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# Standardized angiographic projections allow evaluation of coronary artery side branches with quantitative flow ratio (QFR)



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ARTICLE INFO	A B S T R A C T		
Keywords: Computational fluid dynamics QFR Coronary artery disease Chronic coronary syndrome Non-invasive imaging Side branches Coronary angiography and physiology	Quantitative flow ratio (QFR) is a novel, software-based noninvasive method for the quantitative evaluation of coronary physiology. QFR results correlate with invasive FFR measurements in the three main epicardial coronary arteries. However, QFR data for the evaluation of coronary side branches (SB) are scarce. The evaluation of QFR-performance of SB was retrospective and prospective. Eighty-seven patients with suspected chronic coronary syndrome, who received angiography using routine core lab projections, were retrospectively analyzed. On the second part 37 patients, who received angiography using recommended standardized coronary angiography projections, were prospectively analyzed. Quantitative coronary angiography (QCA) by two certified experts with the software QAngio XA 3D 3.2. Using routine projections, QFR computation in 55 % of the SB were obtained (123 out of 224). Using standardized projections, 85 % of SB were computed by QFR (64 out of 75; p < 0.001 vs routine projections). The fluoroscopy time for recommended projections was not significantly different as opposed to routine projections (3.75 ± 2.2 vs. 4.58 ± 3.00 min, p = 2.6986). Using the standardized projections was associated with a higher amount of contrast medium (53.44 ± 24.23 vs. 87.95 ± 43.73 ml, p < 0.01), longer overall procedure time (23.23 ± 16.35 vs. 36.14 ± 17.21 min, p < 0.01) and a higher dose area product (1152.28 ± 576.70 vs. 2540.68 ± 1774.07 cGycm <sup>2</sup> , p < 0.01). Our study shows that the blood flow of the vast majority of coronary SB can be determined non-invasively by QFR in addition to the main epicardial coronary arteries when standardized projections are used.		

# 1. Introduction

In patients with coronary artery disease, without non-invasive ischemia test present, angiography-based functional assessment remains the state of the art to assess the hemodynamic relevance of intermediate coronary stenosis and guide the percutaneous coronary intervention (PCI). Therefore, these methods are marked with a class I level A recommendation in the current myocardial revascularization guidelines of the European and American Society of Cardiology [1,2]. Pressure wire-based physiological measurements, with (FFR) or without the administration of hyperaemia-inducing agents (iFR, RFR), identifies

more accurately significant lesions than visual angiography alone [3–6]. Although these methods are widely accepted, they are largely underused in real clinical practice. Dattilo et al. demonstrated that FFR, despite a wealth of data demonstrating their utility for the evaluation of intermediate coronary lesions, was only used in a small minority of such cases (6.1 %), analyzing data of 61,874 attempted coronary interventions of intermediate coronary stenoses [7].

The low frequency of use might be due to the long procedural time, lack of availability, potential complications from pressure wire instrumentation, side-effects from hyperemic agents, such as dyspnea, chest pain or arrhythmia, and problems with the reimbursement due to high

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*Abbreviations:* PCI, percutaneous coronary intervention; SB, side branches; CAD, chronic artery disease; DAP, dosis area product; FS, foreshortening; VL, vessel length; FFR, fractional flow reserve; VO, vessel overlap; QFR, quantitative ratio; LAD, Left anterior descending artery; QCA, quantitative coronary angiography; LCx, Left circumflex artery; DB, diagonal branch; OM, obtuse marginal artery; RCA, right coronary artery; RAO, Right anterior oblique; LAO, Left anterior oblique; CAU, caudal; CRA, cranial; AP, anterior posterior; LVEF, left ventricular ejection fraction; MLD, maximum lumen diameter; IA, intermediate artery; PDA, posterior descending artery; PLB, posterolateral branch; CTO, chronic total occlusion.

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#### cost.

In order to overcome some of these obstacles of invasive methods and thereby lower the threshold for functional assessments, a recently introduced method called contrast-flow quantitative ratio (QFR) has been developed. QFR, derived from three-dimensional coronary artery angiography (3D-QCA) and fluid dynamics computations enables the online estimation of the FFR, without the use of a pressure wire or pharmacological agents to induce hyperaemia [8]. Previous studies have shown a high correlation of QFR to associated FFR measurements, a good inter-observer reliability and demonstrated the feasibility and accuracy of online QFR-Measurements in assessing the hemodynamic relevance of coronary stenoses [9,10]. The most recently published FAVOR-III China-Trial was a randomized multicenter trial compared a QFR-guided PCI-strategy with an angiography-guided strategy. This trial showed that the QFR-guided strategy of lesion selection improved the 1-year clinical outcomes compared with the angiography-guided group [11].

