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Functional Evaluation of Coronary Stenosis: is Quantitative Flow Ratio a Step Forward?

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SOUHRN

Závažnost koronárních lézí vždy představovala významný aspekt péče o pacienty během koronarografického vyšetření. Je prokázáno, že léčba vedená na základě hodnot frakční průtokové rezervy (fractional flow reserve, FFR) má pozitivní vliv na klinický výsledný stav pacienta. Zavádění FFR do klinické praxe v celosvětovém měřítku nicméně zpomalily závažné technické nedostatky. V poslední době byla představena a v klinickém výzkumu ověřována jiná kritéria, jako například kvantitativní poměr průtoků (quantitative flow ratio, QFR). Podle jedné studie používající výpočetní mechaniku tekutin a plynů koreluje QFR s hodnotami FFR a ve srovnání s jinými metodami šetří čas i peníze. QFR představuje novou angiografickou metodu, která pomocí moderního softwaru provádí trojrozměrnou rekonstrukci cév a vytváří modely průtoku. Jedná se tedy o technicky vyspělou metodu a o moderní, účinný a praktický nástroj pro hodnocení koronárních lézí. Cílem tohoto přehledu bylo prozkoumat oblasti případného využití QFR v klinické praxi.

Keywords:
Coronary lesions
Fractional flow reserve
Quantitative flow ratio

ABSTRACT

The severity of coronary lesions (CL) has always been an important aspect of patient care during coronary angiography. Fractional flow reserve (FFR)-guided coronary treatments have been shown to have a positive influence on clinical outcomes. However, significant technical flaws in clinical practice have slowed global adoption of FFR. Other indices, such as the quantitative flow ratio (QFR), have recently been created and tested in clinical research. According to a computational fluid dynamics study, QFR has a good correlation with FFR values and saves time and money compared to other methods. QFR is a new angiographic technique that uses modern software to reconstruct three-dimensional vessels and calculate flow models. Modern, effective and usable tool for CL due to significant technical benefits. We aimed to analyze the application areas of the QFR and its potential clinical application in this review.

Introduction

Coronary artery disease (CAD) is a serious cause of mortality worldwide.[1,2] Newer diagnostic and treatment methods have undoubtedly made a major contribution to CAD care during the past decades, considerably improving patient outcomes. Percutaneous coronary intervention (PCI) is a frequently performed invasive procedure globally, improving survival in patients with acute coronary syndromes and relieving symptoms in stable patients with substantial coronary stenosis (CS) and confirmed myocardial ischemia.[3,4] However, both physician visual assessment (PVA) and quantitative coronary analysis (QCA) have demonstrated a weak association with functional CS severity. The use of fractional flow reserve (FFR) has improved decision-making in individuals with moderate CS. FFR-guided PCI for CS in stable CAD patients was emphasized.[5]

In addition to the FFR, many invasive and non-invasive techniques for assessing CS severity have developed in recent years. These methods are intended to assess the lesion in terms of hemodynamics. A good diagnostic performance for CS producing ischemia has been shown using coronary computed tomography (CCTA).[6] Following that, functional evaluation of CS was performed using three-dimensional quantitative coronary angiography (3D-QCA) and blood flow simulation,[7] and FFR was calculated using a combination of 3D-QCA and Thrombolysis In Myocardial Infarction (TIMI) frame count.[8] This minimally

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invasive method, dubbed quantitative flow ratio (QFR), employs three distinct flow simulation models: fixed-flow QFR (fQFR), contrast-flow QFR (cQFR), and adenosine-flow QFR (aQFR), and allows for the differentiation of functionally important and non-significant stenosis. The term "less invasive method" is more accurate than "non-invasive technology", since it may be used on individuals who are still undergoing CA. As a result, it is a less intrusive method than other functional indices such as the FFR and iFR, which both require the use of a pressure wire.[9] QFR is a new approach that offers non-invasive evaluation of significant functional coronary lesions without the need of either an adenosine or pressure wire, which is why we decided to write this review.

We found 2756 references from 2010 to 2021 in PubMed using the keywords (quantitative flow ratio). Duplicate documents were removed from the search. The 224 publications investigated QFR. Non-compliant documents were rejected. So this evaluation focuses on QFR's clinical utility.

