Physiological severity of coronary artery stenosis

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Three fundamental advances in our knowledge underlie the rapidly evolving long-term treatment of coronary artery disease (CAD), summarized briefly here for perspective on the paper by Marques and colleagues (17) in this issue of American Journal of Physiology-Heart and Circulatory Physiology, on quantifying severity of coronary artery stenoses by their pressure-flow velocity relation.

The first of these advances identified sudden plaque rupture and thrombosis as the cause of most acute coronary syndromes associated with inflammation and wall stress of lipid-rich plaques with thin fibrous caps. Consequently, in randomized trials, revascularization procedures in chronic stable CAD do not decrease coronary events or improve long-term survival (13–15). Deferring revascularization based on physiological severity of coronary artery stenosis quantified by coronary flow reserve (CFR) or fractional flow reserve (FFR) improves management of CAD by reducing unnecessary procedures with better outcomes than routine revascularization based on visual stenosis severity on coronary arteriograms (1, 2, 22). Revascularization procedures may be appropriate for acute coronary syndromes or refractory symptoms due to myocardial ischemia but, even with advanced surgical techniques and coated stents, have not improved survival in chronic stable CAD (13–15). However, based on well-documented visual overestimates of stenosis severity, economic incentives, and the well-meaning urge to “do something now” by patients and physicians, these procedures are substantially overutilized without objective measures of ischemia or severity (21), particularly in view of comparable outcomes with deferring revascularization based on objective physiological severity (1, 2, 22).

The second of the major advances was stabilization or regression of coronary atherosclerosis by intense pharmacological and/or lifestyle changes that improve coronary blood flow, reduce atherosclerotic burden, and decrease coronary events by over 90% compared with less intensively treated control subjects (3, 4, 19). Whereas statin monotherapy reduces coronary events and mortality by 30–50% compared with untreated controls, it does not adequately address the risks of low HDL and/or high triglycerides. Multidrug and/or intense combined pharmacological and lifestyle treatment further improve outcomes more than after revascularization procedures with parallel improvement in myocardial perfusion.

The third major advance integrated the anatomic, pressure, and blood flow characteristics of the entire coronary artery tree that explain fundamental coronary artery branching structure, the interacting effects of single or multiple stenosis, and/or diffuse atherosclerosis as the basis for precisely quantifying disease severity in clinically relevant terms, both invasively and noninvasively (6, 7, 20).

CFR was the first physiological measure of stenosis severity (8–12, 16). Relative CFR is the basis of noninvasive stress perfusion imaging. Absolute CFR is the basis of flow velocity measurements using intracoronary Doppler wires or arterial thermodilution catheters during maximum flow after intracoronary adenosine. Absolute or relative CFR is also measured by positron emission tomography (PET) perfusion imaging after intravenous adenosine or dipyridamole. Arteriographic stenosis flow reserve is a calculated flow reserve based on precise integrated stenosis dimensions objectively measured by automated arteriographic analysis using fluid dynamic equations.

Coronary FFR is relative flow reserve determined from pressure wire recordings across a single stenosis at maximum flow after intracoronary adenosine (18). FFR is readily obtained during routine coronary arteriography, is reproducible, and, at a threshold of 0.75 (normal FFR being 1.0), correlates well with exertional ischemia. It serves as a guide for deferring revascularization procedures with better outcomes than visual estimates of severity as the basis for these procedures (1, 2, 22). However, FFR is not valid for multiple stenoses or diffuse disease (18). Neither FFR nor CFR indicates stenosis severity if small vessel disease or diffuse coronary atherosclerosis limits the flow response to pharmacological agents or exercise as commonly occurs in CAD.

These three advances suggest that revascularization procedures are indicated at coronary arteriography only for stenoses that are physiologically severe enough to cause refractory ischemia by objective measurements since visual assessment of severity is grossly inadequate for moderate stenosis of intermediate severity. Stenoses not meeting preestablished thresholds of severity should not be instrumented but treated with intensive lifestyle and pharmacological agents for optimal outcomes. After appropriate noninvasive testing and/or a trial of medical treatment, the question then becomes, What is the best measure of physiological severity of a stenosis at coronary arteriography—automated quantitative arteriographic analysis, CFR, FFR, or dpv50?

