Fractional Flow Reserve Derived from Coronary Imaging and Computational Fluid Dynamics

Ioannis Pantos[1,2] and Demosthenes Katritsis[1]

1. Athens Euroclinic, Athens, Greece; 2. University of Athens, Greece

Abstract

The assessment of functional severity of atherosclerotic stenoses in patients with coronary artery disease by invasive fractional flow reserve (FFR) measurement requires coronary artery cannulation, advancement of a wire and intravenous adenosine infusion with inherent procedure-related risk and costs. Coronary computed tomographic angiography (CCTA) and rotational coronary angiography (RA) have been recently used in conjunction with computational fluid dynamics (CFD) and image-based modelling for the determination of FFR without the need for additional imaging, modification of acquisition protocols or administration of medication. FFR derived from CCTA was demonstrated as superior to measures of CCTA stenosis severity for determination of lesion-specific ischaemia. Estimation of FFR from RA images and CFD provides a less invasive alternative to conventional FFR measurement while estimated values are in agreement with measured values. These new, combined anatomic–functional assessments have the potential to simplify the noninvasive diagnosis of coronary artery disease with a single study to identify patients with ischaemia-causing stenosis who may benefit from revascularisation.

Keywords

Fractional flow reserve, computational fluid dynamics, computed tomography, rotational angiography, coronary artery disease

Disclosure: The authors have no conflicts of interest to declare.
Acknowledgement: Supported by a grant from the Stavros Niarchos Foundation.
Received: 24 April 2014 **Accepted:** 15 August 2014 **Citation:** *Interventional Cardiology Review*, 2014;9(3):145–50
Correspondence: Dr Demothenes Katritsis, Department of Cardiology, Athens Euroclinic, 9 Athanassiadou Str., 115 21 Athens, Greece. E: dkatritsis@euroclinic.gr

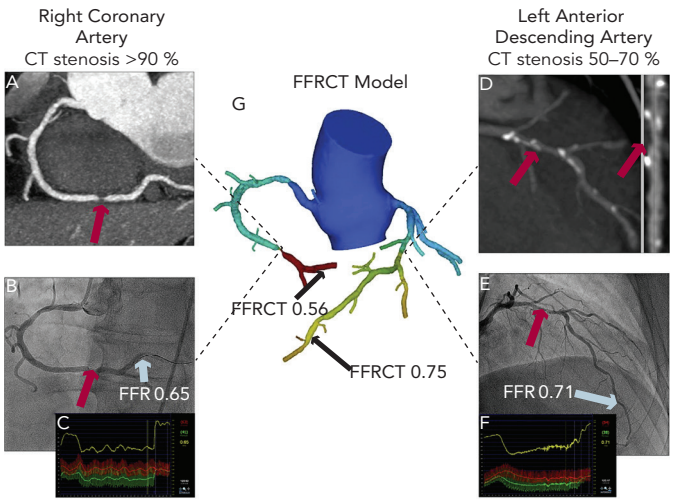
The functional severity of atherosclerotic coronary lesions is the single most important prognostic factor in patients with documented coronary artery disease (CAD). Assessment of the haemodynamic significance of coronary artery lesions by invasive fractional flow reserve (FFR) measurement now has an I-A indication by the European Society of Cardiology (ESC) to identify haemodynamically relevant coronary lesions when evidence of ischaemia is not available.[1] FFR represents the extent to which maximal myocardial blood flow is limited by the presence of a coronary stenosis and in clinical practice FFR is defined as the ratio of distal coronary to aortic pressure at maximal vasodilation.[2] FFR provides a physiologic adjunct to invasive coronary angiography, challenging the notion of coronary revascularisation need on the basis of anatomic coronary stenosis alone.[3] In the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) study, of 1005 patients with multivessel CAD, those who underwent FFR-guided revascularisation experienced lower rates of adverse events with fewer coronary stents and lower healthcare costs, than patients undergoing angiogram-guided revascularisation.[4,5]

