chi-square = 6.300, $p$-Value = 0.033

On evaluating the plaques for Gray–Weale score, majority of the plaques (57%, 16 of 28) were predominantly echogenic, corresponding to a score of 3. In case of multiple plaques, the score of the largest plaque was considered for analysis. ►**Fig. 1** shows grayscale images of carotid plaques with different Gray–Weale scores. Gray–Weale scores of 1 or 2 had a combined sensitivity and specificity of 35.7 and 92.9% for CAD, with diagnostic accuracy of approximately 64%.

On CEUS examination of the same, 8 out of the 28 plaques showed contrast enhancement. More patients from the case group showed CECP (7 out of 14), as compared with the control group (1 out of 14). This difference in proportions was significant with chi-square = 6.300, $p = 0.033$, and presence of CECP was associated with history of ACS. Most of the cases positive for CECP showed minimal enhancement at the margins (5 out of 8). Rest three plaques showed diffuse plaque enhancement. Enhancement in the plaques was seen approximately 45 seconds after administration of contrast in majority of cases. In one case, there was early enhancement seen at approximately 25 seconds from contrast injection, and this plaque showed peripheral enhancement. The sensitivity, specificity, and diagnostic accuracy of CECP for predicting CAD were 50, 92.9, and 71%, respectively.

►**Figs. 2** and **3** show composite grayscale and CEUS images from patients who had CECP.

### Association between Carotid Plaque Characteristics and Severity of Coronary Artery Disease

The frequency of triple vessel CAD was higher in the cases that showed CECP (83% cases of triple vessel disease patients were positive for CECP), and only one case of triple vessel disease did not show plaque enhancement. None of the cases of single vessel disease showed CECP. The sensitivity of CECP for predicting CAD was higher for patients having multivessel disease. The frequency distribution of different imaging features according to the severity of CAD has been tabulated in ►**Table 3**.

Composite grayscale and CEUS images along with the images acquired during coronary angiography for one of the patients have been presented in ►**Fig. 4**.

On comparing the characteristics of the plaques on grayscale ultrasonography with CEUS, hypoechoic plaques (Gray–Weale score ½), and plaques with irregular surface were more likely to show postcontrast enhancement (Fisher's exact test $p$-value 0.048 and 0.038, respectively). The irregular plaque surface represents plaque ulceration, and ulceration is more common in plaques that have a large LRNC or intraplaque hemorrhage (IPH) which is representative of vulnerable plaque morphology.[22]

## Discussion

### Comparison of Diagnostic Performance of Gray–Weale Score and CECP for Predicting CAD

The diagnostic parameters were marginally better for CECP than for Gray–Weale score. The odds ratio of patients with a carotid plaque showing contrast enhancement on ultrasound having CAD was 13 (95% confidence interval 1.32–128.11).