QFR-Computations were evaluated only over epicardial vessels in all studies. Bifurcation lesions, as well as coronary side branch (SB) lesions are still one of the challenging objects during percutaneous coronary interventions (PCI) [12]. Whether QFR bears the potential to apply its benefits to the evaluation of coronary side branches is still unknown.

Taking the relevance of the extent of myocardial ischemia for outcome and long-term prognosis in myocardial revascularization into account, very little is known about coronary side branches and their physiological effects or their effects in myocardial ischemia in coronary artery disease (CAD) [13]. This uncertainty is based on the absence of sufficient data concerning the impact of side branches on myocardial perfusion, resulting in a difficult and often non-standardized assessment and PCI of lesions on SB. Especially given, that a bifurcation-PCI is still constrained by higher long-term adverse events, such as in-stent-restenosis, and particularly periprocedural myocardial infarction, compared to non-true bifurcations [14]. For this reason, it would be useful to know, prior to PCI and preferably noninvasive, whether the target side branch supplies a relevant fractional myocardial mass (amount of myocardium which benefits from a revascularization, %FFM > 10 %), especially considering that side branches > 2.5 mm and longer than 100 mm will probably supply FFM > 10 %, as the proposed treatment algorithm in patients with bifurcation lesions in Sheiban et al. showed [15]. Thus, our PCI-strategy could be adjusted, or an unnecessarily complicated bifurcation-PCI could be avoided. To improve the shortage of evidence-based criteria, this study focused on identifying optimal viewing angles for the assessment of SB. Furthermore, we intended to determine the feasibility of QFR to analyze SB prior to a potential PCI, aiming to improve estimation of stenosis by reducing extensive foreshortening (FS) and vessel overlap (VO) as well as determine anatomical indices such as VL noninvasively with QFR, to potentially consider a PCI-strategy. To define optimal viewing angles, routine cath lab projections were compared to recommended viewing angles, which are provided by the QFR software - QAngio-XA 3D software (Version 3.2, by Medis, Leiden, The Netherlands).

#### 2. Materials and methods

# 2.1. Trial design

The evaluation of QFR-performance of SB was a retrospective and prospective, non-randomized, single-center study at the Department of Cardiology, University Hospital Leipzig, Germany approved by the ethics committee of Leipzig University (369/19-ek). Patients with chronic coronary syndrome (CCS) and indication for an invasive coronary angiography were selected from the hospital database as part one for a retrospective analysis of routine cath-lab projections. Prospectively included patients as part two, underwent angiography using recommended projections of the corresponding main vessel (Table 1). For example, recommended LM/LAD projections were used for the

#### Table 1

Acquisition Aid for QFR<sup>®</sup>, Medis Medical Imaging Systems, Leiden University Medical Center (LUMC) The Netherlands.

Target main vessel	1 <sup>st</sup> X-Ray-Angiography	2 <sup>nd</sup> X-Ray-Angulation
LM & LAD/LCX LAD/Diag. LCX/OM	RAO 20, CAU 45 AP, CRA 45 LAO 10, CAU 25	AP, CAU 10 RAO 30, CRA 20 RAO 25, CAU 25
RCA	LAO 45, CAU 10	LAO 20 , CRA 20

LM: Left main artery; LAD: Left anterior descending artery; LCX: Left circumflex artery; Diag: Diagonal branch; OM: Obtuse marginal artery; RCA: Right coronary artery; RAO: Right anterior oblique; CAU: Caudal; AP: Anterior posterior; CRA: Cranial; LAO: Left anterior oblique.

computation of diagonal branches (DB). As there are multiple recommended viewing angles for each main vessel, the distribution of viewing angles in successful QFR computations was compared.

Assessed side branches were obtuse marginal [OM], diagonal branch [DB], intermediate artery [IA], posterolateral branch [PLB] and posterior descending artery [PDA]. Vessel access for both groups was preferably via radial artery. The application of nitroglycerin i.v. was routinely given.

Exclusion criteria in both groups were acute coronary syndromes within 72 h, coronary artery bypass grafting to the target vessel, more than one chronic total occlusion (CTO), impaired cardiac function with a left ventricular ejection fraction (LVEF) <30 % or kidney function with a glomerular filtration rate (GFR)  $\leq$ 30 ml/min/1.73 m<sup>2</sup> and characteristics limiting QFR computation (ostial stenosis >50 %, ongoing atrial fibrillation and ventricular arrhythmias, poor or insufficient image quality, severe FS or severe VO of the target vessel). SB with a MLD of <2 mm, measured proximately based on QCA, were excluded from further evaluation.