The results from FAME are in accordance with the five-year follow-up of individuals from the Deferral Versus Performance of PTCA in Patients Without Documented Ischemia (DEFER)[6] study which demonstrated that amongst lesions judged angiographically "obstructive," >50 % were haemodynamically insignificant by FFR and no benefit was observed by revascularisation. In patients with stable CAD and functionally significant stenoses, FFR-guided percutaneous coronary intervention (PCI) in combination with medical therapy, as compared with medical therapy alone, decreased the need for urgent revascularisation.[7] Despite these benefits, less than 10 % of PCI procedures in the UK use adjunctive intracoronary measurements, and even fewer diagnostic cases employ FFR to guide management. This is due to the various drawbacks associated with the measurement of FFR, such as the requirement of invasive cardiac catheterisation, an expensive coronary pressure wire and intracoronary or intravenous adenosine infusion which is associated with adverse effects such as AV block, bronchial hyper-reactivity, and chest pain.[8,9] A clinical implication is the inadvertent revascularisation of patients with stable CAD and "innocent" lesions, who clearly do not benefit from intervention.[10] Thus, a tool that could accurately and rapidly calculate FFR without the need of a pressure wire would make this physiologic index become available to a wider population. Recent advances in coronary imaging and computational fluid dynamics (CFD) enable calculation of coronary flow and pressure fields from anatomic image data.[11] Novel techniques of FFR calculation have been developed based on coronary image analysis and CFD techniques which aim to provide an alternate to interventional FFR measurement by abolishing some or most of its limitations.

Computational Fluid Dynamics

CFD is a general term used to account for the numerical solution of the governing equations of fluid flow (Navier-Stokes equations). These equations are solved for the unknown pressure, which varies with position and time, and for the three components (vectors) of blood velocity, each of which are functions of position and time.[12] The physical properties of blood, the fluid density and the fluid viscosity, are known

Figure 1: Example of Fractional Flow Reserve derivation from computed tomography coronary angiography (FFRCT)



Multiplanar reformat (a, d) and straightened curved planar reformat (b, e) of a coronary computerised tomography (CT) angiogram, invasive coronary angiograms (b, e), invasive fractional flow reserve (FFR) measurements (c, f), and fractional flow reserve derived from computed tomography angiography (FFRCT) (g) of the right coronary artery and left anterior descending artery, respectively. The coronary CT angiogram demonstrates obstructive stenosis of the distal portion of the right coronary artery and the mid-portion of the left anterior descending artery (red arrows) and FFRCT values of 0.56 and 0.75 indicating ischaemia. Invasive coronary angiogram demonstrates obstructive stenoses of the right coronary and left anterior descending arteries (red ar rows) and measured FFR values, indicating ischaemia in both vessel territories. Reproduced with permission.[28]

when solving these equations. Although blood exhibits complex rheological properties, it can be approximated as a Newtonian fluid with a constant viscosity in large arteries. These equations were formulated as early as the 19th century, however, their solution only became possible with modern computing power and numerical methods.[13] Typically, a CFD problem consists of flow in a certain vessel model which is subject to certain boundary conditions. The geometric model of the vessel is discretised into a number of smaller entities (finite volumes or finite elements), thus forming the nodes of a computational mesh, on which the unknowns are calculated. The discretisation of the governing differential equations results in systems of algebraic equations, whose solution gives the problem unknowns at the mesh nodes. In order to perform a CFD simulation of flow in a coronary vessel, a 3D description of the vessel lumen is required. Several methods have been used for this purpose, the most widely applied of which are coronary vessel reconstruction based on biplanar coronary angiography,[14,15] rotational coronary angiography,[16] intravascular ultrasound and biplanar coronary angiography,[17] optical coherence tomography (OCT) imaging,[18] 3D quantitative coronary angiography[19] and computed tomography coronary angiography.[20,21]

Boundary flow conditions also need to be specified in order to solve the blood flow problem. Boundary flow conditions are mathematical relationships between the variables of interest, e.g. flow and pressure, defined on the boundaries (entrance and exit) of the vessel model.[12] Coronary flow and pressure at the coronary vessels are technically difficult to acquire both invasively and noninvasively due to the narrow lumens of the coronary vessels, the fact that they are embedded on the beating myocardium and due to the limited spatial and temporal resolution of applicable measurement techniques such as ultrasound, intravascular ultrasound and magnetic resonance imaging (MRI).[22] Thus alternative methodologies are usually utilised such as methods that couple lumped parameter models of the microcirculation to the outflow boundaries,[11] generic boundary conditions are developed and applied to the arterial outlets,[23] or predescribed conditions are assumed.[24,25] The field of CFD has made substantial progress in the past two decades, taking advantage of the availability of fast supercomputer capabilities. In terms of the application of CFD to coronary flow, the main limitations arise from ambiguities associated with inflow boundary conditions, definition of the cardiac and artery motion, etc., result in uncertainties regarding the validity of computational results.

Novel Techniques of FFR Calculation

By taking advantage of the exceptional capabilities of modern modalities for coronary imaging coupled with CFD methodologies, various investigators have presented alternative methods of FFR calculation. In these studies the imaging modality, either a multislice computed tomography (CT) scanner,[20,21,26–29] an angiography unit capable of rotational coronary angiography,[16] or 3D quantitative coronary angiography (3D-QCA) were employed for the acquisition of vessel models of diseased coronary arteries. On the acquired models suitable boundary conditions are applied, the blood is appropriately modelled and the incompressible Navier-Stokes equations are solved with a finite element method using CFD techniques and appropriate hardware. From the simulation results the "virtual" fractional flow reserve is calculated.

