JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 70, NO. 25, 2017
ISSN 0735-1097
https://doi.org/10.1016/j.jacc.2017.10.066

Comparison of Different Diastolic Resting Indexes to iFR

Are They All Equal?

Marcel van't Veer, MSc, PhD,[a,b] Nico H.J. Pijls, MD, PhD,[a,b] Barry Hennigan, MB BCh BAO, BMedSci,[c,d] Stuart Watkins, MBChB, MD,[c,d] Ziad A. Ali, MD, PhD,[e] Bernard De Bruyne, MD, PhD,[f] Frederik M. Zimmermann, MD,[a] Lokien X. van Nunen, MD, PhD,[a] Emanuele Barbato, MD, PhD,[f,g] Colin Berry, MBChB, PhD,[c,d] Keith G. Oldroyd, MD[c,d]

ABSTRACT

BACKGROUND Pressure measurement for the duration of the wave-free period (WFP) is considered essential for resting-state physiological assessment of coronary stenosis severity using the instantaneous wave-free ratio (iFR).

OBJECTIVES The aim of this study was to compare other diastolic resting indexes to iFR.

METHODS In the population of the VERIFY2 (Pd/Pa vs iFR in an Unselected Population Referred for Invasive Angiography) study, iFR calculated by proprietary software (Volcano Harvest, Volcano Corporation, Rancho Cordova, California) was compared with the ratio of resting distal coronary pressure and aortic pressure during the complete duration of diastole (dPR), 25% to 75% of diastole (dPR_{25-75}), and midpoint of diastole (dPR_{mid}), along with Matlab calculated iFR (iFR_{matlab}) and iFR-like indexes shortening the length of the WFP by 50 and 100 ms (iFR_{-50ms} and iFR_{-100ms}), respectively. Mutual differences, Spearman correlations, area under the curve values from receiver-operating characteristic analyses, and diagnostic performance with respect to iFR and fractional flow reserve (FFR) were calculated for all indexes.

RESULTS Median iFR in 197 patients with 257 vessels was 0.91 with an interquartile range of 0.87 to 0.95. The mutual differences ($\pm$ SD) with iFR were 0.006 $\pm$ 0.011 (dPR), 0.001 $\pm$ 0.007 (dPR_{25-75}), 0.001 $\pm$ 0.008 (dPR_{mid}), 0.005 $\pm$ 0.009 (iFR_{matlab}), 0.003 $\pm$ 0.008 (iFR_{-50ms}), and 0.001 $\pm$ 0.009 (iFR_{-100ms}). Correlations for all indexes with iFR were >0.99 ($p < 0.001$ for all). Area under the curve values for predicting iFR were >0.99 for all indexes as well. Diagnostic accuracy compared with FFR was 76% to 77% for all indexes including iFR.

CONCLUSIONS All diastolic resting indexes tested were identical to iFR, both numerically and with respect to their agreement with FFR. A numerically equal value to iFR can be determined without restriction to the WFP. Cutoff values, guidelines, and clinical recommendations for iFR can therefore be extended to these other indexes. (Pd/Pa vs iFR in an Unselected Population Referred for Invasive Angiography [VERIFY2]; NCT02377310) (J Am Coll Cardiol 2017;70:3088–96)

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the [a]Department of Cardiology, Catharina Hospital Eindhoven, Eindhoven, the Netherlands; [b]Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, the Netherlands; [c]British Heart Foundation, Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, Scotland, United Kingdom; [d]West of Scotland Heart and Lung Center, Golden Jubilee National Hospital, Clydebank, Scotland, United Kingdom; [e]Columbia University Medical Center, New York, New York; [f]Cardiovascular Center Aalst, Aalst, Belgium; and the [g]Department of Advanced Biomedical Science, University of Naples, Naples, Italy. Dr. van't Veer has received a speaker fee from Abbott. Dr. Pijls has served as a consultant for Abbott and Opsens; and has equity in Philips, GE, HeartFlow, and ASML. Dr. Ali has received institutional research grants to Columbia University from St. Jude Medical and Cardiovascular Systems Inc.; and has served as a consultant to St. Jude Medical, ACIST Medical, Cordis, and Boston Scientific. Dr. De Bruyne is shareholder for Siemens, GE, Bayer, Philips, HeartFlow, Edwards Lifesciences, Sanofi, and Omega Pharma; his institution, the Cardiovascular Center Aalst, has received grant support from Abbott, Boston Scientific, Biotronik, and St. Jude Medical; and his institution has received consulting fees on behalf of Dr. De Bruyne from St. Jude Medical, Opsens, and Boston Scientific outside of the submitted work. Dr. Barbato's institution, the Cardiovascular Research Institute Aalst, has received speaker and consultancy fees from Abbott Vascular and Boston Scientific on his behalf. Dr. Berry and the University of Glasgow hold research and consultancy agreements with Abbott. Dr. Oldroyd has received consultancy and speaker fees from Abbott; and has received research support from Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Berry and Oldroyd contributed equally.

