Fractional flow reserve based on computed tomography: an overview

Article *in* European Heart Journal Supplements · April 2016

DOI: 10.1093/eurheartj/suw014

9 authors, including:

Francesco Secchi
I.R.C.C.S. Policlinico San Donato
66 PUBLICATIONS **209** CITATIONS
SEE PROFILE

Marco Fedele
University of Pavia
3 PUBLICATIONS **0** CITATIONS
SEE PROFILE

Silvia Tresoldi
Azienda Ospedaliera San Paolo - Polo Univer…
37 PUBLICATIONS **205** CITATIONS
SEE PROFILE

Ferdinando Auricchio
University of Pavia
162 PUBLICATIONS **3,268** CITATIONS
SEE PROFILE

European Heart Journal Supplements (2016) **18** (Supplement E), E49–E56
The Heart of the Matter
doi:10.1093/eurheartj/suw014

Fractional flow reserve based on computed tomography: an overview

Francesco Secchi[1]*, Marco Alì[2], Elena Faggiano[3], Paola Maria Cannaò[4], Marco Fedele[3], Silvia Tresoldi[5], Giovanni Di Leo[1], Ferdinando Auricchio[3], and Francesco Sardanelli[1,6]

[1]*Unit of Radiology, IRCCS Policlinico San Donato, Via Morandi 30, San Donato Milanese, Milan 20097, Italy*
[2]*PhD Course in Integrative Biomedical Research, Università degli Studi di Milano, Via Mangiagalli 31, Milano 20133, Italy*
[3]*Computational Mechanics & Advanced Material Group, Department of Civil Engineering and Architecture (DICAr), Università degli Studi di Pavia, Via Ferrata 3, Pavia 27100, Italy*
[4]*Postgraduation School in Radiodiagnostics, Università degli Studi di Milano, Via Festa del Perdono 7, Milan 20100, Italy*
[5]*Unit of Diagnostic and Interventional Radiology, Azienda Ospedaliera San Paolo, Via A. di Rudinì 8, Milan 20142, Italy*
[6]*Department of Biomedical Sciences for Health, Università degli Studi di Milano, Via Morandi 30, San Donato Milanese, Milan 20097, Italy*

KEYWORDS
Coronary artery disease;
Fractional flow reserve;
Computed tomography;
Transluminal attenuation gradient

Computed tomography coronary angiography (CTCA) is a technique proved to provide high sensitivity and negative predictive value for the identification of anatomically significant coronary artery disease (CAD) when compared with invasive X-ray coronary angiography. While the CTCA limitation of a ionizing radiation dose delivered to patients is substantially overcome by recent technical innovations, a relevant limitation remains the only anatomical assessment of coronary stenoses in the absence of evaluation of their functional haemodynamic significance. This limitation is highly important for those stenosis graded as intermediate at the anatomical assessment. Recently, non-invasive methods based on computational fluid dynamics were developed to calculate vessel-specific fractional flow reserve (FFR) using data routinely acquired by CTCA [computed tomographic fractional flow reserve (CT-FFR)]. Here we summarize methods for CT-FFR and review the evidence available in the literature up to June 26, 2016, including 16 original articles and one meta-analysis. The perspective of CT-FFR may greatly impact on CAD diagnosis, prognostic evaluation, and treatment decision-making. The aim of this review is to describe technical characteristics and clinical applications of CT-FFR, also in comparison with catheter-based invasive FFR, in order to make a cost–benefit balance in terms of clinical management and patient's health.

Introduction

Fractional flow reserve (FFR) was firstly introduced by Pijls *et al.* in 1996,[1] with the aim to describe the maximum achievable blood flow to the myocardium supplied by a stenotic coronary artery in terms of coronary pressure measurements. The value of FFR is given by *the ratio of the mean distal coronary artery pressure to the mean aortic pressure during the period of maximum hyperaemia*.[1] It is usually invasively obtained during catheter-based conventional coronary angiography (CCA) with the normal value of a healthy coronary artery being 1.0, regardless of the patients or the specific vessel examined.[1–3]

In the past years, several trials showed that FFR allows for determining the clinical significance of ischaemia, i.e. for identifying the lesions to be revascularized by percutaneous coronary intervention (PCI), thus contributing

* Corresponding author. Tel: +39 0252774642, Fax: +39 0252774925, Email: francesco.secchi@grupposandonato.it

to a better selection to treatment and patient management.[4,5] According to the European Society of Cardiology, the measurement of CCA-based invasive FFR (I-FFR) is a IA-class indication for identification of haemodynamically significant coronary lesions when non-invasive evidence of myocardial ischaemia is unobtainable.[2]

A non-invasive method for direct visualization of coronary artery disease (CAD) is computed tomography coronary angiography (CTCA). A large body of evidence exists about a high diagnostic accuracy of this technique in the detection of significant coronary artery stenosis.[6] Notably, for a long time, the luminal narrowing of coronary arteries has been used as the main gatekeeper for patient management, even though the detection of a severe stenosis at CCA, or also at CTCA, has only a moderate prognostic value for myocardial ischaemia.[7]

Recent technological innovations allow for a non-invasive calculation of FFR using data already routinely acquired by CTCA. This approach [computed tomographic fractional flow reserve (CT-FFR)] has been demonstrated to be superior to the only anatomical evaluation of stenosis for the detection of coronary stenosis causing myocardial ischaemia. In particular, CT-FFR has been shown to improve the diagnostic accuracy of CTCA by reducing the false-positive rate of stenosis assessment.[8,9]

The purpose of this review is to describe the technical characteristics and clinical applications of CT-FFR, also in comparison with catheter-based I-FFR, in order to make a cost–benefit balance in terms of clinical management and patient's health.

