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Research paper

Clinical effects of physiologic lesion testing in influencing treatment strategy for multi-vessel coronary artery disease

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ABSTRACT

Background: The application of fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) in multi-vessel coronary artery disease (CAD) patients has not been definitively explored. We herein assessed how treatment strategies were decided based on FFR/iFR values in vessels selected clinically. Specifically, we sought to determine whether treatment selection was based on whether the vessel tested was the clinical target stenosis.
Methods: 270 consecutive patients with angiographically determined multivessel disease who underwent FFR/iFR testing were included. Patients were classified initially based on their angiographic findings, then re-evaluated from FFR/iFR results (normal or abnormal). Tested lesions were classified into target or non-target lesions based on clinical and non-invasive evaluations.
Results: Abnormal FFR/iFR values were demonstrated in 51.9 % of patients, in whom 51.4 % received coronary stenting (PCI) and 44.3 % had bypass surgery (CABG). With two-vessel CAD patients, medical therapy was preferred when the target lesion was normal (72.6 %), while PCI was preferred when it was abnormal (78.4 %). In non-target lesions, PCI was preferred regardless of FFR/iFR results (78.0 %). With three-vessel CAD patients, CABG was preferred when the target lesion was abnormal (68.5 %), and there was no difference in the selected modality when it was normal. Furthermore, the incidence of tested lesions was higher in the left anterior descending (LAD) compared to other coronary arteries, and two-vessel CAD patients with LAD stenoses were more frequently treated by PCI.
Conclusion: The use of invasive physiologic testing in multivessel CAD patients may alter the preferred treatment strategy, leading to an overall increase in PCI selection.

1. Introduction

Fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) are the standards for assessing the physiological significance of anatomically ambiguous or intermediate lesions on coronary angiography. Deferral of revascularization based on normal FFR/iFR is cost-effective and associated with good long-term clinical outcomes [1–3]. Functional assessment as an adjunct to anatomic estimates of severity is associated with improved long-term outcomes in intermediate lesions, improving clinical decision-making [4]. These physiologic assessments appropriately influence the decision for coronary revascularization, guide the performance of percutaneous coronary interventions (PCI), and optimize procedural outcomes.

These procedures have been increasingly utilized over the past decade: the rate of FFR utilization among patients with intermediate coronary stenosis (40–70 % diameter stenosis) increased from 14.8 % in 2009 to 18.5 % in 2017 [5]. The gradual increase in utilization may in part be due to the associated decrease in one-year mortality post-FFR-guided revascularization despite the added time and cost of additional invasive procedures and reluctance to employ said procedures unless they yielded more treatment insights [9].

However, the strategic application of invasive physiology in identifying treatment modalities for patients with multi-vessel coronary disease has not been definitively explored. Physiologic lesion evaluation is

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a powerful adjunctive diagnostic modality in the evaluation of intermediate-severity coronary stenoses, but the factors governing its employment and its actual impact on clinical decision-making in this patient population are unknown and likely complex. Consequently, we examined how physiologic testing is applied to select treatment strategy, and whether physiologic testing leads to differences in selection of treatment modality among patients presenting with two- and three-vessel CAD.

2. Methods

2.1. Patient selection

This retrospective study was undertaken to determine how clinicians use invasive physiologic testing to select treatment strategy during catheterization. The primary objective of the study was to determine how FFR/iFR values are used to determine revascularization strategy in patients with angiographic multi-vessel CAD. The secondary objective of the study was to assess if the selection of patients for physiologic testing showed any identifiable predispositions. The Institutional Review Board (IRB) approved the study, and all data were collected in a database that is encrypted and compliant with HIPAA regulations. All patient identifiers were kept confidential in compliance with HIPAA regulations. Over 4 years, 1541 consecutive patients underwent FFR/iFR at a single urban teaching hospital. Of these, 270 patients with angiographically determined multi-vessel (two- or three-vessel) disease underwent FFR and/or iFR testing and were eligible for entry to the study. Patients with previous bypass surgery (CABG) and significant left main stenoses were excluded from this study. The interventional cardiologist decided which vessel to test or not to test.

2.2. Data acquisition

All relevant medical records and reports, including coronary angiograms, were reviewed. Retrospective registry data regarding admission diagnoses, emergency room documentation, past medical history, laboratory results (including troponin levels), cardiac stress test reports, cardiac angiogram reports, electrocardiograms, operative notes, and disposition at discharge were also compiled. Over 50 angiographic, clinical, and physiologic variables were collected and evaluated to determine how these tests altered the initial treatment plan. Patient demographics (including age, gender, BMI, admitting diagnosis, indication for cath/PCI, and FFR/iFR) and other pertinent variables were acquired from data fields within the local NCDR Cath-PCI registry, including angiographically-determined stenosis severity and number of vessels diseased (based on angiographic description of $\geq$70 % diameter stenosis).

2.3. FFR and iFR parameters

FFR is the ratio of mean distal coronary pressure (P_d) to mean aortic pressure (P_a) during maximum hyperemia, which is usually induced by adenosine bolus or infusion, and represents the percentage of normal flow across a coronary stenosis. iFR is measured during a select portion of diastole, the wave-free period (WFP), when the forces that influence coronary flow are quiescent. iFR is calculated by measuring the resting trans-lesional pressure ratio (Pd/Pa) during the WFP. FFR and iFR values were considered abnormal if FFR $\leq$ 0.80 or iFR $\leq$ 0.89.

