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Published in:
Cardiovascular Revascularization Medicine

DOI:
10.1016/j.carrev.2023.03.017

Publication date:
2023

Document version:
Final published version

Cardiovascular Revascularization Medicine 54 (2023) 41–46

Contents lists available at ScienceDirect

Cardiovascular Revascularization Medicine

The Influence of Microcirculatory Dysfunction on the Resting Full Cycle Ratio Compared to Fractional Flow Reserve

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ARTICLE INFO

Article history:
Received 8 March 2023
Received in revised form 16 March 2023
Accepted 27 March 2023
Available online 31 March 2023

Keywords:
Coronary artery stenosis
Resting full cycle ratio
Fractional flow reserve
Coronary microvascular dysfunction
Index of microvascular resistance

ABSTRACT

Background: The relation between the resting full cycle ratio (RFR) and fractional flow reserve (FFR) is not fully understood. This study aims to investigate the influence of coronary microvascular dysfunction, assessed by the index of microvascular resistance (IMR), on RFR compared to FFR in patients undergoing functional assessment for coronary stenosis.

Materials and methods: Two-hundred patients with borderline stenosis underwent functional assessment of RFR, FFR, coronary flow reserve (CFR) and IMR. Retriever operator curve analysis was performed to assess the diagnostic value of RFR in patients with (IMR ≥ 24) and (IMR < 24).

Results: Median RFR did not differ significantly in patients with IMR ≥ 24 compared to patients with IMR < 24: 0.89 (interquartile range (IQR) 0.84, 0.95) vs. 0.90 (IQR 0.84, 0.92), $p = 0.29$). FFR was significantly higher in patients with IMR ≥ 24 compared to patients with IMR < 24: median FFR 0.85 (IQR (0.76, 0.92)) vs. 0.82 (IQR 0.73, 0.86), $p = 0.009$, and median CFR was significantly lower 1.80 (IQR 1.40, 2.55) vs. 2.70 (IQR 1.80, 3.95), $p < 0.001$. The diagnostic value of RFR was high (Area under the curve (AUC) 0.89 95 % Confidence Interval: [0.85, 0.93]) and AUC did not differ between patients with IMR ≥ 24 compared to patients with IMR < 24: 0.89 vs. 0.90, $p = 0.89$. An overall optimal cut off of 0.88 was identified. The cut off did not differ significantly between patients with IMR ≥ 24 compared to patients with IMR < 24: 0.88 vs. 0.90, $p = 0.397$.

Conclusion: In patients with coronary borderline stenosis, the coronary microvascular function did not influence on the cut off values or AUC of RFR compared to FFR.

1. Introduction

Atherosclerosis may lead to the development of coronary artery stenosis and occlusion, which may cause angina pectoris, myocardial infarction or sudden cardiac death [1]. Invasive assessment of coronary stenosis is obtained by a coronary angiogram (CAG) in connection with which a more objective and physiological evaluation of a coronary artery stenosis, fractional flow reserve (FFR) can be performed [2]. The ratio is obtained from measuring the proximal pressure at the tip of the guiding catheter and the distal pressure in a diseased vessel during maximal hyperemia [2]. Due to increased procedure time and cost of adenosine in addition to the patient discomfort following the induction of hyperemia, several non-hyperemic pressure ratios (NHPR) have been developed. All of them have been shown to have similar diagnostic value [3,4]. NHPRs measures the pressure difference across the stenosis to obtain a ratio. However, there is a slight difference in how the ratio is calculated. The Resting Full cycle Ratio (RFR) is calculated by finding the minimum ratio between the distal and proximal transduces during the whole cardiac cycle averaged over 5 heartbeats, and previous studies have observed an optimal cut off ratio at ≤0.89 [5].

Although there is a good diagnostic agreement between the non-hyperemic pressure indices and FFR, disagreement between the two measurements still exists in 15–20 % of cases [6]. Several theories have been proposed to explain this disagreement, and one of them being the influence of coronary microcirculatory dysfunction [6–8].

The coronary microcirculation is comprised of vessels less than approximately 300 μm in diameter responding to vasoactive stimuli [9]. Patients with classical symptoms of angina can sometimes have a normal CAG, and some of these patients may have microcirculatory disease [10]. Smoking, hyperlipidemia and diabetes are all associated with microvascular disease. The microcirculatory function can be assessed invasively as the index of microcirculatory resistance (IMR) and is not

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https://doi.org/10.1016/j.carrev.2023.03.017

Abbreviations and acronyms

LAD	Left anterior descending artery
LM	Left main
CX	Circumflex artery
RCA	Right coronary artery
RFR	Resting full cycle ratio
FFR	Fractional flow reserve
CFR	Coronary flow reserve
IMR	Index of microvascular resistance
AUC	Area under curve
ROC	Retriever operator curve
DM	Diabetes mellitus
MI	Myocardial infarction
LVEF	Left ventricular ejection fraction
BMI	Body mass index
PCI	Percutaneous coronary intervention
CABG	Coronary artery bypass graft
NHPR	Non hyperemic pressure ratio
CAG	Coronary angiogram
iFR	Instantaneous wave-free ratio

affected by epicardial disease, but only by microcirculatory disease [11]. The aim of the present study was to assess the influence of microcirculatory disease on the cut off of the RFR compared to FFR.