Manuscript received September 7, 2017; revised manuscript received October 26, 2017, accepted October 29, 2017.

Assessment of the physiological severity of coronary artery disease by fractional flow reserve (FFR) is superior in guiding coronary revascularization compared with angiography-based strategies and is recommended in European and American guidelines (1,2) based on randomized controlled clinical outcome trials (3-5). Measurement of FFR requires administration of a vasodilatory drug (commonly adenosine) to obtain a reproducible and steady state of coronary hyperemia (3,6,7), which is associated with transient and generally well tolerable symptoms, prolongation of the procedure by a few minutes, and in some countries, extra costs.

SEE PAGE 3097

Recently, the instantaneous wave-free ratio (iFR) was introduced as an adenosine-free alternative for FFR (8). This index is calculated as the ratio of resting distal coronary pressure (Pd) and aortic pressure (Pa) over a specific period in late diastole, the wave-free period (WFP), during which intracoronary resistance is purportedly naturally constant and minimal. The physical basis and even the existence of the WFP have been questioned (9). Moreover, experimental data to support this theory are lacking, and previous studies have shown that both iFR and resistance during the WFP decreased markedly during adenosine infusion (10-12). In fact, in the IDEAL (Iberian-Dutch-English) study, it was even shown that resistance during the WFP is higher than whole-cycle hyperemic resistance (13).

Nonetheless, several clinical studies have reported that use of adenosine can indeed be avoided in a number of lesions using a hybrid approach with a dual iFR cutoff value (10,11,14). Moreover, in 2 recent randomized controlled trials, an iFR-based revascularization approach using a binary cutoff value of 0.89 was noninferior with respect to a composite clinical endpoint in a low-risk population compared with an FFR-based approach (15,16).

In contrast to FFR, which is generic, has been granted open-access, and is not commercially restricted, iFR measurements are limited to proprietary software of 1 single vendor, curtailing clinical application and research more generally. However, other resting indexes can be measured or calculated directly using any measuring equipment available in the catheterization laboratory. Accordingly, the aim of the current study was to compare several nonhyperemic indexes obtained during different parts of diastole or the whole heart cycle to iFR.

ABBREVIATIONS AND ACRONYMS

AUC = area under the curve

dPR = diastolic pressure ratio

FFR = fractional flow reserve

iFR = instantaneous wave-free ratio

IQR = interquartile range

Pa = aortic pressure

Pd = distal coronary pressure

ROC = receiver-operating characteristics curve

WFP = wave-free period

METHODS

This post hoc analysis was performed using the prospectively acquired hemodynamic recordings from the VERIFY2 (Pd/Pa vs iFR in an Unselected Population Referred for Invasive Angiography; NCT02377310) study; the specific details of the study have been described previously (10).

Briefly, Pa (guiding catheter) and Pd (Prestige or Verrata Wire, Volcano Corporation, Rancho Cordova, California) curves were acquired simultaneously in 197 near-consecutive patients from 257 vessels at baseline (resting condition) and during administration of intravenous adenosine (hyperemic condition). For repeatability, all measurements were repeated after a 2-min resting period.

In addition, in this study the following diastolic indexes were pre-specified (**Figure 1**):

