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Diagnostic accuracy of angiography-based vessel fractional flow reserve after chronic coronary total occlusion recanalization

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Abstract

Background: Angiography-based vessel fractional flow reserve (vFFR) demonstrated a strong correlation with invasive fractional flow reserve (FFR) in both a pre- and post-percutaneous coronary intervention (PCI) setting. However, the role of vFFR and its correlation with post-PCI FFR in chronic coronary occlusions (CTO) has not been evaluated yet. We sought to investigate the diagnostic performance of post-PCI vFFR with post-PCI FFR as a reference in patients undergoing successful CTO PCI.

Methods: Between March 2016 and April 2020, a total of 80 patients from the FFR-SEARCH (prospective registry) and FFR REACT (randomized controlled trial) studies underwent successful CTO recanalization with post-PCI FFR measurements.

Results: A total of 50 patients (median age 66 (interquartile range [IQR]: 56–74) years, 76% were male) were eligible for the analysis. Median post-PCI FFR was 0.89 (IQR: 0.84–0.94), while median post-PCI vFFR was 0.91 (IQR: 0.85–0.94) (p 0.10). Suboptimal physiological results, defined as FFR and vFFR <0.90, were identified in 26 (52%) and in 21 (42%) patients, respectively. A strong correlation ($r = 0.82$) was found between vFFR and FFR with a mean bias of 0.013 ± 0.051. Receiver-operating characteristics curve analysis revealed an excellent accuracy of vFFR in predicting FFR <0.90 (area under the curve: 0.97; 95% confidence interval: 0.93–1.00).

Conclusion: Post-PCI vFFR shows a good correlation with post-PCI FFR and a high diagnostic accuracy for post-PCI FFR ≤0.90 in patients undergoing successful PCI of a CTO lesion.

Abbreviations: AUC, area under the curve; CCS, chronic coronary syndrome; CTO, chronic total occlusion; FFR, fractional flow reserve; HR, hazard ratio; IQR, interquartile range; IVUS, intravascular ultrasound; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; ROC, receiver operation characteristics; vFFR, vessel fractional flow reserve.

Alessandra Scoccia and Paola Scarparo contributed equally to this study.

KEYWORDS
3D-QCA, chronic total occlusion, coronary physiology, fractional flow reserve, percutaneous coronary intervention, post percutaneous coronary intervention physiology, quantitative coronary angiography, vessel fractional flow reserve

1 | INTRODUCTION

Chronic total occlusions (CTO) are identified in up to 30% of patients with significant coronary artery disease undergoing coronary angiography.[1] Although percutaneous coronary intervention (PCI) as treatment for CTO is currently associated with success rates of up to 90% of cases in experienced centers, the rate of restenosis and reinterventions is still higher than in standard PCI procedures.[2]

If the role of fractional flow reserve (FFR) in the pre-PCI setting has been fully clarified, there is an increasing interest in the use of FFR in the post-PCI setting, to evaluate the impact of stent deployment on post-PCI physiology. Recent studies demonstrated that, despite adequate angiographic results, suboptimal post-PCI FFR <0.90, is detectable in up to 40% of cases.[3] This is associated with higher risk of major adverse cardiovascular events.[4–7] However, little is known about the role of post-PCI FFR in the setting of CTO, especially considering the peculiar physiological features of CTO lesions, including the presence of collateral, and the restoration of the flow in the vessel.[8]

Angiography-based vessel FFR (vFFR) is a new software method to derive FFR based on three-dimensional quantitative coronary angiography, without the need for a hyperemic agent or intracoronary instrumentation.[9] vFFR demonstrated a strong correlation with invasive FFR in both pre- and post-PCI setting, and had high diagnostic accuracy to identify a post-PCI FFR <0.90.[9–12]

However, the role of post-PCI vFFR and its correlation with post-PCI FFR in the specific subset of CTO PCI has not been evaluated yet. We therefore sought to investigate the correlation between post-PCI vFFR and post-PCI FFR in CTO lesions treated successfully with PCI.