2. Materials and methods

This study was a single center study at Odense University Hospital. A total of 200 consecutive patients had functional assessment performed describing the severity of a stenosis found at CAG. Written and verbal consents were obtained from all patients. If a patient had a borderline lesion (visual lesion assessment of 50–70 % assessed by the operator), a full physiological flow and pressure measurement assessment with RFR, FFR, coronary flow reserve (CFR), and IMR was performed.

Heparin (5000 IE) and nitroglycerin were administrated in correspondence with hospital protocol. The Coroventis CoroFlow Cardiovascular System (Uppsala, Sweden) was used. A pressure wire (Pressurewire X, Abbott) was advanced distal to the stenosis after equalizing at the guiding catheter. The RFR measurements were performed, following the resting flow measurements for the calculation of CFR. Afterwards infusion of adenosine 140 μg/kg/min was administrated via a peripheral vein. During maximal hyperemia the FFR and the hyperemic flow were measured. CFR and IMR were measured with the thermodilution method. Approximately 3 ml of room temperature saline water was rapidly injected 3 times during both resting and hyperemic conditions to measure the transient mean time. Three transient mean times were averaged in both situations. The IMR was calculated using the hyperemic transient mean time multiplied by the distal pressure. CFR was calculated using the ratio of the resting transient mean time and the hyperemic transient mean time.

An FFR of <0.8, RFR of ≤0.89, CFR <2.0 and an IMR ≥24 were considered abnormal. Patients were divided into two groups: patients with microvascular disease (IMR ≥24) and patients without microvascular disease (IMR < 24).

2.1. Statistics

Statistical analysis was executed using STATA 17.0 software (StataCorp, College Station, TX, USA). Categorical data is presented in frequencies and numbers, and compared using chi-squared or Fishers exact test. Continuous data is presented as mean ± standard deviation (SD), and compared using Student's *t*-test. A non-parametric test is used when data is not normally distributed and presented with median and 25 % and 75 % interquartile range. Linear regression is used to evaluate the correlation between RFR and FFR using the regress and pwcorr command. Retriever operator curve (ROC) analysis is performed with the roccomb command for the ability of RFR to predict a FFR of <0.80 in patients with IMR ≥ 24 and for patients with IMR < 24. The confidence intervals for the cut off and the difference in cut off estimated using the bootstrap command and cutpt command. The point maximizing the Youden index defined the optimal cut off value. A p-value <0.05 is considered significant.

3. Results

Between March and October 2022, 200 consecutive patients who had invasive flow and pressure measurements performed were enrolled in the study. Among these, 76 (38 %) had an IMR ≥24 indicating an increased resistance in the microcirculation and 124 (62 %) patients had a normal function of the microcirculation with an IMR < 24. Baseline characteristics did not differ significantly between the two groups (Table 1).

3.1. Flow and pressure measurements

A number of 200 lesions were examined: median RFR 0.90 (IQR 0.84, 0.93), median FFR 0.83 (IQR 0.75, 0.88), median CFR 2.30 (IQR 1.50, 3.35), and median IMR 19.5 (IQR 12.0, 32.0). Median RFR did not differ significantly in patients with IMR ≥ 24 compared to patients with IMR < 24: 0.89 (IQR 0.84, 0.95) vs. 0.90 (IQR 0.84, 0.92), $p = 0.29$). FFR was significantly higher in patients with IMR ≥ 24 compared to patients with IMR < 24: median FFR 0.85 (IQR 0.76, 0.92) vs. 0.82 (IQR 0.73, 0.86), $p = 0.009$, and median CFR was significantly lower 1.80 (IQR 1.40, 2.55) vs. 2.70 (IQR 1.80,3.95), $p < 0.001$). The number of $RFR_{POSITIVE}$ (RFR ≤ 0.89) and $FFR_{POSITIVE}$ (FFR < 0.80) lesions did not differ significantly between the groups. (Table 2).