Measurement of fractional flow reserve

Invasive fractional flow reserve measurement

When a patient presents with a significant occlusive stenosis of a coronary artery, with typical symptoms (such as angina or chest pain) or with a risk to induce an ischaemia using non-invasive methods (such as stress test, myocardial scintigraphy, or stress echocardiography), the cardiologist has no doubts about the need to treat the stenosis, commonly using a PCI strategy. Instead, when the patient presents with a moderate stenosis (between 50 and 70% in PCI) without any evidence of symptoms, a treatment strategy is difficult to establish.[2]

Techniques like CCA only assess the morphological luminal profile of the vessel (and of the atherosclerotic plaque), and a correct interpretation may be limited by vessel foreshortening, heavy calcification, and side-branch overlap.[2] Differently, functional methods may evaluate the FFR. This parameter is of a great importance. In fact, PCI is aimed at increasing blood flow to the heart, but clinical studies showed that if the flow is not significantly obstructed, the lesion does not need to be treated with PCI. In these cases, the patient can be treated safely with medical therapy, and some researches have shown that patients who have been screened out of angioplasty by using FFR did not experience an intensification in adverse outcomes.[5]

As already said, FFR is defined as the ratio of the mean distal coronary artery pressure to the mean aortic pressure during the period of maximum hyperaemia. This value can be measured invasively during a CCA procedure using a thin (0.014-inch) guide wire introduced through a diagnostic catheter.[10] By crossing the stenosis, we can measure the blood flow and pressure after hyperaemic agent infusion (such as adenosine). The small diameter of catheter allows to perform this procedure even in outpatients.[2] For FFR values less than 0.75–0.80, the ischaemia is highly probable. As a consequence, an interventional treatment can be required. Differently, for values higher than this threshold, the stenosis is rarely associated with inducible ischaemia, and the patient may be safely treated with medical therapy without the need of angioplasty.[1–3]

A new computational model that allows assessing with high accuracy the functional significance of intermediate stenosis is the quantitative coronary angiography FFR (QCA-FFR). The high accuracy of QCA-FFR derived from computational fluid dynamics applied to reconstruction of the patient's coronary tree. This is possible using validated three-dimensional QCA and hyperaemic volumetric flow rates derived from a score called *thrombolysis in myocardial infarction* (TIMI) based on clinical data, adjusted to parent and daughter vessel flow distribution in side branches. The inclusion of major side branches allows for a better adjustment for differences in myocardial mass subtended by the interrogated vessel, and the use of individual hyperaemic flow better accounts for distal microvascular disease, providing a better approximation of invasive measures overall. Compared with CT-FFR (that assesses the empiric flow derivation based on average population-based physiological model assumptions under rest conditions), the QCA-FFR is based on individual hyperaemia. This approach leads to a higher accuracy of QCA-FFR compared with the computed tomography (CT) technique.[11]

The FFR measurement can be used to evaluate the robustness of collateral flow in the case of chronic total occlusion (CTO). This measurement differs from the traditional approach because of having to cross the occluded segment with an FFR guide wire. After crossing the CTO segment, the FFR guide wire is advanced into the distal collateralized CTO vessel through a 1.2–1.5 mm over-the-wire balloon. The measurement of FFR is performed in the distal CTO vessel at baseline without inducing hyperaemia after withdrawal of the balloon into the guide. If the CTO is reanalysed via a retrograde approach, all retrograde devices occupying the collaterals will have to be removed prior to FFR measurement in order to allow adequate collateral filling of the distal CTO segment and facilitate measurement of true perfusion pressures. At the end of the revascularization, the final measurement of the FFR is recorded using the same technique.[12] We hypothesize that in the near future, the measurement of collateral flow in the case of CTO could be performed using the CT-FFR, but until now, there are no studies that demonstrate the efficacy of this approach.

Despite the unequivocal evidence supporting the use of FFR to guide clinical decision, the practice of this technique is limited. In fact, FFR is currently used in $<10\%$ of coronary revascularization procedures in the USA.[13] This is partially due to the invasive nature of the technique, the need for pharmacologic vasodilator and for skilled operators, and risks associated to instrumentation of the coronary arteries. Importantly, the cost of this procedure is quite high.[14]

Non-invasive fractional flow reserve measurement

One of the most accurate diagnostic tools for the identification or exclusion of CAD is CTCA. During the past decades, CT underwent a relevant improvement, evolving from single-slice to 640-slice scanners,[15,16] while dual-source units opened new perspectives in cardiac imaging in terms of faster data acquisition and dual-energy (i.e. spectral) studies.[17] Thus, CTCA images can now be acquired within few seconds, with a spatial resolution not so distant from that of CCA.[18] Using at least 64-slice multidetector CT systems, the median sensitivity for significant coronary stenosis on a per-patient level is 98%, and the specificity is 90%, while the high sensitivity reported across most studies turns out into a negative predictive value from 95 to 100%.[19] Of note, radiation exposure has been dramatically reduced, more recently, to <0.1 mSv.[20,21]

However, CTCA cannot determine the haemodynamic significance of coronary lesions, and it often overestimates the clinical relevance of stenosis. In particular, even if most CTCA-detected coronary stenosis are confirmed at CCA, less than half of those studied with FFR cause myocardial ischaemia.[22,23] Thus, at least a percentage of stenosis could be overtreated: the revascularization of such lesions would provide no clinical benefit in terms of improvement of blood flow but exposes the patient to the risks of this procedure.[24]

Improved image-based modelling and computational fluid dynamics allowed for calculating coronary artery pressure and flow using CTCA data, without the need for additional imaging or modification of acquisition protocols.[25] In this way, we could combine the ability of CTCA in anatomical quantification of stenosis with the value of the FFR in the assessment of the functional significance of the identified lesions.