Evaluation and functional implications of CAD

CS, caused by atheromatous thickening or plaque of the arterial wall, reduces maximal vasodilation flow gradient and changes coronary flow control systems. Even while coronary microcirculation reacts to stenosis with vasodilation, it is frequently unable to expand further to meet increasing flow and oxygen demand.[10] In stable CAD, significant CS was defined as a decrease of 70% in lumen diameter.[11] While there is a weak correlation between quantitative stenosis severity on CA and functional flow limitation, a growing body of clinical evidence suggests that a simple percentage definition of CS does not accurately reflect the physiological state of the relevant myocardial area.[12,13]

QFR: FFR by 3D-angiography

There are many significant limitations in CA when evaluating the intermediate CS. The detection of FFR in all major lesions on angiograms enables the identification of those lesions which may cause myocardial ischemia. Without the use of pressure or flow wires, the QFR technique estimates the FFR value using a 3D reconstruction of the target vessel. The QFR functions as a means of communicating the results of the CS examination, which includes both physiological and angiographic testing (Fig. 1). The DISCOVER-FLOW and VIRTU-1 investigations, in particular, paved the way for this.[14]

The inclusion of FFR to CCTA has shown a strong association with FFR. The VIRTU-1 research sought to create a computer model that could correctly predict myocardial FFR from rotational CA angiographic data. The values of virtual FFR and measured FFR were shown to be highly linked.[14] FFR has been predicted using computational fluid dynamics (CFD) analysis using CCTA data in the DISCOVER-FLOW research.[15]

Tu et al.[16] examined the functional relevance of moderately obstructed CAs using a rapid computer model.

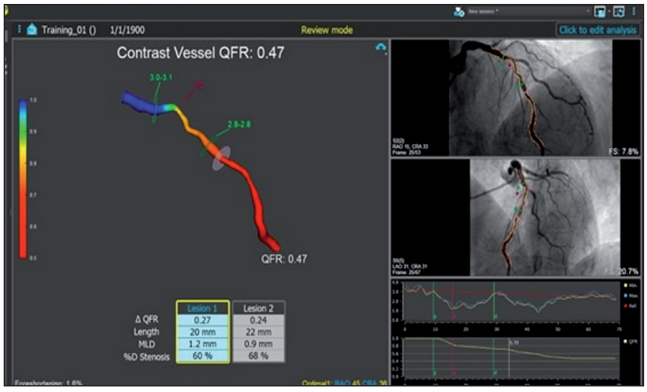

Fig. 1 – Non-invasive physiological assessment: quantitative flow ratio.

They utilized 3D-QCA and computed the mean volumetric flow rate during hyperemia utilizing TIMI frame count in conjunction with 3D-QCA, demonstrating that FFR-QCA calculation is a novel method for determining the functional importance of intermediate CS. Specifically, 77 vessels from 68 individuals were examined, while the testing group included 22 vessels from 20 patients. They discovered a strong connection between FFR-QCA and FFR ($r = 0.81$; $p = 0.001$) and agreement between the two.

FFR-QCA outperforms FFR-CT due to better image resolution and assessment of downstream microcirculation. Additionally, calcified CAD and abnormal cardiac rhythm effect on FFR-CT.[8] CT-FFR is recommended for patients with low-to-moderate risk, for whom a delay in findings is not a concern, and is primarily used to prevent further stress tests and needless invasive procedures. Calculating the severity of intermediate stenoses using the FFR-QCA approach seems to be a safe and cost-effective technique during diagnostic angiography.

The FAVOR Pilot Trial (Functional Assessment by Various Flow Reconstructions)[17] designated this new tool as QFR based on these assumptions. The FAVOR research compared offline QFR calculation against pressure wire-based FFR to see which was better. QFR may be computed both online and offline using a software program (QAngio XA 3D, Medis Medical Imaging System, Leiden, Netherlands) (Fig. 2). Tu et al.[18] found a strong associa-

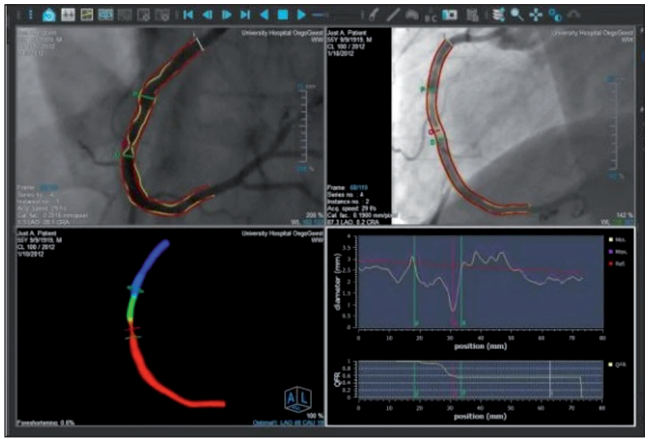

Fig. 2 – Fractional flow reserve (FFR) evaluation using Medis QCA angiography imaging. By eliminating the requirement for pressure wires and adenosine utilized in conventional FFR evaluations.

