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Determining the haemodynamic significance of arterial stenosis: the relationship between CT angiography, computational fluid dynamics, and non-invasive fractional flow reserve

Pang, CL

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Abbreviations

BMI – body mass index

CFD – computational fluid dynamics

CTCA – coronary computed tomography angiogram

CT – computed tomography

DeFACTO - Diagnostic Accuracy of Fractional Flow Reserve from Anatomic CT Angiography

DEFER – deferral of percutaneous coronary intervention

DICOM – Digital Imaging and Communications in Medicine

DISCOVER-FLOW - Diagnosis of Ischaemia-Causing Stenoses Obtained Via Non-Invasive Fractional Flow Reserve

ECG – electrocardiogram

FAME - Fractional Flow Reserve Versus Angiography for Multivessel Evaluation

FFR – fractional flow reserve

FFR_{CT} – fractional flow reserve CT

ICA – invasive coronary angiography

NICE – The National Institute for Health and Care Excellence

NXT - Next Steps

PACS – Picture archiving and communication system

PLATFORM - prospective longitudinal trial of FFR_{CT}: outcome and resource impacts

PROMISE – Prospective Multicenter Imaging Study for Evaluation of Chest Pain

PUPSMED – Plymouth University Peninsula Schools of Medicine and Dentistry

SCOT-HEART - CT coronary angiography in patients with suspected angina due to coronary heart disease

2D – two dimensional

3D – three dimensional

Abstract

Coronary artery disease causes significant morbidity and mortality worldwide. Invasive coronary angiography (ICA) is currently the gold standard investigation. Fractional flow reserve (FFR) complements traditional ICA by providing extra information on blood flow, which has convincingly led to better patient management and improved cost-effectiveness. Computed tomography coronary angiogram (CTCA) is suitable for the investigation of chest pain, especially in the low and intermediate risk groups. FFR generated using CT data (producing FFR_{CT}) may improve the positive predictive value of CTCA. The basic science of FFR_{CT} is like a 'black box' to most imaging professionals. A fundamental principle is that good quality CTCA is likely to make any post processing easier and more reliable. Both diagnostic and observational studies have suggested that the accuracy and the short term outcome of using FFR_{CT} are both comparable with FFR in ICA. More multidisciplinary research with further refined diagnostic and longer term observational studies will hopefully pinpoint the role of FFR_{CT} in existing clinical pathways.

Introduction

Invasive coronary angiography (ICA) is the standard investigation for the evaluation of the coronary arteries and in many centres forms the basis for any subsequent intervention. Coronary revascularisation is performed based on semi-quantitative measures of luminal diameter narrowing of the artery visualised at the time of ICA which may overestimate or underestimate the haemodynamic significance of a lesion, especially in the presence of multi-vessel disease (1, 2). (Figure 1) The FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study showed that angiography can be inaccurate in assessing the functional significance of a coronary stenosis (3). This concern regarding the disparity between anatomical narrowing found during ICA and subsequent clinical outcomes has led to fractional flow reserve (FFR), becoming the established gold standard for the assessment of haemodynamic significance of coronary stenosis (1, 2, 4). FFR is relatively easy to measure during catheter coronary angiography and is reproducible. According to results from the FAME study, FFR directed intervention can improve event free survival and cost effectiveness of coronary intervention compared to angiography alone (3). Hagen-Poiseuille law states that flow is proportional to the difference in

pressure across a stenosis and, consequently this pressure differential can be used as a surrogate for flow under specific conditions, during minimal and constant resistance (5). Maximal hyperaemic conditions are induced using adenosine infusion during the measurement of FFR (6). Adenosine causes vasodilation in arteries, including the coronary arteries. In an artery with pre-existing stenosis, vasodilation takes place due to autoregulation (even before adenosine administration). During adenosine infusion, the normal arteries are relatively more responsive with vasodilation whereas diseased arteries are less responsive, competitively diverting blood away from those diseased segments. FFR is a lesion specific index that is measured by inserting an endovascular pressure wire across a stenosis. Once a wire is optimally placed, the pressure proximal and distal to a lesion causing stenosis can be obtained. A normal coronary artery has a FFR of one. At maximal hyperaemia, the distal pressure would be less than the proximal pressure, giving a value of less than one. In general, a FFR <0.75 is considered to be associated with ischaemia while a FFR value of > 0.80 is considered to be negative for ischaemia (4, 7). Due to the grey area of uncertainty between 0.75 and 0.80 and based on the results from the FAME study, many clinicians now use the FFR cut-off value of 0.8 to guide revascularisation (8). An economic evaluation of the FAME study showed that the overall cost of FFR guided treatment was less than a treatment strategy guided by angiography alone (9). Also of interest, in the FAME 2 trial, FFR-guided therapy reduced the need for urgent revascularisation in patients with stable coronary artery disease and haemodynamically insignificant lesions (10).