The first researches on computational fluid dynamics applied to blood flow were performed in the study of carotid bifurcation and subsequently in the study of image-based modelling of pulsatile blood flow in the abdominal aorta and aortic aneurysms.[26,27] This technology allows for obtaining patient-specific three-dimensional computational models also of the coronary vasculature and stenosis using contrast-enhanced CT. Moreover, the calculation of pressure and velocity of blood flow through the coronary vessels is possible, simulating different situations such as hyperaemia, thus also sparing injection of pharmacologic vasodilator.

The method mostly used for calculating CT-FFR is quite similar to that used for the I-FFR: CT-based computed pressure values are used instead of those measured invasively. In this case, CT-FFR is based on the following three assumptions:

(1) At rest, the total coronary blood flow is proportional to the oxygen demand of myocardial mass, which can be computed using CT data.[13]
(2) At rest, the resistance of the coronary microcirculation is inversely proportional to the size of the feeding vessel.[28–31]
(3) The coronary microcirculation has a predictable response to the vasodilator administration.[32]

Therefore, the condition of maximum myocardial hyperaemia can be simulated using a computational dynamic physiological model that provides a final CT-FFR value.

Two other non-invasive CT-based methods for the assessment of haemodynamic significance of coronary stenosis are transluminal attenuation gradient (TAG) and myocardial perfusion. Transluminal attenuation gradient evaluates the significance of stenosis using the density of contrast material in a series of evenly spaced regions of interest. It is a post-processing defined as the regression coefficient of the line fitting the plot of density vs. distance from the coronary ostium.[33] In fact, in the presence of a functionally significant stenosis, the density of contrast material falls off more rapidly than in the absence of the stenosis.[34] The study of myocardial perfusion is a non-invasive contrast-enhanced CT examination that provides both anatomic and physiological information. However, it is performed in patient rest-stress conditions and involves an additional radiation exposure compared with CTCA.[35]

Computation of fractional flow reserve from computed tomography coronary angiography data

The computation of FFR requires the knowledge of the pressure profile inside a coronary artery before and after the stenosis. Pressure and blood flow can be noninvasively computed by solving the Navier–Stokes equations (which are the equations governing the fluid dynamics) using numerical methods.[36] For the equations to be solved, the physical properties of blood such as density and viscosity are supposed to be known. The solution of the Navier–Stokes equations is the blood pressure profile along the vessel and its time dependence as well as the blood velocity (which is described by three components varying again with position and time). Since the Navier–Stokes equations can be solved analytically only under specific conditions, in the case of a patient-specific model, they must be approximated and solved in a finite number of points (millions of points) and in a finite number of time points (e.g. 100 points for 1 cardiac cycle). This means that millions of equations must be solved simultaneously for each time points using powerful computing workstations.[37]

To compute blood flow and pressure in coronaries, the anatomical domain of interest must be firstly defined. In fact, this is the volume in which the Navier–Stokes equations will be solved (the lumen of the coronary tree). To this aim, CTCA images are processed using segmentation algorithms, which allow the extraction of the luminal surface of coronary arteries and of the aorta.[25] Once the anatomical surface is reconstructed, a mesh consisting in millions of points and elements is generated, and for each of the generated points, the numerical method will compute blood pressure and velocity. Theoretically, an accurate computation of pressure and velocity is obtained if the Navier–Stokes equations are solved in the whole patient-specific circulatory domain. In practice, this is not feasible, and the domain is reduced to the main coronary branches and the aortic root with the first part of the ascending aorta (*Figure 1*). The parts of the circulatory system which are eliminated must be replaced with

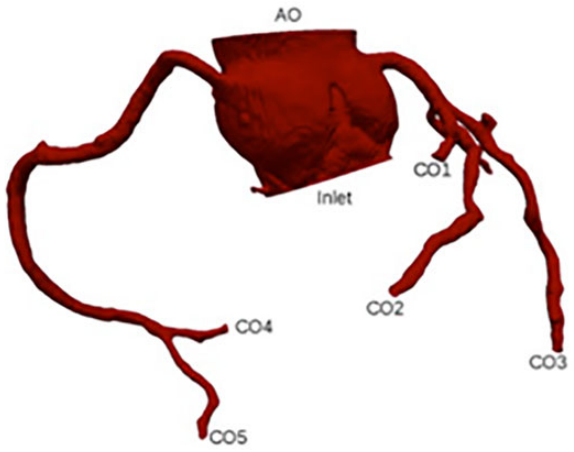

Figure 1 Male patient, 57 year old, with atypical chest pain. Anatomical domain in which the aortic root and the main coronary branches have been reconstructed from one computed tomography coronary angiography (Unit of Radiology, Research Hospital Policlinico San Donato, Milan, Italy). The interfaces between the anatomical domain and the parts of the circulatory system which have not been reconstructed are labelled: the interface with left ventricle (inlet), the interface with the aortic arch (AO), and the interfaces with the truncated coronary tree (CO1, CO2, CO3, CO4, and CO5).

appropriate boundary conditions imposed at the interfaces.[36] These conditions should mimic the missing vessels and the heart. In particular, we can distinguish between the following three types of boundary conditions:

