CTA-Derived Coronary FFR: The "Holy Grail" of Noninvasive Imaging?

FFRCT technology allows new diagnostic opportunities by combining the assessment of anatomy and physiology.

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What is the "state of the state" of noninvasive cardiovascular imaging? Is there a single test that provides adequate, objective data on which clinically appropriate therapeutic decisions can be made? If not, what would such a test entail? Improved functional physiologic data? More precise anatomic delineation? Possibly a combination of the two?

The current standards for the noninvasive diagnosis of obstructive coronary artery disease (CAD) (stress echocardiography and myocardial perfusion scintigraphy) demonstrate good sensitivity and specificity when compared on a per-patient basis to an invasive angiographic reference (Table 1), but looks can be deceiving. Each of these imaging modalities performs significantly worse on a per-vessel or per-lesion basis when compared to an invasively measured objective physiologic reference.

A substudy of the FAME trial demonstrated this shortcoming. Melikian and colleagues showed that perfusion scintigraphy, when used in patients with multivessel CAD, identified specific fractional flow reserve (FFR)-defined ischemic territories < 50% of the time, with an underestimation of ischemia in 36% of cases and overestimation in 22% of cases.[1] These data have raised concerns for the ability of stress tests to effectively screen for specific coronary lesions that might benefit from coronary revascularization.

Since its introduction in 2005, 64-detector row or greater cardiac computed tomographic angiography (CCTA) has emerged as an effective noninvasive method for the anatomic definition of coronary arteries.[2,3] Studies have demonstrated favorable diagnostic performance for CCTA identification and exclusion of invasive, angiographically referenced obstructive coronary disease (Table 1).[4] However, similar to functional studies, when compared to invasively measured FFR, CCTA demonstrates an unreliable relationship to lesion-specific ischemia.[5] It frequently overdiagnoses the degree of coronary obstruction. Meijboom et al showed that coronary lesions that are considered obstructive by CCTA, when compared to an invasively measured FFR reference, were causal of ischemia in < 50% of cases.[6] Thus, while CCTA is highly sensitive for ruling out CAD, it is limited in its ability to define lesion-specific, clinically significant ischemic CAD.

FFR

The cardiac cath lab measurement of FFR is the ratio of maximal, hyperemic, myocardial blood flow through

TABLE 1. NONINVASIVE TESTS VERSUS VISUAL ASSESSMENT OF ANGIOGRAPHY

Test	Sensitivity	Specificity
Exercise ECG treadmill[a]	68%	77%
Exercise echo treadmill[b]	86%	81%
Dobutamine echo[b]	~ 85%	~ 85%
Exercise nuclear treadmill[c]	87%	73%
Pharmacologic nuclear[c]	89%	75%
Coronary CTA[d]	95%	83%

[a] *ACC/AHA 2002 Guideline Update for Exercise Testing.*
[b] *ACC/AHA/ASE 2003 Guideline Update for the Application of Echocardiography.*
[c] *ACC/AHA/ASNC Guidelines for the Clinical Use of Cardiac Radionuclide.*
[d] *ACCURACY study.*

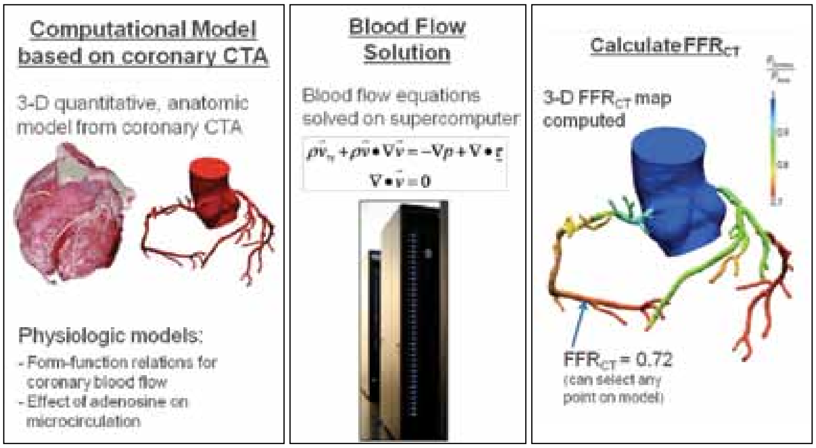

Figure 1. Overview of FFRCT technology combining construction of an accurate model of the epicardial coronary arteries; a mathematical model of coronary physiology to derive boundary conditions representing cardiac output, aortic pressure, and microcirculatory resistance; and the numerical solution of the laws of physics governing fluid dynamics.