3.2. ROC curve analysis

Overall the ROC curve analysis showed a good agreement between RFR and FFR with an AUC of 0.89 95 % CI: [0.85, 0.93]. (Fig. 1A) ROC curve analysis did not differ significantly among the two groups: in the IMR ≥ 24 group AUC was 0.89 95 % CI:[0.82, 0.96] compared to AUC of 0.90 95 % CI:[0.84, 0.95] in the group with IMR < 24, $p = 0.89$. (Fig. 1B).

3.3. Cut off

In the overall population, the optimal cut off for RFR to predict an FFR value of <0.80 was 0.88 (sensitivity 87 %, specificity 74 %). In the IMR ≥ 24 group, the optimal cut off was 0.88 CI: (0.83,0.93) compared to a cut off of 0.90 CI: (0.88,0.93) in the IMR < 24 group (−0.025, CI: (−0.08, 0.03), $p = 0.397$). The cut off values gave a sensitivity and specificity of 82 % and 77 % in the IMR ≥ 24 group and of 74 % and 93 % in the IMR < 24 group, respectively. Assessing only Pd/Pa showed similar cut off value and AUC.

3.4. Positive and negative RFR, FFR, and CFR

Fig. 2A shows a box plot of IMR grouped by four combinations of positive or negative RFR and FFR. Overall IMR did not differ significantly ($p = 0.057$). Fig. 2B shows the same boxplot for CFR. Overall, there was a significant difference between the groups ($p = 0.001$). The CFR was lower in the $FFR_{POSITIVE}$ and $RFR_{POSITVE}$ groups, and was lowest if they both were positive. The $RFR_{POSITIVE}FFR_{POSITIVE}$ group had significantly lower CFR compared to the $RFR_{NEGATIVE}FFR_{POSITIVE}$ ($p < 0.001$) and the $RFR_{NEGATIVE}FFR_{NEGATIVE}$ groups. (p < 0.001) While the $RFR_{POSITIVE}FFR_{NEGATIVE}$ group had lower CFR than $RFR_{NEGATIVE}FFR_{POSITIVE}$ ($p = 0.002$) and the $RFR_{NEGATIVE}FFR_{NEGATIVE}$ groups. ($p = 0.013$).

Table 1
Baseline characteristics.

	IMR ≥ 24	IMR < 24	p-value
N	76	124	
Male gender, n (%)	60 (78.9)	100 (80.6)	0.77
Age, mean (SD)	68.7 (8.9)	66.6 (10.0)	0.15
Body mass index, mean (SD)	27.5 (4.2)	27.3 (4.2)	0.73
Creatinine, mean (SD)	87.4 (23.1)	87.9 (21.4)	0.86
Left ventricular ejection fraction(%), mean (SD)	54.5 (9.6)	54.6 (9.8)	0.96
Hypertension, n (%)	55 (72.4 %)	93 (75.0 %)	0.68
Hyperlipidemia, n (%)	54 (71.1 %)	94 (75.8 %)	0.46
Smoking active, n (%)	17 (22.4 %)	15 (12.1 %)	0.054
Diabetes, n (%)	8 (10.5 %)	25 (20.2 %)	0.075
Insulin treatment, n (%)	1 (1.3 %)	8 (6.5 %)	0.089
Oral antidiabetica, n (%)	7 (9.2 %)	17 (13.7 %)	0.34
Family history, n (%)	37 (48.7 %)	64 (51.6 %)	0.69
Prior myokardial infarction, n (%)	24 (31.6 %)	33 (26.6 %)	0.45
Prior percutaneous coronary intervention, n (%)	31 (40.8 %)	42 (33.9 %)	0.32
Prior coronary artery bypass graft, n (%)	2 (2.6 %)	5 (4.0 %)	0.60
Betablocker usage, n (%)	36 (47.4 %)	46 (37.1 %)	0.15
Calcium antagonist usage, n (%)	33 (43.4 %)	43 (34.7 %)	0.22
Nitroglycerine usage, n (%)	22 (28.9 %)	33 (26.6 %)	0.72
No antianginous medication, n (%)	23 (30.3 %)	42 (33.9 %)	0.60
Acetylsalicylic acid, n (%)	56 (73.7 %)	97 (78.2 %)	0.46
Adenosine diphosphate receptor antagonist, n (%)	20 (26.3 %)	26 (21.0 %)	0.38
Clopidogrel, n (%)	13 (65 %)	16 (62 %)	0.60
Ticagrelor, n (%)	2 (10 %)	1 (4 %)	
Prasugrel, n (%)	5 (25 %)	9 (35 %)	
Statin, n (%)	66 (86.8 %)	111 (89.5 %)	0.57
Other colesterol lowering agents, n (%)	15 (19.7 %)	12 (9.7 %)	0.043
Clinical indication			
Angina pectoris, n (%)	58 (76.3 %)	99 (79.8 %)	0.72
Non ST-elevation myocardial infarction, n (%)	10 (13.2 %)	16 (12.9 %)	
Other*, n (%)	8 (10.5 %)	9 (7.3 %)	

Other*: Valve disease (IMR ≥ 24: 1 vs IMR < 24: 3)) and Arrhythmia (IMR ≥ 24: 3 vs IMR < 24: 6).