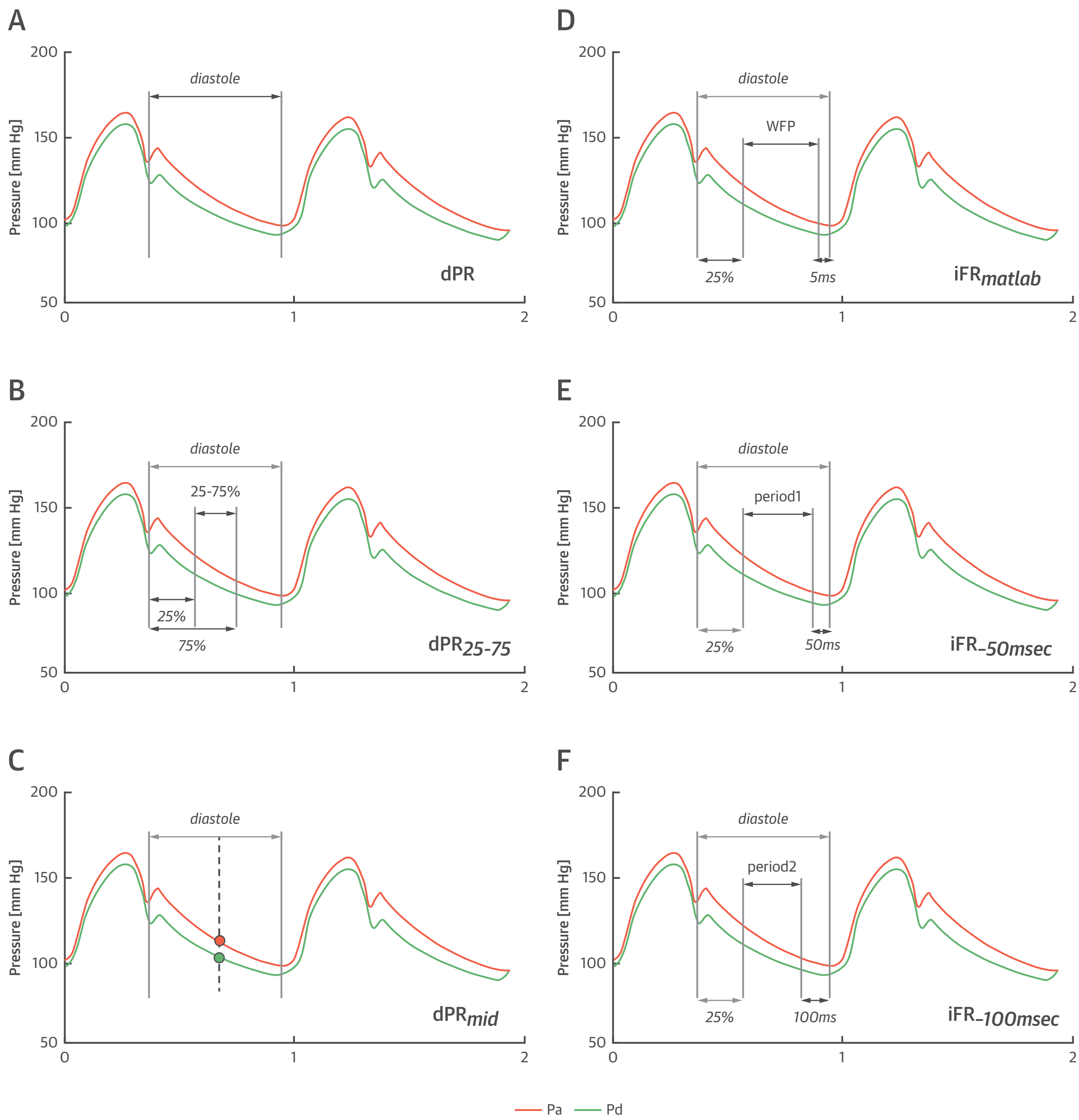
- Diastolic pressure ratio (dPR): average Pd/Pa over the entire diastole.
- dPR_{25-75}: average Pd/Pa from 25% to 75% into diastole.
- dPR_{mid}: Pd/Pa at the single point in time at mid-diastole.
- iFR_{matlab}: average Pd/Pa from 25% into diastole until 5 ms before end of diastole, following the definition of the WFP described by Sen et al. (8); this was not calculated using the proprietary software (Volcano Corporation), but instead by using standard mathematical methods.
- iFR_{-50ms}: average Pd/Pa from 25% into diastole until 50 ms before end of diastole.
- iFR_{-100ms}: average Pd/Pa from 25% into diastole until 100 ms before end of diastole.

Furthermore, as explained in the Online Appendix, the pressure ratios during the intervals defined in the previous text but derived from the curves during hyperemia were also calculated to investigate whether the observed correlations were only confined to resting conditions or would also exist during hyperemia.

Finally, in addition to the diastolic indexes, some other resting indexes that are not confined to diastole were analyzed. Rest Pd/Pa over the whole heart cycle and Pd/Pa_{min} were compared with iFR. This work is further described in the Online Appendix.

DATA HANDLING AND STATISTICS. All curves and iFR values, calculated with the proprietary Volcano

FIGURE 1 Definitions of Diastolic Indexes



Schematic explanation of the diastolic indexes defined in this study. Diastole is defined from the nadir of the dicrotic notch until 50 ms before the upstroke of the next heartbeat. **(A)** The dPR is shown as the Pd/Pa ratio over the entire diastole. **(B)** The dPR over a middle part of diastole defined as 25% to 75% into diastole, $dPR_{25\text{-}75}$. **(C)** The ratio of the Pd/Pa value at mid-diastole, the dPR_{mid}. **(D)** iFR_{matlab} defined as the Pd/Pa value over the period 25% into diastole until 5 ms before the end of diastole; this is comparable to the definition by Sen et al. (8). **(E)** The iFR_{-50ms}, which is the same as iFR_{matlab} except for the fact that Pd/Pa is calculated over the interval used for iFR_{matlab} but shortened by 50 ms (period 1). **(F)** iFR_{-100ms}, which is the same as iFR_{matlab} except for the fact that Pd/Pa is calculated over the interval used for iFR_{matlab} but shortened by 100 ms (period 2). dPR = diastolic pressure ratio; iFR = instantaneous wave-free ratio; Pa = aortic pressure; Pd = distal coronary pressure.