Furthermore, baseline characteristics, anatomical SB parameters such as MLD (mm) and vessel length (VL; mm) of the SB, result of the QFR-computation and procedure parameters, such as use of applicated contrast medium, fluoroscopy time and DAP, were analyzed.

The two QFR-Investigators were blinded. Angiographic SB evaluability was determined by a successful acquisition of QFR computation. To visualize the process of SB evaluation for final analysis a flow chart has been included (Fig. 1).

# 2.2. 3D-QCA and QFR

OFR computation process of SB was performed by two certified and experienced investigators with the above-mentioned software. First, side branches were measured at the largest visible diameter proximally over the end-diastolic phase of the cardiac cycle, using the software's measuring tool based on QCA. QFR computation was performed only for SB with a maximum lumen diameter (MLD) of  $\geq 2$  mm. Second, for each SB, two suitable projections separated at least 25° with a minimum of VO and FS were chosen. In the prospective group all angiograms were obtained with 15 frames per second. On the other hand, in the retrospective group angiograms with 15 frames per second are used, if available. In case of significant VO or FS alternative projections were used. Using the end-diastolic phase of the cardiac cycle in both projections, vessel wall contours were automatically detected and if needed, manually aligned, to generate the reconstruction of a 3D-model of the target SB. QFR-measurement ended at the most distal point that was visible and could easily visualized on both projections. Contrast QFR was computed using the frame count method as previously published [16]. The following outcome parameters were analyzed: baseline characteristics, anatomical SB parameters such as MLD (mm) and vessel length (VL; mm) of the SB, result of the QFR-computation and procedure parameters, such as use of applicated contrast medium (ml), fluoroscopy time (min), procedure time (min) and dose area product (cGycm<sup>2</sup>).



Fig. 1. Trial profile. CCS = chronic coronary syndrome; CABG = coronary artery bypass graft; CTO = chronic total occlusion; LVEF = left ventricular ejection fraction; GFR = glomerular filtration rate; MLD = maximum lumen diameter; SB = side branches; QFR = Quantitative Flow Ratio; Values are given as absolute number or as percentage (%).

#### 2.3. Data collection and endpoints

The patient baseline und procedural characteristics are shown in Table 2. All patient related characteristics were obtained manually from the electronic database system of the University hospital of Leipzig. Specific trial-related data were collected and documented manually.

The primary objective of this trial was to determine the feasibility of QFR to analyze SB and to compare and characterize optimal viewing angles with routine angiographic projections for evaluation of SB.

Secondary endpoints were related to important procedure characteristics, such as (i) use of applicated contrast medium, (ii) fluoroscopy time, (iii) DAP and (iv) procedure time within the two groups.

#### 2.4. Statistical analysis

Baseline and vessel characteristics and QFR are presented as numbers and percentages. Continuous variables are presented as mean  $\pm$  standard deviation (SD) for normal distribution. Normal distribution of variables was checked using Kolmogorov-Smirnov Test of normality.

Normally distributed continuous variables were analyzed using Student's *t*-test or  $\chi^2$ -Test. If not normally distributed, Mann-Whitney *U* Test was used and data were presented as median and interquartile range (IQR). Time applicated contrast medium and fluoroscopy time were compared using Student's *t*-test for independent samples.

Statistical analyses were performed with SPSS software package (IBM Corp. Released 2018. IBM SPSS Statistics for MAC, Version 27.0. IBM Corp., Chicago, IL, USA) and Microsoft Excel (Microsoft Corp. Released 2021. Microsoft Excel for MAC, Version 16.48. Microsoft Corporation, Redmond, WA, USA). A two-sided p-value of  $\leq$ 0.05 was considered statistically significant.

# 3. Results

For retrospective analysis of routine core lab projections 87 patients were selected from the hospital database. Out of 435 potential SB 224 SB were  $\geq 2 \text{ mm}$  (51 %) and 123 SB (55 %) were computable with the use of QFR. Between 2020 und 2022, in the prospective cohort of 37 patients (185 potential SB) with recommended angiographic projections for QFR

#### Table 2

Patient characteristics.