In addition to the previously described studies, the DEFER study added to the validity evidence of the adoption of FFR (11). The investigators assigned patients to

percutaneous coronary intervention based on a FFR value of equal to, lesser than or greater than 0.75. For those with FFR equal to or greater than 0.75, subjects were assigned to intervention (Performance group) or deferred (Deferral group). At follow-up, those assigned to the Deferral group had a risk of death or myocardial infarction of <1%. Therefore, there is significant trial and economic evidence that FFR is a cost-effective strategy in the management of coronary disease.

Evidence for Diagnostic Accuracy of Computed Tomography Coronary Angiography

Apart from ICA, other techniques are available to evaluate the anatomical and functional significance for severe stenosis, these include cardiac magnetic resonance imaging, intravascular ultrasound, echocardiography or single-photon emission computed tomography. Here we focus on the advances of coronary computed tomography coronary angiography (CTCA).

Multiple retrospective and prospective studies have demonstrated that CTCA has high sensitivity and specificity for the non-invasive detection of stenosis (12-17). More recently, the PROMISE and SCOT-HEART studies focused on looking at the longer term benefits of CTCA (18, 19). Regarding diagnostic accuracy, it has been demonstrated that it is capable of excluding luminal stenosis of more than 50% but performs less well in terms of its positive predictive value (16). The differentiation between the 50% to 69% category and >70% category are more difficult possibly due to variable centre expertise and patient characteristics (20, 21). The >70% category is particularly important as it is a widely accepted anatomical threshold for

significant coronary artery disease. Interpretation is particularly difficult in the presence of calcified coronary disease related to blooming artefact and limited spatial resolution bounded by available equipment. Experienced readers would learn to deal with the pitfalls and artefacts on CTCA and access to ICA results provide feedback and improve interpretation (22-24). In view of this, CTCA is primarily used for patients with a low to intermediate risk of coronary disease.

Fractional Flow Reserve by CTCA

Although FFR is the gold standard for determining ischaemic lesions, it requires ICA, expensive consumable equipment and the administration of adenosine to induce maximal hyperaemia (8). To extend the role of CTCA as well as further expand clinical applications of FFR, one major area of interest is the potential generation of FFR values based on the CTCA data set, leading to the generation of FFR_{CT}. Since 2011, there are four trials evaluating this post processing algorithm (25-28). Most recently in 2015, the PLATFORM (prospective longitudinal trial of FFR_{CT}: outcome and resource impacts) trial investigated the impact of FFR_{CT} on survival and downstream investigations (29). CT transluminal attenuation gradient and myocardial perfusion are alternative techniques that are also currently being evaluated. This review explores the pragmatic scientific basis of FFR_{CT} and the potential implications of its application.

The ability to couple FFR and CTCA to generate FFR_{CT} enabled this technique to become a real option in the investigation of chest pain. There were some promising

results from the DISOCOVER-FLOW (Diagnosis of Ischaemia-Causing Stenoses Obtained Via Non-Invasive Fractional Flow Reserve) trial, which was pioneered and sponsored by HeartFlow Inc. (Redwood City, CA, USA), developers of the technology. This group proposed that the computation of FFR_{CT} required construction of anatomical model of coronary arteries, a mathematical model of coronary physiology and a numerical solution for the laws of physics governing fluid dynamics (30). The DISOCOVER-FLOW trial showed that FFR_{CT} improved the accuracy of CTCA by 25.8% (31).