Harvest software, were stored in the Volcano s5 console HDD (Volcano Corporation). Pressure curves were analyzed offline by using Matlab version R2012b (Mathworks, Inc., Natick, Massachusetts) to obtain the different diastolic indexes as described in the previous text. The start of diastole was defined at the nadir of the dicrotic notch on the aortic pressure signal (Pa) and the end of diastole was defined at

50 ms before the upstroke in the aortic pressure signal from the subsequent ventricular contraction. All indexes were determined in a fully automated manner for 5 consecutive beats and were then averaged and compared with acquired iFR values. Spearman's correlation coefficients were determined for all indexes with iFR, and linear regression was applied as well as determination of mutual differences.

Receiver-operating characteristic (ROC) curves with area under curve (AUC) values were determined with iFR as reference standard using a threshold of ≤0.89. Because repeated measurements were available, the average value of the 2 measurements was used for the analyses. To put the AUC values for the different indexes into perspective, an ROC curve analysis was also performed for the second iFR measurement, with the first measurement as the reference standard using a threshold of ≤0.89.

Diagnostic values with respect to FFR ≤0.80 (gold standard) were determined using an identical cutoff value of ≤0.89 for iFR, dPR, dPR_{25-75}, dPR_{mid}, iFR_{matlab}, iFR_{-50ms}, and iFR_{-100ms}. Diagnostic values with respect to iFR ≤0.89 were determined similarly, and the results are shown in the Online Appendix.

Continuous variables are presented as mean ± SD or median with interquartile range (IQR) as appropriate. Analyses were done with Matlab version R2012b.

RESULTS

PATIENT CHARACTERISTICS. A total of 197 patients were included, of whom 136 (69%) were men, 31 (16%) had diabetes, and 73 (37%) had prior MI. Coronary pressure measurements were acquired in 257 coronary arteries, of which 148 (58%) were in the left anterior descending artery, and the mean diameter stenosis was 48 ± 13%. The most frequent indications for angiography were stable angina (50.1%), non-ST-segment elevated myocardial infarction (30.1%), unstable angina (7.0%), and atypical chest pain (5.1%). The median FFR value was 0.81 (IQR: 0.75 to 0.87) and the median iFR was 0.91 (IQR: 0.87 to 0.95). For further characteristics of the VERIFY2 patient cohort, please refer to Hennigan et al. (10).

MUTUAL DIFFERENCES AND CORRELATION BETWEEN iFR AND OTHER DIASTOLIC RESTING INDEXES. Table 1 shows the median values of the various indexes, their respective differences compared with iFR, and their respective correlation with iFR. The differences between any of the indexes and iFR are similar to the test-retest repeatability of iFR, which was found to be −0.0001 ± 0.0156 in this study. Spearman's correlation coefficients are >0.99 ($p < 0.001$) for all of the indexes. The scatterplots for the relation between iFR and the other indexes are displayed in Figure 2.

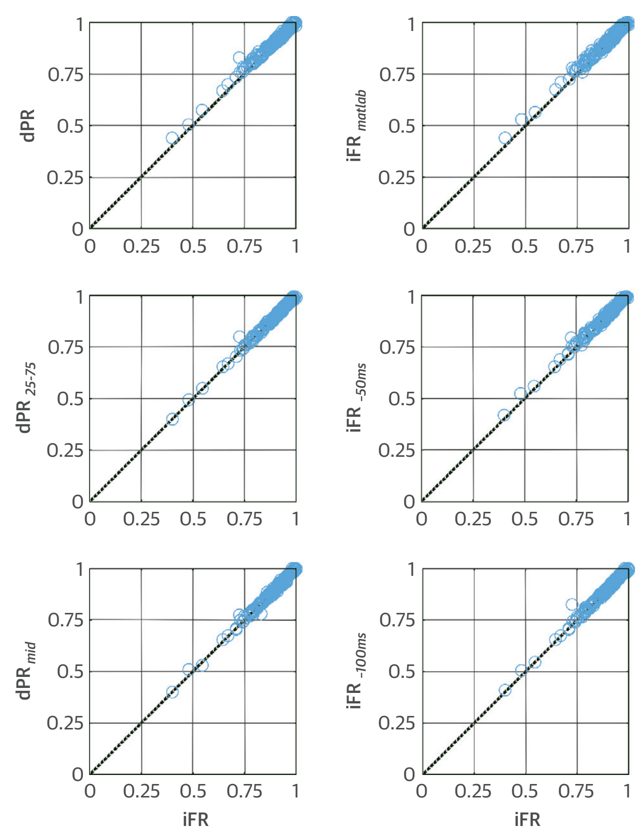
TABLE 1 Median Values and Mutual Differences, Spearman's Correlation Coefficients, Coefficients of Determination, and AUC Values of Resting Diastolic Indexes With Respect to iFR