	Routine Projections (n = 87)	Recommended Projections (n = 37)	p-value < 0.05
Clinical characteristic	s		
Age ( $y \pm SD$ )	$65\pm10$	$65\pm14$	0.94
Female (%)	24	32	0.34
Weight (kg $\pm$ SD)	$78\pm13$	$84\pm15$	0.11
Height (cm)	173 (166–178)	174 (165–178)	0.86
BMI (kg/m <sup>2</sup> $\pm$ SD)	$27\pm4$	$28\pm5$	0.17
Hyperlipidemia n (%)	40 (46)	22 (59)	0.21
Hypertension n (%)	69 (79)	33 (89)	0.27
Diabetes mellitus n (%)	28 (32)	12 (32)	0.96
Smoking n (%)	37 (43)	17 (46)	0.56
- previous n (%)	14 (16)	9 (24)	
Positive Family history n (%)	16 (18)	11 (30)	0.17
RR <sub>sys</sub> (mmHg)	145 (130-155)	147 (131–160)	0.56
RR <sub>dia</sub> (mmHg)	83 (75–90)	85 (73–92)	0.97
HR (/min)	76 (65–85)	71 (65–81)	0.49
Clinical history n (%)			
Myocardial	24 (28)	18 (49)	0.03
infarction			
- STEMI	18 (21)	14 (38)	
- NSTEMI	6 (7)	4 (11)	
Stroke	1 (1)	5 (14)	0.04
PAD	5 (6)	3 (8)	0.65
COPD	7 (8)	2 (5)	0.58
Bronchial asthma	4 (5)	2 (5)	0.87
Heart rhythm disturbances	21 (24)	4 (11)	0.14
Initial LVEF (%)	57 (45–65)	56 (50–60)	0.99
Symptoms n (%)			
Stabile AP	4 (5)	17 (46)	0.33
Unstable AP	69 (79)	7 (19)	0.29
Dyspnea	37 (43)	22 (59)	0.31
Palpitations	14 (16)	2 (5)	0.87
Fatigue	40 (46)	1 (3)	0.03
Troponin-T elevation	62 (71)	16 (43)	0.22

Values are given as median  $\pm$  standard deviation (SD), % or Median (IQR), p-value < 0.05. STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; COPD: chronic obstructive pulmonary disease; PAD: peripheral artery disease; AP: angina pectoris; LVEF: left ventricular ejection fraction; BMI: body mass index; RR: Riva-Rocci; Sys: systolic; Dia: diastolic; HR: heart rate.

analysis of main branches, 75 SB were  $\geq 2 \text{ mm}$  (41 %) and included. 64 of the 75 SB (85 %) were computable with the use of QFR. In total out of overall 299 potential SB  $\geq 2 \text{ mm}$ , 187 (63 %) met the quality criteria for QFR and were analyzed (Fig. 1).

# 3.1. Baseline characteristics

The patient baseline and procedural characteristics are shown in Table 2. The majority of patients in both study groups were male (76 % vs. 68 %). Mean age was 65  $\pm$  10 vs. 65  $\pm$  14 years.

The mean left ventricular ejection fraction (LVEF) was 57 % (45–65 %) vs. 56 % (50–60 %). A high cardiovascular risk profile for patients with coronary artery disease was present in accordance with data published to date. Regarding cardiovascular risk factors in both study groups, there was no significant difference in the presence of hypertension (p = 0.27), hyperlipidemia (p = 0.21), positive family history (p = 0.17), diabetes mellitus (p = 0.96), smoking (p = 0.56) and body weight (p = 0.11). A significant difference in the study populations was found for prior myocardial infarction (28 % vs 49 %; p = 0.03) and prior stroke (1 % vs 14 %; p = 0.04). Fatigue symptoms were more present in the group of routine projections (46 % vs 3 %; p = 0.03).

# 3.2. QFR-analysis

In the retrospective group of routine projections 123 of the included SB were eligible for further analyzation, while 101 SB did not match all criteria for QFR analysis due to projection errors like: missing projection 25° apart, vessel overlap or excessive foreshortening, lack of full vessel filling and panning - resulting in an evaluability of 55 % using QFR software.

The mean MLD was 2.27  $\pm$  0.27 mm, while the mean proximal lumen diameter (PLD) was 2.1  $\pm$  0.3 mm. The mean distal lumen diameter (DLD) was 1.57  $\pm$  0.3 mm, and the mean reference diameter (RD) 1.93  $\pm$  0.4 mm. We found a computable mean vessel length (VL) of 54.1  $\pm$  17 mm.

In the prospective study group, comprising 185 potential SB in total 75 SB met the inclusion criteria of an MLD  $\geq 2$  mm. A successful QFR computation was performed in 64 out of 75 SB. 11 vessels were not eligible for computation due to projection quality and vessel overlap, resulting in an overall evaluability of 85 %. The mean MLD was 2.4  $\pm$  0.38 mm and mean PLD was 2.1  $\pm$  0.6 mm. DLD was 1.5  $\pm$  0.46 mm and mean RD 2  $\pm$  0.55 mm. The computable mean VL was 53.9  $\pm$  17.9 mm. In both groups the dominant reason for not analyzable vessels was due to poor projection quality and vessel overlap.