a diseased artery to the blood flow in the hypothetical case of a normal artery. This technique was first described almost 2 decades ago,[7] but only recently, due to several large randomized clinical trials, has it become recognized as a significant clinical tool and new "gold standard" for the assessment of the physiologic significance of coronary stenoses.[8] In the widely referenced FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study of 1,005 patients with multivessel CAD, FFR-guided revascularization, specifically reserving revascularization for ischemic lesions with an FFR ≤ 0.8, was associated with significantly lower rates of adverse events (28%) and placement of fewer coronary stents compared to patients undergoing an angiographically guided strategy.[9,10]

The results of the FAME study are consistent with the previously reported 5-year follow-up data from the DEFER study.[11] In the DEFER trial, of lesions judged as angiographically obstructive, > 50% were identified as nonischemic by FFR measurement. More significantly, there was no observed clinical benefit derived from revascularizing FFR-defined, nonhemodynamically significant lesions as compared to medical therapy alone.[11] These trials contribute to the growing body of evidence that supports a combined anatomical-physiological evaluation of CAD for improving event-free survival, reducing unnecessary revascularization, and lowering health care costs. Until now, this level of combined evaluation has been only possible with an invasive evaluation in the cardiac cath lab.

FFRCT

FFRCT is FFR measurements obtained from standard CCTA without modification of the usual image acquisition protocols or added medications. It is a major breakthrough in the pursuit of a noninvasive diagnostic imaging technology in that it provides both anatomical and objective physiologic evaluation of the coronary vasculature.[12,13] The question arises, "How can this be done?" As shown in Figure 1, FFRCT technology combines construction of an accurate model of the epicardial coronary arteries; a mathematical model of coronary physiology to derive boundary conditions representing cardiac output, aortic pressure, and microcirculatory resistance; and the numerical solution of the laws of physics governing fluid dynamics. Here, the whole is indeed greater than the sum of its parts. This combination of detailed anatomic modeling with form-function relationships connecting anatomy, physiology, and physics enables the calculation of coronary pressure, flow, and FFR through the application of computational fluid dynamic equations.

COMPUTATIONAL FLUID DYNAMICS

To comprehend the application of computational fluid dynamics (CFD) to coronary blood flow, a basic high school understanding of physics needs to be resurrected. Cardiologists are generally familiar with Bernoulli's equation, proposed in 1738, which describes energy balance for an inviscid (frictionless) fluid and the consequence that an increase in the velocity of a fluid (as occurs as that fluid accelerates going through a stenosis) results in a simultaneous decrease in pressure. In the case of an inviscid fluid, if the vessel downstream of a stenosis enlarges in size to that of the upstream diameter, then this drop in pressure is recovered as the fluid decelerates. However, in the case of a viscous fluid such as blood, the pressure drop is not fully recovered, resulting in a pressure loss due to a stenosis.

The generalization of the theories of Bernoulli, Euler, and Newton to viscous fluids was accomplished by Navier in 1827 and Stokes in 1845. The so-called Navier-Stokes equations described the behavior of viscous (and inviscid) fluids and established the foundation for the quantitative, mathematical description of the universality of fluid dynamic phenomena. For incompressible fluids, such as blood, the Navier-Stokes equations, supplemented by the mass conservation equation, provide the mathematical formalism to quantitatively describe blood flow, pressure, and FFR.

Yet, although the governing equations of fluid dynamics have been known in their current form for more than 150 years, using them to solve most realistic problems had to wait for the development of advanced numerical methods and high-powered digital computers. Once this occurred, the application of the field of CFD became a practical reality. By using physical laws of mass conservation and momentum balance, it became possible to quantify and thus model fluid pressure and velocity.

Today, this technology is used regularly in the automotive and aerospace industry and has had an enormous impact on improving the quality and safety of these products while simultaneously reducing development and testing costs. Advancements in CFD methods and high-performance computing have only recently been directed to the field of medical science.

Through the extensive work performed in Dr. Charles Taylor's lab in the Bioengineering Department at Stanford University, CFD can now be effectively utilized in patient-specific models of human blood flow, initially applied to large vessels, and more recently to the coronary arteries.[14] Coronary arteries require simultaneously solving millions of nonlinear equations and repeating the process for thousands of time intervals within the cardiac cycle.[15] Fortunately, as CFD methods have developed, Moore's Law has worked to reduce computing requirements from those only attainable at NASA to more affordable high-powered computing solutions.