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In this study (17), 77 patients with CAD were studied with dobutamine stress echocardiography (echo), dipyridamole single-photon-emission computed tomography (SPECT) perfusion imaging, quantitative coronary arteriography, and diastolic pressure gradient-flow velocity measurements across stenoses during hyperemia following intracoronary adenosine. The diastolic pressure gradient-flow velocity curves were best fit to a quadratic equation for determining its viscous and separation coefficients. Based on this best-fit quadratic equation, the pressure gradient at a standardized 50 cm/s flow velocity (dpv50) was calculated as a single comprehensive number quantifying stenosis severity derived from the entire pressure gradient-flow velocity relation. The units of dpv50 are millimeters of mercury at 50 cm/s.
The strength of dpv50 is its directly measured pressure-flow velocity relation used to calculate the stenosis pressure gradient at a projected or assumed 50 cm/s flow velocity even if that flow velocity could never be achieved in that patient due to small vessel or diffuse disease. Therefore, it does not depend on maximal CFR, thereby making it independent of small vessel disease or poor response to adenosine.

The sensitivity and specificity for threshold levels of dpv50, FFR, and coronary flow velocity reserve (CFVR) determined at coronary arteriography were then compared for identifying stenosis severity sufficient to cause myocardial ischemia on prior stress echo or perfusion imaging. The threshold value of dpv50 that best differentiated a stenosis causing ischemia from one that did not was 22.4 mmHg, analogous to the FFR threshold of 0.75 for FFR and 1.9 for relative CFVR.

For their respective thresholds, dpv50 had higher sensitivity and specificity than FFR or CFVR for identifying stenosis severe enough to cause ischemia by stress echo of perfusion imaging compared with those stenoses that did not cause ischemia. In essence, the dpv50 measured at coronary arteriography is equivalent to a stress test for identifying ischemia independently of or despite coronary small vessel disease associated with atherosclerosis. The difference between calculated and directly measured dpv50 might be a measure of small vessel disease as well. The dpv50 is therefore the next conceptual step after CFR and FFR for assessing physiological severity of stenosis at coronary arteriography as a guide to revascularization procedures.

LIMITATIONS

Although contributing a valuable concept, the study by Marques and colleagues (17) is not optimal in some respects. The stress echo and perfusion data used for determining the threshold value of dpv50 at 22.4 mmHg were then also used in the same group of patients to calculate the diagnostic sensitivity and specificity of dpv50 compared with FFR and CFVR. Therefore, by definition, the dpv50 would likely have optimal sensitivity and specificity for predicting stress echo and perfusion abnormalities, since the dpv50 threshold itself was originally defined based on this same stress echo and perfusion data.

The threshold values for FFR and CFVR were initially assumed from the literature rather than being predefined by the same stress echo and perfusion data. This assumption potentially biased the study making dpv50 more sensitive and specific than FFR and CFVR. To counter this potential bias, the authors also determined new threshold values of CFVR and FFR from the same stress echo and perfusion imaging data in the same patients so that all the thresholds for dpv50, CFVR, and FFR were determined in the same way from the same stress echo and perfusion imaging data for optimal sensitivity and specificity for each of the severity measures. With this “balanced bias,” dpv50 still best differentiated stenoses causing ischemia from those that did not. A better scientific design would enroll another group of patients for comparative sensitivity and specificity, separately and independently from the initial group of 77 patients used to determine the threshold values of dpv50, CFVR, and FFR. In addition, all of the patients should have had all studies. Stress echo and SPECT perfusion imaging are both limited by suboptimal sensitivity and/or specificity. Although the sensitivity and specificity of dpv50 in this population were impressive, such binomial classification of the continuous spectrum of CAD depends largely on the population selected, the choice of thresholds, and the definition of a positive result, i.e., “disease.”

