Systemic analysis of diagnostic performance and agreement between fractional flow reserve and quantitative flow ratio

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SOUHRN

Úvod: Fyziologicky prováděná perkutánní koronární intervence (PCI) má podporu expertů na celém světě. Přes svoji spolehlivost se nicméně metoda frakční průtokové rezervy (fractional flow reserve, FFR) používá v klinické praxi kvůli její nákladnosti a časové náročnosti i nadále vzácně. Potřeba fyziologicky prováděné PCI podnítila pátrání po rychlejších, levnějších a přitom stejně spolehlivém alternativním způsobu stanovení průtoku krve koronárními tepnami. Od představení nové minimálně invazivní metody výpočtu FFR intervenčním kardiologům se srovnávání této metody jako zlatého standardu a nové alternativy – metody nazvané kvantitativní vyjádření průtoku (quantitative flow ratio, QFR) – stalo předmětem řady studií.

Metody: Bylo nalezeno celkem 23 publikací s výsledky studií s více než 4 000 pacienty srovnávajících reprodukovatelnost a shodu výsledků metod QFR a FFR.

Výsledky: Při vyšetření jiných než zodpovědných tepen pacientů po infarktu myokardu nebo bez něj dosáhla shoda mezi QFR a FFR hodnot 0,88, resp. 0,94. Méně spolehlivá se zdála být metoda QFR u diabetiků, protože shoda mezi QFR a FFR činila 0,74 a 0,83 u diabetiků, resp. nediabetiků. Nejdříve se doporučilo, aby se výsledky všech měření metodou QFR s hodnotami mezi 0,75 a 0,85 ověřovaly metodou FFR. Detailní analýzy mezních hodnot prokázaly pouze minimální neshodu mezi FFR a QFR při dolní mezní hodnotě 0,77 a horní mezní hodnotě 0,86. Srovnání FFR a tří typů QFR (fixní – fQFR, s použitím kontrastní látky – cQFR a s použitím adenosinu – aQFR) neprokázalo vyšší přesnost metody aQFR oproti metodě cQFR s výslednými hodnotami 0,83, resp. 0,87.

Závěry: QFR je pro zkušeného specialistu jednoduchá a rychlá metoda. Je to přesná, specifická a spolehlivá metoda pro fyziologické vyšetření a v blízké budoucnosti by se mohla stát metodou první volby.

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ABSTRACT

Introduction: Physiology guided percutaneous coronary interventions (PCIs) are supported by experts worldwide. Despite its reliability, fractional flow reserve (FFR) method remains rarely used in clinical practice due to its cost and time-duration. The demand of physiology guided PCIs encouraged the search of faster, cheaper and not less reliable alternative coronary flow evaluation method. Since a novel minimally invasive FFR computation method has been presented to interventional cardiologists, the comparison of “golden-standard” method – FFR – and a novel alternative – quantitative flow ratio (QFR) – method has become a subject for numerous studies.

Methods: In total, 23 publication representing results of more than 4000 patients comparing QFR and FFR reproducibility and agreement were studied.

Results: Agreement between QFR and FFR performed in non-culprit arteries in patients with and without previous myocardial infarction was 0.88 and 0.94, respectively. Less reliable QFR seemed in diabetic patients, as agreement between QFR and FFR was 0.74 and 0.83 in diabetic and non-diabetic patients, respectively. Firstly, it was suggested that all QFR with value between 0.75 and 0.85 should be covered by FFR. Detailed analyses of cut-off value showed only a mild mismatch between FFR and QFR when the lower cut-off is 0.77 and the upper 0.86. Comparison of FFR and three types of QFR (fixed – fQFR, contrast – cQFR, and adenosine – aQFR) showed any adenosine based QFR measurement superiority over contrast flow QFR measurements, accordingly 0.83, 0.87, and 0.87.

Conclusions: QFR is a straightforward and quick method for an experienced specialist. QFR is an accurate, specific and reliable method for physiological evaluation which could become the first-line choice in the near future.