Index	Median (IQR)	Difference With iFR	Spearman's Rho	R^2	AUC
dPR	0.920 (0.880-0.960)	0.0059 ± 0.0108	0.993	0.984	0.997
dPR_{25-75}	0.915 (0.870-0.950)	0.0012 ± 0.0065	0.997	0.994	0.999
dPR_{mid}	0.915 (0.870-0.950)	0.0012 ± 0.0081	0.993	0.990	0.997
iFR_{matlab}	0.915 (0.875-0.955)	0.0054 ± 0.0088	0.993	0.989	0.995
iFR_{-50ms}	0.915 (0.870-0.950)	0.0026 ± 0.0083	0.996	0.990	0.998
iFR_{-100ms}	0.915 (0.870-0.960)	0.0009 ± 0.0086	0.996	0.990	0.998

AUC = area under the curve; dPR = diastolic pressure ratio; dPR_{25-75} = average Pd/Pa from 25% to 75% into diastole; dPR_{mid} = Pd/Pa at the single point in time at mid-diastole; iFR = instantaneous wave-free ratio; iFR_{-50ms} = average Pd/Pa from 25% into diastole until 50 ms before end of diastole; iFR_{-100ms} = average Pd/Pa from 25% into diastole until 100 ms before end of diastole; iFR_{matlab} = average Pd/Pa from 25% into diastole until 5 ms before end of diastole; IQR = interquartile range; Pa = aortic pressure; Pd = distal coronary pressure.

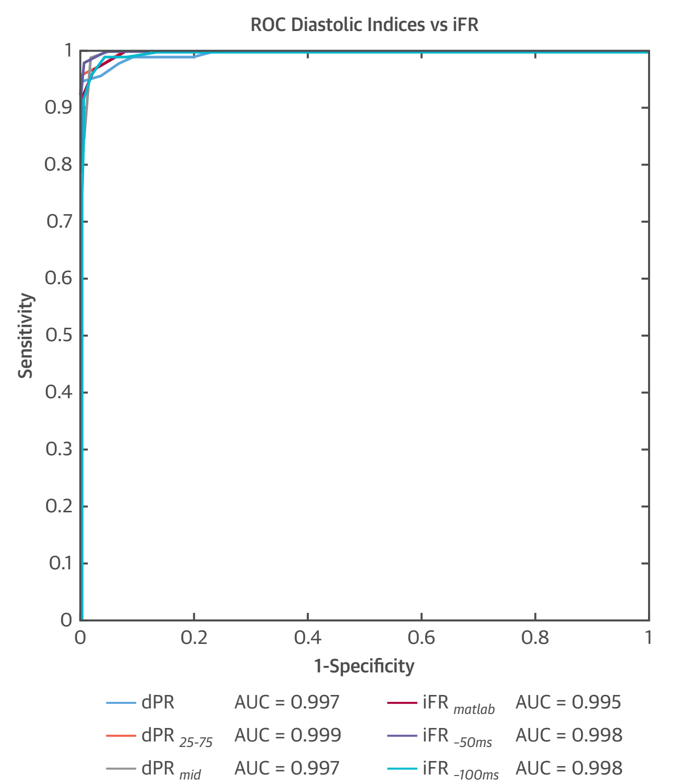
ROC ANALYSES WITH iFR AS THE REFERENCE STANDARD. AUC values from the ROC analyses with iFR as the reference standard for the data at rest

FIGURE 2 Scatterplots of iFR Versus Different Diastolic Indexes



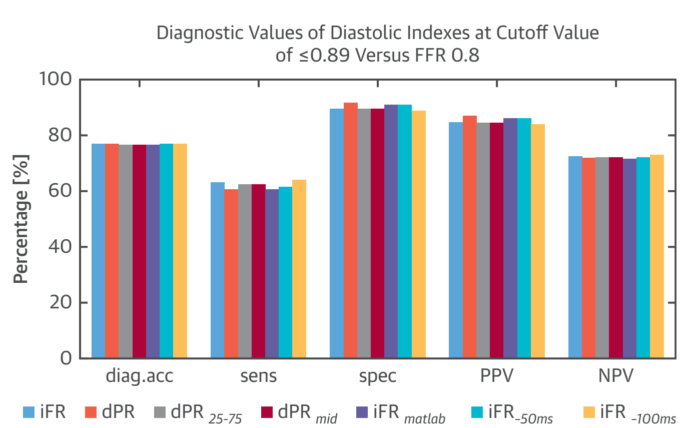
Scatterplots of iFR versus different diastolic indexes. The **dashed lines** indicate the line of identity. Abbreviations as in Figure 1.

FIGURE 3 ROC Curves With iFR as the Reference Standard



ROC curves for all diastolic indexes with corresponding AUC values for all data at rest. AUC = area under the curve; ROC = receiver-operating characteristics curve; other abbreviations as in **Figure 1**.

FIGURE 4 Diagnostic Values of Resting Indexes With Respect to FFR



Diagnostic accuracy (diag.acc), sensitivity (sens), specificity (spec), positive predictive value (PPV), and negative predictive value (NPV) of all diastolic indexes at a cutoff value of ≤0.89 with respect to a fractional flow reserve (FFR) cutoff value of 0.80. Abbreviations as in **Figure 1**.

are >0.99 (**Table 1**) for all of the indexes, indicating near-exact matches (**Figure 3**). The AUC value from the ROC analysis of the second Volcano iFR measurement with the first Volcano iFR measurement as the reference standard was found to be 0.995, corroborating the former statement.

