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Functional assessment of in-stent restenosis with quantitative flow ratio.

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Short title: In-stent restenosis functional assessment with QFR

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Classifications*: In-stent restenosis, Fractional Flow Reserve, QCA*

Abbreviations:

ISR: In-stent restenosis

FFR: Fractional Flow Reserve

QFR: Quantitative Flow Ratio

3D-QCA: Three-dimensional Quantitative Coronary Analysis

DS: Diameter Stenosis

Introduction

Coronary angiography is the most common diagnostic tool to assess in-stent (ISR) severity, both in clinical practice and trials [1]. Yet, given its poor ability to depict functional stenosis relevance, FFR has been proposed as reference standard to ascertain functional ISR severity [2]. More recently, quantitative flow ratio (QFR) has been validated in de novo lesions as angiography-based approach to functional stenosis characterization that does not require intracoronary instrumentation [3]. We investigated the diagnostic performance of QFR in ISR lesions, using FFR as reference standard.

Methods

This is a multi-center, international, retrospective, blinded study, enrolling patients from 3 hospitals in three countries (*Hospital Clínico San Carlos, Spain, Toda Chuo General Hospital, Japan and Sejong General Hospital, South Korea*). Study population consisted of a group of ISR patients in whom FFR was used to guide coronary revascularization in clinical practice. Patients with ISR defined as ≥50% diameter stenosis in-stent, or within 5 mm from the stent edges, luminal narrowing as judged visually were considered for the study. Details regarding data collection and analysis are available in Supplementary Material.

Results

QFR analysis was performed in 78 vessels (73 patients) with ISR, all investigated with FFR (Figure1). Supplementary Table1 shows details on patient demographics and clinical characteristics. Angiographic and physiological variables are shown in Table

1. Stenosis severity was intermediate both in terms of angiography (mean DS%: 51% ± 9%) and FFR (mean value: 0.79 ± 0.09).

Mean difference between FFR and QFR was only 0.01 ± 0.09 (Supplementary Figure1). Classification agreement between FFR and QFR (in terms of dichotomous functional significance) was high, i.e. 83%. Functional assessment of ISR lesions with QFR was comparable to that reported in de novo lesions in previous studies (Supplementary Table 2). Additionally, the area under the ROC curve (AUC) demonstrated high diagnostic performance of QFR regarding its ability to establish ISR relevance, taking FFR as reference [AUC: 0.90 (0.83 – 0.97)] (Figure2). Although, there was a difference in classification agreement between vessels, this was not of statistical significance (Supplementary Table 3). The study also confirmed the low diagnostic yield of angiography in ISR: a 50% DS criterion classified correctly in terms of functional severity only 68% of ISR cases (Table 2). QFR analysis of ISR cases correctly reclassified (as judged by FFR) as functionally non-significant 45% of ISR lesions.

Discussion

Our findings support the use of QFR to outline functional relevance of ISR, with similar diagnostic efficiency as that reported for QFR in major studies in de novo lesions. Compared with available series, classification agreement of QFR and FFR in ISR lesions is similar to two major pivotal studies of QFR-FFR in de novo lesions [4,5]. Importantly, 45% of the ISR cases deemed significant by angiographic criteria, were judged as functionally non-significant both by QFR and FFR, showing that due to its high negative predictive value, QFR can lead to safe deferral of revascularization of significant proportion of ISR lesions. Furthermore, QFR can be useful as research tool in assessing long-term results of stenting.

Limitations

The main limitation of our study was its retrospective character, with exclusion of cases with suboptimal angiography or vessel overlap that may have caused selection bias.

Conclusion

QFR has a high diagnostic performance in assessing ISR lesions, similar to that of de novo lesions, and therefore may facilitate adoption of functional assessment in these lesions.

Impact on daily practice

By not requiring intracoronary instrumentation nor drug administration, QFR may facilitate adoption of functional assessment in ISR. Given its high negative predictive value, QFR will contribute to avoiding unneeded interventions in patients with ISR.

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Conflict of interest statement: None of the authors have conflicts of interest

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Figure legends:

Figure 1: Case example of QFR analysis of intermediate ISR in left anterior descending artery (LAD).

