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Computing Fractional Flow Reserve from Invasive Coronary Angiography: Getting Closer.

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(Invited editorial to accompany manuscript entitled: A Validation Study of Image-Based Fractional Flow Reserve (FFRangio) During Coronary Angiography" by Pellicano et al)

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It is now nearly 25 years since Pijls' first description of the experimental basis for fractional flow reserve (FFR). In that paper, the purpose of FFR was stated as 'assessing the functional stenosis significance severity before and after PTCA'[1]. Since then, and particularly in the last fifteen years, a wealth of evidence has accrued demonstrating that FFR guidance improves outcomes in patients being treated for coronary artery disease when compared with conventional angiographic guidance alone. Adoption into the major guideline documents has since followed [2-4]. Yet FFR measurement is performed in only a small minority of patients. Why is this?

First, FFR requires time to set up, pass the wire and infuse adenosine, all of which increase the procedure time. Second, short-term cost is increased, even though FFR is cost-effective in the longer term. Third, an experienced interventionist may feel that he /she knows which lesion(s) to treat and which not. When faced with lesions of intermediate severity, diffuse disease and long segments, such subjective judgment is inaccurate. Fourth, if non-invasive testing for ischemia has already provided a clear indication of the location of ischemia, FFR may not be necessary. Fifth, the implications of a positive FFR result are that PTCA should be performed, and for this to happen there has to be planning for that procedure, with appropriate anti-platelet agents, counselling, and yet more time scheduled; time which, of course, may not, in the end, be used. Sixth, the weight of evidence supporting FFR is in the context of chronic stable coronary disease, whereas the workload of the interventionist is increasingly made up of acute or unstable disease.

So FFR use remains 'trapped' within the world of (largely elective) PTCA guidance, as originally outlined by Pijls, with less impact in the much larger group of patients undergoing

general diagnostic angiography, investigation and treatment of acute coronary syndromes, or workup for coronary artery bypass surgery.

There are attempts to liberate FFR from some of its limitations, such as abandoning adenosine by using iFR measurement[5], adopting more non-invasive CT imaging allied to FFR estimation[6], or (attempting to) introduce FFR at the time of diagnostic invasive angiography (NCT02892903). All these represent valuable additions and potential improvements in the interventionists' armamentarium; but to address fully the day-to-day lack of physiology in the catheter laboratory, an alternative solution is needed.

The prospect of a computed (in silico or 'virtual') FFR calculated from angiographic images is, therefore, attractive. The goal is to construct a three-dimensional (3D) model of the arterial anatomy in the computer, and simulate blood flow and pressure dynamics through the relevant segments, using well known physical laws, such as those embodied in computational fluid dynamics (CFD) [7]. The attraction is clear. Without the need to pass a guidewire, or infuse a drug, the cardiologist is presented with an FFR 'roadmap' alongside the angiogram, providing all the benefits of physiological guidance without the limitations that restrict use of the invasive technique.

Multiple systems have been described, all with a broadly similar approach: (i) 3D arterial anatomy is reconstructed from ≥2 angiographic projections >25° apart, using image analysis software; (ii) coronary blood flow (Q) and pressure (P) changes are simulated through the model applying fluid dynamic laws and physiological assumptions; (iii) the distal to proximal pressure ratios (P_d/P_a = FFR) are calculated; and (iv) the results are presented graphically to the user. In 2013 Morris et al described the VIRTUheart system which computed FFR from

rotational angiography using a relatively complex transient (time-varying pulsatile flow) 3D CFD analysis coupled to a zero-dimensional modified Windkessel [8]. This proof-of-concept study provided promising early results but lacked general applicability and was slow to compute (>24 hrs). More recent development means VIRTUheart works using standard angiography and has been accelerated to ~3 mins computation time [9]. In 2014 Papafaklis et al used 3D QCA models to compute a novel index called 'virtual functional assessment index' (vFAI) [10]. They used paired steady-state CFD analysis (much faster than transient analysis) to plot the case-specific pressure-flow relationship and derive the Poisuille and Bernoulli constants. vFAI was computed (~7 min), from the P_d to P_a ratio in the range 0-4 ml/s, normalised by the ratio over this range for a normal artery. Although superior to QCA vFAI was entirely a function of the geometry of the stenosis. In the same year, Tu and colleagues introduced their model which also utilised 3D QCA models and CFD analysis but used the TIMI frame counting during hyperaemia to derive a measure of maximal coronary flow thus introducing a physiological parameter with which to tune the models [11]. In 2016, the same group published their Diagnostic Accuracy of Fast Computational Approaches to Derive Fractional Flow Reserve From Diagnostic Coronary Angiography (FAVOR) pilot study [12]. They demonstrated that good results could be generated from thrombolysis in myocardial infarction (TIMI) frame counting during resting conditions, even when hyperaemia was not induced. In the same year Trobs et al published their model of computed FFR [13]. They tuned their simulations using 'published estimates of coronary microvascular resistance' and hyperemic flow was simulated based upon the assumption of a normal physiological response to adenosine. Results were generated in 40 s.

