Onsite Computed Tomography Fractional Flow Reserve in Patients with Suspected Stable Coronary Artery Disease Initial Experience

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Abstract

Introduction Computed tomographic coronary angiographic (CTCA) has evolved into a robust technique to detect significant stenosis; however, there is a discordance in the anatomic and functional significance of stenosis. Therefore, patients with stable coronary artery disease need to be further evaluated before deciding for any revascularization procedure.

Material and Methods A total of 100 consecutive patients of suspected stable coronary artery disease who underwent CTCA were evaluated for functional significance of lesions using onsite computed tomography fractional flow reserve (CTFFR) and the results were compared for detection of both significant and hemodynamically significant/severe stenosis on per vessel and per patient basis and differences were statistically analyzed. Impact of these differences were analyzed for the final outcome and management plan.

Results CTCA detected 33 patients with severe stenosis, while 54 patients had hemodynamically significant stenosis on CTFFR. The sensitivity and specificity of CTCA for the detection of significant coronary artery stenosis per vessel basis were 97.7 and 93.3%, respectively, with a negative predictive value of 98.0%. For severe coronary artery stenosis, sensitivity, specificity, and negative and positive predictive values were 51.6, 89, 68.8, and 80%, respectively, on per vessel basis with CTCA. On per patient basis, CTCA showed as sensitivity and specificity of 61 and 84%, respectively, with area under curve (AUC) being 0.92 and 0.67 for significant and severe stenosis, respectively.

Discussion Onsite CTFFR is a useful tool to calculate functionally significant stenosis and also improves the sensitivity and specificity of CTCA. CTFFR detected 12% more stenotic vessels in the present study on per vessel basis and 21% on per patient basis.

Keywords
► computed tomographic coronary angiography
► coronary artery disease
► CTFFR

Introduction

Advances in the technology of computed tomographic coronary angiography (CTCA) have led to high sensitivity for identification of the disease. Zhang et al[1] showed sensitivity and specificity on per-patient basis of 93.9 and 93.5%, respectively, for significant stenosis for CTCA. The National Institute for Health and Care Excellence (NICE) 2016 guidelines

also recommend CTCA as the first line of investigation for evaluation of patients with typical or atypical angina who are stable and have electrocardiography (EKG) changes of ischemia.[2] Recently concluded PROMISE and SCOT trials[3,4] have also concluded that use of CTCA is better noninvasive diagnostic tool than other noninvasive testing modalities in such patients and helps to reduce future major cardiac events. However, CTCA has also been shown to have a low positive predictive value.[5] Therefore, it is recommended that patients having anatomically significant coronary artery disease with stenosis >50% on CTCA should undergo another test for demonstrable ischemia before revascularization is considered. Invasive FFR was introduced by Pijls et al in 1996[6] for the above purpose to determine the hemodynamic significance of stenosis and FAME trial[7] has proven its value in the detection of clinical significance of lesions which need to be revascularized. Despite the evidence, less than 10% cardiac laboratories do this procedure. The flip side being that it is invasive and adds significant cost and procedure time.[8] Noninvasive FFR using CTCA has evolved since 2019 and uses CTCA images to compute pressure based on the model of fluid dynamics and now with the use of machine learning algorithms, it is possible to get onsite computed tomography fractional flow reserve (CTFFR).[9,10] This study was, therefore, designed to evaluate the role of onsite CTFFR in patients with suspected stable coronary artery disease who underwent CTCA examination in Indian population and clinical cardiology practice.

Materials and Methods

After approval from local ethical review committee, 100 consecutive patients of clinically suspected stable coronary artery disease were enrolled since January 2019 to December 2019. Informed consent was obtained from all the patients. The demographic parameters of all patients, that is, age, sex, body mass index (BMI) along with history of disease, coexisting morbidities like hypertension, diabetes, and hyperlipidemias were recorded. All patients with history of allergy to iodine, arrhythmias, heart rate of more than 100 beats/min, BMI more than 31 kg/m^{2}, increased creatinine levels >1.2 mg/mL, or any prior bypass grafting/angioplasty were excluded from the study. Calcium scoring was not done purposely so that calcified vessels may also be evaluated by CTFFR. CT examination was done on a dual-energy CT 128 scanner (Siemens Go-Top, Forchheim, Germany). Oral 50-mg metoprolol 1 hour before the examination was given followed by sublingual nitroglycerin 0.5 mg to all patients except who had any history of hypotension. A retrospectively gated ECG triggered spiral (pitch 0.3) acquisition was done with collimation of 0.31mm and gantry rotation time of 0.31 ms at a tube voltage of 70 KV along with automated tube current modulation using CARE Dose 4D, Siemens healthineers. The quality reference voltage and current was set to 120 kV, 320 mAs. R-R interval was fixed at 35 to 75%. Noniodinated contrast iomeprol 400 (Iomeron Bracco UK Ltd.) of 35 mL was injected using bolus tracking software with dual head injector (MEDRAD, Stellant, Bayers, Munich, Germany) with flow rate of 4 mL/s followed by

