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EDITORIAL COMMENT

# Building a Fast Virtual Fractional Flow Reserve

## Reductionists or Dreamers?*

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Fractional flow reserve (FFR) is a technique used in cardiac catheterization to determine the likelihood that a coronary artery stenosis impedes oxygen delivery to the heart. FFR can be measured during routine coronary angiography using a pressure sensor guidewire to calculate the ratio between coronary pressure distal to a coronary artery stenosis and aortic pressure under conditions of maximum myocardial blood flow (hyperemia). Over the past decade, the measurement of FFR has been increasingly used in cardiac catheterization laboratories to provide clinicians with a quantitative assessment of the functional severity of coronary artery stenosis, and has become an important factor in the decision to perform coronary revascularization. FFR can also be computed from the 3-dimensional (3D) reconstruction of the coronary artery obtained from computed tomography and invasive angiography, as well as optical coherence tomographic imaging using computational fluid dynamic (CFD) calculations (1-3). The CFD calculations require assumptions of "boundary conditions," that is, pressure input and estimates of outflow resistance across the tube (i.e., arterial conduit). However, until recently, due to the complexity of the calculations, a virtual (v)FFR required >26 h of computational time. Thus, although the clinical correlation between vFFR from coronary angiography and measured invasive FFR is strong (~80%), because of the time involved, the current methodology is impractical for clinical application.

In this issue of *JACC: Basic to Translational Science*, Morris et al. (4), in an extension of previous work (5), presents results related to a faster, novel, and simplified CFD method to produce a vFFR. In 20 patients who underwent percutaneous coronary intervention (PCI) and measurement of FFR, 73 arterial images with segmented 3D geometries obtained by rotational angiography were analyzed. In addition to examining the computing time and correlation with invasive FFR, a sensitivity analysis of which physiologic parameters had the most influence on the variance of the vFFR calculation was also performed.

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The results indicated that vFFR could be measured in 189 s on a personal computer. Accuracy of the measured FFR was high, with a mean error for vFFR of <1% and correlation coefficients between vFFR and FFR of 0.99 ($p < 0.0001$). For FFR ≤0.80, accuracy was 100%. Sensitivity analysis demonstrated that coronary microvascular resistance (CMVR) was the dominant influence on the vFFR value.

Before addressing the strengths and weaknesses of the study by Morris et al. (4), we wanted to provide the perspective of a clinician on the role of *JACC: Basic to Translational Science* as a translational journal. In presenting basic science concepts and extending their applications into clinical practice, *JACC: Basic to Translational Science* is assisting clinicians in interpreting and understanding basic science, while at the same time helping the basic scientist to make sense of clinical syndromes, obscure physiologic conditions, and outcomes. To this end, the study by Morris et al. (4) falls exactly on the continuum of basic to translational work. However,

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**TABLE 1 Basic Science Morris Glossary**

| Term | Translation | Implication |
|---|---|---|
| Transient analysis | Calculations based on full cardiac cycle data computations | More points to compute |
| Pseudo-transient analysis | Calculation based on mean of cardiac cycle data | Fewer points to compute |
| Sobol decomposition, sensitivity analysis index values, variance-based model | Breakdown of factors and their relative contribution to model variance | Potentially allows elimination of unimportant variables and shows most impactful variables |
| vFFR steady | Computed during constant pressure | Less computing time |
| vFFR tms | Computed during transient pressure cycle | More computing time |
| vFFR ps-tms | Computed during pseudo-transient pressure cycle | Less computing time |
| z1, z2 | Coefficients of pressure drop | Components of CMVR, lesion specific |
| Plug velocity profile | Term related to shape of flow velocity profile within a vessel | Blunt flow profile versus bullet-shaped laminar flow profile may influence results |
| Uniform zero pressure outlet | Setting of boundary conditions to presumed zero pressure outside of the system studied | Simplified assumption, but risks not accounting for venous pressure or collaterals. Neglects changes in pressure and flow by wave reflection from downstream vessels. Uncertain impact on vFFR |
| Windkessel parameters | Physiologic model describing the heart and arterial system as a closed hydraulic circuit. Parameters include arterial compliance, resistance, and inertia. | Basis for any model of pressure and flow in the coronary arteries |

CMVR = coronary microvascular resistance; vFFR = virtual fractional flow reserve; ps-tms = computed with pseudo-transient steady-state method; tms = calculated with full transient computational fluid dynamics.

we also realized that, as clinicians, some of the descriptions of technical concepts and mathematical methods are uninterpretable without considerable study and the construction of a glossary (Table 1).