Keywords:

Fractional flow reserve (FFR)
Instantaneous wave-free ratio (iFR)
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Introduction

Nowadays, fraction flow reserve (FFR) is the most widely used method to diagnose the functional significance of coronary artery stenosis.¹ An experienced interventional cardiologist may perform it within 7 minutes.¹ Up today, FFR is considered as a “gold standard” method for the assessment of the significance of coronary artery stenosis and the adoption of further treatment solutions.² This method is Class IA recommendation in Europe² and Class 2A in the United States guidelines³ for the examination of patients with stable coronary artery disease. However, each method has certain disadvantages. FFR requires artificial hyperemia induced by adenosine, which may cause discomfort to the patient, and the pressure wire which increase the cost of the following procedure and may increase the risk of complications during the manipulation.⁴ Adenosine consumption can be prevented by performing the instantaneous wave-free ratio (iFR),⁵ but it has lower specificity and sensitivity than FFR.⁶ However, it is performed through the end of physiological cardiac diastole and adenosine is unused. Nevertheless, as for the FFR, the pressure wire is still used in the iFR measurements.⁶

A breakthrough to identify the significance of coronary artery stenosis is a novel FFR computation method – quantitative flow ratio (QFR). Induced hyperemia and insertion of pressure wire are not necessary for its performance.⁷ An experienced interventional cardiologist can perform it in less than 5 minutes.⁸ However, the use of QFR is not only a financial resource-saving but also time-saving decision. Only ordinary angiograms and a specific computer program are necessary for a certified professional to identify the significance of coronary artery stenosis by QFR.⁸ This method is based on three-dimension reconstruction of the vessel from 2 different angiograms with 25 degrees apart and the fluid flow computation by the specific mathematical formula.⁸

The purpose of this literature review is to analyze the most recent publications comparing FFR and QFR methods, including the analyses of the strengths and weaknesses between the “gold standard” FFR and the innovative, minimally invasive QFR.

Methods

The data for this literature overview were chosen from three databases: PubMed, Oxford Academic, and SpringerLink. The search criteria were two – all articles were published in approved databases within the past five years. Two keywords including “quantitative flow ratio” and “QFR” were used in the search. In general, 30 articles were found. We rejected five of them for inappropriate information about this topic. We also dismissed two meta-analyses because all of them analyzed the same studies. Thus we included QFR results from more than 4000 patients of the 23 articles in the literature review. Patients with diabetes mellitus,⁹ patients who had myocardial infarction a few years ago,¹⁰ and patients with small coronary artery disease¹¹ have been also included. All studies had used FFR as a reference standard to confirm QFR

accuracy, specificity, and sensitivity. All examined articles complied with ethical standards.

Results

QFR meta-analysis¹²

Three meta-analyses where the QFR was analyzed had been detected in PubMed research. The first meta-analyses comprised nine studies which included 1175 blood vessels' results. Main part of patients consisted of a FAVOR II China study,¹³ Emori et al.¹⁰ and Mejia-Renteria et al. studies.¹⁴ All three studies showed that previous myocardial infarction did not affect QFR accuracy to diagnose the significance of stenosis.

Moreover, Spitaleri et al.¹⁵ had demonstrated that revascularization based on the QFR had a reasonable survival rate of up to 5 years.

Yazaki et al.¹⁶ showed that FFR should be performed when QFR is between 0.75–0.85.

QFR diagnostic accuracy between MI culprits and non-culprit arteries

Emori et al.¹⁰ compared the accuracy of QFR to verify the stenosis for patients who had myocardial infarction before. Seventy-five patients with previous MI and 75 with first MI ever have been included in the study. It was found that QFR directly correlates with FFR when comparing patients who had MI with non-previously MI ($r = 0.88$ and $r = 0.94$). There is also no significant difference between QFR and FFR in both cases. Average FFR and QFR values were 0.79 and 0.76, respectively. QFR has been acknowledged as a safe, reliable, effective, and cheaper method for coronary artery stenosis severity assessment.¹⁰

QFR diagnostic accuracy in patients with diabetes mellitus

The QFR in patients with diabetes was examined in two different studies. Smit et al. compared the data of 66 patients with type 2 diabetes mellitus and 193 nondiabetic patients.⁹ There were no significant differences between QFR and FFR in this study group. The correlation between QFR and FFR was good in both subgroups: the correlation coefficient was 0.74 and 0.83 in diabetic and nondiabetic patients, respectively.