Following this the DeFACTO (multi-centre the Diagnostic Accuracy of Fractional Flow Reserve from Anatomic CT Angiography) trial emerged later with a pre-specified primary outcome of whether FFR_{CT} could improve the diagnostic accuracy (32). The pre-specified outcome was not met. Subsequent on this refinements were made in patient selection, CT technique and computational techniques (32). Based on these the NXT (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps) trial was performed (25). This multi-centre study showed an improved diagnostic accuracy of FFR_{CT} on a per-patient basis (see Table 1). In the short-term (less than 90 days), the PLATFORM study was the first study to demonstrate that there was significant increase in event rates of those whom received FFR_{CT} as an alternative test to ICA, suggesting FFR_{CT} is a promising technique. In addition, a normal FFR_{CT} was associated with reduction of finding non-obstructive disease at ICA when referred for downstream testing. However, much longer term follow-up data will be required before the adoption of FFR_{CT} for routine everyday use to evaluate coronary disease.

The Relationship Between Flow & Coronary Anatomy

The calculation of FFR_{CT} requires an understanding of mathematics, fluid dynamics, physics and physiology of blood flow. Combining those functional principles with the anatomical data extracted from the individual patient's coronary arteries and respective arterial system, FFR_{CT} can be estimated for different patients as a combination of physical form and function (Figure 2).

There is a relationship between myocardial mass and coronary flow (33). As a function of mass, myocardial volume can be calculated based on the anatomical data from CTCA. In addition, the anatomical data obtainable from the CTCA data set already contain coronary flow information because flow is evident from physical form (34, 35). For example, if there is a chronic stenosis at a site, the vessel proximal to the stenosis dilates. The physical transformation of this proximal vessel is intimately related to the blood flow at this defined environment. This proportional relationship between vessel size and flow rate can be derived from Hagen-Poiseuille and Murray's laws (5, 36). Murray's law states that when a parent blood vessel branches into daughter vessels, the cube of the radius of the parent vessel is equal to the sum of the cubes of the radii of daughter blood vessels (37). These theoretical equations explain the arterial supply phenomenon of the myocardium: a coronary vessel that supplies a myocardial territory with reduced perfusion will diminish in size whereas an area with increased blood flow as a result of exercise or revascularisation would correspond with an increase in vessel size (30). The above discussion focused on situations where a vessel has a focal stenosis. The flow assumptions that underpin a

vessel with diffusely stenotic diseases present unique challenges and is beyond the scope of this review (38).

Computational Fluid Dynamics

Fluid flows can be modelled mathematically using the Navier-Stokes equations (Figure 3) which are partial differential equations that represent the basic physical conservation laws of energy, momentum (Newton's second law) and mass. Real fluid flow is difficult to measure as it varies in time continuously and is dependent upon the space where it is contained. Computational fluid dynamics (CFD) is a numerical technique that attempts to sample fluid flow at discrete intervals (at a precise time and space) and break down the modelling into numerous but much more manageable chunks that can be solved by computers. CFD provides qualitative and quantitative predictions of fluid flow, for example blood flow, that are difficult or impossible to study.

In practice, the Navier-Stokes equations in their complete form are difficult to solve analytically, except for a limited number of very simple fluid flows. In addition, whilst more complicated flows can conceptually be modelled using CFD, they are often computationally impractical due to the number of calculations needed (39, 40). This situation can be mitigated somewhat by noting that blood is virtually incompressible and isothermal at physiological pressures, consequently this observation allows the simplified "non-compressible" form of the Navier-Stokes equation to be used which significantly reduces the computational overhead.

