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Does the Instantaneous Wave-Free Ratio Approximate the Fractional Flow Reserve?

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Objectives This study sought to examine the clinical performance of and theoretical basis for the instantaneous wave-free ratio (iFR) approximation to the fractional flow reserve (FFR).

Background Recent work has proposed iFR as a vasodilation-free alternative to FFR for making mechanical revascularization decisions. Its fundamental basis is the assumption that diastolic resting myocardial resistance equals mean hyperemic resistance.

Methods Pressure-only and combined pressure-flow clinical data from several centers were studied both empirically and by using pressure-flow physiology. A Monte Carlo simulation was performed by repeatedly selecting random parameters as if drawing from a cohort of hypothetical patients, using the reported ranges of these physiologic variables.

Results We aggregated observations of 1,129 patients, including 120 with combined pressure-flow data. Separately, we performed 1,000 Monte Carlo simulations. Clinical data showed that iFR was +0.09 higher than FFR on average, with ±0.17 limits of agreement. Diastolic resting resistance was 2.5 ± 1.0 times higher than mean hyperemic resistance in patients. Without invoking wave mechanics, classic pressure-flow physiology explained clinical observations well, with a coefficient of determination of >0.9. Nearly identical scatter of iFR versus FFR was seen between simulation and patient observations, thereby supporting our model.

Conclusions iFR provides both a biased estimate of FFR, on average, and an uncertain estimate of FFR in individual cases. Diastolic resting myocardial resistance does not equal mean hyperemic resistance, thereby contravening the most basic condition on which iFR depends. Fundamental relationships of coronary pressure and flow explain the iFR approximation without invoking wave mechanics. (J Am Coll Cardiol 2013;61:1428–35) © 2013 by the American College of Cardiology Foundation This is an open access article under the CC BY-NC-ND

Coronary physiology plays an increasingly important role in interventional cardiology (1). Even as the overall volume of percutaneous coronary interventions declines in the United States, the number of fractional flow reserve (FFR) procedures has grown (2). This growth accelerated after the publication of the FAME (Fractional Flow Reserve Versus

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angiography for multivessel evaluation) trial (3), leading to strong guideline recommendations for physiologic evaluation of an intermediate stenosis lacking definitive functional data.

Measurement of FFR requires an invasive procedure, systemic anticoagulation, instrumentation of the coronary arteries, and pharmacologic vasodilation. In an attempt to avoid the last of these requirements, recent work has proposed the instantaneous wave-free ratio (iFR) (4). While FFR averages the relative distal pressure over the entire cardiac cycle during hyperemia (5), iFR measures the relative distal pressure from mid-to-end diastole at rest. Because coronary flow occurs predominantly in diastole, pressure gradients are higher than during the lower flow period of systole. The fundamental basis of iFR approximation to FFR is the assumption that diastolic resting myocardial resistance equals mean hyperemic resistance (4).

As with any approximation, prerequisites for the successful substitution of iFR for FFR need to be understood, as must its diagnostic performance. Certain general conditions may exist to explain the situations in which iFR does not approximate FFR well. For such cases, pharmacologic vasodilation remains essential to accurately assess stenosis severity. Furthermore, iFR may offer a biased or uncertain estimate of FFR. In this case, iFR could not be used interchangeably with FFR.

Therefore, we first applied a simulation model to study the relationship between iFR and FFR while varying independent anatomic and hemodynamic parameters. Next, we validated our predictions of the iFR approximation by using a large, multicenter cohort of human data. Finally, we tested the assumption that myocardial "resistance at rest is equivalent to time-averaged resistance during FFR measurements" (4).

Methods

Simulation model. Our model applies fundamental principles of coronary and stenosis hemodynamics to a tree network of arterial segments and myocardial beds while allowing for the natural range of normal and abnormal physiology (such as pressure, flow, heart rate, and focal and diffuse atherosclerosis). Full details can be found in the Online Appendix. Our simulation model is not intended to predict iFR or FFR as a diagnostic application but rather to study interactions, physiologic variables, and mechanisms affecting both parameters.

Two general types of simulations were performed. First, parameters such as heart rate, blood pressure, severity of focal and diffuse disease, rest flow, and maximal coronary flow reserve (CFR) in the absence of disease were varied independently to study their relative influences on the iFR/FFR relationship. Results are provided entirely in the Online Appendix. Second, a Monte Carlo simulation was performed. The Monte Carlo method allows for exploration of a complex system when exact mathematical solutions are not feasible because of many parameters whose values are either uncertain or demonstrate innate variability. We repeatedly selected random parameters for the model as if drawing from a cohort of hypothetical patients, using reported ranges of these physiologic variables. The relationship between iFR and FFR was explored after simulation of 1,000 "patients" (repetitions).

Abbreviations and Acronyms

CFR = coronary flow reserve

CI = confidence interval

iFR = instantaneous wave-free ratio

FFR = fractional flow reserve

ROC = receiver-operating characteristic

Human clinical data. Two types of analyses were performed using intracoronary human data: first, the relationship between iFR and FFR; and second, empirical observations and application of physiologic principles to combined pressure-flow measurements. Data were aggregated from multiple centers to produce a large and diverse cohort, as detailed in the Online Appendix. Pressure-only and combined pressure-flow data were acquired using standard equipment and techniques, including both intravenous and intracoronary adenosine for hyperemia. Informed consent approved by the local review board was obtained from each human subject at the time of the original data collection. In most cases, original data had already been analyzed and published as part of other research, occasionally unrelated to iFR, especially for combined pressure-flow data.

Empirical observations from pressure-flow data summarize the signed relative error between iFR and FFR, as ([iFR − FFR]/FFR × 100) across tertiles of hemodynamic parameters (e.g., rest flow velocity, heart rate, mean arterial pressure, and so on). Best-fit parameters, as described in the Online Appendix, were used to test the ability of classical pressure-flow physiology to describe iFR. Myocardial resistance was estimated by dividing distal coronary pressure by its flow velocity only for practical comparison with the results of prior work (4). Conceptually, instantaneous or diastolic myocardial resistance is not correct because of large intramyocardial compliance. Additionally, coronary backpressure should be taken into account, although several issues are controversial and are discussed in detail elsewhere (6).

For our primary analysis, we used the exact definition of the diastolic "wave-free" period as originally proposed, namely "beginning 25% of the way into diastole and ending 5 ms before the end of diastole," where the "onset of diastole was identified from the dicrotic notch" (4). As a secondary analysis, mainly detailed in the Online Appendix, we explored the sensitivities of iFR and myocardial resistance to the exact definition of diastole.

Statistical methods. Statistical analyses were performed using R version 2.14.1 software (R Foundation for Statistical Computing, Vienna, Austria). We used standard summary statistical tests and least squares regression, as detailed in the Online Appendix. Applicable tests were two-tailed,