Zaleska et al. have repeatedly confirmed an excellent correlation between QFR and FFR measurements.¹⁷

QFR accuracy is independent of the individual effect of adenosine on each patient

Mejía-Rentería et al. investigated 294 coronary arteries in 245 patients.¹⁸ Multivessel disease was reported in 64% of patients, and stable coronary artery disease was diagnosed in 70% of them. It was measured as percentage change of mean aortic pressure (% Pa) and resistive reserve ratio (RRR) and has been proved that each patient has severely different responses to adenosine.¹⁸

QFR diagnostic accuracy in non-occluded coronaries for STEMI patients

Sejr-Hansen et al.²⁰ compared the diagnostic accuracy of QFR in non-culprit lesions during the acute phase of myo-

cardial infarction. For QFR analyses in the core laboratory, angiograms from the iSTEMI study were used.¹⁸ The accuracy between QFR and either FFR or iFR in the acute phase was evaluated.¹⁸

The study analyzed 103 acute settings and 72 staged setting angiograms. Match between acute and staged QFR 93%. Acute QFR and staged QFR have exceptionally good diagnostic accuracy. Acute setting QFR has also good diagnostic accuracy when staged FFR is used as the reference standard. In this study, acute QFR showed a slightly higher diagnostic value than acute iFR. However, Sejr-Hansen et al. highlighted that the microvascular resistance index should be known before performing QFR.²⁰

Spitaleri et al. studied QFR accuracy for patients with STEMI and multivessel disease (MVD). Data on 186 patients were collected and demonstrated high diagnostic accuracy of QFR for patients with STEMI and MVD.¹⁵

QFR cut-off when FFR should be forgotten⁸

Smit et al. identified cut-offs when FFR should not be performed to retest QFR. The purpose of this study was to help small hospitals, which are not able to perform FFR or PCI to diagnose significant coronary stenosis by QFR. The average QFR computation time was 4.36 minutes, which is significantly faster than FFR.⁸ Moreover, the possible complications of the FFR and its cost were highlighted, which can become an issue for small hospitals.⁸

In total, 290 patients with an average of 22.8 days between angiogram and FFR were investigated.⁸ 34.7% of them had a history of coronary artery revascularization.⁸ A good correlation between QFR and FFR has been proved.⁸ Smit et al. used a QFR cut-off of 0.77 and 0.86 as chosen in the FAVOR II Europe-Japan trial.¹ A very low percentage of mismatch between FFR and QFR when the lower cut-off is 0.77, and the upper 0.86 has been proved by Smit et al.⁸ Only 9 of 181 QFR patients were above 0.86 when FFR was less than 0.8 and only 4 of 53 diagnosed FFR greater than 0.8 when QFR showed less than 0.77.⁸

Nevertheless, this study demonstrates that using QFR cut-offs of 0.77 and 0.86 enable hospitals to reduce the use of FFR by 50% and increase the prevalence of physiology-guided PCI.⁸ In addition, it supports small hospitals that are unable to perform FFR or PCI to diagnose nonsignificant stenosis.