There was no significant difference between the two groups regarding vessel characteristics of analyzed SB with an MLD > 2 mm (p > 0.05). On the other side there was a significant difference regarding exclusions criteria for QFR-analysis due to projection errors (FS or VO) between the two groups (p < 0.001) resulting in a significant difference between the two groups regarding the QFR evaluability of SB using the recommended projections in comparison with the routine projections (p < 0.001) (Fig. 2).

187 coronary side branches >2 mm have been analyzed. The most frequently analyzed vessels in both groups were the obtuse marginal branches (OM) (30.9 % and 43.8 %), followed by the diagonal branches (DB) (25.2 % and 21.9 %) and posterolateral branch (PLB) (18.7 % and 23.4 %), as shown in Table 3 below.

#### 3.3. Side branches characteristics

Side branches specific data are presented in Table 3 below. The group with routine projections presented 2.5 SB  $\geq$ 2 mm per patient, while the group with recommended projections presented 1.9 SB  $\geq$ 2 mm per patient. This difference was not significant (p = 0.369).

Most assessed vessels showed a better evaluability with the use of recommended projections, except PDA with equal evaluability (p = 0.966) and IA (p = 0.371), as shown in Fig. 2. The highest significant increase in evaluability was found for the PLB from 43 % in routine projections to 93 % in recommended projections (p < 0.001). Overall, there was a significant difference between the two groups regarding evaluability of the SB using the recommended projections vs. routine projections (p < 0.001) as visualized in Fig. 2.

Comparing anatomical indices in both study groups, the measurable mean vessel length was higher but did not increase significantly with the use of recommended projections. The mean maximum lumen diameter (MLD) was also higher, without a significant increase in recommended projections.

#### 3.4. Optimal projections for QFR-analysis of side branches

Analyzing all used projections, we found certain viewing angles that can lead to a better performance in the evaluation of SB, as shown in Fig. 3. OM branches are best evaluated with the combination of RAO25/ CAU35 and LAO10/CAU25. Evaluation success increased by 20 % compared to routine projections. For DB, RAO30/CRA20 and AP/CRA45 were used in over 90 % of successful computations. The evaluability increased by 33 %. This was achieved by the significant reduction of foreshortening in both recommended projections. IA was evaluated best



Fig. 2. A–C: QFR evaluability in overall of side branches using (a) routine projections and (b) recommended projections and as (c) routine projections vs. recommended projections with p-value in overall (all values are given in %). OM: obtuse marginal artery; DB: diagonal branch; IA: intermediate artery; PLB: posterolateral branch; PDA: posterior descending artery; Rout: routine projections; Rec: recommended projections.

with the use of RAO25/CAU35 and AP/CRA45 or LAO10/CAU25. Computation performance of IA was the highest in both study groups. This can be explained by the anatomical appearance of IA, which is comparable to a main vessel in most cases, simplifying the process of QFR computation. The SB of the right coronary artery, PLD and PBA were best evaluated using almost always the same viewing angles, LAO20/CRA20 and LAO45/CAU10 as mentioned in Fig. 3.

# 3.5. Applicated contrast media

The median volume of applicated contrast medium for the recommended projections group was 72.5 ml (IQR 56.25 – 107.3 ml), and 45 ml (IQR 40–62.5 ml) for the routine projections group (Fig. 4). A significant difference was found between the groups (53.44  $\pm$  24.23 vs. 87.95  $\pm$  43.73 ml, p < 0.01).

#### 3.6. Procedure-related fluoroscopy time and dose area product

The median fluoroscopy time for the recommended projections

group was 3.675 min (IQR 2.1–6.475 min), and 3 min (IQR 2–5.5 min) for the routine projections group (Fig. 4). No significant difference was found between the groups ( $3.75 \pm 2.2 \text{ vs.} 4.58 \pm 3.00 \text{ min}, p = 2.6986$ ).

The median dose area product for the group with the recommended projections was 2036 cGycm<sup>2</sup> (IQR 1215.25–2869.25), and 1116 (IQR 1533.5–627.5) for the group with the routine angiographic projections (Fig. 4). A significant difference was found between the groups (1152.28  $\pm$  576.70 vs. 2540.68  $\pm$  1774.07 cGycm<sup>2</sup>, p < 0.01).

#### 3.7. Procedure time in overall

The median procedure time for the recommended projections group was 33.5 min (IQR 21.25–51.75 min), and 20 min (IQR 14–24.5 min) for the routine projections group (Fig. 4). A significant difference was found between the groups (23.23  $\pm$  16.35 vs. 36.14  $\pm$  17.21 min, p < 0.01).

#### 3.8. QFR-results in overall

Out of 187 coronary side branches >2 mm analyzed with QFR only 4

#### Table 3

Anatomical Side branches (SB) characteristics; Values are given as n (%) or mean  $\pm$  standard deviation (SD); p-value < 0.05.