20 mL saline. Image reconstruction was done using iterative reconstruction (SAFIRE, Siemens healthineers level 3) with reconstruction kernel of BV36. All images were transferred to Siemens Syngo. via workstation for post processing in multi planar and volume rendering projections and read by second author (G.M.) who was blinded to the results of CTFFR done onsite on Siemens Syngovia Frontier workstation using CTFFR (version 2.0) software and the results read by first author (A.K.). CTFFR was displayed in the form of color maps of coronary tree with blue being normal and red being ischemic (►Fig. 1). Quantitative analysis was done by marking the analysis site at any point along the vessel. The degree of stenosis was recorded based on per vessel and per patient basis. Vessels with stenosis more than 50% were labeled as significant and more than 70% as severe stenosis. On CTFFR, vessels showing FFR below 0.8 distal to the stenotic site were taken as hemodynamically significant. The results of the impact of CTCA and CTFFR findings on the management plan were obtained from the clinicians in the form of questionnaire, that is, (1) any change in optimal medical management after CTCA and CTFFR and (2) change to intervention plan—elective angioplasty or surgery.

Statistical Analysis

Statistical analysis was done using Analyze-IT software (Leeds, United Kingdom). Distribution and confidence intervals of all continuous variables were done along with Shapiro–Wilk W-test of normality of distribution. Sensitivity and specificity of both CTCA and CTCA with CTFFR were calculated for per vessel and per patient basis along with area under the curve (AUC) analysis. p-Value was fixed at <0.05 as statistically significant with post hoc power of the test at 0.88.

The primary objectives of the study were to determine (1) if on site CTFFR can be computed on images acquired using CTCA, (2) If CTFFR does identify hemodynamically significant stenosis (<0.8), and (3) correlation of anatomic site with
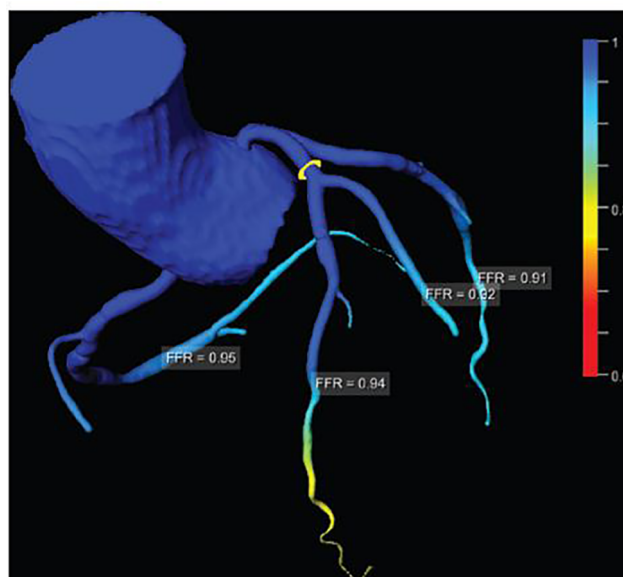

Fig. 1 CTFFR coronary map showing normal FFR in the coronary vasculature. CTFFR, computed tomography fractional flow reserve.

functionally significant stenosis. Secondary objective was to find the impact of CTFFR on the management of patients with stable coronary artery disease.

Results

Demographics of the patients in the study are listed in ►**Table 1**. Mean age of patients was 57 years. There were 74 males and 26 females. Mean heart rate was 72 beats/min. Significant stenosis was observed in 33 patients on per patient basis on CTCA with 125 vessels showing stenosis more than 50% while severe stenosis was seen in all 33 patients on per patient basis and in 72 vessels on per vessel basis. Distribution of stenotic lesions per vessels seen on CTCA were: left anterior descending 66 vessels of which 31 were severely stenotic and 22 had intermediate stenosis, right coronary artery showed stenosis in 48 vessels of which 19 were severely stenotic and 17 had intermediate stenosis, and 23 left circumflex arteries had significant stenosis with 9 being severely stenotic. Left main coronary artery showed 13 vessels with stenosis more than 50% all of which were detected by CTFFR (►**Fig. 2**). Out of these, eight vessels showed calcified plaques, while five were noncalcified (►**Figs. 3A** and **B**). Comparatively, CTFFR detected hemodynamically significant stenosis in 128 vessels, that is, FFR <0.8 in 54 patients