Coronary Computed Tomographic Angiography Derived FFR

Coronary computed tomographic angiography (CCTA) has emerged as a noninvasive test that assesses anatomic CAD stenosis severity.[30] However, CAD as determined by CCTA demonstrates a poor relationship to lesion-specific ischaemia, with the majority of high-grade stenoses detected by CCTA not being associated with ischaemia.[31–34] These findings have raised concerns that widespread use of CCTA might result in excess referral of patients to ICA and unnecessary revascularisation of nonischaemic coronary lesions.[35,36] Thus it would be desirable to be able to calculate the functional severity of CAD stenoses with CCTA. Computational fluid dynamics, as applied to CCTA images, provide the possibility for non-invasive quantitation of coronary blood flow, flow velocity and pressure in the major epicardial coronary arteries. A dedicated algorithm has been developed which facilitated the derivation of FFR based of CCTA (FFRCT) (HeartFlow™; HeartFlow Inc., Redwood City, CA, USA).[37,38]

CCTA can provide a credible coronary geometric model, including patient specific branching and pathology. Based upon this geometric information, a volumetric finite element mesh with anisotropic refinement and boundary layers is generated in order to compute numerical results. Using a proprietary algorithm the heart-vessel interaction can be defined, whereas time-varying coronary resistance for each coronary branch can be determined relative to intra-myocardial pressure and microvasculature impedance. This latter component can be represented by a so-called lumped (zero-dimensional) parameter model, which resembles an electric circuit, including resistive and capacitive elements.[11] The complex fluid properties of the blood are entered into the model, in order to refine the computations.

The methodology of FFRCT computation is based on three key principles[20]: (i) the coronary supply meets myocardial demand at rest; (ii) the resistance of the microcirculation at rest is inversely but not linearly proportional to the size of the feeding vessel; (iii) the microcirculation reacts predictably to maximal hyperaemic conditions in patients with normal coronary flow. FFR can be computed from

typically acquired CCTA scans without any modification of CCTA protocols, additional image acquisition, administration of medications, or additional radiation to the patient (see *Figure 1*).

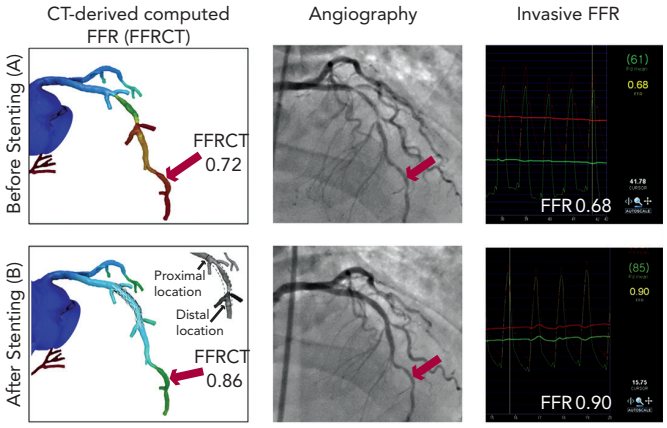
In order to compute FFR, 3D models of the coronary tree and ventricular myocardium are reconstructed from standard coronary CT image datasets and the major epicardial vessels and plaque are segmented, luminal surfaces are identified, and visible side branches are added to the model. Blood is usually modelled as a Newtonian fluid and the incompressible Navier- Stokes equations are solved, subject to appropriate boundary conditions. Since coronary flow and pressure are unknown a priori, a method to couple lumped parameter models of the microcirculation to the outflow boundaries of the 3D model is used to represent the resistance to flow during simulated hyperaemia for each coronary branch of the segmented CT model.

The feasibility and diagnostic performance of the method were evaluated in the Diagnosis of ischaemia-causing stenoses obtained via noninvasive fractional flow reserve (DISCOVER FLOW) study. This trial was conducted at five hospitals internationally, which prospectively enrolled 103 patients (159 lesions) who had undergone coronary CCTA.[20] All patients underwent invasive angiography with FFR. Computed FFR values were found to have a very high degree of correlation with invasively measured FFR. As expected, coronary CT angiography alone showed high sensitivity of 91 % and negative predictive value (NPV) of 89 %, but comparatively low specificity of 40 % and positive predictive value (PPV) of 47 % for the identification of lesion-specific ischaemia defined as an FFR ≤0.80. By comparison, FFRCT produced sensitivity of 88 % and NPV of 92 %, similar to those of coronary CT angiography, but much higher specificity of 82 % and PPV of 74 %, resulting to an overall accuracy increase of 25%.