2 | METHODS

This is a post hoc analysis of the FFR-SEARCH and FFR REACT studies.[3,13] In brief, FFR-SEARCH is a single-center, prospective all comers study evaluating the impact of post-stenting FFR on long-term clinical outcomes. A total of 1000 patients presenting with chronic coronary syndrome (CCS), unstable angina or non-ST-elevation acute coronary syndrome (NSTE-ACS), and ST-elevation myocardial infarction were included in the study.[3]

The FFR REACT study, is a single-center, randomized controlled trial, which included 621 patients with CCS, unstable angina or NSTE-ACS and angiographically successful PCI. All patients underwent post-PCI FFR measurements, and patients with a post-PCI FFR <0.90 were randomized (1:1) to either standard of care (control arm), or intravascular ultrasound (IVUS)-guided optimization (IVUS arm).[13]

Details on inclusion and exclusion criteria and acquisition of diagnostic angiographic projections have been previously described.[3,13]

The Medical Ethics Committee of the Erasmus Medical Center reviewed the study protocol and waived the need for additional informed consent because of the non-interventional character of this retrospective study using anonymous data collection. The investigation conforms to the principles outlined in the Declaration of Helsinki.

2.1 | Patients and study setting

The analysis included patients older than 18 years with CCS or NSTE-ACS and at least one successful CTO recanalization.

Exclusion criteria were (1) target lesion located in or supplied by an arterial or venous bypass graft, (2) unsuccessful CTO recanalization, and (3) adenosine intolerance.

2.2 | Study procedure

2.2.1 | FFR measurement

Coronary angiography was performed using standard techniques. Functional assessments were performed at the end of the procedure when the operator considered the angiographic result acceptable. Post-PCI FFR measurements were obtained using the Navvus™ microcatheter (ACIST Medical Systems, Inc.), advanced at least 20 mm distal to the distal stent edge.

Coronary artery distal pressure (Pd) and aortic pressure (Pa) curves were acquired simultaneously at baseline (resting condition) and during administration of intravenous adenosine (hyperemic condition). Maximal hyperemia was achieved by a continuous intravenous infusion of adenosine at a rate of 140 μg/kg/min through an antecubital vein.

2.2.2 | vFFR computation

vFFR computation was performed off-line using CAAS Workstation 8.2 software (Pie Medical Imaging). The software automatically identified optimal end-diastolic frame from two identical angiographic image projections, and contour detection was performed semiautomatically, by delineating the vessel contour from the ostium to the position at which the pressure wire sensor would be positioned. Contour detecting was not be performed in distal segments with reference vessel diameter <2.0 mm. Manual correction was allowed in case of suboptimal automatic contour