Table 1 Patient demographics

Sl. no	Variable name	Mean	95% CI
1	Mean age (y)	57	54.8–59.2
2	Sex		
	Males	74	
	Females	26	
3	BMI (kg/m^2)	30.16	26.6–30.6
4	Hypertension	80	
5	Diabetes	45	
6	Dyslipidemia	65	
7	Hyperuricemia	21	
8	History of antianginal drugs	28	
9	History of oral statins	44	
10	Mean heart rate	72 beats/min	64–85

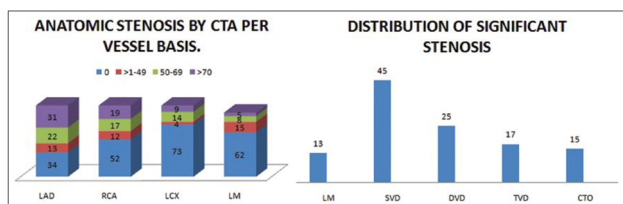Abbreviations: BMI, body mass index; CI, confidence interval.

Fig. 2 Bar charts showing distribution of anatomic stenosis per vessel basis and distribution of significant stenosis by CTCA. CTA, computed tomography angiography; CTCA, computed tomographic coronary angiography.
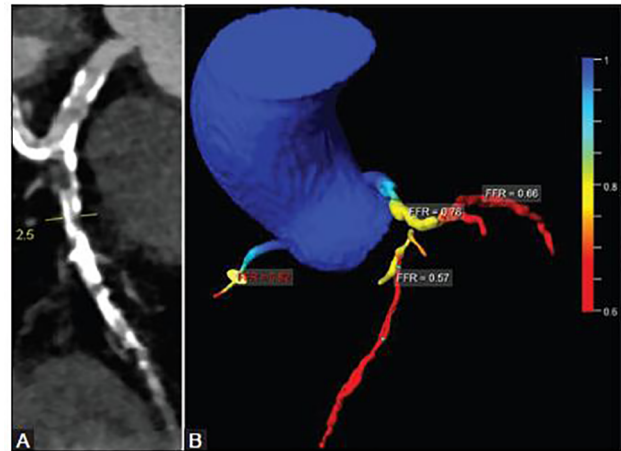

Fig. 3 (**A**) CTCA showing calcified plaque with bifurcation stenosis of left main coronary artery and proximal left anterior descending artery. (**B**) CTFFR showing reduced distal FFR in the same patient. CTCA, computed tomographic coronary angiography; CTFFR, computed tomography fractional flow reserve.
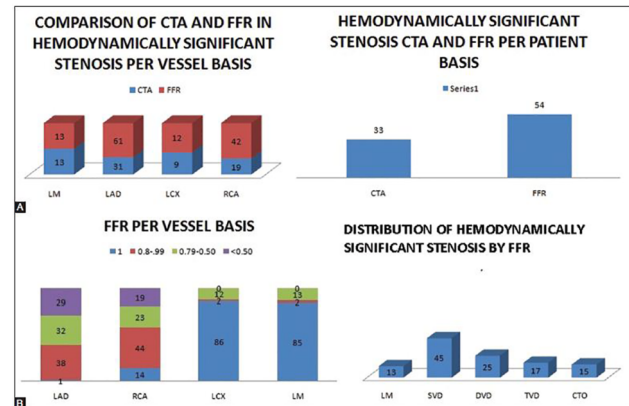

Fig. 4 (**A**) Bar charts showing comparison of CTCA and FFR in hemodynamically significant stenosis on per vessel and per patient basis. (**B**): Bar charts showing distribution of lesions by FFR on per vessel basis and in hemodynamically significant stenosis. CTA, computed tomography angiography; CTCA, computed tomographic coronary angiography; FFR, fractional flow reserve.