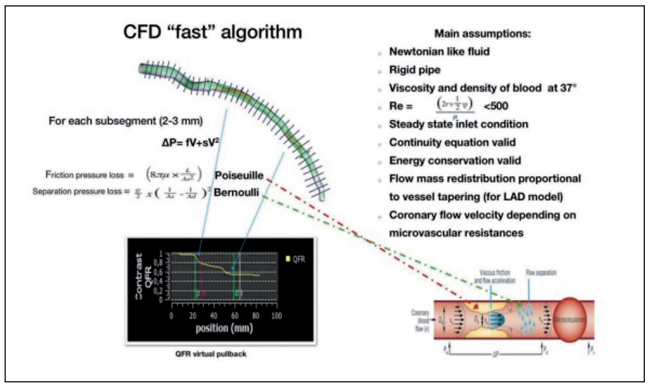

Fig. 3 – The QFR algorithm's key assumptions.

tion between IVUS and optical coherence tomography (OCT) (r = 0.8 and 0.89). Assuming the flow crosses the stenosis and follows fluid-dynamic principles, the mean flow velocity and 3D-QCA reference sizing establish the mass flow rate along the chosen channel. The CFD quadratic mathematical method was used instead of the fully established Navier-Stokes equation because of its speed and correctness. This approach also eliminated the need for side branch reconstruction. The equation and assumptions used to calculate the QFR have been discussed in full before,[17] and are shown in Figure 3.

The FAVOR II China research was the first to test QFR's diagnostic accuracy.[19] Online QFR (0.8 or >0.8) was used to detect functional CS, with FFR (0.8 or >0.8) as the reference standard. 308 individuals were enrolled at 5 centers. The FAVOR II Europe and Japan research found QFR to be better than 2D-QCA for detecting functionally significant lesions.[20] 274 participants out of 329 enrolled in 11 centers had their data evaluated. The positive predictive value with FFR was 78%, whereas negative predictive value was 94%. Another finding from the research, and one of the QFR's many benefits, is the turnaround time. The difference in time between QFR and FFR was 4.8 min (IQR 3.5–6.0) and 7.0 min (IQR 5.0–10.0) (p = 0.001).[20]

The WIFI II research evaluated the feasibility and performance of QFR.[21] FFR was measured in 292 lesions from 191 patients, and QFR in 240 lesions from blinded observers. Here, the QFR was 0.84 (IQR 0.77–0.89), and the QFR calculation revealed r = 0.70 (p = 0.0001), and precision of 0.01 (p = 0.08) with FFR. To enhance accuracy, patients having FFR values between 0.77 and 0.83 (83–87 percent; p = 0.002) near the diagnostic cut point were eliminated. Regarding timeframes, Yazaki et al. provide us with the following information: in their research, the average time required to compute QFR was 266 s (IQR 181–332 s), which included time for two optimum angiographic acquisitions and the completion of the QFR calculation.[22]

The QFR calculation has been used in many patient situations, proving its reliability, safety, and economy. Emori et al.[23] used QFR to evaluate myocardial ischemia in previous MI. It is a single-center research that looked at 75 patients' previous MI-related CA. A comparison of previous MI-related and non-prior MI-related CA using FFR and just two flow models (fQFR and cQFR) revealed no differences in fQFR, cQFR, or FFR correlation. fQFR was lower than FFR in previous MI-related CA. This may be because it uses 3D-QCA anatomic data and ignores the crucial myocardium. Pre-MI CA had substantially lower cQFR vs. FFR values than non-pre-MI CAs, indicating that the vital myocardium was under-represented in the TIMI frame count study.

Despite the proven advantages of physiology-based revascularization, the reference methods for assessing intermediate CS are still employed seldom. Although FFR is recommended in clinical guidelines, its use in coronary catheter labs globally remains low.[24] Indeed, although the use of FFR has increased year after year over the past decade,[25] it varies considerably between nations and locations, accounting for between 3% and 30% of overall PCI volume.[24–26] The FFR's low penetration in everyday practice is most likely related to cost, equipment, and operator preference. The Evolving Routine Standards of FFR Use (ERIS) research[26] is investigator-driven, national, comprising 76 Italian sites. In this context, the QFR may be used more widely since it is less intrusive, less expensive, and more operator-friendly. Thus, QFR may be a useful tool in the cath lab, allowing for better revascularizations.