Table 2
Lesion and procedure characteristics.

	IMR ≥ 24	IMR < 24	p-Value
N	76	124	
RFR, median (IQR)	0.89 (0.84, 0.95)	0.90 (0.84, 0.92)	0.29
Pd/Pa, median (IQR)	0.91 (0.88, 0.95)	0.92 (0.88, 0.95)	0.80
FFR, median (IQR)	0.85 (0.76, 0.92)	0.82 (0.73, 0.86)	0.009
CFR, median (IQR)	1.80 (1.40, 2.55)	2.70 (1.80, 3.95)	<0.001
Index of microvascular resistance (IMR), median (IQR)	36.00 (29.00, 51.00)	14.00 (11.00, 18.00)	<0.001
FFR < 0.80, n (%)	26 (34.2 %)	56 (45.2 %)	0.13
RFR ≤ 0.89, n (%)	39 (51.3 %)	55 (44.4 %)	0.34
CFR < 2, n (%)	44 (57.9 %)	36 (29.0 %)	<0.001
Contrast (ml), median (IQR)	50.0 (40.0, 70.0)	50.0 (40.0, 72.5)	0.95
Procedure time (minutes), median (IQR)	22.0 (15.0, 34.0)	26.0 (18.5, 38.0)	0.11
Flouroscope time (min), median (IQR)	5.0 (3.0, 8.0)	6.0 (3.6, 10.0)	0.22
X-ray dose (Gycm^2), median (IQR)	6.0 (3.0, 11.0)	7.0 (3.0, 10.0)	1.00
Radial access, n (%)	66 (86.8 %)	108 (87.1 %)	0.96
Vessel			0.006
Left main, n (%)	0 (0.0 %)	5 (4.0 %)	0.076
Left anterior acending, n (%)	48 (63.2 %)	85 (68.5 %)	0.43
Left circumflex artery, n (%)	6 (7.9 %)	19 (15.3 %)	0.12
Right coronary artery, n (%)	22 (28.9 %)	15 (12.1 %)	0.003
Consequence			
Medical treatment, n (%)	58 (76.3 %)	79 (63.7 %)	0.14
Percutaneous coronary intervention, n (%)	17 (22.4 %)	40 (32.3 %)	
Coronary artery bypass graft, n (%)	1 (1.3 %)	5 (4.0 %)	

Abbreviation: CFR: coronary flow reserve; FFR: fractional flow reserve; RFR: resting full cycle ratio.

3.5. Agreement between RFR and FFR

Fig. 3 shows a scatter plot of RFR and FFR. RFR was associated with FFR $r = 0.7537$, $p < 0.001$. Patient with negative RFR and positive FFR were significantly younger compared to the other groups. (RFR-FFR+ mean(SD) 60.7 (9.6) vs RFR + FFR+ mean(SD) 68.8(9.5) vs RFR + FFR- mean(SD) 68.6(7.1) vs RFR-FFR- mean(SD) 67.2(10.1), $p = 0.019$). There was a disagreement in 46 (23.0 %) of the values, with 29 (14.5 %) being $RFR_{POSITVE}$ and $FFR_{NEGATIVE}$, and for 17 (8.5 %) the opposite was true. Table 3 compares the baseline variables for the concordant (($RFR_{POSITIVE}$ and $FFR_{POSITIVE}$) and ($RFR_{NEGATIVE}$ and $FFR_{NEGATIVE}$)) and discordant (($RFR_{POSITIVE}$ and $FFR_{NEGATIVE}$) and ($RFR_{NEGATIVE}$ and $FFR_{POSITIVE}$)) groups. Median RFR was significantly lower (0.89 (0.87, 0.90) vs 0.91 (0.83, 0.95), $p = 0.041$) and was more often positive in the discordant group (29 (63.0 %) vs 65 (42.2 %), $p = 0.013$) compared to the concordant group, while FFR, CFR and IMR did not differ significantly. Use of beta blockage was more frequent (29 (63.0 %) vs 53(34.4 %), $p < 0.001$) in the discordant group. Assessed vessel differed significantly ($p = 0.025$), with LAD being assessed more frequent in the discordant group (38 (82.6 %) vs 94 (61.0 %), $p = 0.007$).