details enlisted in ►**Fig. 4A**. Reduced FFR of <0.8 was seen in 61 left anterior descending arteries, 32 right coronary arteries, 12 left circumflex arteries, and 13 left main coronaries these being hemodynamically significant stenosis (►**Figs. 4B and 5A–D**). There were 18 coronary vessels on CTCA which were false positive as having significant stenosis but had normal FFR (►**Figs. 6A** and **B**). A total of 56 vessels were labeled as having intermediate stenosis, that is, 50 to 69% had FFR of <0.8 which leads to 21% difference in severity of stenosis on per patient basis (►**Figs. 7A** and **B**), The sensitivity and specificity of CTCA for detection of significant coronary artery stenosis per vessel basis were 97.7 and 93.3% with a negative predictive value of 98.0%. For severe coronary artery stenosis, CTCA showed a sensitivity, specificity, and negative and positive predictive values of 51.6, 89, 68.8, and 80%, respectively, on per vessel basis (►**Fig. 8A**). On per patient basis, CTCA showed as sensitivity and specificity of 61 and
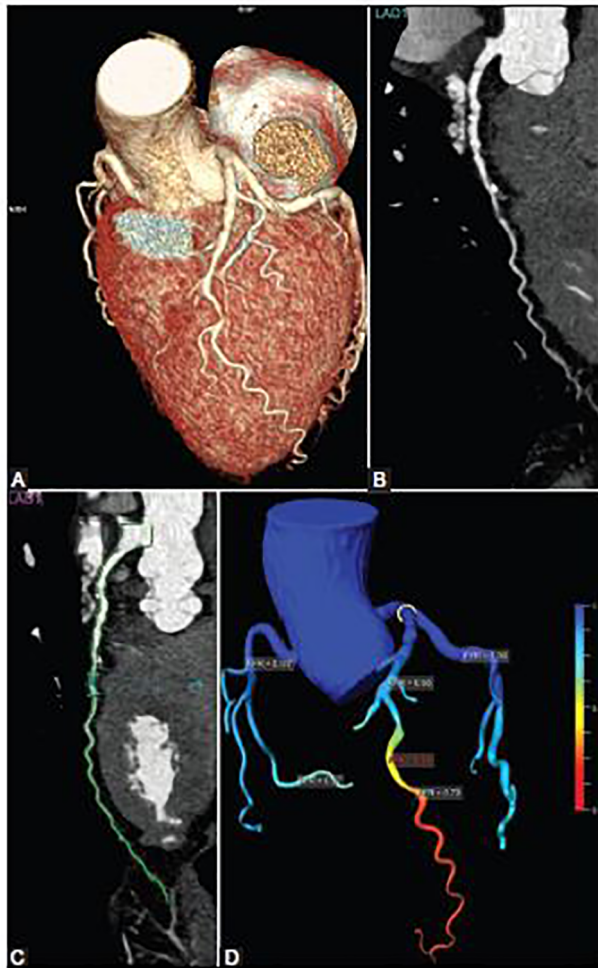
Fig. 5 (**A**) VRT image showing multiple areas of stenosis in left anterior descending artery. (**B**) Multiplanar view of the left anterior descending coronary artery with multiple calcified and soft plaques with indeterminate site of significant stenosis. (**C**) Multiplanar view of the same patient with boundary delineations by CTFFR. (**D**) FFR color map showing hemodynamic significant stenosis in the same patient with triple vessel disease. CTFFR, computed tomography fractional flow reserve.
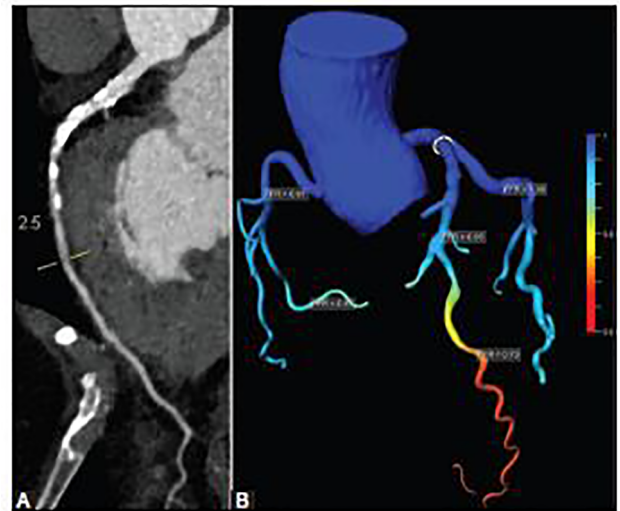