Recent studies

Carlos Cortés et al.[27] found QFR and FFR to be correlated. A QFR below 0.80 best predicts functional importance of CS. This repeatable tool's predictive usefulness is proven. Other clinical applications of QFR are currently missing, necessitating more study. The Q-rFSS model is superior at predicting the risk of MACE.[28] As a consequence of these findings, Cerrato et al.[29] issued strong guidelines for functional assessment of CS. However, advancing a wire into the CA to interrogate the CS has prevented the adoption of coronary wire-based functional assessment in catheterization labs. There are now angiography-derived indices that may be used to assess the functional meaning of stenosis only from angiographic data. QFR is the most researched and verified angiography-derived indicator. This paper will describe the quantitative flow ratio, its present, and prospective uses.

FFR assessment of intermediate CS generated from CA is possible in a radiation-saving mode – 7.5fps and 7pps CA. In these instances, the newly proposed algorithm assists in excluding vessels that are not suitable for angiography-derived FFR analysis, hence increasing the diagnosis accuracy of commercially available software packages. With 7.5fps angiography, cQFR exhibits no incremental benefit over fQFR, and hence fQFR may be the first choice in such instances.[30]

Dai et al.[31] discovered that QFR responded to anatomic and hemodynamic stenosis severity similar to FFR or iFR. Using PET-derived RFR and CFC as a reference, its diagnostic performance was lower than FFR and iFR. Anatomical stenosis severity and individual variability in coronary hemodynamic circumstances were connected with the discordance. The work by Kleczyski et al.[32] demonstrates the excellent diagnostic performance and association of QFR with iFR for diagnosing functional ischemia induced by intermediate lesions in CAs. However, pressure wire testing with iFR may be necessary for around two thirds of patients following QFR measurement.

The QFR is highly consistent with both the FFR and the iFR. Additionally, diagnostic accuracy and discriminant function may be improved when the iFR is utilized as a reference, owing to the complicated nature of cardiac physiology in individuals with severe aortic valve stenosis (AVS). Furthermore, in individuals with severe AVS, the QFR may have the same limits as invasive indicators.[33]

In many clinical contexts and lesion characteristics, cQFR correlated well with FFR. cQFR has better discriminate power for FFR 0.80 than stenosis severity or resting Pd/Pa. 2-year risk of vessel-oriented composite outcomes (VOCO) was substantially higher for low than for high cQFR at the same time point. On this basis, cQFR may be a useful prognostic and diagnostic tool for patients with CAD.[34]

The QFR and OCT-derived intraluminal measures are linked. Our data back up QFR. However, QFR did not correlate with plaque vulnerability, indicating that it could be used in conjunction with intravascular imaging to obtain a contemporary, multimodal assessment of CS. The QFR and OCT-derived intraluminal measures are linked. The data from Milzi and his colleagues' study support QFR. However, QFR did not correlate with plaque vulnerability, indicating that it could be used in conjunction with intravascular imaging.[35]

Physiological assessment by QFR reduces ionizing radiation exposure compared to FFR and iFR. Increasing QFR usage reduced ionizing radiation exposure. Acceptance of standard QFR estimates in ordinary clinical practice may also increase QFR advantages.[36] The reproducibility of QFR computed from identical angiograms varied significantly between observers from different sites, with an average agreement of 0.010.08 for repeated measurements. The reproducibility was observed to be dependent on the observer, the angiographic quality, and the severity of CS as determined by FFR.[37]

Limitations of QFR

Quality angiographic material is critical for accurate QFR calculation. Aiming to automatically evaluate angiographic acquisition quality for QFR analysis is therefore needed. The QFR technology has no systematic cost–benefit assessments. Pricing of QFR is expected to allow for considerable cost reductions linked to pressure wires. In health care systems lacking functional evaluation, a QFR--based method should minimize unnecessary stenting and therefore expenses. Local and national reimbursement schemes will determine the speed of QFR adoption. In the absence of such investigations, randomized trials comparing clinical outcome following QFR and pressure wire-based techniques are set to begin. This enabled for precise analysis for future trial design and clinical use and integration of QFR.

Conclusions

Conventional angiographic assessment of CS in chronic coronary syndrome patients has limits, hence approaches like QCA have emerged. Conventional techniques are inadequate for assessing intermediate stenosis. Guidelines for myocardial revascularization recommend FFR for assessing the significance of CS. The QFR was developed from 2D-QCA to 3D-QCA, which permits reconstruction of the coronary vessel in three dimensions utilizing flow models and TIMI frame count. These results are consistent with the good reproducibility and correlation with FFR. QFR looks to be a safe and cost-effective diagnostic modality that eliminates the need for a pressure wire, uses fewer medications, and reduces procedure time and patient risk.

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