And so we come to the paper by Pellicano et al in this Journal,[14] in which the authors present their FFR_{angio} tool, which reconstructs coronary anatomy in 3D virtual space and computes

the pressure gradients across diseased segments. They applied it in a prospective, randomised, multicentre trial in 184 patients with stable coronary disease, with 203 arteries studied, a modest size of study, but the largest of its kind so far. FFR_{angio} was computed with negligible bias and predicted physiological lesion significance (FFR≤0.80), with a measured FFR as the reference standard, with 88% sensitivity, 95% specificity and 94% overall diagnostic accuracy. The 95% Bland-Altman limits of agreement (±1.96 SD) were -0.10 to +0.10. It is worth discussing what these measures of accuracy mean in the world of FFR and in the day-to-day management of patients.

For computed FFR, accuracy can be defined in several ways. Diagnosing physiological lesion significance, i.e. predicting a binary outcome (FFR ≤0.80), is of most importance and relevance to an interventionist. Most virtual FFR models achieve >85% accuracy in this regard. This is, of course, dependent upon the study-specific distribution of FFR cases, i.e. how closely the cases are clustered around the ≤0.80 threshold. Pellicano et al achieved an overall diagnostic accuracy of 94% with 67% of cases falling between 0.70 and 0.90, which is impressive.

Accuracy can also be judged according to how close an individual virtual FFR result is to the corresponding, directly measured, invasive FFR. The best way to assess this is with a Bland-Altman plot, in which the difference between two measurements is plotted against the mean value. The limits of agreement (±1.96 SD) comprise 95% of the differences; and so the narrower the limits of agreement are, the better is the agreement between the two measures. Amongst the published models of virtual FFR, the limits of agreement are similar, and are of the order of ±0.10, as found in the study of Pellicano, but can be as wide as ±0.15. In the

context of FFR (0.00 to 1.00), ±0.10 is a relatively wide range, and somewhat undermines the value of an individual result.

Given the methods used, Pellicano et al achieve an impressive inter-operator variability (intraclass correlation coefficient = 0.96) which implies a robust and repeatable reconstruction algorithm. This is a real achievement given the challenges of segmenting and reconstructing the anatomical model from invasive coronary angiography. Moreover, the image reconstruction software was said to be automatic with 'minimal manual effort to guide the processing' and can be performed in less than 30 seconds. Overall, the software platform and computational method appear to be simpler than in previous models, and are aimed more at the level of healthcare professionals than the research laboratory, and the authors emphasise its applicability within the clinic. The segmentation method produces an axisymmetric (circular cross section) virtual artery which is used for FFR_{angio} computation. Therefore, unlike intravascular imaging, it is unable to replicate eccentric plaque, which instead is radius-averaged over the selected projections. Again, this is similar to other models and appears to be an acceptable approximation. Recently published data demonstrate that accurately representing the arterial geometry is less important than accurately representing the outlet boundary condition (see below) [9]. A further strength was that the computation of FFR_{angio} did not require any deviation from a standard, routine angiogram, making it potentially widely applicable. Similar to other virtual FFR software platforms, the end result, a graphical 3D physiological roadmap, is attractive and nicely facilitates lesion assessment. In common with the work from other groups, lesions were simple, discrete and 'type A', whilst diffuse disease, ostial lesions and in-stent restenosis were excluded. It will be interesting to see if the same level of accuracy is maintained when more complex and diffuse

disease patterns are included, and if the same level of inter-observer variability is maintained when non-expert users outside of the research team run the analyses.