(1) the inlet boundary condition (inlet, in *Figure 1*), which mimics the blood entering the aorta from the left ventricle of the patient;
(2) the aortic outlet boundary condition (AO, in *Figure 1*), which mimics the expected patient pressure at the ascending aorta;
(3) the coronary outlets (CO1-5, in *Figure 1*), which mimic the expected patient vessel resistance for each of the coronary branch.[25]

For the inlet, a simplified model of the heart is used, which is calibrated to obtain a cardiac output equal to the patient-specific cardiac output computed through an allometric scaling law (of note, *allometry*, also called *biological scaling*, is an empirical science assessing the change in size and shape of organs in relation to changes in body size).[38,39] At the aortic outlet, a pressure equal to the mean brachial pressure of the patient is imposed. Finally, the total coronary flow at rest conditions is computed using a power-law relation which states that total coronary flow is proportional to the myocardial mass to the power of 3/4. From the total coronary flow, the total coronary resistance at rest is estimated, and this is used to estimate the basal resistance of each individual coronary outlet boundary through the assumption that the resistance at rest is inversely proportional to the vessel diameter.[31] Notably, in this model, the movement of the vessels is ignored, and the vascular domain is imposed to be rigid during the solution of the numerical method.

All the described conditions are computed using patient-specific information at rest, i.e. the cardiac output, the myocardial mass, the vessels diameters and the brachial pressure. To compute the FFR, the last step consists in estimating the boundary conditions relative to the maximum myocardial hyperaemia. This is done modelling the effect of vasodilator by reducing the total coronary resistance to 0.24 of the resting value as suggested in Wilson *et al.*[32] After the generation of the vascular domain and the definition of the boundary conditions during hyperaemia, the computational fluid dynamic method computes the hyperaemic pressure field and the blood velocity field in all the points of the vascular domain and for each time point in the cardiac cycle. From these values, the mean over the cardiac cycle of the hyperaemic pressure field is computed, and the CT-FFR is obtained in each domain point by normalizing the mean hyperaemic pressure field by the average mean hyperaemic aortic pressure that means *the ratio of the mean distal coronary artery pressure to the mean aortic pressure during the period of maximum hyperaemia*. Of note, the output of the CT-FFR computation can be presented as an image in which a colour-coded map represents the CT-FFR values over the vascular domain (*Figure 2*).[13,24,25] This allows the evaluation of the CT-FFR across the stenosis and on the whole vascular domain and not only before and after the studied stenosis as is when I-FFR is measured. In *Table 1*, the principal clinical subsets in which either CT or CT-FFR are recommended are reported.

Limitations of computed tomographic fractional flow reserve

Three main factors may limit the clinical value of CT-FFR. The most important one is the *image quality of CTCA*. Image noise, beam-hardening artefacts from metallic devices or from coronary calcifications, and motion artefacts can impair the image quality. These problems may be kept under control following specific guidelines, in particular with the administration of beta-blockers to reduce heart rate and its variability and with the administration of sublingual nitrates to dilate the coronary arteries.[39]

Another limiting factor is the use of *a fluid dynamics model that can be inaccurate in individual patients with abnormal response of the microcirculation to vasodilators and to the physiologic condition that may influence parameters such as the blood viscosity or density*. Blood viscosity, presumed from the concentration of haematocrit and haemoglobin, has minimal influence on CT-FFR in the normal range. Conversely, in condition of severe anaemia, the reduced viscosity can affect the calculation of CT-FFR.[13] Moreover, all the physiological assumptions that must be done to compute CT-FFR (the relationship between total coronary flow and myocardial mass, the relationship between coronary resistance and coronary diameter, and the amount of reduction in resistance due to adenosine) may be incorrect due to variability among patients.[24]

Finally, accuracy of CT-FFR in patients with acute coronary syndrome remains unknown.[13]

Short review of the literature about computed tomographic fractional flow reserve

We performed a literature search on PubMed (MEDLINE) of English studies updated to 26 June 2015. The aim of this