The HeartFlow Inc. model is based on solving these Navier-Stokes equations using CFD to estimate the FFR at areas of coronary artery stenosis which have been computationally modelled from real patients. To solve these equations physical boundaries need to be defined, such as the profile of coronary vessel walls and imaginary apertures where blood enters and leaves. Relevant boundaries of a three-dimensional (3D) model typically include the aortic root and the outlet boundaries of the ascending aorta and the coronary arteries. This geometrical model can be defined using the 3D data obtained in CTCA. As previously alluded to, the Navier-Stokes equations cannot be solved analytically except for a few very simple geometrical problems (with presumptions about the dynamic properties of the fluid materials). Consequently, CFD splits the complex picture into many smaller, interrelated and solvable problems that can be calculated as a set of simultaneous equations by a computer. To apply CFD to CTCA in order to generate FFR_{CT}, requires solving millions of equations simultaneously and repeating this process for thousands of time intervals in a cardiac cycle (30). Due to the nonlinear terms in the equations, the solutions are achieved using iterative techniques that require significant computer power. All these can take time and therefore assumptions such as incompressible flows are used to further simplify the calculations. The results of a CFD simulation are never completely perfect because of a number of factors including imprecise CT input data (either due to noise or restrictions upon temporal and spatial resolutions), the consequences of imperfect mathematical modelling of the coronary geometry, limited computer power (which affects the number of calculations that can be performed within an acceptable processing time) and floating point error due to the large number of calculations.

THE PROCESS

Image Acquisition

Good quality CTCA is the cornerstone of FFR_{CT} as all calculations are based upon it. Inaccurate estimation by subsequent mathematical model is often due to either poor quality CTCA or artefact. It follows that, as with any CTCA, good patient selection, preparation and acquisition are paramount. Improvements in CTCA technology which improve image quality, particularly resolution, will enhance the value of FFR_{CT}.

Computing FFR_{CT} from CFD

CFD is a complex process involving four key steps (see Figure 4-7): segmentation of coronary artery boundaries from the acquired CT data; optimal sampling of the CT data into discrete points in space (discretisation) defined by a surface mesh; application of lumped parameter models of the heart to define the boundary conditions; iterative solution of the resulting complex non-linear simultaneous equations.

Segmentation is a process of partitioning a digital image into multiple segments described by groups of pixels or voxels (volume elements). Applied to CTCA, it is a process of transforming volumetric CT DICOM images into a useful computer model of a patient's coronary vessels by a semi-automated extraction of coronary arterial boundaries (Figure 8). These are represented computationally as the set of voxels that transect the boundaries in space. The first step of segmentation involves applying a mathematical threshold to the DICOM data; that is deciding whether or

not each image voxel has a Hounsfield unit sufficiently high to represent it to reside within a contrast filled coronary artery. This can be achieved using various softwares available commercially. Whilst this conceptually may appear to be a simple process, in practice this procedure is assisted and edited by a trained operator to remove artefacts (e.g. delete any vessel not part of the coronary arterial tree). This process needs to be done with care because the anatomical model generated is the basis for subsequent calculations and therefore it is more than just a graphical representation. Any factor that may impair image quality will impact the accuracy of FFR_{CT}, particularly through erroneous segmentation or artefact due to unwanted image noise, calcified plaque (partial volume artefact perceived as blurring) or the presence of coronary stents (41-43).

The next stage is discretisation of the segmented image data, whereby a surface mesh is fitted to the 3D data describing the coronary arterial tree boundaries. Whereas the segmented data is a set of voxels, the mesh attempts to describe this in terms of a surface defined by a limited number (albeit large) of discrete points. In practice, a mesh composed of numerous adjoining triangular elements is often used although other shapes such as polyhedrals can also be utilised. The resultant mesh can be envisaged as the geometrical outline of a coronary artery without its blood content within; that is a pipe without the fluid. Importantly, the position of the mesh (triangle) element vertices do not need to correspond to the source data voxel coordinates, but is optimised according to the number of surface elements utilised in the model. Whilst maximising the number of surface elements may model computationally the boundaries more accurately, in practice the number of triangles effectively determines the number of problems needed to be solved by CFD.

Therefore, there is an optimum balance between accurately describing the arterial boundaries and computational burden.

The volume encompassed by the surface mesh is next completely filled with many small volume elements, typically tetrahedrals (pyramids). At the boundaries, each triangular mesh element forms the edge of a tetrahedral volume element. The internal edges of these tetrahedrals form the edges of other adjacent tetrahedrals that are more internal within the encompassed volume. Again, the number of these tetrahedral elements defines the number of calculations that need to be solved and therefore there is always a trade-off between better estimate and longer CFD calculation time. Importantly, these smaller and simpler volume elements are utilised because there is a known and relatively simple computational solution to the Navier-Stokes equation of each of these tetrahedral volumes. Each solution is, however, interrelated with that of the next tetrahedral volume element (the boundary of one element forms the boundary of the next); consequently the overall solution is achieved by solving these together as a set of simultaneous interrelated smaller problems.