How is CFD applied to coronary circulation? A common, everyday example of the industrial application of CFD is the calculation of lift and drag on an airplane wing. Data for this calculation include geometry, which are measurements obtained from specific wing design specifications; boundary conditions, which are the velocity of incoming air relative to the wing and atmospheric pressure conditions; and fluid properties (ie, the viscosity and density of air). Inputting these data into CFD equations leads to the calculation of velocity and pressure of air in front of, around, and behind the wing, and the important aeronautical calculations of lift and drag, which are simply calculated from the velocity and pressure fields.

When using CFD for the calculation of FFR from static CTA images, the inputted data include geometry (precise, personalized, three-dimensional reconstruction of the coronary tree, including branching structure and pathology extracted from the CCTA anatomic data); boundary conditions (total coronary blood flow calculated from myocardial mass [extracted from the CT data], aortic [brachial] blood pressure, and coronary microcirculatory resistance [derived using form-function relationships from vessel anatomy]); and fluid properties (viscosity [derived from hematocrit] and density of blood [varying minimally]). Inputting these data into high-performance, proprietary, flow-solving equations of CFD provides point-specific velocity and pressure of blood throughout the coronary arteries and allows for the calculation of FFR.

FORM FOLLOWS FUNCTION

The anatomical data set obtained from a CCTA provides significant information related to coronary blood flow because form follows function in the circulatory system.[16] The form-function relationships adhere to allometric scaling laws, which relate the mass (size) of an object to shape, anatomy, and physiology. Common examples of this include left ventricular enlargement associated with increased flow or resistance (ie, athlete's heart and hypertension), chronic vessel enlargement due to increased flow (ie, collaterals or arteriovenous fistulas), and reduction in vessel caliber due to decreases in blood flow (ie, stenotic, ischemic segments).

Overall derivation of FFRCT is based on three predefined scientific principles. The first principle is that resting, nonischemic coronary blood flow is proportional to myocardial mass (measured from the CT data set). The second principle is that resistance of the microcirculatory vascular bed in a resting state is inversely, but not linearly, proportional to the size of the feeding vessel. Namely, the size of coronary arteries offers clues to relative flow, with smaller coronary artery branches having a higher resistance to flow than larger branches.

The third principle is that the microcirculation has a predictable response to adenosine. Total coronary resistance at maximum hyperemia decreases to approximately one-quarter of its resting value and can be brought on with a dose of 140 ug/kg/min of intravenous adenosine, the recommended dose for the cath lab measurement of FFR.[17] The reproducible, predictable nature of this response allows it to be effectively modeled.

OVERVIEW OF THE FFRCT PROCESS

The methodology for obtaining FFRCT involves downloading a routinely acquired CCTA DICOM data set (ie, 64-slice or better prospective or retrospective image acquisition with no additional medications required) through the internet to a protected storage site.
The accompanying required clinical data include the patient's brachial blood pressure and hemoglobin. The initial images are then evaluated by a scientist/analyst (HeartFlow, Inc., Redwood City, CA) for quality assurance. Image resolution and quality need to be adequate to define the vascular lumen (Figure 2). The myocardial

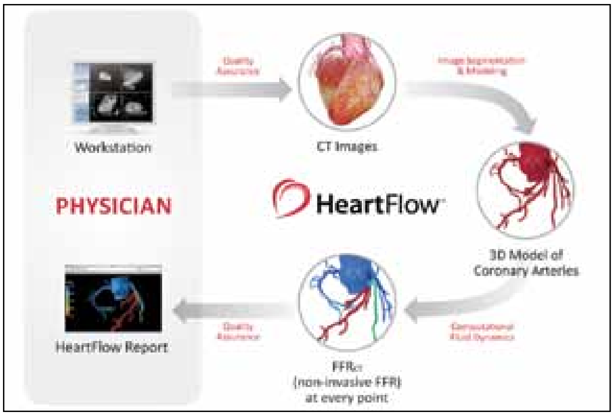

Figure 2. HeartFlow FFRCT Workflow Process in which a CCTA DICOM data set is downloaded to a protected server. The data are processed by HeartFlow and returned to the physician in an interactive format.