4. Discussion

The present study confirmed the cut off value of RFR to FFR from previous trials [6,8,12–18] and showed that the microvascular function did not influence on this cut off. The AUC and the cut off were similar between patients with microvascular dysfunction and healthy microvascular function. Overall, we found a disagreement of the RFR and FFR in nearly one fourth of the patients, however, most of these values were borderline values and close to the cut off values.

Other studies have found similar AUC of the RFR compared to FFR as in the present study [6,8,12–18]. Most of these studies did not measure

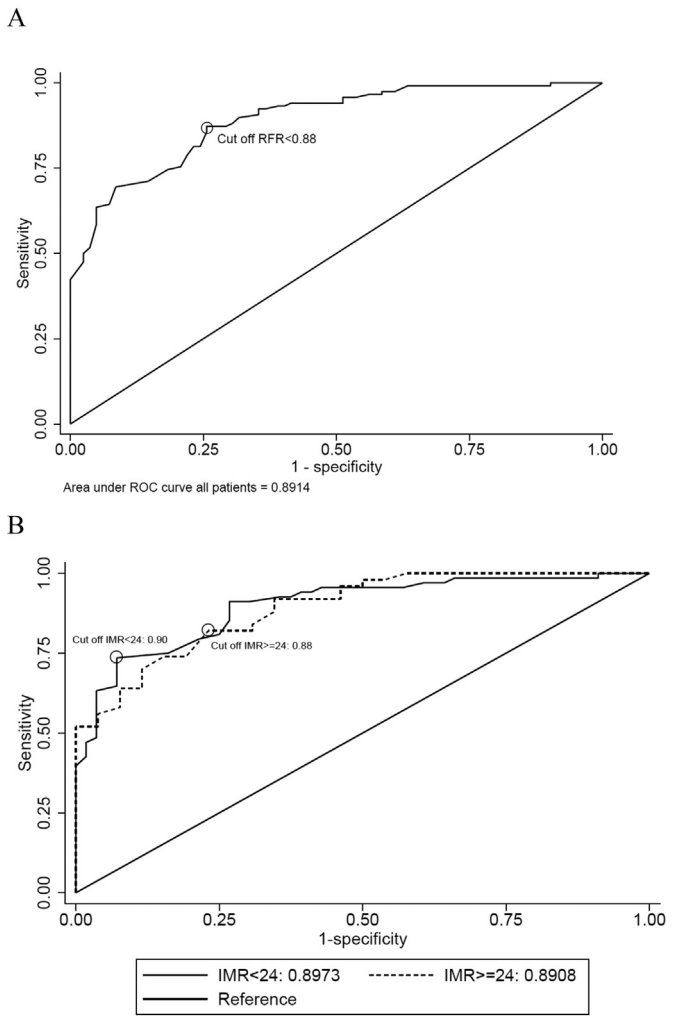

Fig. 1. A: ROC curve of RFR in patients with coronary artery stenosis ($n = 200$). B: ROC curve of RFR in patients with coronary stenosis with IMR ≥ 24 ($n = 76$) and IMR < 24 ($n = 124$). Abbreviations: ROC: Retriever operator curve, AUC: Area under curve, RFR: Resting full cycle ratio, FFR: Fractional flow reserve, IMR: Index of microvascular resistance.