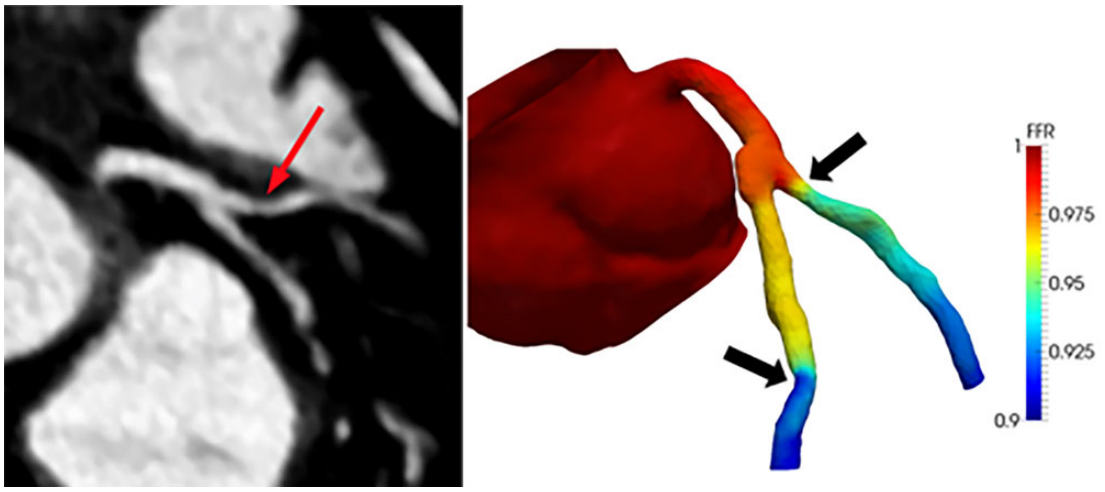

Figure 2 Male patient, 57 year old, with atypical chest pain (same patient shown in *Figure 1*). Computed tomography coronary angiography was performed at the Unit of Radiology of the Research Hospital Policlinico San Donato, Milan, Italy using a 64-row computed tomography (Definition AS, Siemens, Enlargen, Germany) with prospective gating, and 80 mL of iomeprol with an iodine concentration of 400 mg I/mL (Iomeron 400, Bracco, Milan, Italy). Computed tomography scan (left panel) showed a 50% stenosis at origin of circumflex coronary artery and a 50% stenosis at middle left anterior descending coronary artery. Computed tomographic fractional flow reserve (right panel) was calculated and represent as a colour-coded map by the Computational Mechanics & Advanced Material Group, Department of Civil Engineering and Architecture, University of Pavia, Pavia, Italy, showing for both stenoses a fractional flow reserve of >0.8, i.e. haemodynamically not significant, clinically not deserving conventional coronary angiography.

Table 1 Criteria of appropriateness for computed tomography and/or computed tomographic fractional flow reserve in principal clinical subsets

	CT	CT-FFR
Pretest probability of CAD		
Low	R	I
Intermediate	R	R
High	I	I
Setting		
Graft patency	R	R
Stent with diameter >3 mm	R	NC
Stent with diameter <3 mm	I	I

CT-FFR, computed tomographic fractional flow reserve; I-FFR, CCA-based invasive fractional flow reserve; R, recommended; I, inappropriate; NC, not clear.

search was to show and summarize the progresses of CT-FFR measurement in the assessment of CAD. The key words used for this search were *fractional flow reserve* AND *computed tomography*, restricting to only *clinical trials* or *meta-analyses*.

We found 16 original articles and 1 meta-analysis (*Table 2*). Eight of them compared CT-FFR with I-FFR as a reference standard.[37–47] The systematic review and meta-analysis included articles published up to August 2014, evaluating the diagnostic performance of CT-FFR using I-FFR as a reference standard.[48] Five studies for a total of 706 patients and 1165 vessels or lesions were included. The pooled per-patient sensitivity and specificity were 90 and 72%, respectively; pooled LR+ and LR− were 3.70 and 0.15, respectively. The pooled per-vessel or per-lesion sensitivity and specificity were 83 and 78%, and pooled LR+ and LR− were 3.75 and 0.22, respectively. The area under the summary receiver operating characteristic curve was 0.94 (per patient) and 0.91 (per vessel). The authors concluded that 'The existing evidence suggests that non-invasive FFR-CT has high diagnostic performance compared with invasively measured FFR for the detection of ischemia-causing stenosis in stable patients with suspected or known coronary artery disease'.

One study evaluated the reproducibility of repeated CT-FFR measurements.[49] FFR-CT and I-FFR measurements were performed in 28 patients with suspected stable CAD, for a total of 58 vessels examined. The standard deviation for the difference ($P = 0.722$) between first and second FFR-CT analyses was 0.034 vs. 0.033 for I-FFR repeated measurements. Limits of agreement were −0.06 to 0.08 for FFR-CT and −0.07 to 0.06 for I-FFR. The coefficient of variation of FFR-CT was 3.4 vs. 2.7% for I-FFR.[46] Therefore, the reproducibility of CT-FFR is similar to that of I-FFR.

Two articles discussed the use of TAG for predicting the haemodynamic significance of coronary artery stenosis.[50,51] However, Yeonyee *et al.*[52] compared the diagnostic performance of TAG and CT-FFR and concluded that CT-FFR provides better diagnostic performance for detecting and excluding coronary artery lesions-specific ischaemia compared with TAG or visual stenosis grade on CCTA.

Two of these studies analysed the economical and clinical impacts of incorporating CT-FFR into future pathways.[53,54] In particular, the study performed by Kimura *et al.*[53] on 254 patients showed that the use of CT-FFR for selecting patients for PCI would result in 32% lower cost and 19% fewer cardiac events at 1 year compared with I-FFR trial. On the other hand, the retrospective analysis performed at the RACPC hospital in UK by Rajani *et al.*[54] on 410 patients showed that using FFR-CT in patients with a pre-test likelihood of CAD between 10 and 90% predicted a reduction of 48% in CCA and 49% in PCI. Furthermore,

Table 2 Original articles and meta-analysis regarding computed tomographic fractional flow reserve measurement in the assessment of coronary artery disease

First name, year (reference)	CT-FFR vs. I-FFR	Reproducibility	Cost analysis	TAG	Other
Deng, 2015[48]					Meta-analysis
Hulten, 2015[55]					CT-perfusion vs. CT-FFR
Rajani, 2015[5]			x		
Thompson, 2015[56]					CT-FFR vs. CTA, I-FFR and ICA
Baumann, 2014[45]	x				
Coenen, 2015[46]	x				
Gaur, 2014[49]		x			
Kim, 2014[43a]	x				
Kimura, 2014[53]			x		
Leipsic, 2014[57]					CTA vs. Ct-FFR
Miyoshi, 2014[47]	x				
Nørgaard (HFNXT), 2014[42a]	x				
Renker, 2014[44a]	x				
Stuijfzand, 2014[50]				x	
Wong, 2014[51]				x	
Min (DeFACTO), 2012[41a]	x				
Koo (DISCOVER-FLOW), 2011[40a]	x				
Total	8	1	2	2	4

CT-FFR, computed tomographic fractional flow reserve; I-FFR, CCA-based invasive fractional flow reserve; TAG, transluminal attenuation gradient.
[a]Studies included in the systematic review and meta-analysis by Deng *et al.* (2015).

the FFR-CT allowed for saving £200 per patient and a reduction in relative adverse event rates of 4%.