Ties et al. have demonstrated the great correlation between QFR and FFR.⁴ They also noted that hospitals should not verify QFR when it is more than 0.9.¹⁹ In this study, 101 blood vessels were analyzed and there was not a single positively false result when QFR value was more than 0.9. This solution would allow us to avoid up to 39% of FFR without any risk.⁴

Three types of QFR

Three types of QFR computations were investigated in FAVOR pilot trial.²¹ A fixed QFR (fQFR) that uses information from a database based on previously performed FFR; a contrast QFR (cQFR) – when the individual contrast flow velocity is included into FFR computation; and an adenosine QFR (aQFR) which calculates the contrast flow velocity after artificial hyperemia induction. The last one still required adenosine, so it is more valuable than FFR only that no pressure wire is used. The analyses of 73 patients

showed the best diagnostic accuracy with aQFR (87%), followed by cQFR (86%) and finally fQFR (80%).

A similar research was performed by van Rosendaal et al. in two independent laboratories.²² Twenty left coronary arteries were investigated. However, this study showed similar results. The correlation coefficients between FFR data and fQFR, cQFR, and aQFR were 0.83, 0.87, and 0.87, respectively.

Later, encouraged by the FAVOR pilot study,²¹ Xu et al. conducted FAVOR II China trial.¹³ The primary purpose of which was to achieve the highest possible diagnostic accuracy and demonstrate it in a big group of patients. As a result, 328 coronaries were studied in both “online” and “offline” settings. “Online” – QFR calculated in the operating room. “Off-line” – QFR recalculated in an independent laboratory whose specialists performed QFR analyses from the same angiograms blinded to the “online” results. This was the first research demonstrating such high QFR accuracy with FFR (“online” – 92.7%; “offline” – 93.3%). Only 18 FFR were estimated to be higher than 0.8 when QFR was less than 0.8. Following these impressive results, Chang et al.²³ have repeatedly performed QFR analyses for the FAVOR II China trial angiograms.²² High QFR correlation and accuracy of FFR have been proved repeatedly.^{22,23}

Moreover, Zhang et al.²⁴ have discovered a way to make QFR even more accurate. Previously, the flow rate required for QFR computations was calculated by the frame count-based flow velocity (Vcount) marked by the physician, a new automatic approach (Vauto) enables automatic contrast flow computation. By this, the diagnostic accuracy becomes even higher.²⁴ This was proved by analysis of 328 coronary arteries. An excellent correlation of 0.96 between QFRauto and QFRcount was found. Even more, compared to FFR as a reference, the diagnostic accuracy was 93.2%. Thus, this study demonstrated another way of improving QFR, which, although not strong, but still increased diagnostic accuracy.

Discussion

Seventeen publications about QFR accuracy, sensitivity, and specificity compared to FFR were included for the analysis (Table 1). Mean accuracy, sensitivity, and specificity of QFR were 86%, 94%, and 90%, respectively. Moreover, the studies conducted in our center have shown excellent results – 94.2% accuracy, 84.2% specificity, and 100% sensitivity.²⁶

These studies have assessed QFR accuracy in various situations including stable patients, non-culprit artery stenosis in patients treated for acute ischemic syndrome. Even more studies investigating patients with diabetes mellitus have demonstrated 88% of QFR accuracy, 95% specificity, and 75% sensitivity.⁹ Excellent correlations between QFR and FFR for diabetic patients opened new perspectives of QFR adoption in clinical practice. The use of QFR may reduce the risk of wire insertion complications in the diabetic patients group. According to Smit et al., QFR could be the method of choice for the assessment of the functional significance of coronary artery stenosis.⁹