Fig. 6 (**A**) CT angiogram multiplanar reconstruction showing multiple calcified plaques with high-grade stenosis in proximal left anterior descending artery. (**B**) CTFFR showing no hemodynamically significant stenotic lesion. CTFFR, computed tomography fractional flow reserve.
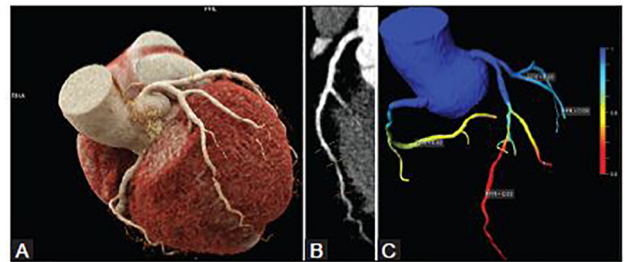

Fig. 7 (**A**) VR 3D image on CT angiogram showing stenosis in mid left anterior descending artery. (**B**) Multiplanar reconstruction image of the same vessel showing 65% stenosis in mid segment. (**C**) CTFFR showing reduced FFR distal to the stenosis in mid segment in the same patient. 3D, three-dimensional; CTFFR, computed tomography fractional flow reserve.

Fig. 8 (**A**) Sensitivity and specificity of CTCA in severe and significant stenosis, respectively. (**B**) Sensitivity and specificity of CTCA, a per-patient basis in severe stenosis. CTCA, computed tomographic coronary angiography.

84%, respectively (►**Fig. 8B**). There were 7% patients in the study who had either heavily calcified vessels where CTCA could not assess the lumen and stenosis due to blooming artifacts of calcium (►**Fig. 9A** and **B**). Eighteen vessels were calcified and were falsely labeled as stenotic on CTA, while three vessels were falsely labeled as normal but were positive
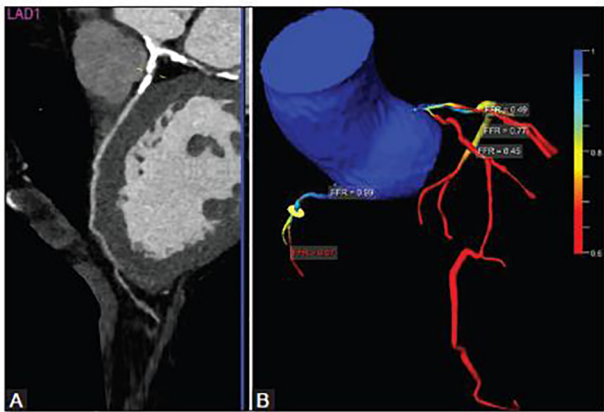
Fig. 9 (**A**) CTCA showing heavily calcified lumen of left anterior descending, left circumflex and left main coronary arteries. (**B**) CTFFR showing normal FFR in left main with ischemia in proximal left anterior descending and circumflex arteries. CTCA, computed tomographic coronary angiography; CTFFR, computed tomography fractional flow reserve.
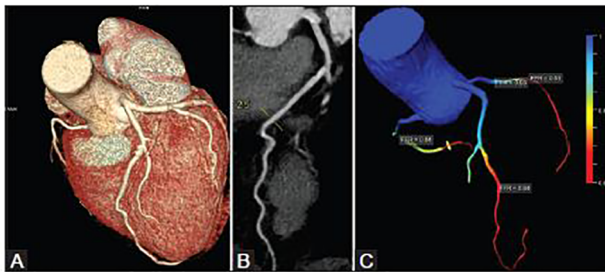

Fig. 10 (**A**) VRT image showing normally opacified left anterior descending artery. (**B**) Multiplanar reconstruction of left anterior descending artery with absent stenosis. (**C**) FFRCT showing nonobstructive coronary ischemia in mid segment with FFR of 0.64. CTFFR, computed tomography fractional flow reserve.
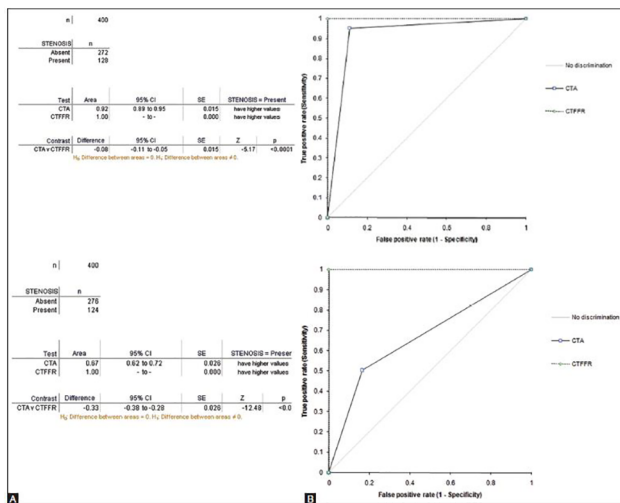

Fig. 11 (**A**) Area under curve for CTCA in detection of significant coronary stenosis per vessel basis. (**B**) Area under curve for CTA in severe coronary stenosis on per vessel basis. CTA, computed tomography angiography; CTCA, computed tomographic coronary angiography.