DIAGNOSTIC VALUE OF ALL DIASTOLIC RESTING INDEXES WITH FFR AS THE REFERENCE STANDARD. The diagnostic accuracy to predict an FFR value with a binary cutoff value of 0.80 was 77% for iFR, which is equal to all other indexes (76% to 77%), all with the same cutoff value of 0.89. Negligibly small differences were observed for sensitivity, specificity, and negative and positive predictive values (**Figure 4**).

CORRELATION BETWEEN THE DIFFERENT DIASTOLIC PRESSURE RATIOS IN THE HYPEREMIC CURVES. As displayed in Online Figure 1 (and in Online Table 1), under hyperemic conditions, the Pd/Pa ratios corresponding with the time intervals of the investigated indexes showed the same correlation with identical numerical values compared with iFR, showing that the equality of all indexes is not dependent only on resting conditions.

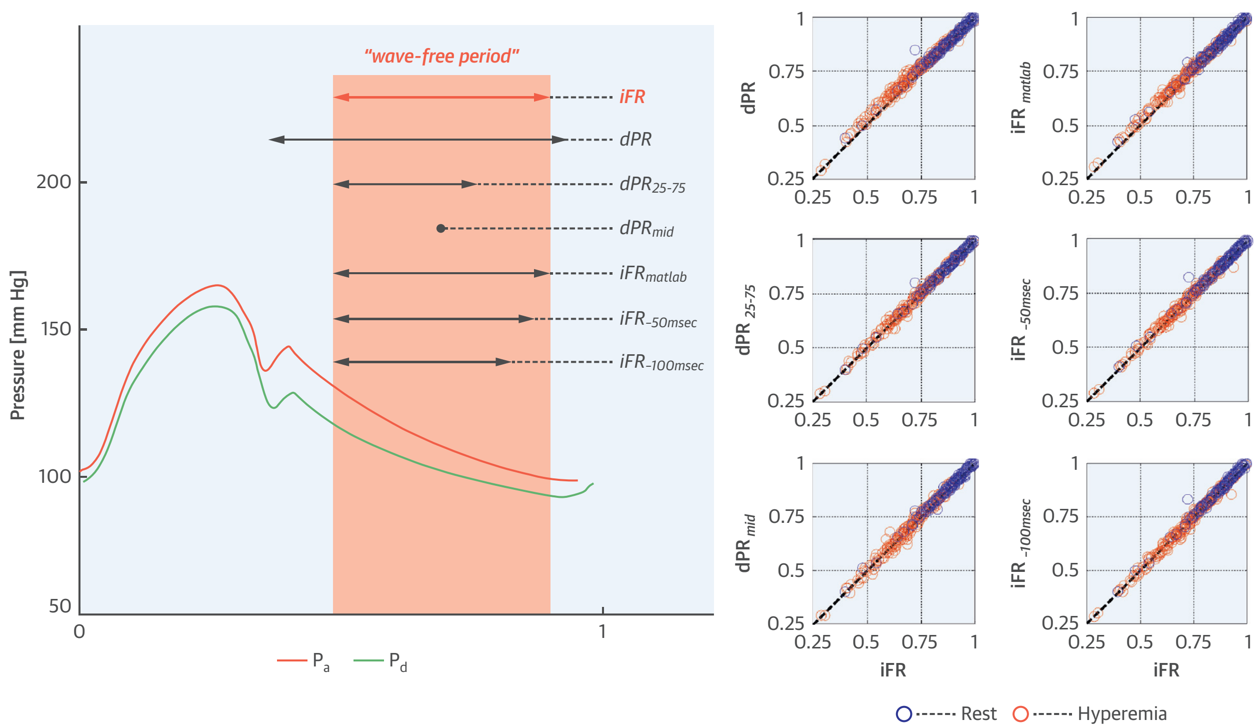
NONDIASTOLIC RESTING INDEXES. Comparison of nondiastolic resting indexes with iFR showed an equally similar linear correlation for Pd/Pa at rest during the whole heart cycle and for Pd/Pa_{min}, but with slightly different numerical values (Online Table 2). ROC curves with iFR as the reference standard are shown in Online Figure 2.

DIAGNOSTIC VALUE OF ALL DIASTOLIC INDEXES WITH IFR AS THE REFERENCE STANDARD. The diagnostic accuracy of all indexes with iFR as the reference standard was equal to the diagnostic accuracy of the second iFR measurement compared to the first iFR measurement as measured by the Volcano console (Online Figure 3).

