Aerodynamics in Cardiac CT

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It seems not long ago that invasive coronary angiography was considered as the undisputed diagnostic standard and management determining test for patients with ischemic heart disease. Registry data have shown that reliance on noninvasive testing for myocardial ischemia, positioned as a gatekeeper to restrict referral to the catheterization laboratory, is far from optimal in clinical practice. Coronary computed tomographic (CT) angiography (CCTA), which was developed and validated during the past decade, allows noninvasive visual confirmation of the presence or absence of coronary artery disease (CAD). Meanwhile the cardiology community has rediscovered an appreciation for functional parameters of CAD, particularly for clinical decision making. Cardiac CT is arguably the most accurate noninvasive technique to exclude CAD, with sensitivities and negative predictive values >95% as reported in meta-analyses. Unfortunately, CCTA has a tendency to overestimate the severity of CAD, particularly in the presence of coronary calcifications. More than ever before, we are aware of the complex and unpredictable relation between angiographic stenosis and myocardial ischemia. Compared with invasive fractional flow reserve (FFRcath), which is currently considered stenosis and myocardial ischemia. Compared with invasive fractional flow reserve (FFRcath), which is currently considered the clinical standard of lesion-specific hemodynamic significance, both invasive and noninvasive coronary angiography overestimate the functional severity of CAD. Current clinical practice guidelines recommend consideration of both anatomic and functional parameters in the treatment of stable CAD. There seems to be no prognostic benefit from revascularizing hemodynamically nonsignificant stenosis, whereas on the other hand, mechanical treatment of myocardial ischemia is difficult in the absence of focal narrowing of the epicardial coronary branches. In that context, a diagnostic modality able to provide both angiographic and functional information during a single, noninvasive examination would be highly desirable.

For decades, (computer) simulations of air flow around objects have defined the design of aircrafts and automobiles. Based on the shape of the design and the boundary conditions, air velocity, pressure, and mechanical behavior can be predicted by a computer. Based on similar principles, the developers of CT-based computation of fractional flow reserve (FFRct) have found a way to estimate the flow and pressure within the coronary arteries and calculate pressure gradients for stenotic lesions during simulated peripheral vasodilation. Although the complex methodology and inherent limitations of these algorithms are fully comprehended by few, several studies have demonstrated that FFR simulations based on CT images are feasible, and that the numbers correlate with FFRcath. The largest of these technical validation studies is the Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography (DeFACTO) study by Min et al., which was published in 2012. In this international, multicenter study, the performance of FFRct in comparison with coronary CT angiography, was validated against FFRcath. CCTA (diameter stenosis >50%) had a sensitivity of 84%, specificity of 42%, and accuracy of 64% for the detection of hemodynamically significant CAD as defined by invasive angiography and FFRcath. FFRct improved the sensitivity to 90%, the specificity to 54%, and the overall accuracy to 73%. C-statistics showed a significant improvement in the area under the curve from 0.68 by CCTA to 0.81 by FFRct. Although the accuracy by FFRct was slightly less than anticipated, DeFACTO showed that FFRct has the potential to improve the diagnosis of hemodynamically significant CAD by cardiac CT.