A) Long LAD stented segment analyzed. **B)** Two angiographic projections > 25° apart allow 3-diamensional vessel reconstruction. **C)** QFR computed based on 3D-QCA and TIMI frame count, resulting in QFR value of 0.89 (non-significant). **D)** FFR value was 0.89. Green lines represent proximal and distal borders of the segment with the most significant lesion and red line represents the most severe stenosis level.

Figure 2: Significant difference in diagnostic performance of QFR and %DS in identifying significant lesions in ISR population.

The area under the curve using FFR as reference standard shows high diagnostic accuracy of QFR but low diagnostic accuracy of %DS for ISR lesions.

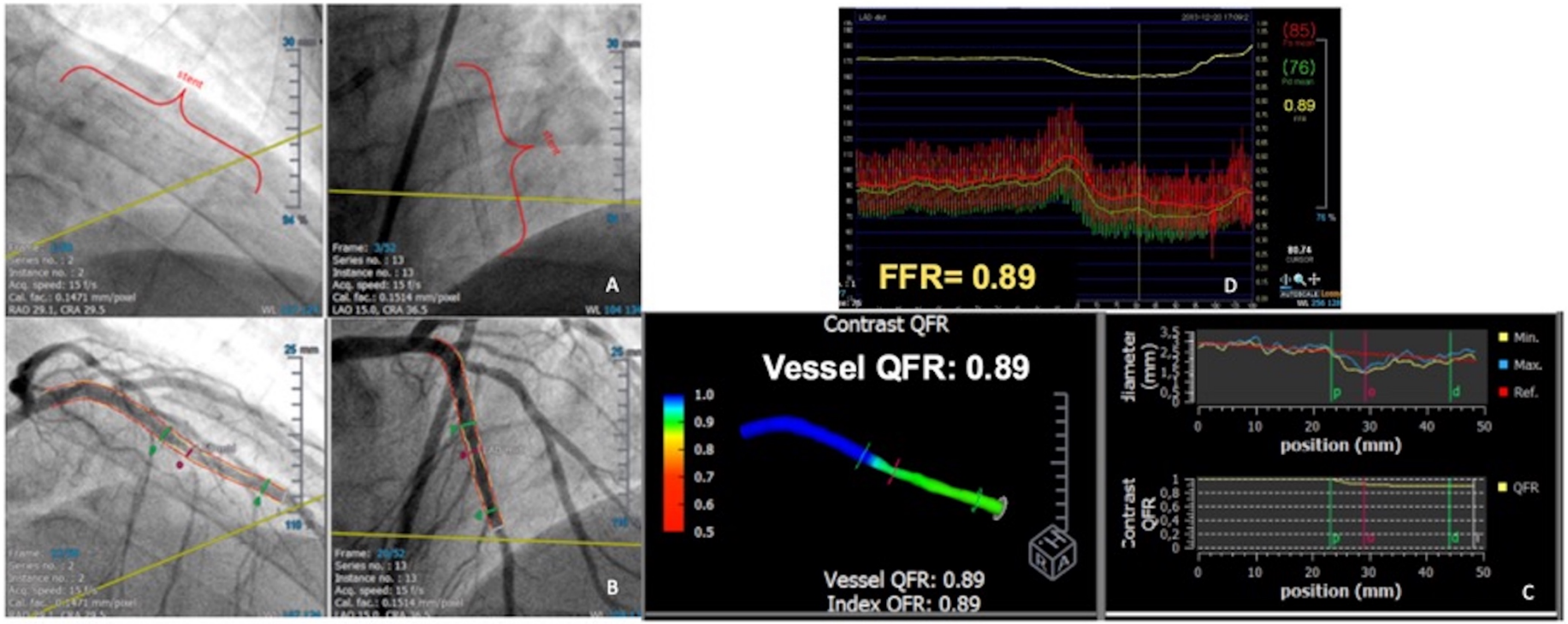