	Routine Projections (n = 87)	Recommended Projections (n = 37)	p-value < 0.05		
Maximum Lumen Diameter (MLD) in mm ± SD					
OM	$\textbf{2.28} \pm \textbf{0.26}$	$2.35\pm0.35$	0.33		
DB	$2.25\pm0.27$	$2.26\pm0.2$	0.23		
IA	$2.37\pm0.31$	$3\pm0,27$	0.47		
PLB	$2.3\pm0.33$	$2.55\pm0.42$	0.13		
PDA	$2.18\pm0.18$	$2.2\pm0.32$	0.62		
Vessel Length (VL) in mm $\pm$ SD					
OM	$59.2 \pm 22.26$	$63.3\pm17.17$	1		
DB	$49.1 \pm 13.1$	$\textbf{48.19} \pm \textbf{10.9}$	0.37		
IA	$73.1\pm20.9$	$64.72 \pm 22.8$	0.93		
PLB	$36.9 \pm 14.5$	$46.28 \pm 15.3$	0.19		
PDA	$52.3 \pm 14.4$	$40.1\pm14.6$	0.34		
Side branches	Routine ( $n = 123$ )	Recommended ( $n = 64$ )			
(SB) overall					
OM	38 (31)	28 (44)			
DB	31(25)	14 (22)			
IA	7 (5)	2 (3)			
PLB	23 (19)	15 (23)			
PDA	24 (20)	5 (8)			

vessels showed a positive and therefore hemodynamically relevant QFRcomputation <0.8 (2,1% - IA, PLD and 2xOM). IA (QFR = 0.69) and one case of OM (QFR = 0.74) were intervened using PTCA. The second case of OM (QFR = 79) was not intervened because of a negative FFRmeasurement (FFR = 0.85). The last case of PLD (QFR = 0.78) was also not intervened due to lack of suitable evidence of relevant ischemia in noninvasive stress-CMR. The majority of the SB computation showed in 91.4 % (171) of the cases in overall a QFR > 0.9. Approximately 6 % of the SB (12) showed a QFR between 0.8 and 0.89 and 2.1 % (4) a hemodynamic relevant QFR < 0.8.

#### 4. Discussion

The main novel finding of this study is that QFR is feasible for the routine assessment of side branches (SD) with MLD  $\geq 2$  mm. Furthermore, the use of the QFR-recommended projections significantly improved the quality and evaluability of the SB analysis apart from PDA and IA, without increasing the fluoroscopy time during coronary angiography. Finally, we are able to recommend specific projections for the analysis of each SB with QFR. We found a significant difference regarding the use of contrast medium, procedure time and dose area product between the groups. Overall QFR could increase the use of physiologically guided coronary interventions, not only for the main epicardial vessels, but also for the relevant big SB using the new novel virtual FFR-method. To our knowledge this is the first study evaluating QFR for SB analysis.

#### 4.1. QFR-performance of side branch-analysis

The main finding of the present study is that QFR-analysis is feasible for the assessment of large SB with a MLD >2 mm, especially while using recommended angiographic projections. Importantly, 85 % of all SB with a MLD  $\geq 2$  mm were eligible using the recommended projections and were analyzable with the QFR in contrast to 55 % of the computated SB with QFR from the group of the routine core lab projections. This led to a significant difference between the two groups regarding the QFR evaluability of coronary SB (p < 0.001). Most assessed vessels showed a better evaluability with the use of recommended projections, except PDA with equal evaluability (p = 0.966) and IA (p = 0.371). This can be explained by a larger, vessel specific, anatomic variation. Difficulties in the evaluation of the RCA using 3D-quantitative coronary angiography (3D-QCA) are known from other studies and were explainable by the specific course of the RCA with two rectangular deviations in comparison to the LCA [16,17]. In particular, Kirigaya H. et al. showed moreover, that 15 % of the lesions of this trial had a discordant result between QFR and FFR, despite the overall good correlation between the two methods [16]. Specifically, these lesions were localized either in the very proximal LAD or at the distal RCA. The reason of this mismatch was



Fig. 3. Majority distribution in recommended projections per side branch in %. RAO: Right anterior oblique; CAU: Caudal; AP: Anterior posterior; CRA: Cranial; LAO: Left anterior oblique; OM: obtuse marginal artery; DB: diagonal branch; IA: intermediate artery; PLB: posterolateral branch; PDA: posterior descending artery.