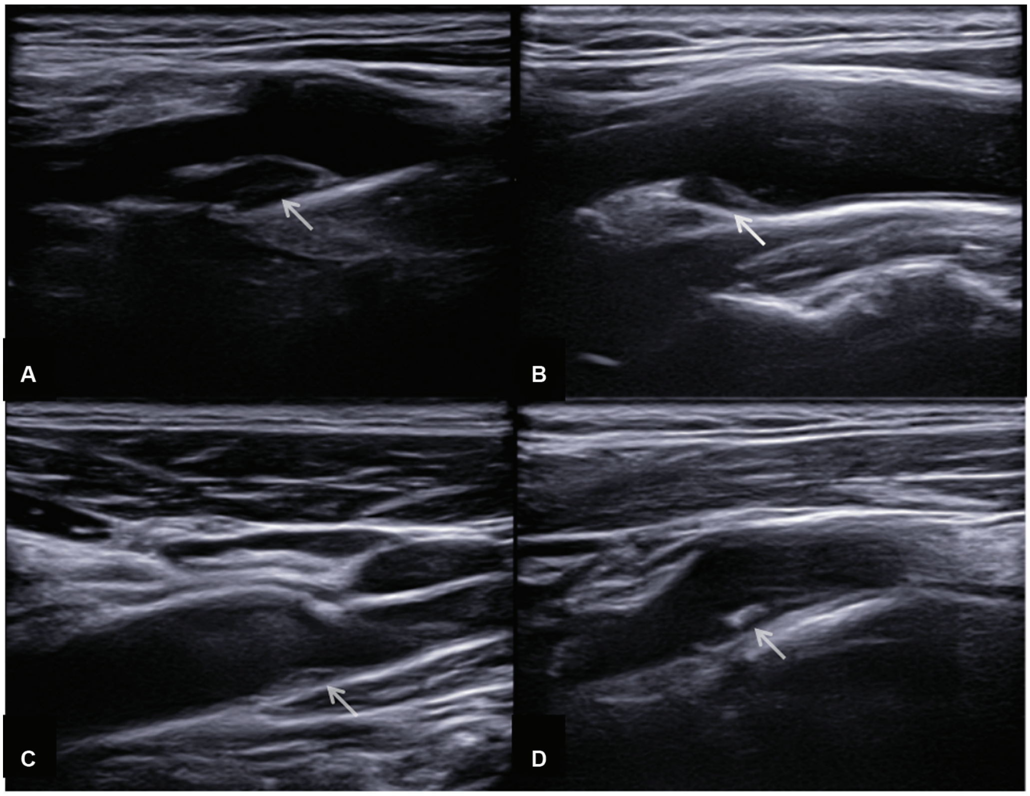
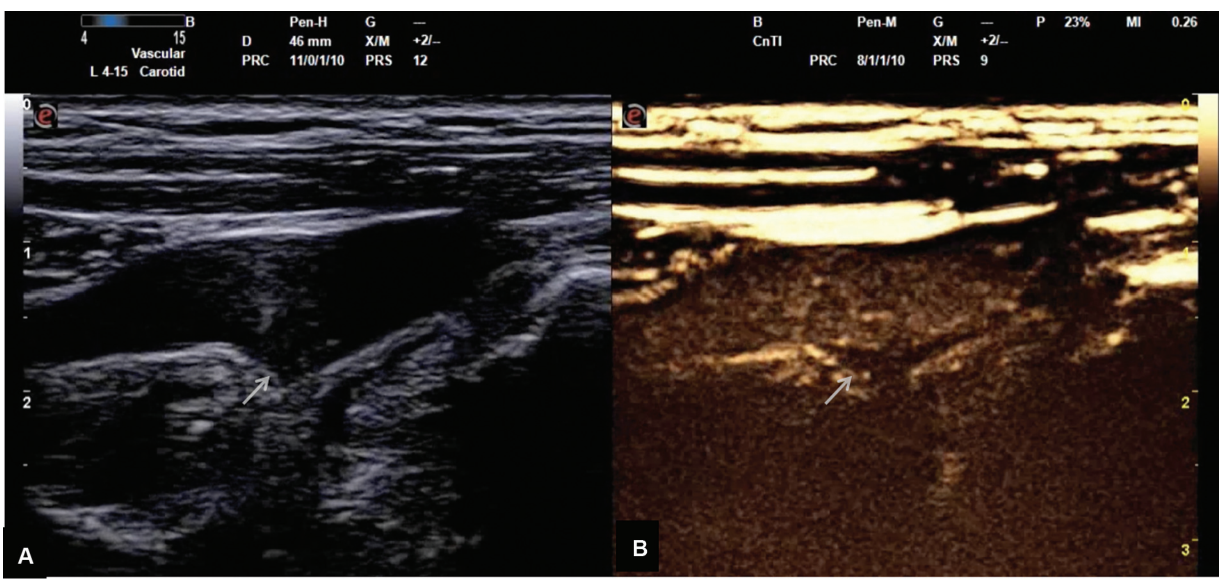



**Fig. 1** Representative images of carotid plaques with different Gray–Weale scores. The arrows indicate the plaque under study. (**A**) Homogeneously (> 85%) hypoechoic plaque. (**B**) Predominantly hypoechoic plaque (> 50% area). (**C**) Predominantly hyperechoic plaque. (**D**) Homogeneously hyperechoic plaque.