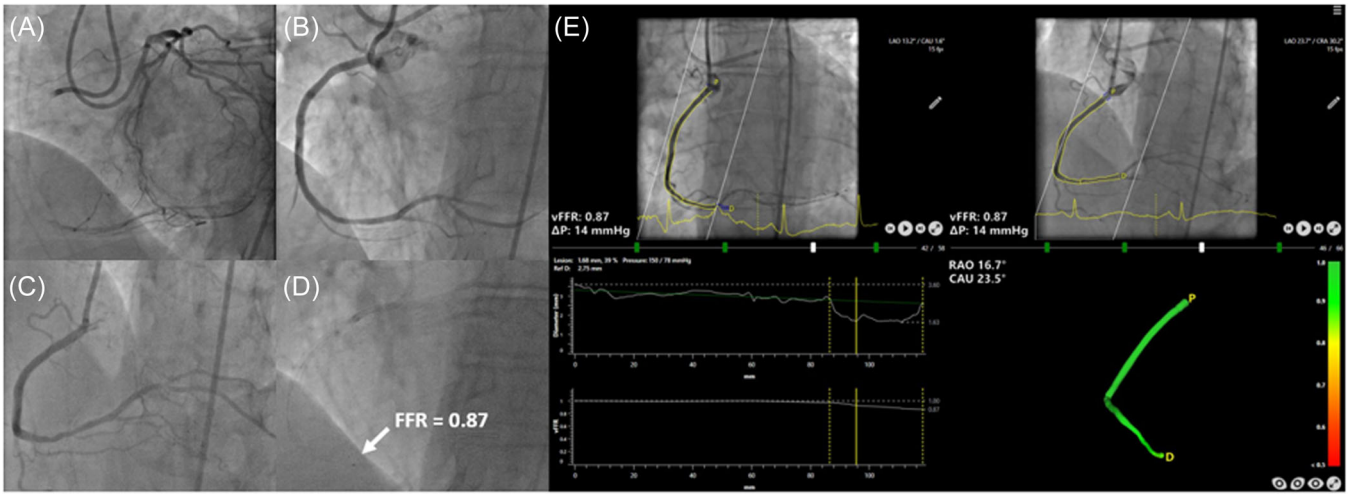

FIGURE 1 Successful percutaneous coronary intervention of a chronic total occlusion of the right coronary artery (A–C). At the end of the procedure the FFR microcatheter is advanced in the distal segment (D). vFFR computation is performed from two angiographic image projections of the right coronary artery (E). vFFR, vessel fractional flow reserve. [Color figure can be viewed at wileyonlinelibrary.com]

detection following a standard operating procedure.[9] vFFR analysis were performed by a trained cardiologist (A. S.), blinded to the FFR values.

2.3 | Data collection and statistics

Demographic data, cardiovascular risk factors, and procedural details were collected for each patient and stored in an electronic database.

Categorical variables are expressed as number and percentages, while continuous variables are expressed as mean ± standard deviation or median and interquartile range (IQR), as per distribution. The Shapiro–Wilk test was used to evaluate whether continuous variables followed normal distribution.

The relation between vFFR and FFR was assessed using Spearman's correlation coefficient (*r*). The agreement between both indices was assessed by Bland–Altman plots with corresponding 95% limits of agreement. Receiver operation characteristics (ROC) curve with area under the curve (AUC) was determined with FFR as a reference standard using a threshold of 0.90. A two-sided $p < 0.05$ was considered statistically significant. Statistical analyses were conducted using SPSS (version 24.0; SPSS Inc.).

3 | RESULTS

Between March 2016 and April 2020, a total of 80 patients from the FFR-SEARCH and FFR REACT studies underwent successful CTO recanalization. A total of 30 patients were excluded due to insufficient angiographic views precluding vFFR computation. Subsequently, 50 patients (50 vessels) were included in the analysis (Figure 1 and Supporting Information: Figure 1).

The baseline and procedural characteristics of the population are summarized in Table 1.

TABLE 1 Baseline and procedural characteristics

Patient-level variables	All (*N* = 50)
Age, in years	66 (56–74)
Male gender	38 (76%)
Clinical presentation	
Stable/unstable angina	42 (84%)
NSTE-ACS	8 (16%)
Cardiovascular risk factors	
Hypertension	27 (54%)
Hypercholesterolemia	31 (62%)
Diabetes mellitus	12 (24%)
Current smoker	14 (28%)
Cardiovascular history	
Peripheral arterial disease	2 (4%)
Prior PCI	15 (30%)
Prior CABG	2 (4%)
Vessel-level variables	
Vessel	
Right coronary artery	30 (60%)
Left anterior descending	13 (26%)
Left circumflex artery	7 (14%)
Post-PCI FFR	0.89 (0.84–0.94)
Post-PCI vFFR	0.91 (0.85–0.94)
n of FFR lesion <0.90 of total lesion evaluated (%)	26 (52)
n of vFFR lesion <0.90 of total lesion evaluated (%)	21 (42)

Note: Values are displayed as median (IQR) or *n* (%).

Abbreviations: CABG, coronary artery bypass grafting; FFR, fractional flow reserve; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; vFFR, vessel fractional flow reserve.

Median age was 66 (IQR: 56–74) years and 76% of the patients were male. Clinical indication for coronary angiography was stable or unstable angina in 84% of cases, and NSTE-ACS in 16% of cases.