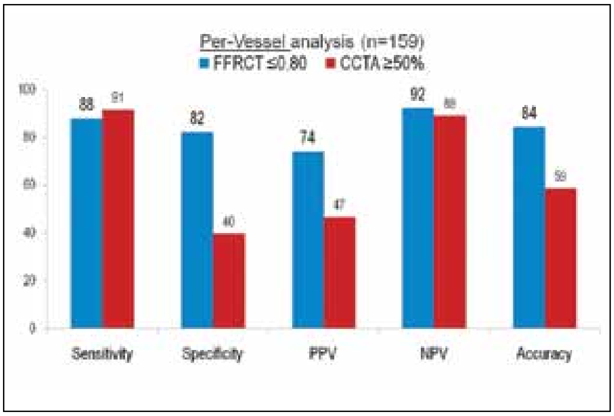

Figure 3. Per-patient comparison of FFRCT and CCTA demonstrating a 25% improvement in accuracy with FFRCT. Reprinted with permission from Koo BK, Erglis A, Doh JH, et al. from the DISCOVER-FLOW Study. *J Am Coll Cardiol.* 2011;58:1989–1997.[18]

mass is determined from CTA data, and a precise three-dimensional model of the vascular tree is created by the trained analyst.

This geometric information is introduced into a high-powered computer-processing algorithm that calculates blood flow and pressure at millions of data points in the coronary arteries. FFRCT is then defined throughout the coronary tree as the mean point-specific coronary pressure divided by the mean blood pressure in the aorta under conditions of modeled maximum hyperemia. The resulting FFR color-coded vascular analysis is reviewed for quality assurance and subsequently returned to the evaluating physician in a user-friendly interactive format.

FFRCT VALIDATION

The HeartFlow FFRCT endeavor has, for the last several years, focused on the validation of the technology compared to invasive cath lab measurements of FFR. The first presentation on this subject was by Dr. Andrejs Erglis's team at the European Society of Cardiology meeting in September 2010. They described the initial 20 patients who underwent FFRCT compared to measured FFR. The cath lab FFR-to-FFRCT correlation showed an *r* value of 0.74, and the addition of the FFRCT measurement provided a three-fold reduction in false-positive CCTAs.

A significantly larger, prospective, multicenter, international DISCOVER-FLOW study (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) was presented by Dr. Bon-Kwon Koo at the EuroPCR meeting in May 2011 and then published in *JACC*.[18] This trial enrolled 103 stable patients at four sites (159 vessels in total) who had both CCTA studies and coronary angiography with FFR measurements. Based on the CCTA, all patients had a stenosis ≥ 50% in a major coronary artery. The CCTAs and FFRCT evaluations were blinded and read in independent core labs. Ischemia was defined as an FFR or FFRCT of ≤ 0.8.

Fifty-six percent of patients had ≥ one vessel with an FFR ≤ 0.8. FFRCT, when compared to an invasive FFR reference standard, demonstrated a per-vessel accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of 84.3%, 87.9%, 82.2%, 73.9%, and 92.2%, respectively. The performance of FFRCT was superior to CCTA for the diagnosis of lesion-causing ischemia, demonstrating an accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of 58.5%, 91.4%, 39.6%, 46.5%, and 88.9%. FFRCT thus retained the high sensitivity and negative predictive value of CCTA while reducing the number of false-positives by more than three-fold (Figure 3).[18]

A larger, 285-patient, multicenter trial of FFRCT, (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography [DeFACTO]) has completed patient enrollment and core lab analysis under the leadership of Dr. James K. Min. The primary endpoint of this trial is the diagnostic accuracy of FFRCT compared with invasively measured FFR as the reference standard and is adequately powered on both a per-vessel and per-patient basis. Additional secondary endpoints are per-patient (as well as per-vessel) diagnostic performance characteristics, including sensitivity, specificity, positive predictive value, and negative predictive value.[19] If the DeFACTO results support and further qualify the DISCOVER-FLOW data, FFRCT has the potential for being a significant addition to the nonin-

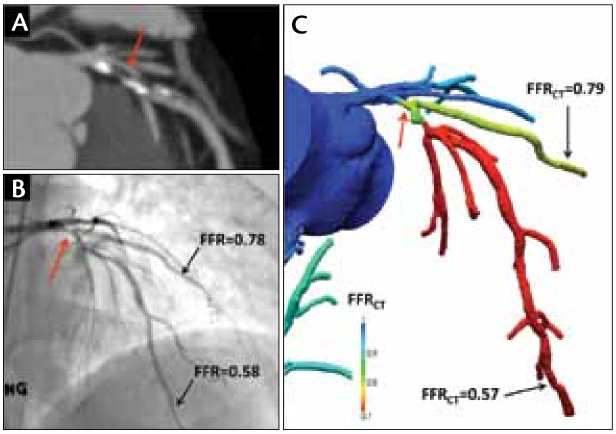

Figure 4. FFRct case example. CCTA (A). Coronary angiography with measured FFR (B). Result from FFRCT (C). Reprinted from *J Am Coll Cardiol,* 58, Koo BK, Erglis A, Doh JH, et al. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. 1989–1997, 2011, with permission from Elsevier.[18]

vasive cardiac imaging armamentarium. A representative example of a patient with lesion-specific ischemia is shown in Figure 4.