DISCUSSION

The present analysis shows that all diastolic indexes are essentially identical to iFR both numerically and in terms of diagnostic performance. In addition, all indexes had the same agreement with FFR as the reference standard with a diagnostic accuracy of 76% to 77%. This implies that all of these resting indexes can be used interchangeably, and all cutoff values, clinical recommendations, and guidelines used for iFR are directly applicable to the diastolic indexes investigated in this study (**Central Illustration**). Our results simplify the clinical translation of coronary physiology measurements in the catheterization

CENTRAL ILLUSTRATION Correlations and AUC Values >0.99 for All Resting Pd/Pa Ratios Over Different Periods in Diastole Compared With iFR as the Reference Standard



van't Veer, M. et al. J Am Coll Cardiol. 2017;70(25):3088-96.

Different periods are defined in diastole and compared with the "wave-free period." Scatterplots of the Pd/Pa ratios versus iFR for the defined diastolic periods at rest **(blue)** and during hyperemia **(orange)**. All correlations between the diastolic indexes investigated and iFR were >0.99 and were not different during rest or hyperemia. AUC values from ROC analyses with iFR as a reference standard were >0.99 for all indexes, indicating essentially identical values. AUC = area under the curve; dPR = diastolic pressure ratio (average Pd/Pa over the entire diastole); dPR_{25-75} = average Pd/Pa from 25% to 75% into diastole; dPR_{mid} = Pd/Pa at the single point in time at mid-diastole; iFR = instantaneous wave-free ratio; iFR_{-50ms} = average Pd/Pa from 25% into diastole until 50 ms before end of diastole; iFR_{-100ms} = average Pd/Pa from 25% into diastole until 100 ms before end of diastole; iFR_{matlab} = average Pd/Pa from 25% into diastole until 5 ms before end of diastole; Pa = aortic pressure; Pd = distal coronary pressure; ROC = receiver-operating characteristics curve.

laboratory and should facilitate adoption of functional testing.

The negligible differences between iFR and the diastolic indexes presented in this study (Table 1) indicate that measurements during a specific period of diastole and the exact definition of the end of diastole are not essential for the clinical utility of diastolic resting indexes of stenosis severity. These differences are within the test-retest limits of each parameter. The AUC values of >0.99 for every diastolic index from ROC curve analyses when using iFR as the reference standard, questions the proposed uniqueness of the iFR algorithm. Shortening the definition of the WFP by 50 or 100 ms (or extended to earlier diastole), does not influence the calculated values. Resting Pd/Pa from the whole heart cycle and Pd/Pa_{min} can be used, but with a slightly different cutoff value. This was shown in a recent study by Kobayashi et al. (17), which demonstrated an AUC value of 0.98 when the resting whole cycle Pd/Pa was compared to iFR, which is similar to values from this study (Online Appendix). An iFR value can be predicted from whole cycle resting Pd/Pa by a simple linear transformation (18). Moreover, both of these indexes are independent of a specific period in diastole, but need to be further investigated in further studies.

The fact that the equivalence between investigated indexes and iFR was maintained when also making the calculations from the hyperemic curves indicates that there is no specific physiological basis for preferring one index over another. In other words, the dependency of all of these indexes on hyperemia is identical, consistent with the findings from the

VERIFY study (11). Finally, repeatability of all indexes was equally good.

So far, research with iFR has been restricted to users of Volcano/Philips equipment. The results from the current study indicate that any diastolic resting index can be used with the same advantages and disadvantages inherent to iFR. VERIFY2 is the only comparatively large, publicly available database that includes iFR measured with proprietary software and rest Pd/Pa. This resource becomes all the more relevant given the lack of published data supporting rest Pd/Pa.

MERITS OF iFR. The merit of iFR, and the subsequent discussions and studies investigating whether hyperemia is mandatory for clinical decision making for ischemia and necessity of revascularization, is that use of adenosine can be omitted in some of the patients undergoing invasive functional testing of stenosis severity. Using a hybrid approach, hyperemia can be avoided in about 50% of the population without seriously affecting diagnostic accuracy. These results represent a worthwhile advance, provided safety is not compromised (19). The longer-term follow-up results from DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation) (15) and SWEDE-HEART (Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome) (16) and application of resting indexes in higher-risk patients will be important in this regard.

SHORTCOMINGS OF iFR. iFR has been described as a very specific index based upon particular pathophysiological phenomena present during a select part of diastole. Experimental studies supporting the hypothesis are lacking. The existence of the WFP, upon which iFR is based, has been questioned (9), and our data indicate, in fact, that a particular WFP does not exist.

iFR has been shown to be strongly influenced by hyperemia, with resistance during the WFP falling between 150% and 200% after administration of adenosine. The numerical correspondence of iFR to FFR was described in the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study (8) but was later discarded, and the best cutoff value for indicating ischemia increased from 0.83 to the range of 0.89 to 0.91. The reasons for the comparatively low iFR values in the ADVISE study and the shift to a higher cutoff value are not completely understood, but were attributed to patient selection (20).