A total of 30 (60%) interrogated vessels were right coronary arteries, 13 (26%) were left anterior descending arteries, and 7 (14%) were left circumflex arteries.

Median post-PCI FFR was 0.89 (IQR: 0.84–0.94), while median post-PCI vFFR was 0.91 (IQR: 0.85–0.94) (p 0.10). Distribution of FFR and vFFR value are shown in Figure 2. Suboptimal physiological results, defined as post-PCI FFR <0.90 and post-PCI vFFR <0.90, were identified in 26 (52%) and in 21 (42%) patients, respectively.

A strong correlation ($r = 0.82$) was found between vFFR and FFR with a mean bias of 0.013 ± 0.051 (Figure 3 and Supporting Information: Figure 2). ROC curve analysis revealed an excellent accuracy of post-PCI vFFR in predicting post-PCI FFR <0.90 (AUC: 0.97; 95% confidence interval: 0.93–1.00) (Figure 4).

4 | DISCUSSION

This is the first study that investigates the correlation between post-PCI vFFR and post-PCI FFR in patients undergoing successful CTO PCI. The main findings of the study are as follows: (1) post-PCI vFFR showed a good correlation with post-PCI FFR; (2) post-PCI vFFR shows a high diagnostic accuracy for post-PCI FFR <0.90 in patients undergoing successful PCI of a CTO lesion.

Suboptimal post-PCI FFR is associated with suboptimal stent deployment and residual disease.[14] Several studies demonstrated that low post-PCI FFR is linked to higher rates of target vessel failure and to an increased risk for major adverse cardiovascular events.[4,15–19] As a consequence, post-PCI FFR has the potential to be a useful tool for the assessment of PCI results and could play a role in optimization of procedural results.

Despite these observation, its adoption into daily practice is limited, due to several reasons including the need for relatively expensive pressure wires or microcatheters, prolongation of procedural time, occurrence of drift, and side-effects associated with the use of hyperemic agents. These aspects are particularly relevant in complex CTO PCI already burdened by high costs and long procedural time. Consequently, the option of wire-free post PCI physiological analysis using angiography based FFR to identify individuals requiring additional diagnostics and subsequent specific management is of particular clinical interest in the post-PCI CTO setting.

There is an increasing number of evidence supporting the use of angiography based FFR in post-PCI setting. In the HAWKEYE study,