Table 2 Impact on Management plan after use of CTA and CTCA + CTFFR (fl/=100)

Sl. No modality	OMT	INVCA	PCI	CABG
1 Non invasive	45	55	nil	nil
2 CTCA	67	33	12	11
3 CTCA + CTFFR	34	66	33	23

Abbreviations: CABG: coronary artery bye pass graft; CTCA, computed tomographic coronary angiography; CTFFR, computed tomography fractional flow reserve; INVCA: Invasive coronary angiogram; OMT: optimal medical management; PCI: percutaneous coronary intervention.

on CTFFR (►**Fig. 10A–C**). The AUC showed values of 0.92 and 0.67 for CTCA in detection of significant and severe stenosis, respectively, compared with CTFFR (p <0.0001; ►**Figs. 11A and B**). The results from questionnaires from treating clinicians showed that the use of CTFFR reclassified management of 21% patients with hemodynamic significant stenosis from optimal medical management to percutaneous interventions (PCI) and in 12% of patients from PCI to bypass grafting ►**Table 2**.

Discussion

This study shows that it is possible to calculate FFR noninvasively on site using CTFFR software based on imaging data of CTCA acquired with proper technique and modern state of art scanners in not more than 10 to 15 minutes which was the first prime objective of study. CTFFR accurately depicted the site of hemodynamically significant stenosis on colored FFR flow maps of the coronary tree map and also quantified FFR at the sites identified by the user. CTCA alone was accurate in identifying significant stenosis on per vessel basis with sensitivity and specificity of 97.7 and 93%, respectively, with a negative predictive value of 98% which was very good to confirm the diagnosis. However, CTCA showed a reduced sensitivity of 51.6% for detection of severe stenosis with negative predictive value of 68.8% which meant that used alone it cannot plan revascularization procedures in such patients. On per patient basis, sensitivity and specificity of CTCA for severe stenosis were 61 and 84%, respectively, which made 21% difference leading to misclassification of the management protocol based on CTCA alone. Our study also showed that the maximum difference was seen in patients with intermediate stenosis which on CTFFR was reclassified as hemodynamically significant or functionally severe. Ihdayhid et al[11] also showed in their study that addition of FFRCT improved AUC of CTCA from 0.78 to 0.93 in the detection of severe stenosis and was even better than using CT myocardial perfusion which had AUC of 0.87 similar to what is seen in the present study. This has a major implication on the selection of patient management protocol as use of FFRCT increases the rate of percutaneous angioplasties in these patients who had discordance between anatomical and functionally significant stenosis. The use of CTFFR also modified the selection of vessels in 12% patients in the present study which changed the choice of treatment to bypass

grafting. Similar results were shown by SYNTAX III trial[12] in patients with three-vessel coronary artery disease; use of CTFFR changed treatment decisions and procedural planning in 20% patients and in 7% patients from angioplasty to surgery. There were 7% patients in the study who had either heavily calcified vessels where CTCA could not assess the lumen and stenosis due to blooming artifacts of calcium. Also, 2% patients in the study were falsely misclassified as severe stenosis due to similar effect. Although calcium scoring was not done by us as all patients who were enrolled in the study were symptomatic, these were false positive or not assessable on CTCA. Study shows that with FFRCT, these vessels could be evaluated and coronary calcium did not impair the functional evaluation as was seen in the determination of anatomic stenosis. NXT trial[13] also showed that sensitivity of ischemia detection was high irrespective of coronary calcium scores and the Agatston scores up till 3,500 did not affect the results. There were three patients with ischemia in nonobstructive coronary arteries (INOCA) in our study, all of which were females in the study which is now emerging as an important clinical entity and has important implications on the prognosis of such patients.[14]

Conclusion

To conclude, the present study shows that use of on-site CTFFR is an accurate and quicker option not only to detect hemodynamically significant stenosis on CTCA but also to improve the sensitivity and specificity of noninvasive CT angiography which has a bearing on the patient management plan and treatment and can be frontline road map tool to evaluate such patients.

Conflicts of Interest
There are no conflicts of interest.

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