To enable these calculations to be performed, boundary conditions need to be set at the coronary arterial ostia (or within the aorta/ coronary sinuses), the vessel boundaries as defined by the mesh, and the downstream endpoints (i.e. the coronary outlets) of the modelled coronary arterial tree. These can be set using “lumped parameter models” of the heart as follows (30). Firstly, the entrance flow conditions at the coronary sinuses can be simulated using a Windkessel model of the aortic

arch which predicts aortic flow according to cardiac output and systemic resistance (44, 45). It is possible to include more parameters to portray a more authentic model at the cost of more computing time (44). Aortic pressure is assumed to be equivalent to the (measurable) brachial arterial pressure and the total blood flow down the coronary arteries is estimated from the total myocardial wall volume which can be quantified from the CTCA data (30). Secondly, there is the so called 'non-slip' condition in fluid dynamics for viscous fluids. In this particular case, the lateral coronary arterial boundaries defined by the surface mesh are assumed to have zero flow. Lastly, at each of the downstream coronary arterial tributary outlets a model relating localised pressure to blood flow is utilised for the coronary microcirculation, relating outlet resistance to flow and therefore the local pressure at these boundaries to vessel diameter utilising Murray's morphology law (30, 36). A potential source of error here is the assumption of equivalence between coronary arteries and brachial pressure. Furthermore, the downstream calculations require assignment of more values in different parts of the circulatory system, therefore making more assumptions. After these steps, simulations of flow and pressure characteristics within the coronary arteries can be applied (at rest and maximal hyperaemia) and FFR_{CT} obtained (30).

The last step is to solve the resultant numerous simultaneous equations that are generated, each of which is a solution of the Navier-Stokes equation for a specific tetrahedral volume element and is interrelated to the neighbouring volume element or boundary. This can be performed using one of several different computational techniques including Finite Difference, Finite Element or Finite Volume methods (46-48). In practice, many hundreds or thousands of tetrahedral volume elements are

required to give an adequate model. Meshing and further re-meshing requires the expertise of a CFD specialist and is far from being a single click of a button on a workstation (49).

Issues of Using Patient-Specific Data

In terms of population-based medicine, we often hope to achieve a ‘one-size-fits-all’ approach and therefore a generalisable model is desirable. However, in terms of individual based care, decisions made according to unique personalised information are best. The overall accuracy of the FFR_{CT} calculation can be viewed as a trade-off between these principles. The quality of the information put into a model is also an important consideration. Most importantly, the boundaries of a 3D model can be limited by image quality and the robustness of the segmentation algorithms relies on accuracy of this (48). Establishing the ‘true’ boundaries of lumen for a calculation, remains a challenging task even for clinicians experienced in cardiac CT applications (41). Inaccurate segmentation is commonly encountered in the presence of blooming artefacts and coronary stents. This poses an additional ambiguity in constructing an anatomically accurate coronary artery model (48). To compute FFR_{CT}, it currently requires appropriately four to six hours per case (27, 48). This post processing time remains a hurdle in the clinical application of assessing acute chest pain. Taking computing time into account, there has been increasing interest in using reduced-order models for predicting coronary flow, namely the one-dimensional model for solving the Navier-Stokes equations, compared with the more detailed but more resource intensive 3D model proposed by HeartFlow Inc (50-53). Given the inherent simple nature of the one-dimensional approach, the refinement of prediction

accuracy remains at the experimental stages. These simplified strategies can potentially over simplify coronary physiology but may be no greater than the errors that occur with more complex models currently in use. Simpler models have the advantage of reduced processing time, cost and the ability to deliverer to a PACS or workstation based solution. With the rise of parallel processing, a complicated task can be achieved quicker by dividing the job among multiple processors. High performance computing such as parallel processing and the utilisation of graphics processing units (GPUs) for computation are likely to significantly reduce post processing time in the future.