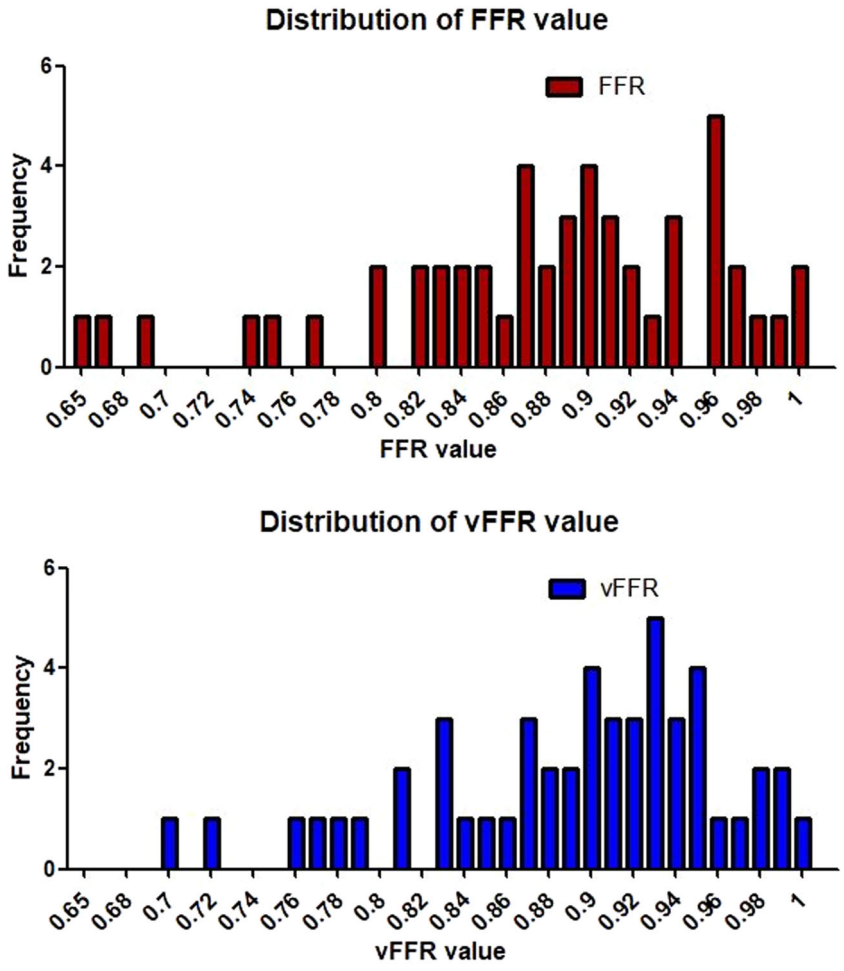

FIGURE 2 Distribution of FFR and vFFR values. vFFR, vessel fractional flow reserve. [Color figure can be viewed at wileyonlinelibrary.com]

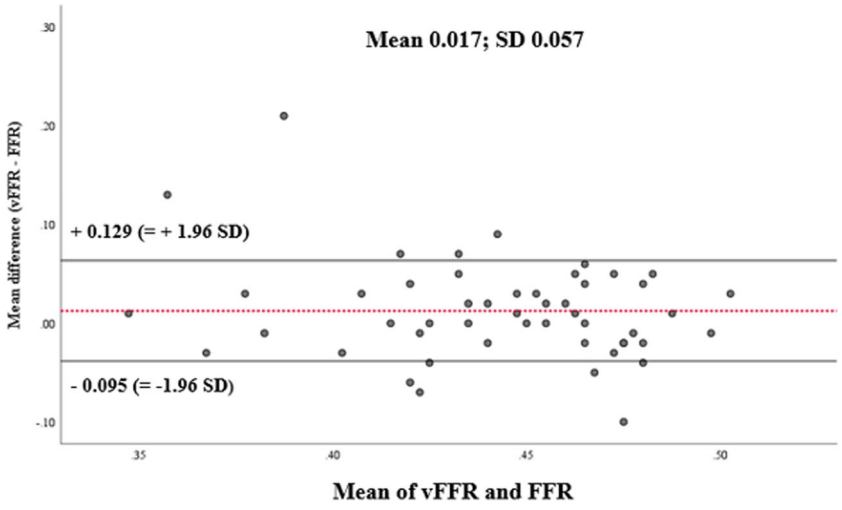

FIGURE 3 Bland–Altman plots of differences against the means. The mean bias is represented by the solid red line and the 95% confidence interval is represented by the dashed line. vFFR, vessel fractional flow reserve. [Color figure can be viewed at wileyonlinelibrary.com]

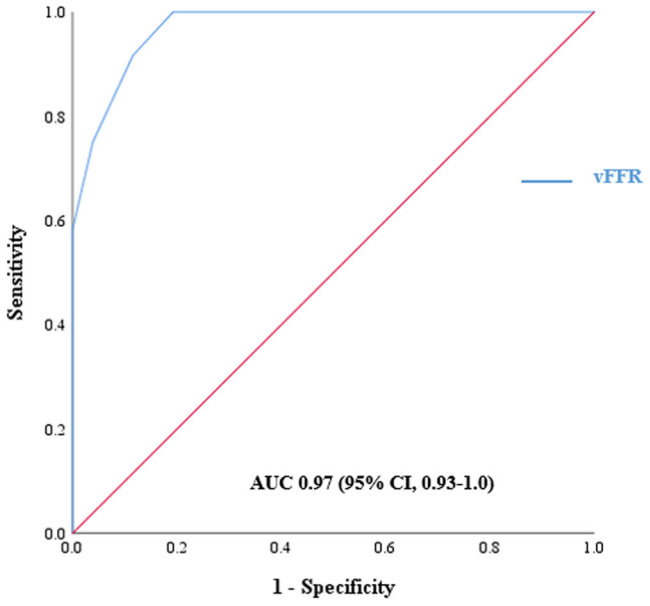

FIGURE 4 ROC curve of vFFR to predict FFR lesions <0.90. AUC, area under the curve; CI, confidence interval; ROC, receiver operation characteristics; vFFR, vessel fractional flow reserve. [Color figure can be viewed at wileyonlinelibrary.com]