**Fig, 2** (**A**) Grayscale examination image of a patient in the case group depicting concentric plaque (indicated by arrow) located in the carotid bulb. (**B**) Contrast-enhanced ultrasound (CEUS) image shows enhancement in the periphery of the plaque as marked by the arrow.

The low sensitivity is explained by presence of variation in the plaque morphology in different vascular beds (carotid and coronary) in the same patient.[23]

On correlating the Gray–Weale score with the findings on CEUS, four out of the seven cases who were positive for CECP had a score of 1 or 2 (predominantly hypoechoic plaques) and three were predominantly hyperechoic plaques which had some hypoechoic areas. The only patient in the control group who had CECP also had a predominantly hyperechoic plaque on grayscale imaging.

The percentage of plaques with score 2 showing CECP was 66% (4 out of 6) and for score 3 it was 25% (4 out of 16). On

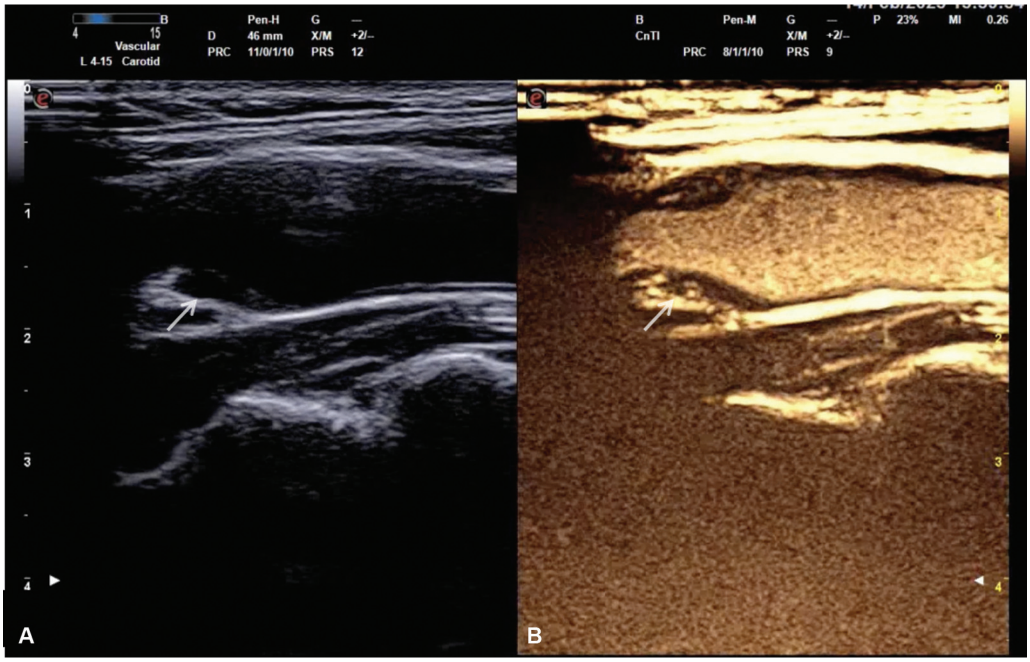



**Fig. 3** (**A**) Grayscale examination image of a patient in the case group showing mixed, predominantly hypoechoic plaque (indicated by arrow) and the hypoechoic portion of the plaque shows diffuse postcontrast enhancement as seen in (**B**).

**Table 3** Lists the frequency distribution of the imaging findings among the cases divided according to the severity of disease (number of major coronary vessels involved)

| Parameters | Vessels involved | | | *p*-Value |
|---|---|---|---|---|
| | SVD ($n = 4$) | DVD ($n = 4$) | TVD ($n = 6$) | |
| Stenosis | | | | |
| < 50% | 4 (75.0) | 3 (75.0) | 3 (50.0) | 0.65[a] |
| > 50% | 1 (25.0) | 1 (25.0) | 3 (50.0) | |
| Surface | | | | |
| Regular | 3 (75.0%) | 2 (50.0%) | 4 (66.7%) | > 0.99[a] |
| Irregular | 1 (25.0%) | 2 (50.0%) | 2 (33.3%) | |
| GW scale | | | | |
| Score 1/2 | 1 (25.0%) | 1 (25.0%) | 3 (50.0%) | 0.660[a] |
| Score 3/4 | 3 (75.0%) | 3 (75.0%) | 3 (50.0%) | |
| Obstruction (present) | 0 (0.0%) | 1 (25.0%) | 1 (16.7%) | > 0.99[a] |
| Enhancement (present) | 0 (0.0%) | 2 (50.0%) | 5 (83.3%) | 0.058[a] |