2.4. Lesion classification

Patients with normal and abnormal FFR/iFR values were categorized based on whether the target lesion was involved in the treatment or if the treatment included other vessels. Target lesions were identified as the clinically apparent culprit lesion by morphology or severity ($\geq$70 % diameter stenosis pre-treatment) and believed clinically to be causing an acute coronary syndrome based on EKG or abnormal stress test. Non-target lesions were stenoses in other vessels identified by the angiogram to be intermediate-to-high severity ($\geq$70 % narrowing) but not directly related to the clinically affected area of the myocardium (i.e. in a contralateral vessel). Clinical correlation with ECG changes, non-invasive evaluation, and other factors were used to make this determination, which was blinded to physiologic outcomes and the revascularization strategy employed.

Each group was then subdivided based on the number of diseased vessels (i.e. two- vs. three-vessel CAD). The initial appraisal was performed based on angiographic interpretation. Functional assessment was undertaken in stenoses classified as primary targets identified clinically or a secondary vessel, how many $\geq$70 % diameter stenoses and consequent diseased vessels were present, and if the FFR/iFR outcomes were normal or abnormal. Angiographic reports and clinical notes were reviewed to find the rationale behind selecting treatment strategy (e.g. medical treatment vs. PCI vs. CABG) as well as assessing lesion location by vessel (e.g. LAD vs. left circumflex (LCX) vs. right coronary artery (RCA) vs. other vessels). Age, gender, BMI, COPD, diabetes, and other demographic variables were collected and did not independently predict the use of FFR/iFR in patients. No patient had revascularization (PCI or CABG) done in a vessel shown to have a normal FFR or iFR. When revascularization was performed in a patient classified as having a normal test result, it was always performed in a different vessel than the one tested.

2.5. Statistical analysis

Ordinal variables were analyzed using GraphPad Prism 8.4 (GraphPad Software) and presented as absolute values and percentages. One-way ANOVA followed by Dunnett's test was used to determine if differences existed among the subgroups before chi-square testing. The chi-square goodness of fit test was used to determine whether the treatment modality was chosen based on FFR/iFR values and lesion classification. The statistical analysis (chi-square) was run on every possible facet and combination concerning FFR/iFR evaluations and the number of diseased vessels. Chi-square goodness of fit is an ideal statistical choice for this study as the expected outcome frequency for each treatment modality in each patient group (two-vessel and three-vessel) is based on the FFR/iFR outcomes. Thus, chi-square analyses comparing the observed outcomes with the expected outcomes for each treatment modality in each patient group would allow the detection of biases (deviations from the expected) in the treatment modality chosen in different patient groups. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 270 patients with multivessel CAD who underwent FFR/iFR during coronary angiography or stenting comprised the study group. Baseline patient characteristics (e.g. demographics, clinical characteristics, admitting diagnosis) are summarized in Table 1. Of the total number of patients, 113 (41.9 %) underwent angiography with NSTEMI/STEMI as their main indication, whereas 91 (33.7 %) underwent the procedure due to an abnormal stress test (Table 1). The remaining patients had testing for malignant arrhythmias or other causes, such as new onset cardiomyopathies, worsening congestive heart failure, and valvular heart disease. No notable differences in baseline characteristics nor admitting diagnosis between patients with normal and abnormal FFR/iFR testing were detected (Table 1). There were also no differences in baseline characteristics between patients receiving PCI, CABG, and medical treatment. There was, however, a discernible trend favoring PCI regardless of the admitting diagnosis (i.e. acute coronary syndrome, abnormal stress test, malignant arrhythmia, and other

Table 1
Patient characteristics.

	Total (n = 270)	Normal FFR/iFR (n = 130)	Abnormal FFR/iFR (n = 140)	p-value	PCI (n = 132)	CABG (n = 72)	Med Mx (n = 66)	p-value
Baseline characteristics								
Age (SD)	65 (10)	65 (11)	66 (10)	0.861	65 (10)	65 (9)	66 (11)	0.885
Sex: Male	207 (76.7 %)	101 (48.8 %)	106 (51.2 %)	0.781	102 (49.3 %)	58 (28 %)	47 (22.7 %)	0.554
Race: White	122 (45.2 %)	52 (42.6 %)	70 (57.4 %)	0.104	57 (46.8 %)	38 (31.1 %)	27 (22.1 %)	0.343
Weight (SD)	87 (19)	87 (20)	85 (19)	0.808	89 (19)	87 (18)	85 (20)	0.855
BMI (SD)	30 (7)	31 (7)	29 (7)	0.796	31 (7)	29 (6)	29 (7)	0.803
Clinical characteristics								
Diabetes	129 (47.8 %)	60 (46.5 %)	69 (53.5 %)	0.428	71 (55 %)	32 (24.8 %)	26 (20.2 %)	0.498
HbA1c of diabetics (SD)	7.1 (1.9)	7.3 (2.1)	6.9 (1.7)	0.769	7.0 (1.8)	7.0 (1.5)	7.3 (2.4)	0.884
Congestive heart failure	58 (21.5 %)	28 (48.3 %)	30 (51.7 %)	0.793	27 (46.6 %)	17 (29.3 %)	14 (24.1 %)	0.724
Previous PCI	101 (37.4 %)	47 (46.5 %)	54 (53.5 %)	0.486	45 (44.6 %)	30 (29.7 %)	26 (25.7 %)	0.561
Admitting diagnosis								
NSTEMI/STEMI	113 (41.9 %)	58 (51.3 %)	55 (48.7 %)	0.778	58 (51.3 %)	25 (22.2 %)	30 (26.5 %)	0.804
Positive stress test	91 (33.7 %)	43 (47.3 %)	48 (52.7 %)	0.753	43 (47.3 %)	28 (30.8 %)	20 (21.9 %)	0.478
Arrhythmia	6 (2.2 %)	2 (33.3 %)	4 (66.7 %)	0.414	3 (50 %)	2 (33.3 %)	1 (16.7 %)	0.846
Others	60 (22.2 %)	27 (45 %)	33 (55 %)	0.439	28 (46.7 %)	17 (28.3 %)	15 (25 %)	0.718