Table 1 – Results of the included studies

Study	Main point of the study	Patients	QFR and FFR correlation	Diagnostic accuracy	Sensitivity	Specificity
Ties et al., 2018	QFR cut-offs	96	0.70	90%	67%	96%
Hwang et al., 2019 ⁶	FFR vs iFR vs QFR	264	0.863	90.8%	92.3%	89.8%
Emori et al., 2018	Prior-MI and non-prior-MI QFR	150	0.94 (non-prior- MI) 0.88 (prior-MI)	92%	95%	88%
Chang et al., 2018	FAVOR II China Study Double checked QFR value performing “online” and “offline” analyses in the core laboratory	304	0.86	93.3%	94.96%	92.8%
Westra et al., 2018	FAVOR II QFR vs FFR	Europe-Japan 329	0.83	86.8%	86.5%	86.9%
Zaleska et al., 2019	QFR vs FFR	196	0.78	89%	94.6%	91.7%
Smit et al., 2019	Diabetic patients	259	0.74	88%	71%	95%
Yazaki et al., 2017	QFR vs FFR	142	0.8	88.7%	89.1%	88.6%
Tu et al., 2016	cQFR, fQFR, aQFR	73	0.77	86%	74%	91%
Erbay et al., 2019	QFR vs FFR (patients with multivessel disease)	436	0.84	94.1%	80%	98.5%
Sejr-Hansen, et al., 2018	QFR vs FFR for STEMI patients	72 103	0.89 staged 0.81 acute	93%	92%	94%
Stähli et al., 2018 ²⁵	QFR vs FFR	436	0.82	93.4%	75%	97.8%
Xu et al., 2017	“Online” and “offline” QFR	308	0.86	92.4%	94.6%	91.7%
Smit et al., 2018	QFR vs FFR. QFR cut-off	290	0.81	86%	70%	92%
Zhang et al., 2018	Auto-QFR vs count-QFR	304	0.84	93.2%	92.4%	93.7%
Spitaleri et al., 2017	QFR STEMI patients with multivessel disease	304	0.9	94%	88%	97%
Mejia-Renteria et al., 2018	QFR for patients with high microvascular resistance index	248	0.83	90%	89%	87%

aQFR – adenosine was used in quantitative flow ratio; cQFR – a contrast quantitative flow ratio; FFR – fraction flow reserve; fQFR – a fixed quantitative flow ratio; iFR – instantaneous wave-free ratio; QFR – quantitative flow ratio; STEMI – ST-segment elevation myocardial infarction.

Accuracy of QFR assessed in patients with previous MI and non-culprit artery functional assessment during acute coronary syndrome in addition to its accuracy in diabetic patients group, encouraged the wider QFR adoption to clinical practice improving physiology guided PCI with the least possible risk for patients mostly associated with pressure wire insertion.⁸ The correlation between QFR and FFR in patients treated for the first time with MI is 0.94¹⁰ and patients who had a history of myocardial infarction is 0.88.¹⁰

Erbay et al.¹¹ we have performed a fascinating study analyzing QFR accuracy dependence on the diameter of the investigated artery. They grouped all QFR into two groups according to coronary artery diameter: small arteries <2.8 mm and large arteries >2.8 mm. It was found the accuracy of 94.1% and the specificity of 98.5% in the analysis of small diameter coronary arteries. It is essential because pressure wire insertion into small coronaries is much more dangerous and has an extremely high complication rate. Therefore, QFR should be the first choice for functional assessment for patients with microvascular disease.

Despite that a high-quality QFR analysis requires a long period of learning; this is an accurate and fast method.

Based on the experience of our center, a specialist who has enough experience can perform it within 3–7 minutes. In QFR investigator opinion, it is necessary to perform about 50 high-quality QFR analyses to become an expert. Chang et al.²³ have proved excellent agreement between separately working QFR expert observers. As it was mentioned, they were performing QFR analyses in two independent laboratories, for the analyses using the same angiogram images and with blinded QFR results to each other. The differences between all three analyses were no more than 0.004±0.03. The excellent values of QFR analysis were also identified in our center study. The specialist three times analyzed the same occlusion and the correlation was 0.997, $p < 0.001$.²⁶ All these prove that QFR is a feasible, easy to use, and accurate method for the physiological assessment of intermediate coronary artery stenosis.

Conclusions

Despite a certain learning curve needed, QFR is a straightforward and quick method for an experienced specialist. Based on the accuracy and specificity of the method in

specific patient groups, QFR can be used reliably to assess the functional significance of coronary artery stenosis in patients with intermediate coronary artery lesions in any patient group. Even more, it could become the first-choice method in the near future.

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