A substudy of DISCOVER-FLOW demonstrated considerable accuracy of FFRCT for diagnosis of lesion-specific ischaemia of coronary lesions of intermediate stenosis severity (40 % to 69 %).[39] A larger, prospective multicentre clinical trial, the Determination of fractional flow Reserve by anatomic computed tomographic angiography (DeFACTO) study is similarly designed to determine the diagnostic performance of FFRCT for the noninvasive assessment of lesion-specific ischaemia using invasively measured FFR as the reference standard.[27] This multicentre diagnostic performance study involving 252 stable patients with suspected or known CAD observed that FFRCT demonstrated improved diagnostic accuracy versus CT alone for diagnosis of ischaemia, although the study did not satisfy its prespecified primary end point of diagnostic accuracy of greater than 70 % of the lower bound of the one-sided 95 % confidence interval. Refinements in FFR computation technology become recently available which included updated proprietary software with quantitative image quality analysis, improved image segmentation, refined physiological models, increased automation, as well as emphasis on the coronary CTA image acquisition protocol to reflect current guidelines.[28]

By adopting this refined methodology a recent prospective multicentre trial on 254 patients showed that FFRCT exhibits a very high diagnostic performance compared with invasively measured and high specificity of FFRCT, which was markedly better than in a previous evaluation of FFRCT.[21] Moreover, compared with coronary CTA, FFRCT led to a marked reduction in false-positive results. A novel study expedited the application of FFRCT to virtual stenting for the prediction of the functional outcome of stenting prior to the invasive procedure.[29] Virtual

Figure 2: Example of Functional Assessment Before and After Revascularisation



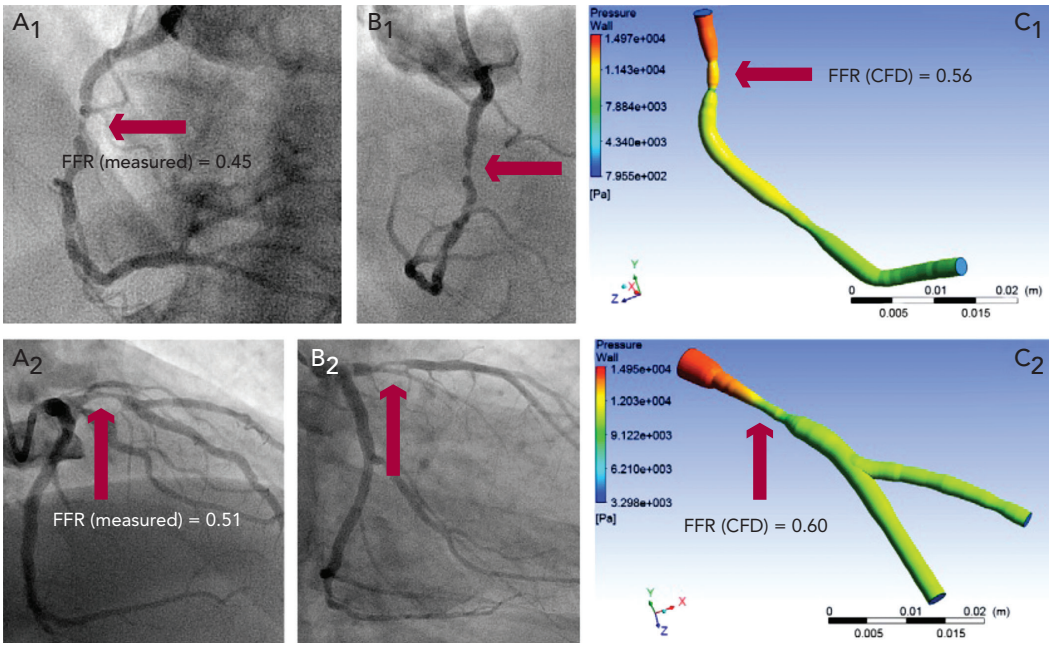
(A) The functional significance of a stenosis of the left anterior descending (LAD) coronary artery was calculated by noninvasive fractional flow reserve (FFR) from coronary computed tomographic angiography data (FFRCT=0.72) and by FFR measurement during invasive coronary angiography (FFR=0.68). (B) Fractional flow reserve derived from computed tomography angiography FFRCT demonstrated no ischemia in the LAD after virtual stenting, with a computed value of 0.86. Invasive FFR after stent implantation was 0.90. Reproduced with permission.[29]