BMI = body mass index; HbA1c = hemoglobin A1c; NSTEMI = non-ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction; FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; Med Mx = medical treatment/management; SD = standard deviation.

indications).

3.2. Overall proportions of treatment selections and lesion locations

140 patients (51.9 %) had abnormal FFR/iFR testing of at least one lesion, while the remaining 130 patients (48.1 %) had normal FFR/iFR testing. Of the patients with abnormal FFR/iFR testing, very few were treated medically (6 patients, 4.3 %) when compared to either PCI (72 patients, 51.4 %) or CABG (62 patients, 44.3 %) (Fig. 1A). Of the patients with normal FFR/iFR, substantially more were treated medically or with PCI (60 patients, 46.2 %) than with CABG (10 patients, 7.5 %) (Fig. 1A). Thus, abnormal physiologic assessment led to overall increased revascularization and decreased medical management.

The relationship between the lesions selected for invasive physiologic measures (target vs. non-target) and the subsequent treatment strategy was also assessed. Of the 123 patients with non-target lesions tested, substantially more patients received PCI (83 patients, 67.5 %) than were treated medically (22 patients, 17.9 %) (Fig. 1B). However, there was not a notable difference between the number of patients who underwent bypass surgery (18 patients, 14.6 %) and the number of patients treated medically (Fig. 1B). This skew was not observed with the treatment employed in the 147 patients with target lesions tested. There were no differences in the distribution of patients receiving medical therapy (44 patients, 30.0 %) compared to patients receiving PCI (49 patients, 33.3 %) or undergoing CABG (54 patients, 36.7 %) (Fig. 1B). Consequently, in addition to physiologic testing results and whether the lesion tested was the clinical target stenosis, the suitability for revascularization (PCI or CABG) versus medical therapy also depends on the number of vessels with significant stenoses.

Patients were also examined based on the lesion location by vessel. In normal FFR/iFR group, the majority of the lesions were located in the LAD (49 patients, 37.7 %), followed by LCX (31 patients, 23.8 %), RCA (28 patients, 21.5 %), and lastly the other branches (22 patients, 16.9 %) (Fig. 1C). The distribution of lesions in patients with abnormal FFR/iFR also highlighted lesions predominant in the LAD (96 patients, 68.6 %) (Fig. 1C). Similarly, analyses of both target and non-target lesions showed substantially more lesions located in the LAD (52.4 % and 54.5 %, respectively) compared to the LCX, RCA, or other branches (Fig. 1D). Overall, lesions were primarily located in the LAD regardless of physiologic assessment values or lesion classification.

3.3. Proportions of treatment selections and lesion locations in two-vessel CAD patients

149 patients with two-vessel CAD underwent FFR/iFR testing. 44 patients with two-vessel CAD had normal FFR/iFR testing in the target lesion, and the majority were treated medically (32 patients, 72.6 %) compared to either PCI or CABG (6 patients, 13.8 %) (Fig. 2A). Intriguingly, substantially more patients with abnormal FFR/iFR in the target lesion received PCI (29 patients, 78.4 %) and CABG (7 patients, 18.9 %) than medical therapy (1 patient, 2.7 %) (Fig. 2A). These results highlight a marked preference for revascularization with abnormal FFR/iFR testing in the target lesions of two-vessel CAD patients. 24 patients with two-vessel CAD had abnormal FFR/iFR testing in non-target lesions, where the majority received PCI (18 patients, 75.0 %) over CABG (6 patients, 25.0 %), and no patients were treated medically (Fig. 2B). The remaining patients with normal FFR/iFR in non-target lesions either received PCI (35 patients, 79.5 %) or were treated medically (9 patients, 20.5 %), with no patients undergoing CABG (Fig. 2B).

68 two-vessel CAD patients with non-target lesions were tested, and the majority received PCI (53 patients, 78.0 %) instead of medical therapy (9 patients, 13.2 %) or CABG (6 patients, 8.8 %) (Fig. 2C). 81 two-vessel CAD patients with target lesions were tested, and the majority of patients were treated medically (33 patients, 40.7 %) or with PCI (35 patients, 43.2 %) than with CABG (13 patients, 16.1 %) (Fig. 2C). Thus, with two-vessel CAD patients, abnormal FFR/iFR testing in either target or non-target stenoses led to an overall increase in revascularization (PCI or CABG) and decrease in medical management. The skew favoring PCI was especially prevalent when testing non-target lesions in two-vessel CAD patients, where more PCIs were performed than medical management or CABG regardless of FFR/iFR results.