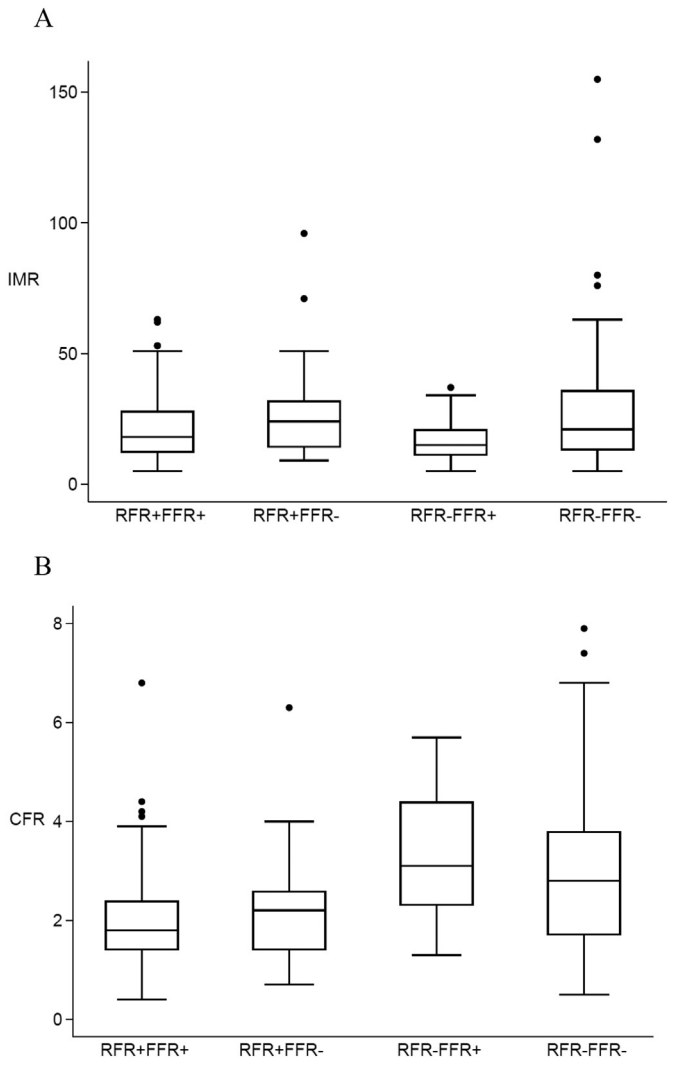

Fig. 2. A: Box plot of IMR by groups of RFR and FFR. B: Box plot of CFR by groups of RFR and FFR. Abbreviations: RFR: Resting full cycle ratio, FFR: Fractional flow reserve, IMR: Index of microvascular resistance.

IMR and mainly focused on the overall diagnostic value of RFR, and other factors influencing the disagreement of RFR and FFR. The patient characteristics and comorbidity differed among the different studies. Other studies have found an optimal cut off ranging from 0.88 to 0.92 [5,8,12–14]. and the cut off of 0.88 in the present study clinical was close to the clinical used cut off of 0.89. RFR shows similar results between studies in a wide range of indications and comorbidities, this strengthens the results of RFR as having a good diagnostic performance.

The microcirculation is of great significance on the functional assessment of a stenosis. The coronary arteries differentiate itself from other arteries due to the changing influence of the microcirculation. During the cardiac cycle, resistance in the microvascular bed is not constant. Pressure indices relay on the linear relationship between pressure and flow. However, a change in resistance influences this relationship. In FFR, adenosine induces hyperemia and thereby reduces and creates a constant resistance. The pressure difference is measured and averaged over several heart beats [19]. Other NHPR – like the instantaneous wave-free ratio (iFR) – generally measure the pressure difference on moments where the resistance is constant [19]. The RFR is calculated by finding the greatest pressure drop during the whole cycle [5]. Increased resistance in the microcirculation affects how the vascular bed response to adenosine, and potentially influence the linear relationship

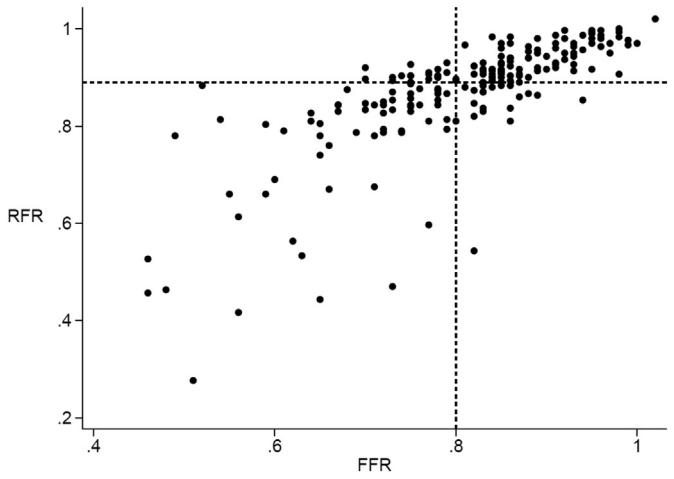

Fig. 3. Scatterplot of FFR and RFR. Abbreviations: RFR: Resting full cycle ratio, FFR: Fractional flow reserve.

Table 3
Concordant/discordant for RFR and FFR: baseline, lesion and procedure characteristics.