stenting is performed by modification of the computational model to restore the area of the target lesion according to the proximal and distal reference areas. FFRCT is computed before and after virtual stenting thus providing not only diagnosis of lesion-specific ischaemia but additionally predicts the therapeutic benefit of coronary revascularisation (see *Figure 2*). FFRCT had a diagnostic accuracy of 96 % in predicting or ruling out myocardial ischaemia after stenting as defined by a post-stent FFR of >0.80 while the mean difference between FFR after stenting and FFRCT after virtual stenting was 0.02 ± 0.05.[29] Thus, it appears that comprehensive planning of a revascularisation strategy and selection of the optimal target coronary lesion(s) for revascularisation is possible using this novel technology, which can provide both anatomical and functional information for each lesion before the invasive procedure.

FFRCT is a promising noninvasive method for identification of individuals with ischaemia and the prediction of the functional outcome of revascularisation. These findings can be considered proof of concept of the feasibility of this novel technology and represent the first large-scale prospective demonstration of the use of computational models to calculate rest and hyperaemic coronary pressure fields from typically acquired CCTA images. The calculation of FFR from CT images requires uploading the CT scan digital imaging and communications in medicine (DICOM) image dataset to particular workstations for image analysis, geometric modelling and supercomputer computation. At present, this data is only provided as a service by a single company, which performs the image analysis, geometric modelling and supercomputer computation[20,21,26,28,29,39,40] and thus results are not generated at the clinical site. Moreover, this process currently takes several hours per exam, however iterative improvements in automation are expected reduce processing time in the near future.[26]

A recent investigation sought to project the potential clinical and economic consequences of using FFRCT to guide clinical management, in comparison with commonly used alternative strategies for the diagnosis and treatment of patients with known or suspected CAD and reported that use of FFRCT to select patients for invasive coronary angiography and revascularisation would result in 30 %

Figure 3: Examples of Fractional Flow Reserve Estimation in the Right Coronary Artery (Upper Panel) and Left Anterior Descending (Lower Panel) for Two Patients by Rotational Angiography



Two single frames (A and B) from the rotation were selected for each artery. The arrows indicate the stenosis. The angiographic data were processed for anatomic and physiological reconstruction, which is displayed in image C. The colours represent pressure (Pa) according to the scale shown. The invasively measured and estimated by computational fluid dynamics (CFD) values of fractional flow reserve (FFR) are shown for each stenosis. Reproduced with permission.[16]

lower costs and 12 % fewer events at one year compared with the most commonly used strategies.[41] Derivation of FFRCT is hampered by certain limitations at the extraction of the vascular structures from CT images, formulation of boundary flow conditions and definition of modelling equations of flow.[38] Erroneous segmentations are usually encountered in clinical practice, due to the presence of high attenuation objects such as calcified plaques or stents which produce image artefacts. Following image segmentation the entire volume occupied by the coronary artery is discretised into a large number of small elements, a process known as meshing, which allows for the solution of the blood flow problem at the location of each element. This meshing process is usually user-dependent and potentially introduces further uncertainty in blood flow modelling.

Finally, realistic inflow and outflow boundary flow conditions are required to perform the CFD simulation, however blood pressure cannot be directly measured by CCTA and brachial blood pressure is often used as a surrogate for pressure in large arteries. The outlet boundary condition (which models the effect of the distal vascular system, such as small arteries, microcirculatory vessels and veins and returning blood to the heart) is difficult to determine in practice. Outlet boundaries are derived by coupling the lumped parameters, which approximate the haemodynamic conditions of the distal vascular system.[42] The estimated flow distribution of each of the major coronary arteries is a consequence of the relationship between vessel size and resistance, while cardiac output is based on the measurement of myocardial mass that is derived from the cardiac CT dataset. Furthermore, the coronary venous resistance is calculated based on the assumption of mean coronary blood flow at the expense of incorporating patient-specific factors.

Rotational Coronary Angiography Derived FFR

A proof-of-concept, single-site study explored the feasibility of FFR estimation on 19 patients with stable coronary artery disease using CFD techniques and angiographic images acquired from rotational angiography (RA).[16] The workflow has been developed to create simplified virtual models of the major epicardial arteries with or without one major side branch from a single rotational coronary angiogram. With a CFD solver and with generic boundary conditions,[23] the pressure and flow solution can be calculated (see *Figure 3*). The estimated FFR values agree well with the measured values, with an overall average deviation from the measured values of ± 0.06. Lesions requiring PCI (measured FFR <0.80) were identified from nonsignificant lesions (measured FFR >0.80) with 97 % accuracy. This methodology does not require the induction of hyperaemic flow, additional procedure time, the hazard of passing an intracoronary wire, or additional equipment, training or cost. However, the authors acknowledge the study can be only considered as hypothesis generating since it is hampered by various limitations. The most evident being the limited patient cohort and the fact that only a limited subgroup of cases (n= 3) had an measured FFR falling between 0.75 and 0.85. In several patients with measured FFRs equal to 1.0 the calculated value varies between 0.85 and 0.95.