Tables

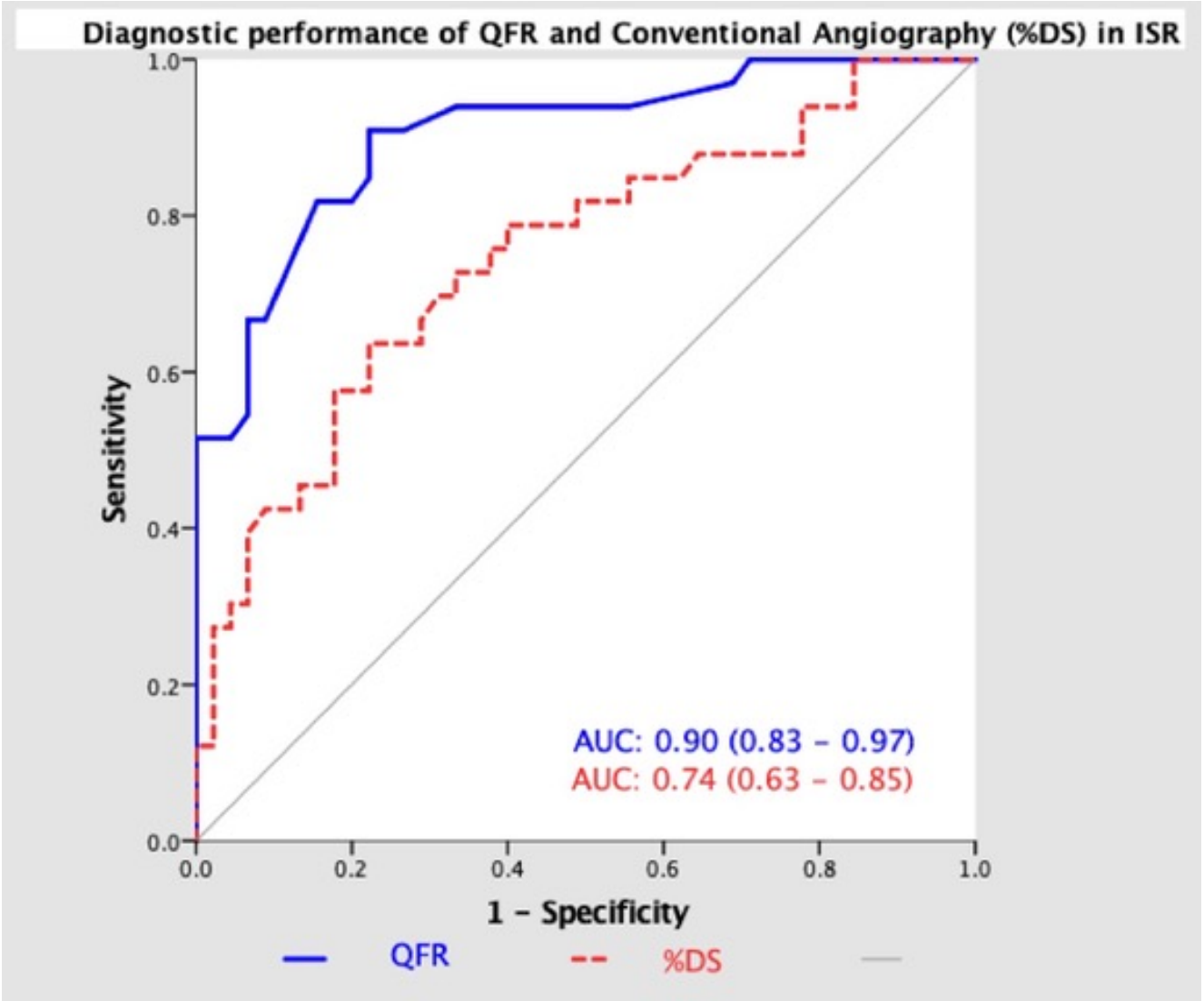
Table 1. Vessel characteristics

QFR analysis in ISR N=78 vessels			
Lesion location N, (%)		**Minimal lumen diameter (mm)**	1.3 (1.0 – 1.5)
Left anterior descending	46 (59)	**DS % (mean)**	51 ± 9
Left circumflex artery	12 (15)	**Vessels with DS by 3D-QCA ≥50%, N (%)**	38 (49)
Obtuse marginal branch	4 (5)	**Area stenosis % (mean)**	67 ± 10
Right coronary artery	16 (21)	**Lesion length, mm**	19.2 (12.9 – 31.4)
Segment location N, (%)		**FFR (per vessel)**	0.81 (0.75 – 0.87)
Proximal	33 (42.3)	**Vessels with FFR ≤ 0.80 (%)**	33 (42)
Mid	41 (52.6)	**QFR (per vessel)**	0.80 (0.72 – 0.87)
Distal	4 (5)	**Vessels with QFR ≤ 0.80 (%)**	40 (51)
Reference vessel diameter (mm)	2.7 (2.2 – 3.0)		