CONCLUSION

CCTA provides substantial anatomical definition of the coronary arteries noninvasively and has produced dramatic improvements in both accuracy and resolution since the introduction of the 64-detector scanners in 2005. Further improvements in spatial and temporal resolution and reductions in radiation dose will continue to affect the quality of the anatomical data provided by this technology. The additional application of CFD algorithms to CCTA-derived, patient-specific models now enables the noninvasive, objective determination of FFR on a precise, lesion-specific basis. This ability to obtain clinically relevant physiologic data without the need to take a patient to the cardiac cath lab will have a dramatic impact on improving the diagnosis and management of patients who have CAD and therefore has the potential to be "game-changing" technology.

To take it a step further, the CFD-derived, patient-specific models could enable the prediction of changes in coronary blood flow after a proposed interventional treatment, whether it be a stent or even coronary artery bypass surgery. The opportunity to precisely diagnose and then plan the optimal management strategy for patients well before they get to the cardiac cath lab is an extraordinary concept. Computational coronary artery modeling could possibly be the "Holy Grail" of noninvasive cardiovascular imaging. ■

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Charles Taylor, PhD, is Cofounder and Chief Technology Officer of HeartFlow. He has disclosed that he is an employee and shareholder in HeartFlow.

1. 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 Cardiovas Interv. 2010;3:307-314.
2. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med. 2008;359:2324-2336.
3. Meijboom WB, Meijs MF, Schuijf JD, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective 64-slice computed tomography coronary angiography: a prospective, multicenter multivendor study. J Am Coll Cardiol. 2008;52:2135-2144.
4. Rispler S, Keidar Z, Ghersin E, et al. Integrated single photon emission computed tomography and computed coronary angiography for the assessment of hemodynamically significant coronary artery lesions. J Am Coll Cardiol. 2007;49:1059-1067.
5. Hacker M, Jacobs T, Hack N, et al. Sixty-four slice spiral CT angiography does not predict the functional relevance of coronary artery stenosis in patients with stable angina. Eur J Nucl Med Mol Imaging. 2007;34:4-10.
6. Meijboom WB, Van Mieghem CA, van Pelt N, et al. Comprehensive assessment of coronary artery stenosis: computed tomography coronary angiography versus conventional coronary angiography and correlation with fractional flow reserve in patients with stable angina. J Am Coll Cardiol. 2008;52:636-643.
7. Pijls NH, Van Gelder B, Van der Voort, et al. Fractional flow reserve: a useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. Circulation. 1995;92:3183-3193.
8. Kern MJ, Samady H. Current concepts of integrated coronary physiology in the catheterization laboratory. J Am Coll Cardiol. 2010;55:173-185.
9. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Eng J Med. 2009;360:213-224.
10. Fearon WF, Bornschein B, Tonino PA, et al. Economic evaluation of fractional flow reserve-guided percutaneous intervention in patients with multivessel disease. Circulation. 2010;122:2545-2550.
11. 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;49:2105-2111.
12. Kim HJ, Vignon-Clementel IE, Figueroa CA, et al. Developing computational methods for three-dimensional finite element simulations of coronary blood flow. Finite Elements Analysis Design. 2010;46:514-525.
13. Taylor CA, Steinman DA. Image-based modeling of blood flow and vessel wall dynamics: applications, methods and future directions. Ann Biomed Eng. 2010;38:1188-1203.
14. Taylor CA, Draney MT, Ku JP, et al. Predictive medicine: computational techniques in therapeutic decision-making. Comput Aided Surg. 1999;4:231-247.
15. Kim HJ, Vignon-Clementel IE, Figueroa CA, et al. On coupling a lumped parameter heart model and a three-dimensional finite element aorta model. Ann Biomed Eng. 2009;37:2153-2169.
16. LaBarbara M. Principles of design of fluid transport systems in zoology. Science. 1990;249:992-1000.
17. Wilson RF, Wyche K, Christensen BV, et al. Effects of adenosine on human artery circulation. Circulation. 1990;82:1595-1606.
18. 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;58:1989-1997.
19. 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;5:301-309.