Cost Considerations

HeartFlow Inc. offers a commercial fee charging service to calculate FFR_{CT} on a per patient basis. Each case needs to be uploaded to the company's secure cloud prior to generation of results. There was a small economic analysis based on 96 patients from the DISCOVER-FLOW trial which claimed that FFR_{CT} led to 30% lower costs and 12% fewer events at one year (54). The latest PLATFORM study was a well-conducted multicenter prospective observational follow-up study demonstrating that the FFR_{CT} was a safe alternative to ICA (comparable events rates at 90 days follow-up) and was linked with a reduction of finding obstructive coronary disease during ICA (61% risk difference between FFR_{CT} and ICA) (29). No cost analysis was however performed between CTCA with and without FFR_{CT}. The latter being recognised by NICE as the most cost effective initial investigation in patients with chest pain (55). FFR_{CT} may fit in the current pathway by positioning itself as a tool that guides referral for ICA due to its ability to distinguish obstructive and non-

obstructive lesions. A long-term cost-effectiveness analysis based on a representative population will be required to illustrate how FFR_{CT} would fit in relevant clinical pathways. The development of new mathematical models will require modification of existing CFD tools and therefore ongoing software updates will be required. For instance, there is some interest regarding the Lattice-Boltzmann equation in the CFD field which may be a potential alternative to traditional CFD techniques. All these will have implications on the negotiation of software licenses and future additional costs upon any new version being released.

Conclusion

CTCA is currently an anatomical investigation used for the evaluation of chest pain in the low to intermediate risk categories. FFR_{CT} promises the exciting proposition of obtaining both anatomical and inferred functional data from the same investigation. FFR_{CT} is being compared to the current gold standard of invasive FFR which increases its validity. There is promising evidence that FFR_{CT} may enhance the positive predictive value of CTCA and therefore potentially extend its role. The addition of FFR_{CT} provides patient-specific flow information generated from readily available anatomical data from CTCA which may enable it to predict the need for coronary intervention by detecting flow limiting plaque disease. A number of issues regarding the fundamental scientific challenges remain, in particular the evolving mathematical models used in CFD, the assumptions made about boundary conditions and physiological flow. The development of FFR_{CT} requires ongoing interdisciplinary research across mathematics, physics, computer science, radiology and cardiology. There is also potential to add FFR_{CT} to other existing CT applications,

for example, lower limb CT angiography. One point to bear in mind is perhaps not to over simplify coronary physiology in order to save post processing time. More validation studies, especially longer term observational studies in representative population, will help to evaluate the safety and cost-effectiveness of FFR_{CT}.

Highlights

- CTCA is suitable for the investigation of chest pain, in particular in the low and intermediate risk groups
- The available diagnostic accuracy studies of FFR_{CT} suggest that it may potentially extend the role of CTCA by improving its positive predictive value
- More observational studies are required to confirm the safety and explore the value of FFR_{CT} within existing clinical pathways

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Table and Figure Legends

Table 1. Diagnostic performance of FFRCT on a per-patient basis when compared to invasive coronary angiography

Figure 1. An left anteior oblique projection with cranial angulations showing a left anterior descending artery with mid segment stenosis.

Figure 2. An example of the output from a steady state FFR CFD model underdevelopment. The same left anterior descending artery stenosis as shown in figure 1.

Figure 3. An example of Navier-Stokes equations.

Figure 4. A section of a transverse coronary CT slice showing a contrast opacified coronary artery.

Figure 5. Segmentation of the transverse coronary CT slice (as seen in figure 4) into a group of voxels describing the boundary of the coronary artery.

Figure 6. Discretisation step whereby a geometric triangular mesh is fitted to the segmented CT data (as seen in figure 5). Here this is schematically represented such that each line in this 2D diagram represents the edge of a triangle in 3D space.

Figure 7. Filling of the geometric mesh (as seen in figure 6) with tetrahedral volume elements. Here the tetrahedrals in 3D space is represented by triangles in this 2D schematic slice.

Figure 8. An example of a coronary arterial tree segmentation.