The accuracy of the methods seems to be lesion severity dependent since for haemodynamically insignificant stenoses the calculated FFR values are more likely to be accurate whereas for most lesions with FFR <0.80, the virtual FFRs underestimates severity. Other limitations are the adoption of generic rather than patient specific boundary flow conditions and the long computational time currently required to process data. Inherent limitation is the requirement of a rotational coronary angiogram which is an invasive procedure not universally available and cumbersome to perform.

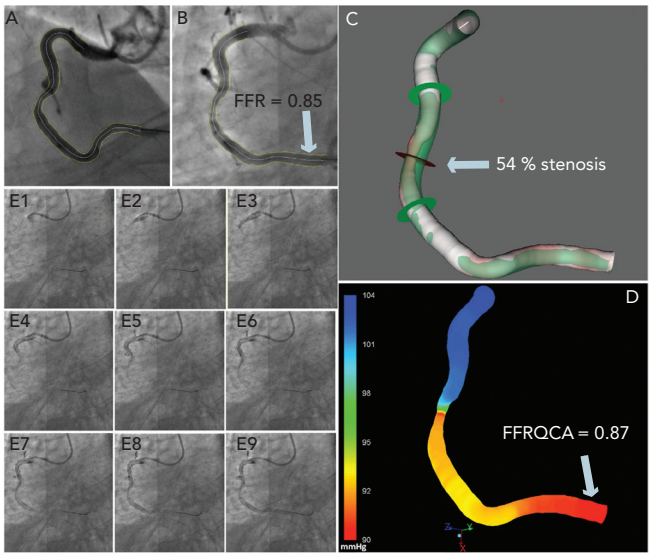
3D QCA and TIMI Frame Count Derived FFR

A methodology for FFR computation based on 3D quantitative coronary angiography (QCA) and thrombolysis in myocardial infarction (TIMI) was recently presented.[19] The methodology uses 3D QCA (QAngio® XA 3D, Medis Special BV[43,44]) to obtain the anatomical

models and applies CFD subsequently, using the hyperaemic flow rate to calculate FFRQCA. To calculate flow rate, the contrast medium transport time in the reconstructed vessel was measured on hyperaemic projections using TIMI frame count. The mean volumetric flow rate (VFR) at hyperaemia was derived using the lumen volume of the reconstructed coronary tree divided by the mean transport time. The same calculation was applied to the baseline angiography, from which the baseline VFR was obtained. Coronary flow reserve (CFR) was derived by dividing the hyperaemic VFR by the baseline VFR. For the CFD part of the methodology, blood was modelled as incompressible Newtonian fluid and blood's density and viscosity were derived using the haematocrit value of individual patients. The mean hyperaemic VFR and the mean pressure at the guiding catheter tip were applied at the inlet, whereas outflow (fully developed flow) condition was applied at the outlets. After simulation, FFRQCA was defined as the mean pressure at the outlet divided by the mean pressure at the inlet (see *Figure 4*). The diagnostic performance of the computed FFRQCA was assessed using wire-based FFR as reference standard on 77 vessels in 68 patients with intermediate coronary stenoses (40–70 % diameter stenosis by visual estimation). FFRQCA correlated well with FFR ($r = 0.81$, $p < 0.001$), with a mean difference of 0.00±0.06 ($p=0.541$). Applying the FFR cutoff value of ≤0.8 to FFRQCA resulted in 18 true positives, 50 true negatives, four false positives and five false negatives.

FFRQCA provides a more patient-specific approach than previously presented methodologies since rather than assuming that microcirculation reacts predictably to maximal hyperaemic condition, it calculates hyperaemic directly on the angiographic projections during hyperaemia. It also appears that FFRQCA is more accurate than FFRCT which, according to the investigators, can be attributed to the higher image spatial resolution of conventional coronary angiography versus coronary computed tomography angiography, as well as by the presence of downstream microcirculatory disease. Another plausible advantage of the technique is the processing time which according to the authors is less than 10 minutes, which implies that it has the potential to be adopted in clinical practice if the methodology is further optimised. Limitations of the study include its limited patient cohort and validation exclusively on de novo lesions. Another limitation of the method is that since 2D projections are used to reconstruct the 3D arterial model, vessel overlap, foreshortening and poor image quality may hamper the process.

