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Anatomy is Destiny, But Physiology is Here Today

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Author(s):
James R. Wilentz, MD

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In the current busy catheterization laboratory, the operator is under constant pressure to get cases accomplished with dispatch, yet under obligation to ask, as Barry Rutherford has often reminded us, not what we can do, but what we should do. Coronary angiography, long considered the “gold standard” for decision-making regarding treatment of coronary stenoses in both acute and chronic coronary artery disease (CAD), has known limitations. The dye-filled artery

projects a shadow which is a two-dimensional representation of a three-dimensional structure. The diameter of the most severe stenosis can be relatively easily chosen and measured, but the choice of a non-diseased reference diameter may be hampered by the fact that on post-mortem studies it is clear that coronary plaque is ubiquitous, and thus it is somewhat arbitrary where one defines the reference segment.[1] To better understand the three-dimensional nature of coronary plaque and its physiologic significance, non-angiographic assessments including anatomic intravascular ultrasound (IVUS)[2] and physiologic flow measurements, fractional flow reserve (FFR)3 have been increasingly utilized. For IVUS, accepted definitions have evolved to discriminate between "significant" and "non-significant" lesions in the proximal portions of the major coronary arteries[4] and in the left main stem.[5] Specifically, lesions with minimal luminal cross-sectional areas ≥ 4.0 mm^2 in a proximal coronary artery or ≥ 7.5 mm^2 in the left main stem may be left for medical therapy rather than treated by intervention. IVUS can also give information about the nature and potential vulnerability of the obstructing plaque[6,7] and its overall amount8 which may be useful both for research purposes and for the prognosis and treatment decisions regarding the patient. Similarly, for FFR, the finding of a distal coronary/aortic pressure ratio of ≥ 0.75 at peak distal vasodilatation with adenosine predicts a benign course for the lesion treated non-interventionally.[3,9] A number of different studies have been done looking at outcomes with FFR-guided intervention, and the most recent guidelines of the ACC-AHA regarding this suggest that

there may be a “gray zone” such that lesions with FFR < 0.75 should surely be considered ischemic and thus candidates for intervention, those between 0.75 and 0.8 allocated to either intervention or medical treatment at the option of the physician within the context of the clinical setting, and those with ratios ≥ 0.8 clearly suitable for deferral of intervention.[10]

In this issue of the Journal, Dr. Lockie and colleagues[11] report a series of real world consecutive cath lab cases in which patients with moderate (50–75% angiographic diameter stenosis) coronary lesions were investigated with intravenous adenosine-stimulated maximal hyperemic flow and decisions regarding intervention were made with a discriminant cutoff for FFR of 0.75. Of the 5,609 interventional patients seen during the time period studied, 300 patients underwent pressure wire measurements with the important finding that 75% of the patients studied avoided a revascularization procedure on one of the arteries studied as a result of the FFR measurement. This is another brick solidly cemented into the structure of evidence surrounding the safety of deferring intervention in patients whose stenoses are not physiologically flow-impairing. That edifice, with a foundation dating back to the original Doppler coronary flow reserve measurements, has been further strengthened recently with the results of the DEFER study,[12] which used a randomization schema to show that performance of intervention on patients with a FFR ≥ 0.75 showed no benefit over medical therapy and that both the medically treated and interventional patients with initial FFR ≥ 0.75 did better

than the interventional patients whose FFR had initially been < 0.75. Finally in the FAME study,[13] randomizing to FFR-guided intervention (with a trigger for intervention of FFR ≤ 0.8) versus angiographically-driven intervention resulted in the placement of fewer stents (1.9 versus 2.7) per patient in the FFR group and a lower incidence of the adverse primary endpoint of death, myocardial infarction and repeat revascularization (13.2% versus 18.3%). Finally there was also a cost savings ($5,332 in the FFR group versus $6,007 in the angiography group) and a length of stay advantage (3.4 versus 3.7 days), and both were statistically significant.

Having established that angiography is not the be-all and end-all of the decision-making process in how to treat stable coronary disease, do we chose IVUS or FFR as the supplementary modality in evaluating the intermediate lesion, and why? If we want to intervene, we better do IVUS. This is suggested by Nam and colleagues in their recent study[14] of 167 consecutive patients with intermediate lesions (40–70% diameter stenosis), in which either FFR < 0.80 or IVUS MLA < 4mm2 was chosen by operator preference as the pivotal test in determining whether or not to intervene. All vessels had to be at least 2.5 mm in reference diameter to be included in this study. The striking finding is that if FFR is chosen as the key determinant, intervention is performed on only 33.7% of lesions vs. 91.5% if IVUS is used! In the 12-month follow up period in this study, there was no difference in the measured outcomes of target vessel revascularization or MACE (death, myocardial infarction and ischemia-driven TVR) with these

two strategies despite the different utilization of interventions. This has led John Hodgson to suggest the use of FFR for assessment of intermediate lesions (physiologic test to assess physiology) and IVUS to guide the performance of an intervention once intervention is determined to be needed.[15]

Perhaps it would be wise to turn back to where we were at the beginning and ask again not what we can do, but what we should do. At this point the complementarity of FFR and IVUS should be clear, but are we still missing the point? It is easy with a well-understood basis to treat a patient who has disabling angina, and easier still to stop a heart attack in progress with an elegant intervention, but further research and thought remains needed to find those intermediate lesions which may become unstable and cause heart damage and death. It seems obvious from the data that for the majority of intermediate lesions, physiologic assessment rules the day and benign outcomes are expected, but better assessment techniques such as optical coherence tomography, as well as fast, low radiation dose CTA, and possibly newer probes that may be used with PET imaging to view the areas of inflammation in the vessel wall are required to enhance our understanding of how this disease evolves clinically from its stable state into a dangerous taker of lives and sapper of strength. Meanwhile let's perform FFR on those intermediate lesions and not be tempted to use IVUS to increase our clinical volume!

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From the Lenox Hill Heart and Vascular Institute, New York New York.The author reports no conflicts of interest regarding the content herein.Address for correspondence: J.R. Wilentz, MD, FACC, Lenox Hill Heart and Vascular Institute, 130 East 77th St, New York NY 10075. E-mail: wilentz@gmail.com [4] [5]

• Commentary