Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 61, No. 13, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.01.034

Diagnostic Classification of the Instantaneous Wave-Free Ratio Is Equivalent to Fractional Flow Reserve and Is Not Improved With Adenosine Administration

Results of CLARIFY (Classification Accuracy of Pressure-Only Ratios Against Indices Using Flow Study)

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Objectives This study sought to determine if adenosine administration is required for the pressure-only assessment of coronary stenoses.

Background The instantaneous wave-free ratio (iFR) is a vasodilator-free pressure-only measure of the hemodynamic severity of a coronary stenosis comparable to fractional flow reserve (FFR) in diagnostic categorization. In this study, we used hyperemic stenosis resistance (HSR), a combined pressure-and-flow index, as an arbiter to determine when iFR and FFR disagree which index is most representative of the hemodynamic significance of the stenosis. We then test whether administering adenosine significantly improves diagnostic performance of iFR.

Methods In 51 vessels, intracoronary pressure and flow velocity was measured distal to the stenosis at rest and during adenosine-mediated hyperemia. The iFR (at rest and during adenosine administration [iFRa]), FFR, HSR, baseline, and hyperemic microvascular resistance were calculated using automated algorithms.

Results When iFR and FFR disagreed (4 cases, or 7.7% of the study population), HSR agreed with iFR in 50% of cases and with FFR in 50% of cases. Differences in magnitude of microvascular resistance did not influence diagnostic categorization; iFR, iFRa, and FFR had equally good diagnostic agreement with HSR (receiver-operating characteristic area under the curve 0.93 iFR vs. 0.94 iFRa and 0.96 FFR, $p = 0.48$).

Conclusions iFR and FFR had equivalent agreement with classification of coronary stenosis severity by HSR. Further reduction in resistance by the administration of adenosine did not improve diagnostic categorization, indicating that iFR can be used as an adenosine-free alternative to FFR. (Classification Accuracy of Pressure-Only Ratios Against Indices Using Flow Study [CLARIFY]; NCT01118481) (J Am Coll Cardiol 2013;61:1409–20) © 2013 by the American College of Cardiology Foundation

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Manuscript received July 25, 2012; revised manuscript received December 5, 2012, accepted January 8, 2013.

Abbreviations and Acronyms

AUC = area under the curve
FFR = fractional flow reserve
HSR = hyperemic stenosis resistance
iFR = instantaneous wave-free ratio
iFRa = instantaneous wave-free ratio during adenosine
ROC = receiver-operating characteristic

Use of intracoronary physiological indices to guide revascularization improves clinical outcomes and reduces procedural costs (1,2). Because of the simplicity of measuring intracoronary pressure and the wealth of outcome data, fractional flow reserve (FFR) is the most frequently used measure of stenosis severity. However, intracoronary pressure distal to a stenosis reflects not only the severity of the stenosis but also pressure generated from the microcirculation (3). FFR is calculated as a ratio of mean distal to aortic coronary pressures over the entire cardiac cycle. To separate the hemodynamics of the stenosis from that of the microcirculation, FFR is calculated under conditions of constant (and minimal) microvascular resistance (4). This is achieved with the administration of vasodilators, such as adenosine (5).

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The instantaneous wave-free ratio (iFR) is a pressure-only index that takes an alternative approach to the isolation of the hemodynamics of a stenosis from the microcirculation (6). It does not use vasodilators; instead, it samples intracoronary pressure during the diastolic "wave-free" period—a period in the cardiac cycle when intrabeat microvascular resistance is inherently stable and minimized. This wave-free window provides a phase in which microvascular resistance is significantly lower than that over the whole cardiac cycle, and coronary hemodynamics are most suited for assessment of the hemodynamic effects of a stenosis (6,7). However, it is possible that microvascular resistance during the wave-free period can be lowered even further with the administration of adenosine, and it has been suggested that calculating iFR during adenosine administration may improve its ability to accurately discriminate flow-limiting stenoses (8).

In the ADVISE (Adenosine Vasodilator Independent Stenosis Evaluation) study, the classification of stenosis severity was good between iFR and FFR, but in the absence of a true gold standard, where differences in classification occurred, it was difficult to know which index was correct.

The absence of a true ischemic gold standard has hampered the development of new indices in the past. Previously, noninvasive imaging modalities have been used to further evaluate new intracoronary physiological tools. However, these techniques have limitations in multivessel disease and can only isolate ischemia at the level of a territory rather than a specific vessel (9). Therefore, in this study, we use the hyperemic stenosis resistance (HSR) index, an invasive pressure- and flow-based index, as the reference standard to determine which of the pressure-based indices most accurately represents the hemodynamic severity of the stenosis. HSR falls back to the fundamental importance of simultaneously measuring pressure and flow as first described by Gould (7), and in doing so, circumvents many of the limitations of a pressure-only index. It is recognized to be more stenosis specific, and less dependent on adenosine-mediated hyperemia than pressure-only indices (10–14).

In the first part of this study, we compared the diagnostic classification of iFR, iFRa, and FFR to HSR. We then assessed the changes in resistance that occur during the 3 pressure-derived indices to determine how adenosine administration influences diagnostic categorization.

Methods

Study population. This study included 51 stenoses (subjects 66.2 ± 9.2 years of age; 82.4% male) (Table 1) scheduled for coronary angiography or percutaneous coronary intervention at Guys and St. Thomas' NHS Trust or Imperial College London, UK. In addition to new data, patients were included from part 1 of the ADVISE study (6). Exclusion criteria were limited to significant valvular pathology, previous coronary artery bypass surgery, and weight >200 kg. All subjects gave written informed consent in accordance with the protocol approved by the local ethics committee (NRES 09/H0712/102; NCT01118481).

Study protocol. Pressure and flow velocity recordings were made distal to the target vessel coronary stenosis in 51 vessels at rest and during adenosine-induced hyperemia (76.5% intravenous [140 μg/kg/min] and 23.5% intracoronary [120 μg]).

Cardiac catheterization. Cardiac catheterization was undertaken through the femoral approach. After diagnostic angiography, a 0.014-inch pressure and Doppler sensor-

Table 1 Demographics

	Stenoses, n (%)
Male	42 (82.4)
Age, yrs	66.2 ± 9.2
Risk factors	
Smoker	15 (29.4)
Diabetic	14 (27.4)
Hypertension	18 (35.2)
Family history of ischemic heart disease	13 (25.5)
Vessel	
LAD	28 (54.9)
Cx	12 (23.5)
RCA	11 (21.6)
Adenosine route	
IV	39 (76.5)
IC	12 (23.5)

Cx = circumflex; HSR = hyperemic stenosis resistance; IC = intracoronary; IV = intravenous; LAD = left anterior descending artery; RCA = right coronary artery.