lower values of quantitative flow ratio (QFR) after complete and successful revascularization demonstrated to predict subsequent adverse events.[20] Consistent observations were also reported by Kogame et al.,[21] with vessels presenting post-PCI QFR values >0.91 having lower risk of target vessel revascularization at 2 year, as compared to vessels with post-PCI QFR ≤0.91 (3.6% vs. 15%, $p < 0.001$).

In the FAST POST study, vFFR demonstrated good correlation and a high diagnostic accuracy to identify FFR <0.90 in post-PCI.[11] Subsequent data from the FAST OUTCOME study demonstrated that post-PCI vFFR <0.88 were associated with a significantly increased risk of target vessel failure and target vessel revascularization at 5-years follow-up.[22]

To our knowledge, the present study is the first to compare the diagnostic performance of vFFR using FFR as a reference in patients undergoing successful PCI of a CTO lesion. This is of particular interest, since the coronary physiology in the setting of CTOs has important differences from that in the setting of coronary lesions with intermediate stenosis grade. These include the potential competitive flow through collaterals and the altered microcirculatory physiology in hibernating but viable myocardium which can lead to a different hyperemic response.[23]

Conversely, vFFR, which does not require TIMI frame count for computation, can be less affected by changes in the microvasculature or an impaired hyperemic response.

However, whether physiology-guided incremental optimization strategy is achievable and beneficial remains subject of debate.

Two dedicated trials, TARGET FFR (post-stenting FFR vs. coronary angiography for optimization of PCI) and FFR REACT (FFR guided PCI optimization directed by high-definition IVUS vs. standard of care), addressed this question.[13,24]

TARGET FFR failed to show that a physiology-guided incremental optimization strategy was beneficial at improving the proportion of physiologically optimal PCI (FFR >0.90). Conversely, FFR REACT demonstrated IVUS-guided PCI FFR optimization led to a significant increase in post-PCI FFR values, but was unable to improve target vessel failure at 1-year follow-up (IVUS-guided optimization arm: 4.2%, control arm: 4.8%, $p = 0.79$). Of note, the low proportion (31%) of patients who underwent PCI optimization in TARGET FFR and the low events rates in FFR REACT has to be taken into account when interpreting the results of these studies.

Dedicated trials aimed to evaluate whether functional PCI optimization based on unsatisfactory post-PCI values of physiological indices improves patient outcome are currently awaited (FFR REACT: ongoing follow-up and DEFINE GPS: NCT04451044).

4.1 | Limitations

Some limitations of the analysis need to be addressed. First, this is retrospective analysis, so acquisition of specific angiographic projection was not mandatory, leading to the exclusion of almost 40% of patients. Second, in both FFR SEARCH and FFR REACT studies post-PCI FFR was measured with a microcatheter instead of a pressure wire, which could have led to slightly lower post-PCI FFR values.[25]

5 | CONCLUSION

In conclusion, post-PCI vFFR shows a good correlation with post-PCI FFR and a high diagnostic accuracy for post-PCI FFR ≤0.90 in patients undergoing successful PCI of a CTO lesion.

CONFLICTS OF INTEREST

Dr Diletti has received institutional research grant support from ACIST Medical Systems, Inc. Joost Daemen received institutional research support from Astra Zeneca, Abbott Vascular, Boston Scientific, Acist Medical, Medtronic, Pie Medical, ReCor medical and Pulse Cath. Nicolas M. Van Mieghem received research grant support from Edwards, Medtronic, Abbott, Boston Scientific, Pulse Cath, Acist Medical, and Essential Medical. Tara Neleman received institutional research grant support from Acist Medical. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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