Figure 4: Example of Fractional Flow Reserve derivation by quantitative coronary angiography (FFRQCA)



(A,B) Example of FFRQCA calculation of 54 % diameter stenosis of the RCA with a wire-based FFR measurement of 0.85. (C) 3D reconstruction of the arterial lumen. (D) Simulated pressure distribution at hyperemia and computation of FFRQCA (0.87). (E1 to E9) Consecutive angiographic image frames at hyperaemia. Reproduced with permission.[19]

Conclusions

Comprehensive noninvasive anatomical and functional imaging would be desirable to identify patients who are likely to benefit from invasive coronary angiography and revascularisation. Advances in computational technology now permit calculation of FFR using resting CCTA, RA or QCA image data, without the need for additional radiation or medication. Early data from various studies demonstrate improved accuracy and a discriminatory ability of FFRCT to identify ischaemia-producing lesions compared with CCTA alone. FFR estimation from RA provides a less invasive alternative to conventional FFR measurement which is not widely applied yet, however early results are promising. Computation of FFRQCA allows safe and efficient assessment of the functional significance of intermediate stenosis. Acknowledging the various limitations of each technique, these combined anatomic–functional assessments have the potential to simplify the noninvasive diagnosis of coronary artery disease with a single study to identify patients with ischaemia-causing stenosis who may benefit from revascularisation. ■

1. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: The task force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013.
2. De Bruyne B, Sarma J. Fractional flow reserve: A review: Invasive imaging. *Heart* 2008;94:949–59.
3. Melikian N, De Bondt P, Tonino P, et al. Fractional flow reserve and myocardial perfusion imaging in patients with angiographic multivessel coronary artery disease. *JACC Cardiovasc Interv* 2010;3:307–14.
4. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;360:213–24.
5. Fearon WF, Bornschein B, Tonino PA, et al. Economic evaluation of fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease. *Circulation* 2010;122:2545–50.
6. Pijls NH, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the defer study. *J Am Coll Cardiol* 2007;49:2105–11.
7. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided pci versus medical therapy in stable coronary disease. *N Engl J Med* 2012;367:991–1001.
8. Smits P, Thien T. Effects of adenosine on human coronary arterial circulation. *Circulation* 1991;84:2208–10.
9. Kern MJ, Deligonul U, Tatineni S, et al. Intravenous adenosine: Continuous infusion and low dose bolus administration for determination of coronary vasodilator reserve in patients with and without coronary artery disease. *J Am Coll Cardiol* 1991;18:718–29.
10. Katritsis DG, Ioannidis JP. Pci for stable coronary disease. *N Engl J Med* 2007;357:414–5; author reply 417–8.
11. Kim HJ, Vignon-Clementel IE, Coogan JS, et al. Patient-specific modeling of blood flow and pressure in human coronary arteries. *Ann Biomed Eng* 2010;38:3195–209.
12. Taylor CA, Fonte TA, Min JK. Computational fluid dynamics applied to cardiac ct for noninvasive quantification of fractional flow reserve: Scientific basis. *J Am Coll Cardiol* 2013.
13. Meijs MF, Cramer MJ, El Aidi H, Doevendans PA. Ct fractional flow reserve: The next level in non-invasive cardiac imaging. *Neth Heart J* 2012;20:410–8.
14. Johnston BM, Johnston PR, Corney S, Kilpatrick D. Non-newtonian blood flow in human right coronary arteries: Steady state simulations. *J Biomech* 2004;37:709–20.
15. Johnston BM, Johnston PR, Corney S, Kilpatrick D. Non-newtonian blood flow in human right coronary arteries: Transient simulations. *J Biomech* 2006;39:1116–28.
16. Morris PD, Ryan D, Morton AC, et al. Virtual fractional flow reserve from coronary angiography: Modeling the significance of coronary lesions: Results from the virtu-1 (virtual fractional flow reserve from coronary angiography) study. *JACC Cardiovasc Interv* 2013;6:149–57.
17. Bourantas CV, Kourtis IC, Plissiti ME, et al. A method for 3d reconstruction of coronary arteries using biplane angiography and intravascular ultrasound images. *Comput Med Imaging Graph* 2005;29:597–606.
18. Kousera CA, Nijjer S, Torii R, et al. Patient-specific coronary stenoses can be modeled using a combination of oct and flow velocities to accurately predict hyperemic pressure gradients. *IEEE Trans Biomed Eng* 2014;61:1902–13.
19. Tu S, Barbato E, Koszegi Z, et al. 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;7:768–77.
20. Koo BK, Erglis A, Doh JH, et al. 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;58:1989–97.
21. Min JK, Leipsic J, Pencina MJ, et al. Diagnostic accuracy of fractional flow reserve from anatomic ct angiography. *JAMA* 2012;308:1237–45.
22. Katritsis D, Kaiktsis L, Chaniotis A, et al. Wall shear stress: Theoretical considerations and methods of measurement. *Prog Cardiovasc Dis* 2007;49:307–29.
23. Westerhof N, Lankhaar JW, Westerhof BE. The arterial