Fig. 4. A–D: Comparison of (A) the applied contrast in ml, of (B) fluoroscopy time in min, of (C) dosis area product in cGycm<sup>2</sup> and of (D) the overall-procedure time in min between the 2 groups. Rout: routine projections; Rec: recommended projections.

bad visualization of the target lesion, in the proximal LAD due vessel overlap with the DB or interventricular septal branches. Discrepancies in the distal RCA were mainly due to vessel tortuosity. In the present study a major issue even with recommended projections was that the PDA was partially obscured by the PLB in at least one of the two angulations, hindering a correct QFR computation. No discordance between QFR and FFR was detected in the LCX in the aforementioned trial, attributable to clearer visualization of the LCX-segments by less frequent VO in contrast to LAD and RCA-analysis. This aspect is consistent with the present study due to the relatively high evaluability of OM using both routine and recommended projections (73 % vs. 93 %, p = 0.025). This observation could also be confirmed in a previous study of our group, where the sensitivity of QFR in relation to stress-CMR was reduced for the RCA compared to LAD and LCX. Especially QFR-measurements of the LCX showed in that study the highest diagnostic accuracy [16]. The nonsignificant improvement, regarding IA, of the evaluability of QFR using recommended projections might be due to the small vessel-cohort with 7 analyzed IA in the group of routine projections and 2 IA in the group of recommended projections (70 % vs. 100 %, p = 0.371).

Overall, the use of recommended projections did not lead to a change in the computation of anatomical vessel indices in both study groups, like measurable VL or MLD, as demonstrated in Table 3. This underlines the general robustness of this method. Once the evaluation of the SB of interest is possible with a routine viewing angle, the analysis and QFR computation is equivalent to the computation in recommended projections. The main benefit of using recommended projections is found in the increased overall evaluability. Finally, we are able to recommend certain projections for the QFR-analysis of SB as visualized in Fig. 3, which might help increase the possibility of evaluating intermediate stenoses using a reasonable amount of time, radiation and contrast medium.

# 4.2. Secondary endpoints

The second major finding of the present study addresses a significant difference regarding the use of contrast medium (53.44  $\pm$  24.23 vs. 87.95  $\pm$  43.73, p < 0.01) and procedure time (23.23  $\pm$  16.35 vs. 36.14  $\pm$  17.21, p < 0.01) between the groups, as our data reveal. This is conceivable due to the main QFR-requirement of high-quality angiograms with 15 frames per second (fps) for optimal computation of the angiographic images in addition to sufficient contrasting of the vessels and thus to equitable contour detection, leading to an accurate 3D-QCA. However, recent studies showed that angiography derived FFR-assessment of intermediate coronary stenosis is nonetheless feasible under radiation save-mode coronary angiography (7.5 fps), which can lead to a "mini-revolution" in the context of virtual FFR [18].

Another possible reason of the additional use of contrast medium in the group of recommended projections might be the execution of the recommended angiographic projections for all coronary arteries seen in Table 1, in a high-quality fashion in contrast to the cath lab routine performance. Because of the use of the potential kidney-damaging iodine-based contrast medium, leading to a contrast medium-induced nephropathy (CIN), patients with impaired kidney function were excluded in this study (Fig. 1) [19]. Recent studies demonstrated the frequency of a CIN after a routine cardiac catheterization up to approximately 20 % [20]. This fact could not be confirmed in our study and especially in the group with the recommended projections with the high-quality fashion. How can now nevertheless a reduction of the use of contrast medium, and thus the risk of CIN, be achieved, despite further use of the recommended angiographic projections? This purpose could be achievable through the implementation of a targeted use of these recommended projections for the selected vessel instead of all recommended projections. In this respect, QFR could still be of interest to people with impaired kidney function undergoing invasive coronary angiography.

The significant difference between the two groups regarding the procedure time might be also due to the execution of all recommended angiographic projections, which certainly leads to more time consumption. This aspect can also be solved in the same way as mentioned above.

Interestingly, according to the presented data, QFR computation of the SB using recommended projections is feasible without increasing the procedure-related fluoroscopy time during the invasive coronary angiography (3.75  $\pm$  2.2 vs. 4.58  $\pm$  3.00, p = 2.6986) but with significant higher dose area product (1152.28  $\pm$  576.70 vs. 2540.68  $\pm$  1774.07, p < 0.01). Radiation exposure during coronary angiography remains a substantial concern for patients as well as interventional cardiologists, because of the cancer risk and its effects on superficial skin reactions to patients and catheterization suite staffs [21]. For this reason, the fundamental clause regarding radiation exposure ought to be "as low as possibly attainable".