Other studies compared CT-FFR with different techniques such as CT perfusion,[55] invasive coronary angiography,[56] or CT angiography.[56,57]

Conclusion

The non-invasive measurement of FFR based on CTCA data is a promising tool for the assessment of the haemodynamic significance of intermediate coronary arteries stenosis. The possibility to use the data routinely acquired with CTCA may greatly help physicians in selecting patients for medical therapy vs. invasive CCA, improving clinical outcomes while reducing healthcare costs. Further large-scale clinical trials are warranted to support the implementation of CT-FFR in clinical practice.

Conflict of interest: none declared.

References

1. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek J, Koolen JJ, Koolen JJ. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med* 1996; **334**:1703–1708.
2. Elgendy IY, Conti CR, Bavry AA. Fractional flow reserve: an updated review. *Clin Cardiol* 2014;**37**:371–380.
3. Stergiopoulos K, Boden WE, Hartigan P, Möbius-Winkler S, Hambrecht R, Hueb W, Hardison RM, Abbott JD, Brown DL. Percutaneous coronary intervention outcomes in patients with stable obstructive coronary artery disease and myocardial ischemia: a collaborative meta-analysis of contemporary randomized clinical trials. *JAMA Intern Med* 2014; **174**:232–240.
4. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Möbius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Jüni P, Fearon WF. FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012;**367**:991–1001.
5. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, Bär F, Hoorntje J, Koolen J, Wijns W, de Bruyne B. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER study. *J Am Coll Cardiol* 2007;**49**: 2105–2111.
6. Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, Gottlieb I, Paul N, Clouse ME, Shapiro EP, Hoe J, Lardo AC, Bush DE, de Roos A, Cox C, Brinker J, Lima JA. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med* 2008;**359**:2324–2336.
7. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF, FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;**360**:213–224.
8. Grunau GL, Min JK, Leipsic J. Modeling of fractional flow reserve based on coronary CT angiography. *Curr Cardiol Rep* 2013;**15**:336.
9. McGeoch RJ, Oldroyd KG. Pharmacological options for inducing maximal hyperaemia during studies of coronary physiology. *Catheter Cardiovasc Interv* 2008;**71**:198–204.
10. Leone AM, Porto I, De Caterina AR, Basile E, Aurelio A, Gardi A, Russo D, Laezza D, Niccoli G, Burzotta F, Trani C, Mazzari MA, Mongiardo R, Rebuzzi AG, Crea F. Maximal hyperemia in the assessment of fractional flow reserve: intracoronary adenosine versus intracoronary sodium nitroprusside versus intravenous adenosine: the NASCI (Nitroprussiato versus Adenosina nelle Stenosi Coronariche Intermedie) study. *JACC Cardiovasc Interv* 2012;**5**:402–408.
11. Tu S, Barbato E, Köszegi Z, Yang J, Sun Z, Holm NR, Tar B, Li Y, Rusinaru D, Wijns W, Reiber JH. Fractional flow reserve calculation from 3-dimensional quantitative coronary angiography and TIMI frame count: a fast computer model to quantify the functional significance of moderately obstructed coronary arteries. *JACC Cardiovasc Interv* 2014;**7**: 768–777.
12. Sachdeva R, Agrawal M, Flynn SE, Werner GS, Uretsky BF. The myocardium supplied by a chronic total occlusion is a persistently ischemic zone. *Catheter Cardiovasc Interv* 2014;**1**:839–816.
13. Zarins CK, Taylor CA, Min JK. Computed fractional flow reserve (FFTCT) derived from coronary CT angiography. *J Cardiovasc Transl Res* 2013;**6**: 708–714.