When examining the lesion distribution in target vessels of two-vessel CAD patients, we found substantially higher lesion counts in the LAD than in other arteries, which were seen with normal and abnormal FFR/iFR testing (Fig. 2D). Similar observations were found regarding lesion distribution in non-target vessels of two-vessel CAD patients (Fig. 2E). Lastly, in patients with two-vessel CAD regardless of whether a target or non-target lesion was being tested, lesion counts were notably

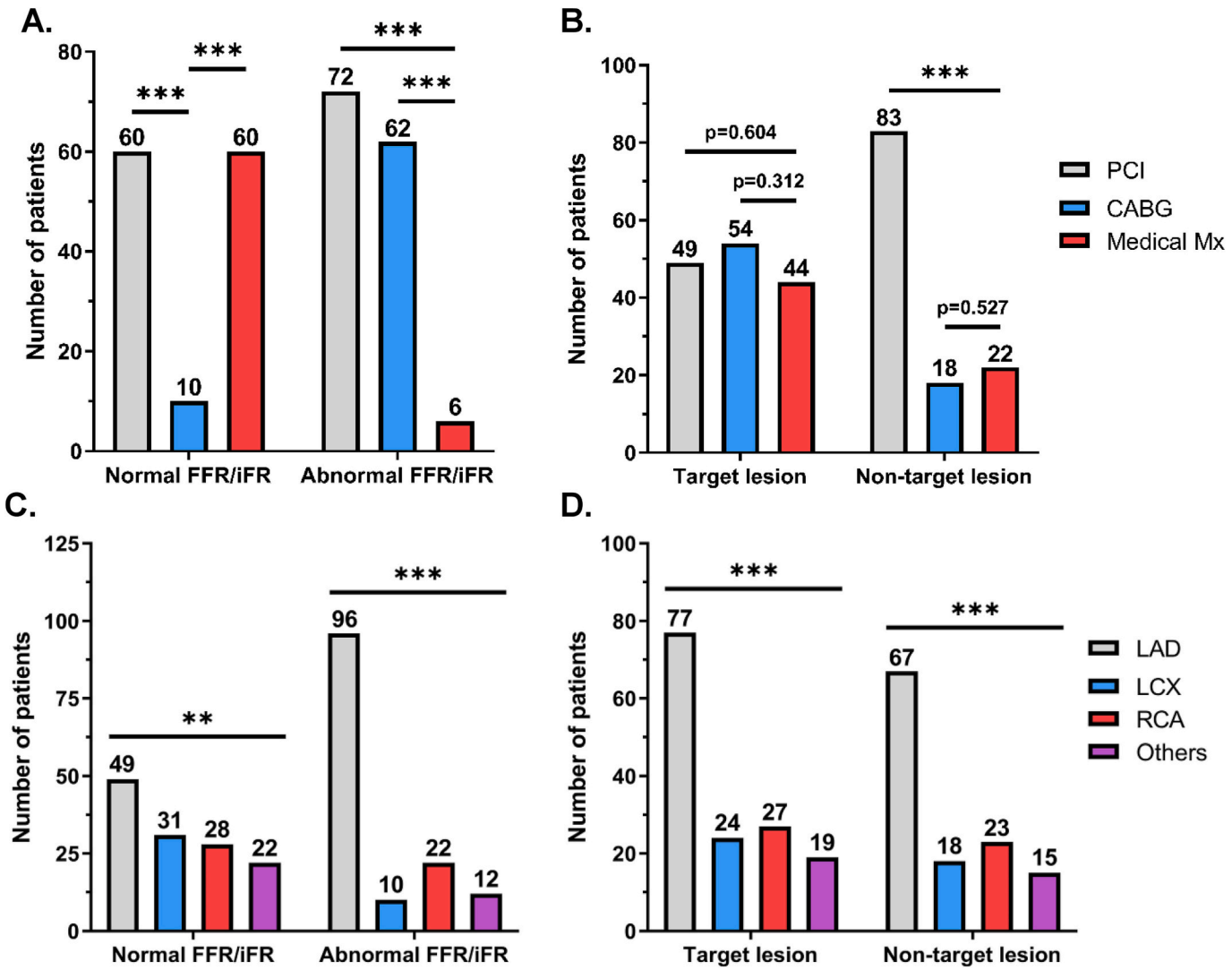

Fig. 1. Overall proportions of treatment modalities and lesion locations by FFR/iFR results and lesion classification. Patients were categorized based on the selected treatment strategy (percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), and medical treatment (Med Mx)) as well as by FFR/iFR values (normal and abnormal) **(A)** or lesion types (target and non-target) **(B)**. Patients were further categorized based on the location of the lesion involved in the treatment (left anterior descending (LAD), left circumflex (LCX), right coronary artery (RCA), and other vessels) in addition to FFR/iFR values **(C)** or lesion types **(D)**. ** indicates $p < 0.01$, and *** indicates $p < 0.001$.

higher in LAD than in other arteries (Fig. 2F). Taken together, these findings demonstrate that two-vessel CAD patients with LAD stenosis were more frequently treated by PCI.