Table 2. Diagnostic Performance of QFR and 3D-QCA DS in ISR population using FFR as reference

	QFR	DS by 3D-QCA ≥50%
Classification agreement N, (%)	65 (83%)	53 (68%)
Spearman/ Pearson correlation, (rho/r)	0.731	0.433
AUC	0.90 (0.83-0.97)	0.74 (0.63-0.85)
Sensitivity (%)	91 (74-97)	70 (51-83)
Specificity (%)	78 (62-88)	67 (50-79)
PPV	75 (58-86)	61 (43-75)
NPV	92 (77-97)	75 (58-86)
+ LR	4.1 (2.3-7.1)	2.0 (1.3-3.3)
- LR	0.1 (0.0-0.3)	0.4 (0.2-0.7)





Functional assessment of in-stent restenosis with quantitative flow ratio. Supplementary Appendix.

Methods

Study design

This study enrolled patients from 3 hospitals in three countries (*Hospital Clínico San Carlos, Spain, Toda Chuo General Hospital, Japan and Sejong General Hospital, South Korea*). Patients' demographic and clinical characteristics, procedural reports, angiographic views and raw coronary physiology data were collected from the participating hospitals and sent to the core laboratory (Hospital Clínico San Carlos) where the QFR analysis was performed in a blinded fashion regarding FFR values.

Study population

The study group consisted of patients with ISR in whom FFR was used to guide coronary revascularization in the clinical practice. Patients with ISR defined as ≥50% diameter stenosis in-stent, or within 5 mm from the stent edges, luminal narrowing as judged visually were considered for the study. In cases of acute myocardial infarction, the investigated vessel was not the culprit one.

The initial study population consisted of 202 vessels (190 patients): 56% derived from Hospital Clinico San Carlos, 12% from Toda Chuo Hospital and 32% from Sejong Hospital. Out of them, 90 vessels had to be excluded before starting QFR analysis due to the following exclusion criteria: history of coronary artery bypass surgery, ostial left main or ostial right coronary artery lesions, occlusive restenosis, bioresorbable scaffolds, incompatibility of angiographic images

with QFR software. Another 34 vessels were excluded after starting QFR analysis due to inherent QFR exclusion criteria: lack of at least two angiographic projections >25^{o} apart, severe vessel tortuosity and/or overlap limiting QFR analysis. The final study population included a total of 73 ISR patients (78 vessels).

Pressure wire assessment

FFR values were obtained both from raw physiology studies and procedural reports. Intracoronary nitrates were administered before physiology measurements and hyperemia was induced by intravenous infusion of Adenosine (140 mcg/kg/min) through a femoral or antecubital vein during a minimum of 2 minutes. FFR was calculated as the minimum ratio between intracoronary distal pressure and aortic pressure during steady state hyperemia. In the majority of cases pressure drift was checked with the wire sensor at the tip of the guiding catheter.

QFR analysis

Two angiographic images separated > 25^{o} were selected to perform three-dimensional reconstruction of the target vessel using a dedicated software (QAngio-XA 3D, research edition, version 1.0, Medis, Leiden, The Netherlands). Calibration was automatically performed. End-diastolic frames properly opacified by contrast were selected. Two anatomical markers e.g. bifurcations were identified as reference points in the two angiographic views for automated correction of system distortions. A distal landmark in the target vessel was selected, matching the original position of the pressure-wire sensor. Whenever required, the lumen contour automatically delineated by the software algorithms was manually corrected following standard procedure. The proximal (beginning) point of QFR analysis was placed in the proximal segment of the vessel ensuring that it could serve as a reference "healthy" segment (i.e. devoid from angiographic stenosis). The proximal reference size was automatically calculated with the "Automatic" function in most cases, unless there was an ostial LAD or LCX lesion: in these cases, in order to deal with the dimensional gap with LM, the reference size was selected using

the “Normal” or the “Fix” reference function taking into account the sex and BMI of the patient. The detailed methodology has been previously described. The percent diameter stenosis (DS%), percent area stenosis (AS%), lesion length, minimum lumen diameter and reference vessel diameter were automatically derived from three-dimensional reconstruction. The contrast flow model, which uses TIMI frame count to derive contrast flow velocity from coronary angiography without pharmacologically induced hyperemia, was used for final QFR computation.