	Concordant	Discordant	p-Value
N	154	46	
Male gender, n (%)	124 (80.5)	36 (78.3)	0.74
Age, mean (SD)	67.92 (9.83)	65.72 (8.90)	0.18
Body mass index, mean (SD)	27.25 (3.89)	27.85 (5.03)	0.39
Creatinine, mean (SD)	87.71 (22.39)	87.74 (20.81)	0.99
Left venticular ejection fraction(%), mean (SD)	54.29 (9.63)	55.54 (9.80)	0.44
Hypertension, n (%)	114 (74.0 %)	34 (73.9 %)	0.99
Hyperlipidmia, n (%)	111 (72.1 %)	37 (80.4 %)	0.26
Smoking active, n (%)	27 (17.5 %)	5 (10.9 %)	0.28
Diabetes, n (%)	23 (14.9 %)	10 (21.7 %)	0.28
Insulin treatment, n (%)	6 (3.9 %)	3 (6.5 %)	0.45
Oral antidiabetica, n (%)	17 (11.0 %)	7 (15.2 %)	0.44
Family history, n (%)	76 (49.4 %)	25 (54.3 %)	0.55
Prior myocardial infarction, n (%)	42 (27.3 %)	15 (32.6 %)	0.48
Prior percutanous coronary intervention, n (%)	58 (37.7 %)	15 (32.6 %)	0.53
Prior coronary artery bypass graft, n (%)	6 (3.9 %)	1 (2.2 %)	0.58
Betablocker usage, n (%)	53 (34.4 %)	29 (63.0 %)	<0.001
Calcium antagonist usage, n (%)	54 (35.1 %)	22 (47.8 %)	0.12
Nitroglycerine usage, n (%)	41 (26.6 %)	14 (30.4 %)	0.61
No antianginous medication, n (%)	56 (36.4 %)	9 (19.6 %)	0.033
Acetylsalicylic acid, n (%)	119 (77.3 %)	34 (73.9 %)	0.64
Adenosine diphosphate receptor antagonist, n (%)	35 (22.7 %)	11 (23.9 %)	0.87
Clopidogrel, n (%)	22 (63 %)	7 (64 %)	0.57
Ticagrelor, n (%)	3 (9 %)	0 (0 %)	
Prasugrel, n (%)	10 (29 %)	4 (36 %)	
Statin, n (%)	136 (88.3 %)	41 (89.1 %)	0.88
Other colesterol lowering agents, n (%)	20 (13.0 %)	7 (15.2 %)	0.70
Clinical indication, n (%)			
Angina pectoris, n (%)	118 (76.6 %)	39 (84.8 %)	0.49
Non ST-elevation myocardial infarction, n (%)	22 (14.3 %)	4 (8.7 %)	
Other*, n (%)	14 (9.1 %)	3 (6.5 %)	
RFR, median (IQR)	0.91 (0.83, 0.95)	0.89 (0.87, 0.90)	0.041
FFR, median (IQR)	0.84 (0.72, 0.90)	0.82 (0.78, 0.84)	0.47
CFR, median (IQR)	2.20 (1.50, 3.50)	2.35 (1.60, 3.10)	0.65
IMR, median (IQR)	19.0 (12.0, 32.0)	21.0 (14.0, 32.0)	0.81
FFR < 0.8, n (%)	65 (42.2 %)	17 (37.0 %)	0.53
RFR ≤ 0.89, n (%)	65 (42.2 %)	29 (63.0 %)	0.013
CFR < 2, n (%)	62 (40.3 %)	18 (39.1 %)	0.89
IMR ≥ 24, n (%)	57 (37.0 %)	19 (41.3 %)	0.60
Contrast (ml), median (IQR)	50.0 (40.0, 70.0)	55.0 (40.0, 80.0)	0.14
Proceduretime (minutes), median (IQR)	24.0 (16.0, 35.0)	25.0 (20.0, 40.0)	0.40
Flouroscope time (min), median (IQR)	5.0 (3.0, 8.0)	6.1 (4.7, 10.0)	0.21
X-ray dose ($Gycm^2$), median (IQR)	6.0 (3.0, 10.0)	7.0 (3.0, 11.0)	0.44
Radial access, n (%)	133 (86.4 %)	41 (89.1 %)	0.62
Vessel			0.025
Left main, n (%)	4 (2.6 %)	1 (2.2 %)	0.87
Left anterior decending, n (%)	94 (61.0 %)	39 (84.8 %)	0.003
Left circumflex artery, n (%)	23 (14.9 %)	2 (4.3 %)	0.057
Right coronary artery, n (%)	33 (21.4 %)	4 (8.7 %)	0.051
Consequence			
Medical treatment, n (%)	102 (66.2 %)	35 (76.1 %)	0.062
Percutaneous coronary intervention, n (%)	49 (31.8 %)	8 (17.4 %)	
Coronary artery bypass graft, n (%)	3 (1.9 %)	3 (6.5 %)	

Abbreviations: CFR: coronary flow reserve; FFR: fractional flow reserve; IMR: Index of microvascular resistance; RFR: Resting full cycle ratio. Other* Valve disease (IMR ≥ 24: 2 vs IMR < 24: 2) and Arrhythmia (IMR ≥ 24: 1 vs IMR < 24: 8).

between flow and pressure. A coronary artery stenosis may be less flow limiting in case of microcirculatory dysfunction because of less dilation of the vascular bed to the adenosine stimuli compared to a healthy microcirculation.