3.4. Proportions of treatment selections and lesion locations in three-vessel CAD patients

121 patients with three-vessel CAD underwent FFR/iFR testing. 54 patients with three-vessel CAD had abnormal FFR/iFR values in the target lesion, and the majority underwent CABG (37 patients, 68.5 %) instead of PCI (12 patients, 22.2 %) or medical treatment (5 patients, 9.3 %) (Fig. 3A). Conversely, of the patients with normal FFR/iFR testing in the target lesion, there were no notable differences between the number of patients treated medically (6 patients, 50.0 %) compared to those who received PCI (2 patients, 16.7 %) or CABG (4 patients, 33.3 %) (Fig. 3A). These results highlight a preference towards CABG with abnormal FFR/iFR values in the target vessel of patients with three-vessel CAD. 25 patients with three-vessel CAD had abnormal testing in non-target lesions, and patients either received PCI (13 patients, 52.0 %) or underwent CABG (12 patients, 48.0 %) (Fig. 3B). Interestingly, the remaining patients with normal FFR/iFR in non-target lesions either received PCI (17 patients, 56.7 %) or were treated medically (13 patients, 43.3 %), and no patients underwent CABG (Fig. 3B).

55 three-vessel CAD patients with non-target lesions were tested, and the majority received PCI (30 patients, 54.6 %) instead of medical therapy (13 patients, 23.6 %) or CABG (12 patients, 21.8 %) (Fig. 3C). 66 three-vessel CAD patients with target lesions were tested, and substantially more patients underwent CABG (41 patients, 62.1 %) than medical treatment (11 patients, 16.7 %) or PCI (14 patients, 21.2 %) (Fig. 3C). These findings demonstrate that with three-vessel CAD patients, abnormal FFR/iFR testing in the target stenoses led to a dramatic increase in CABG. However, PCI was favored when the non-target stenoses were tested regardless of FFR/iFR results, paralleling our observations seen with two-vessel CAD patients.

When examining the lesion distribution in three-vessel CAD patients with abnormal FFR/iFR testing, we found higher lesion counts in the LAD than in other arteries, which were seen with both target and non-target lesions (Fig. 3D, E). Conversely, no notable differences were observed regarding lesion distribution in three-vessel CAD patients with normal FFR/iFR testing in either target or non-target lesions (Fig. 3D, E).