Fluid dynamics purists may be critical of the method by which FFR_{angio} was computed because the authors considered only Poiseuille's law. Trans-lesional fluid mechanics are complex and the Bernoulli pressure drop, due to convective acceleration through an arterial narrowing, is actually more dominant than the Poiseuille drop, due to viscous friction across a stenosis [15]. But even these laws of fluid dynamics are superseded by CFD which invokes the Navier-Stokes equations (the governing equations of fluid flow), which better characterise trans-lesional pressure and flow changes, including incomplete pressure recovery distal to the lesions. The downside of 3D CFD is that, typically, it is complex, computationally expensive, and time-consuming; but recent advances have demonstrated that even complicated CFD methods can be accelerated and simplified enough for 'on-table' use [9].

A challenge in the area of modelling FFR lies in understanding the dominant, accuracy-defining factors; those which need to be accurately represented, and those which can be averaged or assumed. Sophisticated models may be accurate, but complexity can render them impractical outside the research laboratory. Simpler models may be quicker and easier to use, but may not provide sufficient accuracy in all patients. A key question is therefore: what is the simplest model that provides sufficient accuracy for clinical use? Put another way, what is the optimal trade-off between accuracy and ease-of-use? If sufficient accuracy can be provided by simpler models (where the user interface is simplified but underlying scientific methods retain sophistication) and /or methods (where the scientific method itself is simplified) then this is highly advantageous. The latter appears to have been achieved by Pellicano and co-workers.

When computing FFR, aside from the accuracy of the segmented anatomical model, the major accuracy-defining factor is how the model is 'tuned' to represent the resistance of the distal myocardial microvessels [9]. This parameter determines coronary blood flow and is heterogeneous in healthy and diseased states. For this reason, a model which performs fluid dynamics from imaging alone cannot actually compute FFR, a physiological index; and is, in effect, nothing more than a 'fancy QCA'. Models therefore apply a prediction of microvascular resistance (or, conversely, hyperaemic blood flow) using assumptions. Maximum coronary flow is related to the accumulated sum of the distal luminal volume. Although not explicitly laid out in the paper Pellicano et al applied recognised allometric scaling (non-linear proportionality between diverse variables) laws to estimate normal blood supply demand from the volume of the reconstructed arterial tree. Applying the correct resistance or flow is important. If the applied resistance is lower (or higher) than the true microvascular resistance, then flow will be too high (or low) and the virtual FFR will be falsely decreased (or increased) thus over- (or under-) estimating lesion significance with the obvious potential consequence of stenting (or not) inappropriately. If a method can be developed which can accurately predict or approximate to coronary microvascular resistance (or alternatively hyperaemic blood flow) on an individual case-by-case basis, then virtual FFR results will more closely match invasive FFR results, and limits of agreement will improve. This is a major challenge for researchers in this field [16].

Beyond such methodological challenges, the interventional and regulatory communities will need to decide what constitutes 'sufficient accuracy' for routine clinical use – a question which was asked in the same journal last year [17]. Because neither index is perfect, and since virtual FFR will almost certainly never match invasive FFR perfectly in all cases, perhaps

this is better assessed in randomised outcome trials than in observational numerical comparisons, notwithstanding the limitations of serial non-inferiority trials. HeartFlow, Inc (Redwood City, CA), the company behind $_{CT}$FFR, has demonstrated that in silico techniques can be successfully translated routine clinical practice and gain regulatory approval [18]; an important step forward in the introduction of computer modelling to assist decision making in heart disease.

Whether computed 'virtual' physiology represents part of the future for invasive coronary angiography remains to be seen. It is likely that several systems will be developed along similar lines, and there remain methodological and regulatory challenges which need to be resolved. But the critical leap, of which this is the first step, will be to open up coronary physiology to the majority of patients undergoing a diagnostic invasive coronary angiogram, either offline, or preferably in the catheter laboratory, using images recorded in-house or from elsewhere, in stable, unstable, PTCA or potential CABG patients. In silico techniques have the potential to achieve this. The introduction of a practical computer model which brings physiology into an otherwise anatomical test is to be welcomed. In the longer term, it will be interesting to see if in silico techniques can be used to develop an index which is not simply equivalent (or non-inferior) to FFR, but that can improve upon it.

Disclosures

The authors of this editorial are developing their own models of cardiovascular pathophysiology but have no commercial conflicts to declare.

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