windkessel. *Med Biol Eng Comput* 2009;47:131–41.
24. Berne R, Levy M. *Cardiovasular physiology* St. Louis, USA: Mosby inc. 2001.
25. Matsuo S, Tsuruta M, Hayano M, et al. Phasic coronary artery flow velocity determined by doppler flowmeter catheter in aortic stenosis and aortic regurgitation. *Am J Cardiol* 1988;62:917–22.
26. Yoon YE, Choi JH, Kim JH, et al. 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;5:1088–96.
27. Min JK, Berman DS, Budoff MJ, et al. Rationale and design of the defacto (determination of fractional flow reserve by anatomic computed tomographic angiography) study. *J Cardiovasc Comput Tomogr* 2011;5:301–9.
28. Norgaard BL, Leipsic J, Gaur S, et al. 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;63:1145–55.
29. Kim KH, Doh JH, Koo BK, et al. A novel noninvasive technology for treatment planning using virtual coronary stenting and computed tomography-derived computed fractional flow reserve. *JACC Cardiovasc Interv* 2014;7:72–8.
30. Min JK, Shaw LJ, Berman DS. The present state of coronary computed tomography angiography a process in evolution. *J Am Coll Cardiol* 2010;55:957–65.
31. Budoff MJ, Dowe D, Jollis JG, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: Results from the prospective multicenter accuracy (assessment by coronary computed tomographic angiography of individuals undergoing invasive coronary angiography) trial. *J Am Coll Cardiol* 2008;52:1724–32.
32. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row ct. *N Engl J Med* 2008;359:2324–36.
33. Meijboom WB, Meijs MF, Schuijf JD, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: A prospective, multicenter, multivendor study. *J Am Coll Cardiol* 2008;52:2135–44.
34. Meijboom WB, Van Mieghem CA, van Pelt N, et al. 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;52:636–43.
35. Lauer MS. Ct angiography: First things first. *Circ Cardiovasc Imaging* 2009;2:1–3.
36. Redberg RF, Walsh J. Pay now, benefits may follow-the case of cardiac computed tomographic angiography. *N Engl J Med* 2008;359:2309–11.
37. Serruys PW, Girasis C, Papadopoulou SL, Onuma Y. Non-invasive fractional flow reserve: Scientific basis, methods and perspectives. *EuroIntervention* 2012;8:511–9.
38. Rajani R, Wang Y, Uss A, et al. Virtual fractional flow reserve by coronary computed tomography - hope or hype? *EuroIntervention* 2013;9:277–84.
39. Min JK, Koo BK, Erglis A, et al. Usefulness of noninvasive fractional flow reserve computed from coronary computed tomographic angiograms for intermediate stenoses confirmed by quantitative coronary angiography. *Am J Cardiol* 2012;110:971–6.
40. Min JK, Koo BK, Erglis A, et al. Effect of image quality on diagnostic accuracy of noninvasive fractional flow reserve: Results from the prospective multicenter international discover-flow study. *J Cardiovasc Comput Tomogr* 2012;6:191–9.
41. Hlatky MA, Saxena A, Koo BK, et al. Projected costs and consequences of computed tomography-determined fractional flow reserve. *Clin Cardiol* 2013;36:743–8.
42. Vignon-Clementel IE, Figueroa CA, Jansen KE, Taylor CA. Outflow boundary conditions for 3d simulations of non-periodic blood flow and pressure fields in deformable arteries. *Comput Methods Biomech Biomed Engin* 2010;13:625–40.
43. Tu S, Xu L, Ligthart J, et al. *In vivo* comparison of arterial lumen dimensions assessed by co-registered three-dimensional (3d) quantitative coronary angiography, intravascular ultrasound and optical coherence tomography. *Int J Cardiovasc Imaging* 2012;28:1315–27.
44. Tu S, Huang Z, Koning G, et al. A novel three-dimensional quantitative coronary angiography system: In-vivo comparison with intravascular ultrasound for assessing arterial segment length. *Catheter Cardiovasc Interv* 2010;76:291–8.