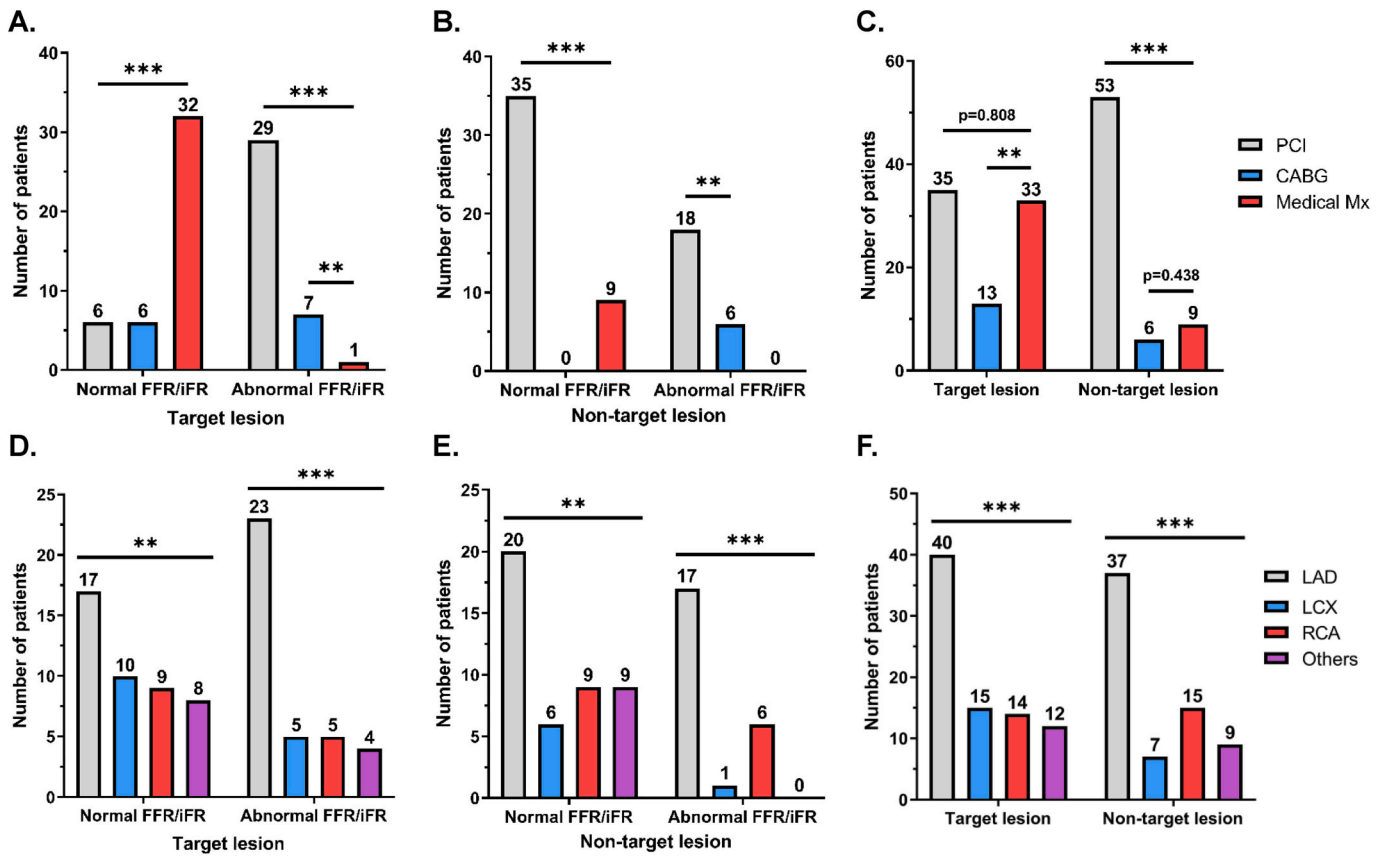

Fig. 2. Proportions of treatment modalities and lesion locations by FFR/iFR results and lesion classification in two-vessel CAD. Two-vessel CAD patients were categorized by the selected treatment strategy (percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), and medical treatment (Med Mx)) in addition to FFR/iFR values (normal and abnormal). Patients were subcategorized based on whether target lesions were involved in the treatment **(A)** or if the treatment included non-target lesions **(B)**. Patients were then separated based on the selected treatment strategy and lesion types (target and non-target) regardless of FFR/iFR results **(C)**. Two-vessel CAD patients were further categorized by the location of the lesion involved in the treatment (left anterior descending (LAD), left circumflex (LCX), right coronary artery (RCA), and other vessels) in addition to FFR/iFR values. Patients were subcategorized based on whether target lesions were involved in the treatment **(D)** or if the treatment included non-target lesions **(E)**. Patients were then separated based on the lesion location and lesion types regardless of FFR/iFR results **(F)**. ** indicates $p < 0.01$, and *** indicates $p < 0.001$.

Lastly, in patients with three-vessel CAD regardless of whether a target or non-target lesion was being tested, lesions counts were markedly higher in LAD than in other arteries (Fig. 3F). Overall, these observations indicate that three-vessel CAD patients with abnormal testing and LAD stenosis were more frequently treated by either PCI or CABG, while no definitive inferences could be made regarding patients with normal testing.

4. Discussion

FFR/iFR testing is the standard invasive assessment of the physiologic impact of lesions on the myocardium in coronary angiography. In this retrospective study, we examined how treatment strategy was decided based on FFR/iFR outcomes in vessel locations selected clinically. Furthermore, we assessed if differences in the selection of treatment modality were based on whether the vessel tested was the clinical target stenosis vessel.

Here, we demonstrate an overall increase in revascularization (PCI and CABG) and decreased medical management both with abnormal FFR/iFR assessment and in non-target lesions. With two-vessel CAD patients, abnormal FFR/iFR testing in both target and non-target lesions resulted in a notable preference towards PCI selection and a decrease in medical management. With three-vessel CAD patients, however, abnormal FFR/iFR values led to a marked increase in CABG in target lesions only. Moreover, tested lesions were primarily located in the LAD when compared to other coronary arteries. While two-vessel CAD patients with LAD stenosis were more frequently treated by PCI regardless of FFR/iFR values, revascularization was preferred in three-vessel CAD patients with LAD stenosis only with abnormal testing.

These findings demonstrate the use of functional revascularization in contemporary practice. The performance of a functional test is itself a marker for consideration of a revascularization procedure. When a target lesion is tested, the test itself reflects a leaning towards revascularization. When non-target stenoses are tested, it suggests that the presence of a significant lesion in another vessel would alter the treatment strategy by impacting the number of vessels diseased.

The number and identity of affected vessels chosen for testing when proving the severity of a lesion will alter the preferred treatment strategy. In real-world contemporary practice, invasive physiological testing is not applied randomly, but rather it is used in focused situations when ascertaining the functional number of vessels diseased may alter the preferred treatment strategy. In most situations, this resulted in increased PCI as the revascularization strategy over CABG. This skew can be identified by case selection for these tests, as the treatment modality changes based on the lesion classification (target vs. non-target) as well as the number of diseased vessels involved (two-vessel vs. three-vessel).

Since the introduction of FFR in 1993 [6] and most recently iFR in 2012 [7], physiology-guided revascularization has provided an evidence-based approach to managing patients with CAD. Multiple landmark trials [8,10] [9] have shown the FFR-guided revascularization strategy to be safe, cost-effective, and associated with reduced adverse