Other studies have reported on the influence of microvascular function on the diagnostic performance of RFR and disagreements between RFR and FFR [7,12]. In a study from Legutko et al. [12], 101 patients (157 lesions) with stable coronary disease were assessed with RFR and FFR, the influence of coronary microvascular dysfunction defined as IMR ≥ 25 were investigated. They found that IMR ≥ 25 was an independent predictor of disagreement RFR/FFR vessels in a population with high rates of hypertension (96 %), dyslipidemia (91 %), and diabetes mellitus (42 %), all factors important in microvascular disease. The study had less FFR positive lesions (around 30 %) than our study. However, they had more patients with coronary microvascular dysfunction (47 %). When investigating the influence of the IMR measurement, treated as a continuous value, they, similar to our study, could not find an influence.

In another study from Lee et al. [7], the influence of IMR on the NHPR iFR was evaluated. In that study, 596 patients (840 lesions) underwent functional assessment of stenosis with iFR, FFR, CFR, and IMR. They found an overall difference in IMR when lesions were divided in four combination groups ($RFR_{POSITVE}$ and $FFR_{POSITIVE}$ – $RFR_{POSITIVE}$ and $FFR_{NEGATIVE}$ – $RFR_{NEGATIVE}$ and $FFR_{POSITIVE}$ – $RFR_{NEGATIVE}$ and $FFR_{NEGATIVE}$), whereas IMR did not differ significantly between the groups, indicating little influence of IMR.

IMR is an independent prognostic factor in patient with angina [1]. Due to similar symptoms, it may be difficult to differentiate coronary obstructive diseases and microvascular dysfunction. In RFR and FFR borderline cases, the IMR could have the potential to guide the operator in decision-making. If IMR is increased, the patient may not be free from symptoms after revascularization and further medical treatment may be needed op top of revascularization to reduce or remove the patient's symptoms.

Overall, we found a disagreement of the NHPR RFR and FFR in nearly one fourth of the patients, however, most of these values were borderline values and close to the cut off values. In clinical practice, this would translate to a higher degree of reliability in the RFR if the value is further away from the cut off. An earlier study found greater diagnostic ability, if the RFR was not in the grey area (0.86–0.93) [17]. Three studies [13–15] have tried to make a hybrid method to achieve a higher sensitivity and specificity, while still minimizing the need for adenosine and shortening the procedural time: (1) Casanova-Sandoval et al. [13] found a greater diagnostic ability and a decreased need for adenosine with a hybrid method of only using adenosine in borderline cases, RFR 0.86–0.92, (2) Lei et al. [14] found a better diagnostic agreement and less need for adenosine with a hybrid strategy in a RFR 0.85–0.93 region and (3) Di Serafino et al. [15] used a hybrid method of 0.86–0.93 with iFR, RFR, and the diastolic pressure ratio (DPR) to achieve the same. A similar hybrid method would also achieve greater diagnostic value in the population of this study.

4.1. Impact on daily clinical practice

Our study found a good diagnostic performance of the RFR. Today's guidelines with a cut off of 0.89 is almost similar to the 0.88 in the present study. The impact of microvascular diseases seems to be small in a clinical practice, with no influence on the diagnostic ability and importantly no influence on the clinically used cut off value. The results of this study show that the RFR is safe to use in clinical practice and that the diagnostic performance are not influenced by the coronary microvascular function.

4.2. Limitations

This study has several limitations. The decision to use flow and pressure measurements was up to the operator, which may lead to bias. However, this study acts like a real-world scenario, with a population treated in a real clinical situation. The wide inclusion criteria can be viewed as a strength of the study, as it increased the external validity. The termodiluation methods is limitated by the need for true resting and hyperemic conditions, and is sensitive for a correct volume during the injections. Adenosine was infused by a standard recommendation dose, and the patients had either symptoms of the adenosine infusion or pressure changes. However, we did not increase the adenosine dose to test if total hyperemiae was obtained.

5. Conclusion

Coronary microvascular dysfunction did not influence the cut off and the diagnostic ability of the adenosine-free non-hyperemic pressure

ratio RFR in patients undergoing functional assessment of coronary artery stenosis compared to FFR.

CRediT authorship contribution statement

JT and LOJ formulated the study design. JT was responsible for data management and for design and implementation of the statistical analysis. All other authors took part in patient enrollment and data collection. JT and LOJ contributed to the design of the statistical analysis and the interpretation of results. JT drafted the article, which was subsequently seen and reviewed by all authors. All authors have seen the final submitted article, and they agree with its contents. JT and LOJ had full access to all the data in the study.

Declaration of competing interest

LOJ has received research grants from Biotronik and Biosensors to her institution and honoraria from Biotronik. JT, KNH, MN, JEG, AJ, KTV, MH, COF and HSH declare that they have no conflicts of interest.

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