## STUDY STRENGTHS

On a pragmatic level, this study represents a promising proof of concept. A translesional pressure drop across a narrowed arterial segment is computed, in which the drop in pressure is described by a quadratic function of flow during steady state over a pressure cycle in the Morris model, as opposed to requiring calculations at all points over the complete phasic cycle as required in most computed tomography angiography FFR original algorithms. The original vFFR technique is a function of 9 parameters (proximal pressure, coefficients of pressure loss [z1, z2], CMVR, CMV compliance, and additional parameters that describe myocardial systolic contraction). In the steady-state computation, all these parameters are reduced to a single time average value of resistance, becoming a function of 4 parameters (mean pressure, z1, z2, and total resistance), with the advantage that with far fewer parameters, far less computational power and time was required. Using this simplified methodology, all 73 cases were processed successfully on the first attempt with an average processing time of just >3 min.

Sensitivity analysis was then performed to evaluate the influence of interdependent individual model inputs, quantifying and ranking them in terms of their effects on the modeled output, which in this case was the vFFR (6). We learned 2 things: 1) the accuracy of the FFR was remarkably high, with an interclass correlation coefficient between the vFFR and FFR of 0.999, with 100% sensitivity, specificity, and positive predictive and negative accuracy for lesions with FFR <0.80; and 2) that vFFR could be accurately computed from 3D (rotational) coronary angiography in <4 min provided an accurate CMVR input was available.

One of the most mysterious and difficult issues to understand was the semiautomatic optimization algorithm used to derive the CMVR from invasive measured pressure values (7). CMVR had the greatest influence, which accounted for 59.1% of the vFFR variance, whereas 33% of the variance was accounted for by stenosis geometry. Only 7.5% variance was caused by higher order interaction effects. The influence of CMVR was also demonstrated by reanalyzing cases using a generic CMV value as a distal boundary condition that had a marked effect on accuracy over the range studied, which means vFFR was influenced less by geometry than by CMVR.

## STUDY LIMITATIONS

First, CMVR was derived from invasive pressure wire measurements, something that might not be needed in the future. Second, rotational angiography is not yet widely available and may produce asymmetric coronary segmentations, a concern for future analysis. Third, the true amount of time required to

acquire and process the data to produce vFFR was probably longer than the 3-min computation time, and should include additional time to account for the difficulties of angiographic image acquisition, elimination of artifacts, time to upload the study for CFD analysis, and creating the 3D volumetric mesh. The study did not address interpatient sensitivity and potential errors of vFFR prediction due to clinical uncertainties. Although the investigators claimed the most important result of their study was not whether the vFFR matched FFR, but rather that the simplified and accelerated methods generated results without sacrificing accuracy relative to the transient 3D analysis. On this point, we beg to differ. It is equally or more important to have a high correspondence between vFFR and FFR; otherwise, all this mathematical machinations is unimportant.

The depth and novelty of most basic science experiments often leaves the clinician on the outside, uncertain of its downstream, real-world application. As the raison d'etre for *JACC: Basic to Translational Science*, the laboratory bench and the catheter laboratory usually appear worlds apart. However, this study attempts to close that gap for vFFR. Although the language of the basic science used in this study requires translation for minimal understanding, the bottom line is that any model that can reduce the number of parameters and complexity while maintaining the same accuracy is a winning strategy in both directions.

The original CFD computational methods are probably unnecessarily complex, incorporating multiple factors that ultimately may contribute little to the final result. In the pursuit of accuracy to provide an unassailable proof of concept, researchers often attempt to model every possible contributing factor, regardless of importance, time, and cost. As Morris et al. (4) have shown, only by simplifying, testing, and retesting can we discover and carve away what is excessive and unnecessary, and reveal the essential sculpture underneath, while not cracking and destroying the desired result.

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