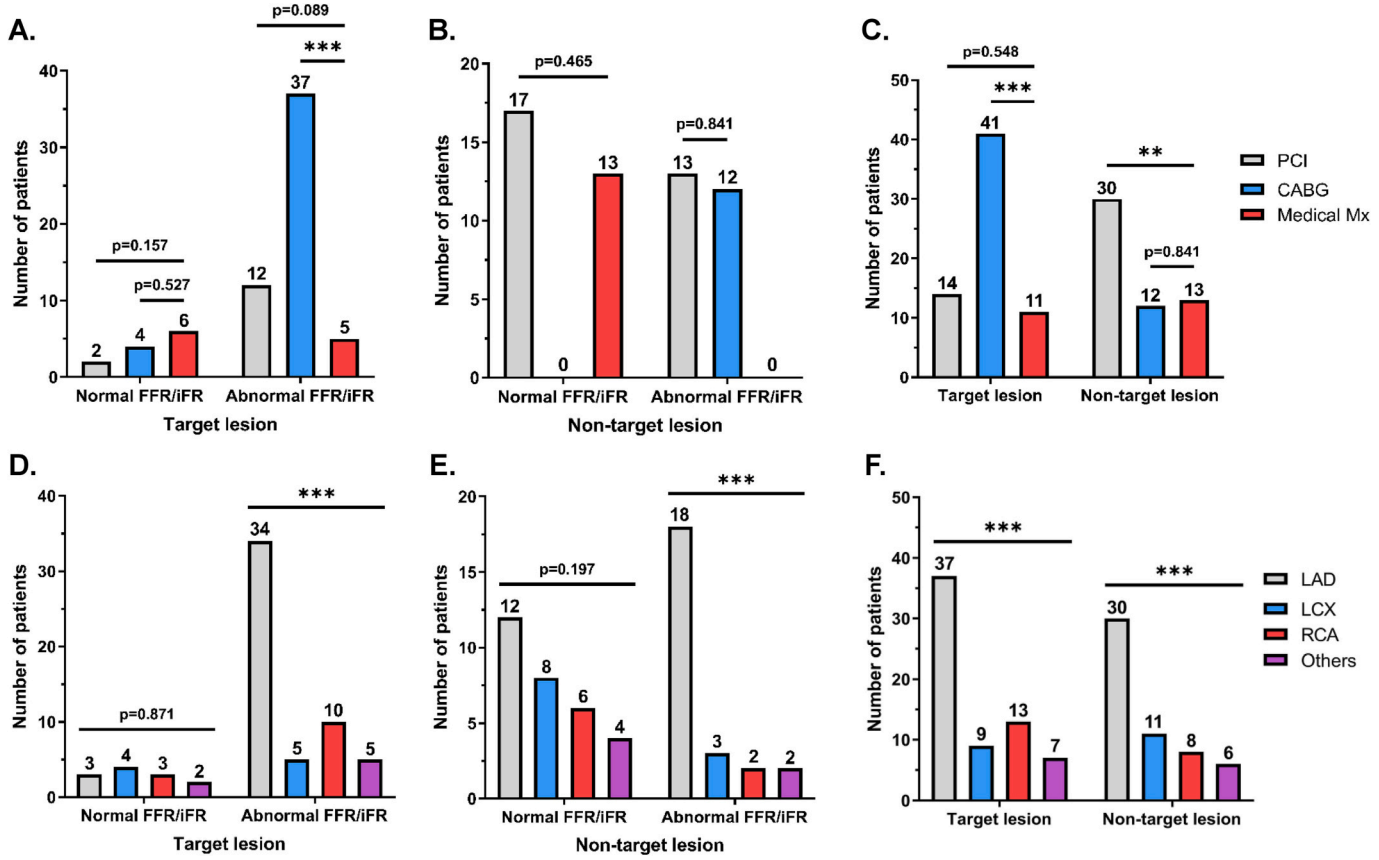

Fig. 3. Proportions of treatment modalities and lesion locations by FFR/iFR results and lesion classification in three-vessel CAD. Three-vessel CAD patients were categorized by the selected treatment strategy (percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), and medical treatment (Med Mx)) in addition to FFR/iFR values (normal and abnormal). Patients were subcategorized based on whether target lesions were involved in the treatment **(A)** or if the treatment included non-target lesions **(B)**. Patients were then separated based on the selected treatment strategy and lesion types (target and non-target) regardless of FFR/iFR results **(C)**. Three-vessel CAD patients were further categorized by the location of the lesion involved in the treatment (left anterior descending (LAD), left circumflex (LCX), right coronary artery (RCA), and other vessels) in addition to FFR/iFR values. Patients were subcategorized based on whether target lesions were involved in the treatment **(D)** or if the treatment included non-target lesions **(E)**. Patients were then separated based on the lesion location and lesion types regardless of FFR/iFR results **(F)**. ** indicates $p < 0.01$, and *** indicates $p < 0.001$.

cardiac events compared to the angiography-guided strategy. The non-inferiority of iFR to FFR in predicting cardiovascular outcomes and a reasonable alternative for physiologic assessment has also been demonstrated. In patients with multi-vessel disease, non-invasive testing often underestimates the burden of coronary stenosis [11,12]. Even though non-invasive tests, such as stress echocardiography and myocardial perfusion scintigraphy, provide information regarding ischemic burden, these tests have poor discrimination in identifying which lesions cause ischemia, especially in patients with multi-vessel disease [11,12]. Hence, there is a strong need for accurate functional testing to identify if a specific coronary lesion produces ischemia or not.