14. Meijboom WB, Van Mieghem CA, van Pelt N, Weustink A, Pugliese F, Mollet NR, Boersma E, Regar E, van Geuns RJ, de Jaegere PJ, Serruys PW, Krestin GP, de Feyter PJ. Comprehensive assessment of coronary artery stenoses: computed tomography coronary angiography versus conventional coronary angiography and correlation with fractional flow reserve in patients with stable angina. *J Am Coll Cardiol* 2008;**52**:636–643.
15. Di Cesare E, Gennarelli A, Di Sibio A, Felli V, Splendiani A, Gravina GL, Barile A, Masciocchi C. Assessment of dose exposure and image quality in coronary angiography performed by 640-slice CT: a comparison between adaptive iterative and filtered back-projection algorithm by propensity analysis. *Radiol Med* 2014;**119**:642–649.
16. Di Cesare E, Gennarelli A, Di Sibio A, Felli V, Splendiani A, Gravina GL, Masciocchi C. Image quality and radiation dose of single heartbeat 640-slice coronary CT angiography: a comparison between patients with chronic atrial fibrillation and subjects in normal sinus rhythm by propensity analysis. *Eur J Radiol* 2015;**84**:631–636.
17. Kim SM, Chang SA, Shin W, Choe YH. Dual-energy CT perfusion during pharmacologic stress for the assessment of myocardial perfusion defects using a second-generation dual-source CT: a comparison with cardiac magnetic resonance imaging. *J Comput Assist Tomogr* 2014; **38**:44–52.
18. Sabarudin A, Sun Z. Coronary CT angiography: diagnostic value and clinical challenges. *World J Cardiol* 2013;**5**:473–483.
19. Meinel FG, Bayer RR II, Zwerner PL, De Cecco CN, Schoepf UJ, Bamberg F. Coronary computed tomographic angiography in clinical practice: state of the art. *Radiol Clin North Am* 2015;**53**:287–296.
20. Cademartiri F, Maffei E, Arcadi T, Catalano O, Midiri M. CT coronary angiography at an ultra-low radiation dose ($<$0.1 mSv): feasible and viable in times of constraint on healthcare costs. *Eur Radiol* 2013;**23**:607–613.
21. Kim Y, Kim YK, Lee BE, Lee SJ, Ryu YJ, Lee JH, Chang JH. Ultra-low-dose CT of the thorax using iterative reconstruction: evaluation of image quality and radiation dose reduction. *AJR Am J Roentgenol* 2015;**204**: 1197–1202.
22. Schuijf JD, Bax JJ. CT angiography: an alternative to nuclear perfusion imaging? *Heart* 2008;**94**:255–257.
23. Nissen SE. Limitations of computed tomography coronary angiography. *J Am Coll Cardiol* 2008;**52**:2145–2147.
24. Patel MR. Detecting obstructive coronary disease with CT angiography and noninvasive fractional flow reserve. *JAMA* 2012;**308**:1269–1270.
25. Taylor CA, Fonte TA, Min JK. Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve: scientific basis. *J Am Coll Cardiol* 2013;**61**: 2233–2241.
26. Perktold K, Resch M, Peter RO. Three-dimensional numerical analysis of pulsatile flow and wall shear stress in the carotid artery bifurcation. *J Biomech* 1991;**24**:409–420.
27. Taylor CA, Hughes TJR, Zarins CK. Computational investigations in vascular disease. *Comput Phys* 1996;**10**:224–232.
28. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med* 1987;**316**:1371–1375.
29. Zarins CK, Zatina MA, Giddens DP, Ku DN, Glagov S. Shear stress regulation of artery lumen diameter in experimental atherogenesis. *J Vasc Surg* 1987;**5**:413–420.
30. Kamiya A, Togawa T. Adaptive regulation of wall shear stress to flow change in the canine carotid artery. *Am J Physiol* 1980;**239**:H14–H21.
31. Choy JS, Kassab GS. Scaling of myocardial mass to flow and morphometry of coronary arteries. *J Appl Physiol* 2008;**104**:1281–1286.
32. Wilson RF, Wyche K, Christensen BV, Zimmer S, Laxson DD. Effects of adenosine on human coronary arterial circulation. *Circulation* 1990;**82**: 1595–1606.
33. Ko BS, Wong DT, Nørgaard BL, Leong DP, Cameron JD, Gaur S, Marwan M, Achenbach S, Kuribayashi S, Kimura T, Meredith IT, Seneviratne SK. Diagnostic performance of transluminal attenuation gradient and noninvasive fractional flow reserve derived from 320-detector row CT angiography to diagnose hemodynamically significant coronary stenosis: an NXT substudy. *Radiology* 2015;**6**:150383, in press.
34. Einstein AJ. TAG-is it it?: improving coronary computed tomography angiography with the isotemporal transluminal contrast attenuation gradient. *J Am Coll Cardiol* 2013;**61**:1280–1282.
35. Cannaò PM, Schoepf UJ, Muscogiuri G, Wichmann JL, Fuller SR, Secchi F, Varga-Szemes A, De Cecco CN. Technical prerequisites and imaging protocols for dynamic and dual energy myocardial perfusion imaging. *Eur J Radiol* 2015;**84**:2401–2410.
36. Formaggia L, Quarteroni A, Veneziani A. *Cardiovascular Mathematics: Modeling and Simulation of the Circulatory System*. Vol. 1. Heidelberg, Germany: Springer Science & Buisness Media; 2010.
37. Murray CD. The physiological principle of minimum work: I. The vascular system and the cost of blood volume. *Proc Natl Acad Sci* 1926;**12**: 207–214.
38. West GB, Brown JH, Enquist BJ. A general model for the origin of allometric scaling laws in biology. *Science* 1997;**276**:122–126.
39. Nam CW, Mangiacapra F, Entjes R, Chung IS, Sels JW, Tonino PA, De Bruyne B, Pijls NH, Fearon WF, FAME Study Investigators. Functional SYNTAX score for risk assessment in multivessel coronary artery disease. *J Am Coll Cardiol* 2011;**58**:1211–1218.
40. Koo BK, Erglis A, Doh JH, Daniels DV, Jegere S, Kim HS, Dunning A, DeFrance T, Lansky A, Leipsic J, Min JK. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained via Noninvasive Fractional Flow Reserve) study. *J Am Coll Cardiol* 2011;**58**:1989–1997.
41. Min JK, Leipsic J, Pencina MJ, Berman DS, Koo BK, van Mieghem C, Erglis A, Lin FY, Dunning AM, Apruzzese P, Budoff MJ, Cole JH, Jaffer FA, Leon MB, Malpeso J, Mancini GB, Park SJ, Schwartz RS, Shaw LJ, Mauri L. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. *JAMA* 2012;**308**:1237–1245.
42. Nørgaard BL, Leipsic J, Gaur S, Seneviratne S, Ko BS, Ito H, Jensen JM, Mauri L, De Bruyne B, Bezerra H, Osawa K, Marwan M, Naber C, Erglis A, Park SJ, Christiansen EH, Kaltoft A, Lassen JF, Bøtker HE, Achenbach S, NXT Trial Study Group. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). *J Am Coll Cardiol* 2014;**63**:1145–1155.
43. Kim KH, Doh JH, Koo BK, Min JK, Erglis A, Yang HM, Park KW, Lee HY, Kang HJ, Kim YJ, Lee SY, Kim HS. A novel noninvasive technology for treatment planning using virtual coronary stenting and computed tomography-derived computed fractional flow reserve. *JACC Cardiovasc Interv* 2014;**7**:72–78.
44. Renker M, Schoepf UJ, Wang R, Meinel FG, Rier JD, Bayer RR II, Möllmann H, Hamm CW, Steinberg DH, Baumann S. Comparison of diagnostic value of a novel noninvasive coronary computed tomography angiography method versus standard coronary angiography for assessing fractional flow reserve. *Am J Cardiol* 2014;**114**:1303–1308.
45. Baumann S, Wang R, Schoepf UJ, Steinberg DH, Spearman JV, Bayer RR II, Hamm CW, Renker M. Coronary CT angiography-derived fractional flow reserve correlated with invasive fractional flow reserve measurements—initial experience with a novel physician-driven algorithm. *Eur Radiol* 2015;**25**:1201–1207.
46. Coenen A, Lubbers MM, Kurata A, Kono A, Dedic A, Chelu RG, Dijkshoorn ML, Gijsen FJ, Ouhlous M, van Geuns RJ, Nieman K. Fractional flow reserve computed from noninvasive CT angiography data: diagnostic performance of an on-site clinician-operated computational fluid dynamics algorithm. *Radiology* 2015;**274**:674–683.
47. Miyoshi T, Osawa K, Ito H, Kanazawa S, Kimura T, Shiomi H, Kuribayashi S, Jinzaki M, Kawamura A, Bezerra H, Achenbach S, Nørgaard BL. Non-invasive computed fractional flow reserve from computed tomography (CT) for diagnosing coronary artery disease – Japanese results from NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). *Circ J* 2015;**79**:406–412.
48. Deng SB, Jing XD, Wang J, Huang C, Xia S, Du JL, Liu YJ, She Q. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in coronary artery disease: a systematic review and meta-analysis. *Int J Cardiol* 2015;**184**:703–709.
49. Gaur S, Bezerra HG, Lassen JF, Christiansen EH, Tanaka K, Jensen JM, Oldroyd KG, Leipsic J, Achenbach S, Kaltoft AK, Bøtker HE, Nørgaard BL. Fractional flow reserve derived from coronary CT angiography: variation of repeated analyses. *J Cardiovasc Comput Tomogr* 2014;**8**:307–314.
50. Stuijfzand WJ, Danad I, Raijmakers PG, Marcu CB, Heymans MW, van Kuijk CC, van Rossum AC, Nieman K, Min JK, Leipsic J, van Royen N, Knaapen P. Additional value of transluminal attenuation gradient in CT angiography to predict hemodynamic significance of coronary artery stenosis. *JACC Cardiovasc Imaging* 2014;**7**:374–386.