Abbreviations: DVD, double vessel disease; SVD, small vessel disease; TVD, triple vessel disease.
Note: Different statistical tests were applied for each of these and resultant *p*-Values are given in the last column.
[a]Fisher's exact test.

scrutinizing these plaques further, it was observed that only the hypoechoic portion of the heterogeneous plaques (score 3) showed enhancement. This heterogeneity of the plaques probably explains why CECP had slightly better sensitivity than Gray–Weale score for predicting presence of CAD. The hypoechoic portion of the plaques has been shown to correlate with lipid-rich areas within the plaque on histopathological examination which correlates with plaque vulnerability.[24,25]

## Association of Carotid Plaque Enhancement with Severity of CAD

More patients (70%) with multivessel disease had CECP. All patients with single vessel disease (four in number) did not show CECP. This result suggests that carotid plaque enhancement may indicate more extensive involvement of coronary arteries. One previous study has evaluated the same and suggested that a higher sum average of grade of enhancement of all the carotid plaques combined was associated with greater complexity of

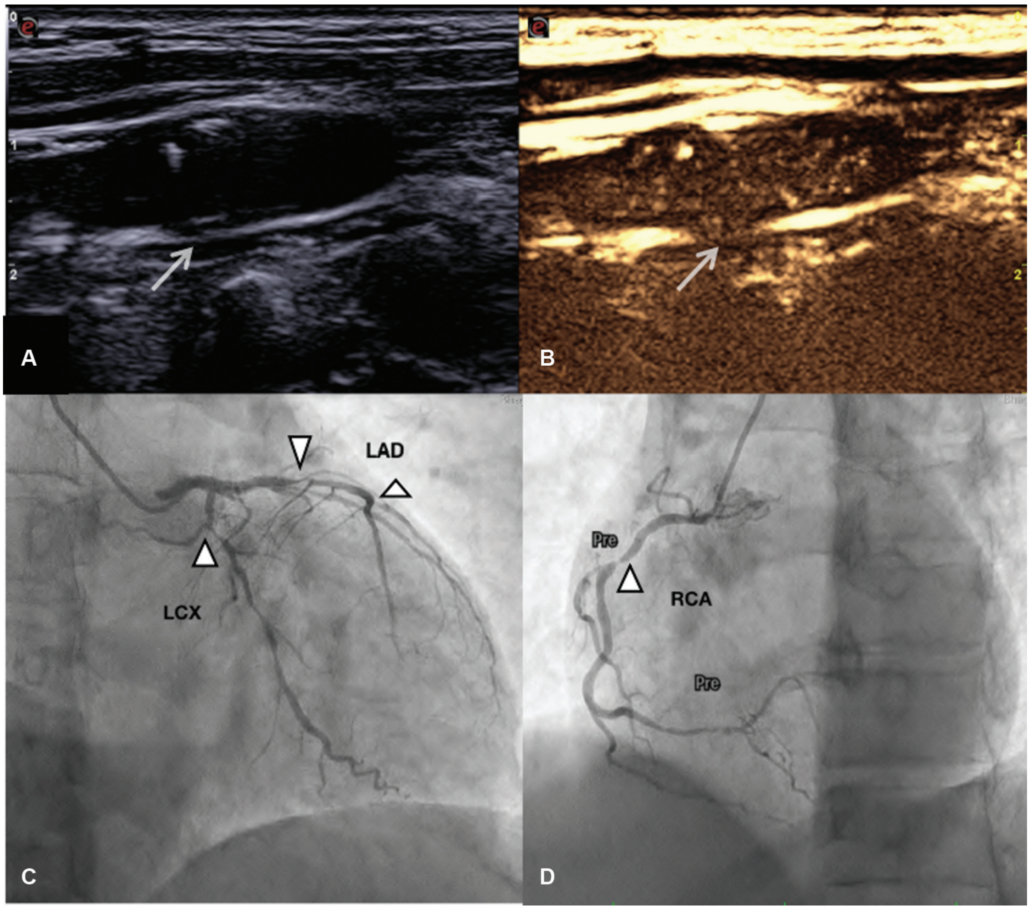



**Fig. 4** Grayscale (**A**) and contrast-enhanced ultrasound (CEUS) images (**B**) from another patient in the case group. (**A**) Nonobstructive predominantly hypoechoic carotid plaque having few foci of calcification. (**B**) Homogeneous contrast enhancement. Coronary angiography (**C** and **D**) revealed multifocal severe stenosis (marked by arrowheads) involving left anterior descending artery (LAD), left circumflex coronary artery (LCX), as well as right coronary artery (RCA).

coronary lesions.[26] Other studies have also concluded that enhancement of carotid plaque on CEUS was associated with increased risk of future adverse coronary events[27–29]; however, all these studies recruited all patients who were already diagnosed with CAD. A prospective study conducted on 50 asymptomatic patients with carotid artery stenosis who were kept under follow-up concluded that a higher grade of carotid plaque enhancement could predict future adverse events.[30]

### Association of Carotid Plaque Enhancement with Gray–Weale Score

Our study also explored the association between enhancement characteristics and the Gray–Weale score of the carotid plaques. We found that plaques with scores of 1 or 2 were more likely to show CECP than plaques with scores 3 or 4. This association was significant with a $p$-value of $< 0.05$. This result was concordant with another study which suggested that more hypoechoic plaques showed a higher grade of IPN as evidenced by CECP, when compared with more echogenic plaques.[31]