Although the DeFACTO study included lesions extending the full range of angiographic severity, in clinical practice the need for functional assessment will be most relevant in lesions of intermediate severity, which is the question Dr Nakazato and colleagues set out to answer in this issue of Circulation: Cardiovascular Imaging. The CT exams were performed using contemporary scanner technology and standard acquisition protocols. The FFRct calculation was performed offline by the developer of the algorithm. FFRcath was performed after administration of nitroglycerine with intracoronary injection of adenosine using a 0.80 threshold for hemodynamic significance. Invasive and noninvasive angiographies, as well as the FFRcath were interpreted by separate core laboratories in a blinded fashion. Of the original DeFACTO cohort of 252 patients, 82 patients had 150 vessels with a maximum CT stenosis of 30% to 69%. In approximately a quarter of these vessels, the FFRcath measured <0.80, with fairly similar proportions of hemodynamic significance above and below the CT angiographic threshold of 50% diameter reduction. The overall conclusion from the subanalysis is that the addition of FFRct improves the diagnostic performance of CCTA to identify vessels and patients with functionally relevant coronary obstruction. The C-statistics demonstrated superior discrimination by FFRct in comparison with CT angiography alone and improved the area under the curve from 0.50 to 0.81. Which is not to say that FFRcath performed perfectly. On average FFRct overestimated the severity of functional obstruction, with fairly wide limits of agreement compared with FFRcath. Despite the ingenuity of the FFRct algorithm, methodological objections exist concerning...
the allometric assumptions, the physiological modeling, and attention to biological variability, which would suggest that it is difficult to extract a functional parameter from static anatomic images. But even if a perfect algorithm would be created, its feasibility would remain dependent on the quality of the anatomic input data. The effective spatial resolution of cardiac CT is 0.4 mm at best. Accurate depiction of the vessel lumen is further affected by blurring from residual cardiac motion and blooming artifacts because of calcifications in the vessel wall. Accurate depiction of tightly narrowed vessels (with calcifications) is difficult, whereas the absolute size of the stenotic lumen has a large effect on the FFR\textsubscript{CT} result. Fortunately, because FFR\textsubscript{CT} on average overestimated the severity of CAD in comparison with FFR\textsubscript{Cath}, the number of false-negative results remained acceptable. The net reclassification analysis showed that FFR\textsubscript{CT} was able to correctly reclassify many patients after CCTA interpretation. However, it should be noted that CCTA in this study showed different performance compared with what is usually seen in clinical practice. Typically, cardiac CT overestimates disease severity, resulting in high sensitivity and lower specificity, particularly when compared with a functional reference.\textsuperscript{2,4} Interestingly, in this study, the per patient specificity of CCTA (64%) was relatively high, at the expense of a lower sensitivity of 37%. This may be explained by the selection of intermediate lesions, or the lack of the clinically common practice of defensive reading to avoid false-negatives.

Then, what would be the role of FFR\textsubscript{CT} in clinical practice? The anticipated benefit is that in case of intermediate coronary lesions on CCTA further testing can be avoided after demonstrating the absence of hemodynamic significance. FFR\textsubscript{CT} is appealing because it can be performed without additional testing, radiation exposure, or contrast injection. The drawbacks are that this particular FFR\textsubscript{CT} simulation is performed offsite and requires transfer of CT data and several hours of preparation and computation, which makes the analysis relatively expensive. FFR\textsuperscript{CT} computation requires image quality that exceeds what is generally needed for visual evaluation of the coronary arteries. Of the original DeFACTO cohort, 12% of CT scans was excluded because of insufficient image quality. Our own experiences indicate that the number of nonanalyzable CT scans can be even higher.\textsuperscript{10} Image quality will improve with further advanced scanner technology as well as medical preparation of the patients (nitroglycerine and heart rate reduction). There is the potential threat that higher image quality requirements will oppose current trend toward lower radiation and contrast medium exposures associated with CCTA. Without doubt, FFR\textsubscript{CT} algorithms will further evolve, become available onsite, providing faster and more accurate calculations. But how about our conventional alternatives? Functional testing using nuclear technologies, magnetic resonance imaging, and echocardiography have established roles in the diagnostic workup of stable CAD. Although myocardial perfusion imaging may not pinpoint the lesion that is hemodynamically most severe, information about the overall ischemic effect of the total atherosclerotic burden is equally relevant to the patient. Stress myocardial perfusion imaging by CT is currently under development, which would also provide comprehensive information by a single modality. Although this technique does require a second scan with contrast injection, there is the advantage of immediate availability of directly measured functional information, independent of the image quality of the CT angiogram.

FFR\textsubscript{CT} is an ingenious and fascinating new technique that could bridge the gap between anatomic imaging and clinical decision making. Although the concept of computed fluid dynamics was initially received with skepticism, the DeFACTO investigators are to be congratulated for demonstrating in a robust manner that FFR\textsubscript{CT} is feasible with better-than-expected diagnostic performance compared with FFR\textsubscript{Cath}. This study by Nakazato et al, which focused on the intermediate lesions where implementation of FFR\textsubscript{CT} seems most efficient, demonstrated its incremental diagnostic value to CCTA and supports its potential value to avoid further testing. There are advantages and practical limitations to FFR\textsubscript{CT}. Future studies will need to assess the technical performance and clinical benefit of FFR\textsubscript{CT} in comparison with its functional competitors.

Disclosures

None.

References

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