51. Wong DT, Ko BS, Cameron JD, Leong DP, Leung MC, Malaiapan Y, Nerlekar N, Crossett M, Troupis J, Meredith IT, Seneviratne SK. Comparison of diagnostic accuracy of combined assessment using adenosine stress computed tomography perfusion + computed tomography angiography with transluminal attenuation gradient + computed tomography angiography against invasive fractional flow reserve. *J Am Coll Cardiol* 2014;**63**:1904–1912.
52. Yoon YE, Choi JH, Kim JH, Park KW, Doh JH, Kim YJ, Koo BK, Min JK, Erglis A, Gwon HC, Choe YH, Choi DJ, Kim HS, Oh BH, Park YB. Noninvasive diagnosis of ischemia-causing coronary stenosis using CT angiography: diagnostic value of transluminal attenuation gradient and fractional flow reserve computed from coronary CT angiography compared to invasively measured fractional flow reserve. *JACC Cardiovasc Imaging* 2012;**5**:1088–1096.
53. Kimura T, Shiomi H, Kuribayashi S, Isshiki T, Kanazawa S, Ito H, Ikeda S, Forrest B, Zarins CK, Hlatky MA, Norgaard BL. Cost analysis of noninvasive fractional flow reserve derived from coronary computed tomographic angiography in Japan. *Cardiovasc Interv Ther* 2015;**30**:38–44.
54. Rajani R, Webb J, Marciniak A, Preston R. Comparative efficacy testing—fractional flow reserve by coronary computed tomography for the evaluation of patients with stable chest pain. *Int J Cardiol* 2015;**183**:173–177.
55. Hulten E, Ahmadi A, Blankstein R. CT assessment of myocardial perfusion and fractional flow reserve. *Prog Cardiovasc Dis* 2015;**57**:623–631.
56. Thompson AG, Raju R, Blanke P, Yang TH, Mancini GB, Budoff MJ, Norgaard BL, Min JK, Leipsic JA. Diagnostic accuracy and discrimination of ischemia by fractional flow reserve CT using a clinical use rule: results from the determination of fractional flow reserve by anatomic computed tomographic angiography study. *J Cardiovasc Comput Tomogr* 2015;**9**:120–128.
57. Leipsic J, Yang TH, Thompson A, Koo BK, Mancini GB, Taylor C, Budoff MJ, Park HB, Berman DS, Min JK. CT angiography (CTA) and diagnostic performance of noninvasive fractional flow reserve: results from the Determination of Fractional Flow Reserve by Anatomic CTA (DeFACTO) study. *AJR Am J Roentgenol* 2014;**202**:989–994.