Determining dpv50 for routine clinical application requires a small flexible guidewire that records both pressure and flow velocity by Doppler. Very small size is important to avoid further compromising the narrowed lumen of a stenotic segment by the wire passed through the stenosis to record distal pressure and flow velocity. In addition, Doppler signals vary with the angle of incidence to blood flow that is not always controllable. Finally, the Doppler wire measures primarily peak flow velocity, not average cross-sectional flow velocity, where the velocity profile may change with time, range of flow velocities, and location along length of an artery. A wide-field Doppler wire that recorded true mean cross-sectional flow velocity might improve the reproducibility of flow velocity recording to be comparable to the excellent reproducibility of pressure recordings by current pressure wires.

THE NEXT STEP

Validating the clinical usefulness of dpv50 requires a series of clinical studies like those published for FFR demonstrating diagnostic accuracy in a separate group of patients using the threshold values derived in the current paper. Just as that done for FFR, it would be important to demonstrate improved outcomes in randomized trials of deferring revascularization procedures based on the threshold of dpv50.

As reported in this paper, dpv50 is applicable only to a single segmental stenosis, as is true for CFR and FFR. None of these measurements account for or quantify multiple stenoses in series or in parallel, or for diffuse disease throughout the entire branching coronary artery tree. We have shown that multiple stenoses and/or diffuse narrowing throughout the coronary artery tree have tremendous interactions (6, 7, 20). Consequently, the pressure-flow (or flow velocity) characteristics integrated throughout the entire coronary artery tree are markedly different from and cannot be determined by the pressure-flow characteristics of single isolated stenosis.

This more comprehensive analysis would require a slow pull-back recording of pressure and flow velocity from the distal to proximal segments of each major coronary artery after intravenous adenosine or dipyridamole with a dpv50 determined for each increment of each coronary artery. The resulting comprehensive pressure-flow velocity map would provide a precise physiological measure of every stenosis, in series or in parallel, of diffuse disease and their interactions. Pull-back pressure along the length of a coronary artery after intracoronary adenosine has demonstrated this principle for identifying diffuse CAD in the absence of significant arteriographic segmental stenosis (5).

Interestingly, the fundamental concepts for determining stenosis severity by physiological pressure-flow relations, by quantitative arteriographic analysis of the whole coronary artery tree, by intracoronary echo, and by perfusion imaging using PET are simultaneously evolving toward the comprehensive integrated analysis of the entire branching coronary arterial tree as affected by diffuse and multigeminal disease.

Why bother? First, the comprehensive analysis of the entire coronary artery tree relating function, anatomy, and vascular
physiology is good science and worth the intellectual investment. Second, such analysis identifies which stenoses need revascularization or not for better patient outcomes and lower cost. Such comprehensive analysis could in principle predict the physiological effects of opening a stenosis before the procedure was done to assess the residual pressure flow effects of remaining diffuse or other segmental disease.

CONCLUSIONS

In this era of randomized trials, evidenced-based medicine and well-documented quantitative alternatives, visually assessing percent diameter stenosis on coronary angiograms remains, astonishingly, the single dominant determinant of subsequent procedures, enormous costs, lack of survival benefit, and proven gross inadequacy for determining stenosis severity or for identifying early diffuse coronary atherosclerosis causing most sudden coronary events.

The paper by Marques and colleagues (17) is a significant step toward a more rational basis for revascularization procedures based on physiological severity of narrowing—the dp50. The pressure gradient at a flow velocity of 50 cm/s calculated from pressure gradient-flow velocity curves obtained with a pressure-Doppler wire at coronary arteriography is valid for quantifying severity of stenosis even in the presence of small vessel disease or submaximal flow response to adenosine, an advantage over CFR and FFR. Determination of dp50 is the next logical step on the way to the complete integrated analysis of the entire branching coronary artery tree for interacting diffuse and multisegmental stenoses by pressure-flow velocity recording along the length of each major coronary artery, by precise anatomic-fluid dynamic analysis of the entire coronary arteriographic tree, by intracoronary echo, or by noninvasive PET perfusion imaging.

REFERENCES


