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VERIFY (VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice)

A Multicenter Study in Consecutive Patients

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Objectives This study sought to compare fractional flow reserve (FFR) with the instantaneous wave-free ratio (iFR) in patients with coronary artery disease and also to determine whether the iFR is independent of hyperemia.

Background FFR is a validated index of coronary stenosis severity. FFR-guided percutaneous coronary intervention (PCI) improves clinical outcomes compared to angiographic guidance alone. iFR has been proposed as a new index of stenosis severity that can be measured without adenosine.

Methods We conducted a prospective, multicenter, international study of 206 consecutive patients referred for PCI and a retrospective analysis of 500 archived pressure recordings. Aortic and distal coronary pressures were measured in duplicate in patients under resting conditions and during intravenous adenosine infusion at 140 μg/kg/min.

Results Compared to the FFR cut-off value of ≤0.80, the diagnostic accuracy of the iFR value of ≤0.80 was 60% (95% confidence interval [CI]: 53% to 67%) for all vessels studied and 51% (95% CI: 43% to 59%) for those patients with FFR in the range of 0.60 to 0.90. iFR was significantly influenced by the induction of hyperemia: mean ± SD iFR at rest was 0.82 ± 0.16 versus 0.64 ± 0.18 with hyperemia ($p < 0.001$). Receiver operating characteristics confirmed that the diagnostic accuracy of iFR was similar to resting Pd/Pa and trans-stenotic pressure gradient and significantly inferior to hyperemic iFR. Analysis of our retrospectively acquired dataset showed similar results.

Conclusions iFR correlates weakly with FFR and is not independent of hyperemia. iFR cannot be recommended for clinical decision making in patients with coronary artery disease. (Comparison of Fractional Flow Reserve Versus Instant Wave-Free Ratio for Assessment of Coronary Artery Stenosis Severity in Routine Practice; NCT01559493) (J Am Coll Cardiol 2013;61:1421–7) © 2013 by the American College of Cardiology Foundation

Fractional flow reserve (FFR) is a pressure-derived index of coronary stenosis severity and represents the ratio of maximal blood flow in a stenotic artery to maximal flow in the same artery in the absence of any stenosis (1–4). It has been well validated (5–7), and in patients with multivessel coronary disease undergoing percutaneous intervention (PCI), FFR guidance improves health and economic outcomes

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Abbreviations and Acronyms

ACC = American College of Cardiology

ESC = European Society of Cardiology

FFR = fractional flow reserve

iFR = instantaneous wave-free ratio

Pa = aortic pressure

Pd = distal coronary pressure

PCI = percutaneous coronary intervention

compared to treatment based on angiography alone (8–10). As a result, FFR guidance during PCI has received a class 1A recommendation from the European Society of Cardiology (11) and a class IIA recommendation from the American College of Cardiology (12). FFR measurements require that myocardial resistance is minimal and constant. In clinical practice, intravenous adenosine infusion is used to establish these conditions. Although most patients experience some breathlessness and chest tightness during adenosine infusion, these symptoms are generally well tolerated (13). The instantaneous wave-free ratio (iFR) has been proposed as an index of stenosis severity that is independent of hyperemia and can be measured without the need for adenosine (14). The concept of iFR is based on the hypothesis that there is a diastolic "wave-free" period (WFP) when microvascular resistance is already constant and minimal. An iFR value of ≤0.83 has been suggested as having diagnostic accuracy comparable to the commonly used FFR cutoff of ≤0.80. We studied consecutive unselected patients referred for angiography with or without PCI to compare FFR to iFR and to determine whether iFR is independent of hyperemia.

Methods

The study protocol was approved by the institutional review board or ethics committee at each participating center, and all patients provided written informed consent. This study is registered at the National Institutes of Health Clinical Trials website (NCT01559493). All consecutive patients referred for FFR-guided angiography with or without PCI during a 5-week period from January 4 to February 10, 2012,

Table 1 Baseline Characteristics (n = 206)

Age (yrs)	65.2 ± 10.2
Male	146 (71)
Mean body mass index (kg/m^2)	27.7 ± 4.6
Risk factors	
Cigarette smoker	64 (31)
Diabetes	50 (24)
Hypercholesterolemia	127 (62)
Treated hypertension	137 (67)
Family history	71 (35)
Mean % of left ventricular ejection fraction	56 ± 11
Stable angina	140 (68)
Unstable angina	46 (22)
No. of previous MIs in the culprit artery territory	28 (14)
Index artery	
LAD	133 (64)
Cx	28 (14)
RCA	45 (22)
No significant disease	16 (8)
Single-vessel disease	85 (41)
Two-vessel disease	64 (31)
Three-vessel disease	41 (20)
Medication	
Aspirin	181 (88)
Clopidogrel or ticagrelor or prasugrel	94 (46)
ACE inhibitor or ARB	139 (68)
Beta-blocker	161 (78)
Statin	169 (82)
Calcium antagonist	49 (24)
Long-acting nitrate	45 (22)
Insulin	19 (9)
Oral antidiabetes medication	33 (16)

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; Cx = circumflex coronary artery; LAD = left anterior descending coronary artery; MI = myocardial infarction; RCA = right coronary artery.

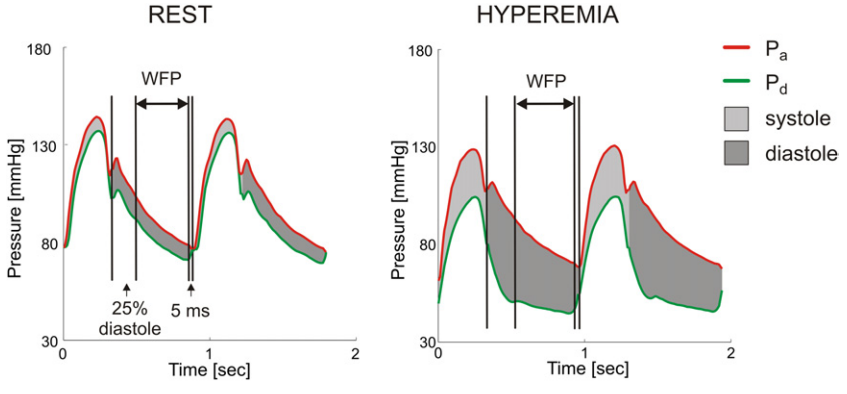

Figure 1 Pressure Tracings of 2 Sequential Heartbeats at Rest and During Hypermia Induced by Adenosine

The wave-free period (WFP) begins 25% into diastole and ends 5 ms before the end of diastole. Aortic pressure is in **red** and distal coronary artery pressure is in **green**. Both the systolic pressure gradient **(light shade)** and diastolic pressure gradient **(dark shade)** increase substantially during hyperemia.