About 70 % of patients referred for PCI have multi-vessel CAD [13], and in these patients, non-invasive testing is often unreliable. FFR/iFR can be used to aid decision-making, especially in cases where there is discordance between lesion severity/location and non-invasive testing. The FAME-2 trial demonstrated the superiority of FFR-guided PCI plus medical therapy over medical management alone in patients with multi-vessel CAD. The FFR-guided group showed lower rates of the primary endpoint of all-cause death, non-fatal MI, and repeat revascularization. This difference was largely driven by a greater need for urgent revascularization in patients managed with medical therapy alone [14]. These findings raise curious questions about the utility of physiologic parameters in the selection of patients for CABG, where the anticipation that non-significance in one or more vessels would prevent a patient from open-heart surgery and instead receive a coronary stent. A study led by Fearon et al. [15] observed about 1500 patients from 48 centers, and they found that in patients with CAD, FFR-guided PCI was not found to be inferior to CABG with regards to incidence of death, MI, stroke, or repeat vascularization at 1-year.

Multiple trials including SYNTAX, SYNTAX II l, FAME, and FAME II have evaluated the impact and use of FFR on PCI and revascularization. FAME demonstrated lower rates of major adverse cardiac and cerebrovascular events with the use of FFR. FAME II also used an FFR-guided modality for revascularization in combination with medical management, and their outcomes demonstrated a benefit against patient mortality with physiologic revascularization [2]. A recent meta-analysis analyzed the prognostic value of FFR, where linking physiologic severity to clinical outcomes suggested that FFR-guided strategy leads to revascularization approximately half as often as anatomic-based strategies [16]. FFR-guided strategy was also associated with a 20 % lesser incidence of adverse events and 10 % better angina relief [16]. An evolving discussion regarding the appropriateness of stenting a lesion is based on its functionality that may lead to significant occlusion. FFR can help us distinguish lesions, which are functionally significant and obstructive, from non-obstructive lesions, and thus assist in guiding treatment selection when choosing PCI vs. bypass graft [3].

Society guidelines summarize the value of physiologic testing in appropriate treatment selection for patients to direct them to either PCI or CABG [18]. The functional syntax score will differ based on angiographic interpretation and inclusion of intermediate but non-ischemic

lesions. This might lead to the reclassification of an angiographic three-vessel CAD to a two-vessel CAD, which would therefore benefit from PCI rather than CABG. A direct comparison between the outcomes of SYNTAX II and SYNTAX I was performed, where iFR was performed in 74 % of lesions and consequently led to deferring treatment in 31 % of interrogated lesions. At 1 year, PCI with this treatment strategy had similar outcomes to the CABG cohort in SYNTAX I. The PCI cohort, however, had lower MACE scores compared to the SYNTAX-I PCI cohort (HR 0.58 (95 % I 0.39–0.85)). The two-year follow-up for this study is still pending [18].

Long-term data on the effects of CABG on angiographically borderline stenoses are still unknown. Moreover, there are data to support that there was no difference in MACE at 3 years if patients underwent CABG vs. FFR-guided PCI [18]. These data further confirm that the transition towards physiologic assessment with FFR/iFR, which gives more objective evidence of the severity of a lesion, should be given key importance in clinical decision-making. This is especially important in lesions where there are no stress tests available or the results of the anatomic lesions and stress tests are discordant [3].

Recently, the RIPCORD2 trial discussed the blanket use of FFR as a diagnostic tool for all patients undergoing coronary angiography. In the 1100-patient study, there was no significant difference between in-hospital costs and quality of life at 1 year when testing with angiography alone when compared to angiography plus FFR usage. Interestingly, routine FFR did not reduce costs, improve quality of life, or reduce major adverse cardiac events or revascularization rates compared to angiography alone. It was instead associated with higher complication rates, contrast use, and procedural times [19]. The study, however, was likely unable to demonstrate the benefits of FFR since it was utilized as a blanket tool and not selectively.

There have been various studies assessing the use of FFR in the context of CABG selection. Spadaccio et al. [20] accounted for all the different trials conducted worldwide on the subject. The conclusions were based on the mechanisms of flow competence and whether the grafts used were arterial or venous. This study concluded that preoperative use of FFR reduces the number of distal anastomoses and simplifies CABG procedure, however, the data on improved early clinical outcomes were limited. Furthermore, preoperative data showed some correlation with arterial grafts but evidence of FFR usage in venous grafts was lacking. While the use of FFR in surgical revascularization is not definitively explored, there are some benefits of physiological testing in deciding treatment strategy [20].

The main limitation of the current study is that it was a single-center, non-randomized observational study. The data accurately reflects the use of these tests in current practice, however, several of the subgroups had too few patients to be certain that the lack of significant differences seen would be verifiable in a larger population. Angiographic reporting of stenosis severity is known to be subjective and inaccurate. Without a doubt, the angiographer had a sense of severity before FFR/iFR usage, and there is no feasible way to retroactively determine how the use of physiologic assessment may have impacted the lesion severity reported.

In conclusion, despite the use of invasive physiologic testing in patients with multi-vessel coronary artery disease, the functional number of diseased vessels may alter the preferred treatment strategy. In most situations, this may lead to a substantial increase in the use of PCI as the treatment strategy.

Ethics disclosures

This study has been approved by the human research ethics committee of the Advocate Health Care Network (Ref. No. 1243433-1).

CRediT authorship contribution statement

Harsh Rawal: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Data curation, Conceptualization. **Tung D. Nguyen:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis, Data curation. **Efehi Igbinomwanhia:** Investigation, Formal analysis, Data curation. **Lloyd W. Klein:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that there is no conflict of interest regarding the publication of this paper. There was no funding associated with the study.

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