The novel virtual-FFR assessments, like QFR, require for the 3D-QCA vessel reconstruction at least 2 angiographic images with 25° apart acquired with 15 fps, according to a currently recommendation. This is necessary for good vessel contour detection, which provides an accurate 3D-vessel geometry, leading to a precise vessel reconstruction and consequently QFR-computation. Unfortunately, high-quality angiographic images with >15 frames per second are associated with higher radiation exposure to patients, physicians and circulating support stuff. As a compromise, one could start with a targeted SB-strategy using QFRrecommended projections only for the culprit vessel, under radiation save-mode [18]. Targeted QFR-based SB-diagnostic strategy with the recommended projections could thereby lead to a pronounced reduction of cumulative exposure to ionizing radiation, while maintaining QFRfeasibility and accuracy. Future studies will have to prove this concept. For this reason, Shengxian Tu et al. tried to evaluate the diagnostic accuracy of computation of fractional flow reserve using QFR from a single angiographic view in patients with intermediate coronary stenosis of the FAVOR II China study population. The aim of this study was also to increase the feasibility of routine use of computational FFR in the daily routine. An artificial intelligence algorithm was used for the automatic delineation of the main epicardial coronary arteries and their side branches. The study showed a high feasibility and brilliant diagnostic accuracy of µQFR (Murray law-based quantitative flow ratio) computation from a single angiographic view in identifying hemodynamically significant coronary stenosis [22]. It is unknown whether single view µQFR analyzing coronary bifurcation lesions of the main coronary arteries in overall might perform in this setting. Kotoku Nozomi et al. showed also a high feasibility of  $\mu QFR\mbox{-}computation$  using a single angiographic view in bifurcation lesions of left main coronary artery using FFR-CT as reference [23]. From this point of view further studies are needed to perform the robustness of µQFR evaluating coronary side branches.

#### 4.3. The possible potential of side branches

The amount of myocardium that benefits from a revascularization is described as fractional myocardial mass (FFM), the ratio of vessel specific myocardial mass to whole myocardial mass. It is significant at % FFM > 10 %. As Kim et al. showed, a significant SB-specific FFM can reasonably be identified by a SB vessel length of  $\geq$ 73 mm [24]. Furthermore, side branches  $\geq$ 2.5 mm and longer than 100 mm will be probably supply a significant FFM > 10 % according to the proposed treatment algorithm in patients with bifurcation [15]. The QFR software

and its recommended viewing angles calculate the anatomical vessel length (VL) and MLD. Therefore, new possibilities arise if we could use QFR-based VL- and MLD-measurements in the decision making of SB interventions. This may help with the uncertainty in determining the relevance of SB lesions on myocardial perfusion. Compared to the wire based-FFR measurement, QFR analysis allows the investigator to assess all SB of interest in one session without the needed wire placement. Ideally, the use of the two recommended projections per SB category could be sufficient for SB examination and evaluation. This may lead to a significant reduction in procedure time, needed contrast agent and exposure to radiation, as above mentioned.

# 4.4. Limitations

Firstly, due to the retrospective analysis in the group of routine projections and the prospective analysis of recommended projections, selection bias cannot be ruled out. Secondly, the difference in sample size (n = 87 vs. n = 37) may add variability to the overall SB evaluability. Thirdly, the values could strongly depend on the investigating interventional cardiologist and on the patient's stature, which was not considered in the evaluation, especially with reference to DAP. Finally, as this is the first study concerning SB evaluation with QFR with a small-sized study group in one single center and without evidence, how single view QFR might perform in this setting, further studies are needed to evaluate the significance of QFR-based SB evaluation, as such as further ideal projection für SB for the QFR-analysis.

# 5. Conclusions

QFR is a novel virtual angiography-based method evaluating the hemodynamical relevance of coronary lesions. The presented study shows for the first time the feasibility of evaluation of coronary SB using QFR. Especially, the execution of the recommended angiographic projection for the three main epicardial vessels leads to a significantly higher evaluability of coronary SB. QFR also demonstrates the robustness of the method in computation of SB, using routine angiographic projections. With its possibility to reduce procedure time, contrast medium and exposure to ionizing radiation when a targeted SBrecommended QFR-strategy is used, QFR could improve the adjustment of physiological based revascularization of SB, determined from VL and FFM. This might be advantageous to the currently applied strategies. Based on these results, further studies can be designed to investigate the significance, possibilities, and advantages of a targeted QFR computation of the SB for clinical purposes.

# 6. Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of University of Leipzig (369/19-ek) for studies involving humans.

# 7. Informed consent statement

Informed consent was obtained from all subjects involved in the study.

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# CRediT authorship contribution statement

**M. Antoniadis:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **M. Blum:**  Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft. **M. Ussat:** Supervision, Writing – review & editing. **U.** Laufs: Resources, Supervision, Writing – review & editing. **K. Lenk:** Conceptualization, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101349.

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