## Study Limitations and Future Directives

This study was time bound and long-term follow-up of patients was not obtained, due to which eventual outcome of the asymptomatic patients who had carotid plaques with features suggesting plaque vulnerability could not be determined. The sample size was limited which reduced the power of the study for comparison of subgroups. This can be attributed to multiple factors—only the patients who underwent coronary angiography were included as cases, limited patient inflow due to coronavirus disease 2019, and the stringent exclusion criteria employed to prevent adverse events in the population suffering from CAD and associated cardiac diseases. The lack of preexisting data regarding the safety of the contrast agent in our population was a cause of concern.

For each patient only the largest plaque was evaluated as only one plaque could be focused at the time of injection. Focusing instead on the hypoechoic plaques might improve the sensitivity of the examination. Examining the plaques individually would require an increase in the dose of the contrast to be administered, which raises cost and also makes it more time consuming. Future research should focus on whether this results in a rise in sensitivity or diagnostic accuracy with an acceptable cost–benefit ratio.

The patients with stable CAD were not included in the study. Evaluation of the patients with stable CAD can help in determining the association between CECP and severity of CAD.

The results from this study indicate that CECP can indicate presence of severe CAD. However, patients in the control group, although asymptomatic, could still have had CAD. Further research with a larger study population and concurrent imaging of the carotid plaques with CEUS and of coronary vasculature (preferably by noninvasive methods such as CT coronary angiography) for symptomatic as well as asymptomatic patients can be done to determine the role of CEUS in screening of asymptomatic patients for severe CAD.

## Conclusion

B-mode ultrasonography has been utilized for the detection of plaques in carotid arteries. With further advancements in technology such as Doppler imaging and CEUS, it has become possible to characterize these plaques in terms of their shape, size, surface morphology, and presence of IPN and IPH. These characteristics, specifically IPN as detected on CEUS, are more common in patients having recent history of ACS. This study also shows that diffuse CECP can predict multivessel CAD with high specificity. It is better than all the grayscale plaque characteristics at predicting symptomatic disease.

### Availability of Data

The underlying research data of this article is not publicly available for patient privacy. The data are available from the corresponding author on reasonable request.

### Ethical Approval

All the patients were explained the study and gave written and informed consent before enrollment. All procedures performed were in accordance with the ethical standards of the Institutional Ethics Committee and with the 1964 Helsinki Declaration and its later amendments. None of the figures submitted reveal the identity of the participants.

### Funding

None.

### Conflict of Interest

None declared.

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