Statistical Analysis

All continuous variables were tested for normality of distribution using the Kolmogorov-Smirnov test. Continuous variables are presented as mean values ± standard deviation or median 25^{th} – 75^{th} percentile) depending on normality of their distribution. Categorical variables are presented as count and percentage (%). Differences between two continuous variables were assessed using Student’s t-test or Mann-Whitney U test accordingly. Associations between categorical variables were evaluated with the Fisher exact test. Associations between continuous variables were quantified by Pearson’s or Spearman’s correlation coefficient, as appropriate. Demographic and clinical data were analyzed on per-patient basis, while the remaining calculations were analyzed on per-vessel basis. Diagnostic performance of QFR and 3D-QCA-derived DS% were assessed by the area under the ROC curve (AUC), taking FFR as reference. Classification agreement between QFR and FFR was obtained according to the threshold ≤0.80 for both techniques. The relationship and agreement between QFR and FFR were assessed by Spearman correlation coefficient and Bland-Altman plot respectively. A p-value <0.05 was considered statistically significant. SPSS statistics, version 19 (IBM Corp., Armonk, NY, USA) and MatchIt package of R software were used for statistical analysis.

Results

Demographic, clinical and lesions' characteristics

A total number of 78 vessels (from 73 patients), that had been treated with stent implantation and developed ISR, were included in the study. Demographics and clinical characteristics are shown in Supplementary Material Table 1.

Overall, the left anterior descending artery was the most frequently studied vessel. Mean length of implanted stent in ISR was 21±7 mm. The stenoses had intermediate angiographic severity (DS% derived by 3D-QCA 51% ± 9%).

Coronary physiology characteristics

The investigated ISR lesions had intermediate functional severity, as judged both by FFR and QFR (mean FFR value: 0.79 ± 0.09, mean QFR value: 0.78 ± 0.11). Mean difference between FFR and QFR values was not significant (Supplementary Figure 1). ISR lesions were functionally non-significant in 58% and 49% of cases according to FFR and QFR values respectively.

The classification agreement between FFR and QFR (in terms of dichotomous functional significance) was as high as 83%, similar to the one reported in two previous studies (Supplementary Table 2). The mean difference between FFR and QFR was low (0.01 ± 0.09). A strong correlation between FFR and QFR values was additionally found (rho=0.73, $p<0.001$). Although, there was a difference in classification agreement according to investigated vessel, this was not of statistical significance (Supplementary Table 3).

Functional assessment of ISR lesions with QFR showed a high diagnostic performance (AUC 0.90 [95% CI, 0.83 – 0.97]). Sensitivity, specificity, positive and negative predictive values were 91%, 78%, 75% and 92% respectively.

Assessment of stenosis severity with 3D-QCA

The correlation between DS% and FFR was only moderate ($r= -0.43$, $p<0.001$), and its diagnostic performance in assessing functionally significant lesions was notably inferior to QFR (table 2, figure 2).

Supplementary Figure legend:

Supplementary Figure 1: Agreement between QFR and FFR

Bland – Altman plot shows good agreement between QFR and FFR in ISR lesions. The lines illustrate the mean difference ± 2SD.

Tables

Supplementary Table 1. Demographic and clinical characteristics of the ISR population

Age	67.5 ± 11
Male, N (%)	59 (81)
BMI (kg/m^2)	26.5 (24.3 – 28.9)
HTN, N (%)	52 (71)
Dyslipidemia, N (%)	52 (71)
Smoke, N (%)	11 (15)
Diabetes Mellitus, N (%)	22 (30)
CKD, N (%)	9 (12)
Previous MI, N (%)	42 (58)
Clinical Presentation	
Stable Angina, N (%)	50 (69)
Unstable Angina, N (%)	19 (26)
Acute MI, N (%)	4 (6)

BMI: Body Mass Index, HTN: Hypertension, CKD: Chronic Kidney Disease, MI: Myocardial Infarction

Supplementary Table 2. Classification agreement between QFR and FFR in previous large studies.

Study	Classification Agreement
FAVOR II Europe – Japan Study	86.8%
FAVOR II China Study	92.7%
WIFI II Study	83%
Current ISR study	*83%*

Supplementary Table 3. Classification agreement according to vessel analysis

N=78

Vessel	N	Classification Agreement	p-value
LAD	46	76%	
LCX-OM	16	94%	0.120
RCA	16	94%