The present analyses show that any resting index, taken from different parts of diastole, yields factually identical diagnostic results, both numerically and in relation to FFR. Our results also show that microvascular resistance in rest is minimized not only during the WFP but also in other periods of diastole, supporting the critique of Westerhof et al. (9).

CAVEATS OF RESTING INDEXES IN GENERAL. Although the present study shows that iFR and all other diastolic indexes are "clinically equal" and that concordance is present between all resting indexes and FFR in 76% to 77% of cases, some caveats exist when using resting indexes only.

First, independent superiority studies to show improved outcome with iFR have never been performed. Resting indexes including iFR have only been compared with FFR. Second, outcome studies in comparison to FFR have only been performed in low-risk populations (15,16). Especially in proximal stenoses in large coronary arteries (left main, proximal left anterior descending, proximal right coronary artery), false-negative iFR is present in up to 30% of patients (21). Also, in large perfusion territories, short tight lesions, young patients with good microvascular function, and dominant right coronary arteries, minimal resting gradients can be associated with significant coronary artery disease, as reflected by FFR. Third, hyperemic gradients in a coronary artery are usually 2 to 3× larger than resting gradients. Therefore, avoiding adenosine decreases the signal-to-noise ratio of the pressure pull-back recording and the sensitivity to unmask the significance of diffuse disease and cross-talk between different lesions in 1 coronary artery. Fourth, the decreased signal-to-noise ratio at rest also enhances confounding by drift, which is a troublesome phenomenon associated with most pressure wires. As drift is an absolute phenomenon (mm Hg/unit of time), its influence is larger when using resting indexes. Fifth, post-PCI assessment by physiology—an increasingly important issue (22)—is not possible by resting indexes because a variable state of submaximal hyperemia often exists for a prolonged time after a complex PCI. Finally, resting indexes do not allow quantification of the rate of improvement by stenting. So, when using hyperemia and FFR, an increase of FFR from 0.60 to 0.90 indicates an improvement of 50% of maximum myocardial perfusion by PCI. Such useful information is lost when only using resting indexes.

STUDY LIMITATIONS. First, this study was not a prespecified post hoc analysis. However, the results indisputably show that selecting the exact WFP is not essential for calculating iFR. Second, one could argue about the definition of the end of diastole.

Physiologically, the start of the consecutive left ventricular contraction precedes the upstroke of the aortic pressure by about 30 to 50 ms, the isovolumetric contraction period. Therefore, the end of diastole was chosen 50 ms before the upstroke of the next heartbeat.

Initially, electrocardiogram signals were used as a marker for determination of the end of diastole in the iFR algorithm. Later, some authors have described that left ventricular contraction observed in the distal coronary signal may be sufficient, making the electrocardiogram superfluous (23). The results presented in this study, based on the aortic signal alone, show that a simple time difference of 50 or even 100 ms before the Pa upstroke yields exactly the same results.

Third, the choice for the different diastolic periods investigated was arbitrary but intuitive. Investigating the complete diastole instead of part of it is straightforward, but many other (diastolic) resting indexes perform equally well. Calculating Pd/Pa during other parts of diastole makes little difference.

Finally, the number of investigated curves to conclude that iFR and other diastolic indexes are similar is arbitrary. But, we believe that the similarity in this dataset of 250 $\times$ 2 curves will not change when extending this comparison to thousands of curves (24).

CONCLUSIONS

Many diastolic resting indexes are identical to iFR, both numerically and with respect to agreement with FFR. Consequently, all cutoff values, guidelines, and clinical recommendations for iFR can be extended 1:1 to any of these other diastolic resting indexes.

ADDRESS FOR CORRESPONDENCE: Dr. Marcel van't Veer, Department of Cardiology, Catharina Hospital Eindhoven, Michelangelolaan 2, 5623 EJ Eindhoven, the Netherlands. E-mail: marcel.vh.veer@catharinaziekenhuis.nl.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The nonhyperemic iFR can be used for physiological assessment of coronary artery stenosis severity at rest. The iFR can also be calculated from the ratio of mean Pd/Pa during specific periods in diastole other than the WFP.

TRANSLATIONAL OUTLOOK: Further studies of functional tests are needed to expand the utility of physiological measurements in the catheterization laboratory.

REFERENCES

1. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2014;35:2541–619.

2. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease. J Am Coll Cardiol 2014;64:1929–49.

3. Pijls NHJ, de Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N Engl J Med 1996;334:1703–8.

4. Tonino PAL, De Bruyne B, Pijls NHJ, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213–24.

5. De Bruyne B, Pijls NHJ, Kalesan B, et al. Fractional flow reserve–guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;367:991–1001.

6. De Bruyne B, Pijls NHJ, Barbato E, et al. Intracoronary and intravenous adenosine 5′-triphosphate, adenosine, papaverine, and contrast medium to assess fractional flow reserve in humans. Circulation 2003;107:1877–83.

7. van Nunen LX, Lenders GD, Schampaert S, et al. Single bolus intravenous regadenoson injection versus central venous infusion of adenosine for maximum coronary hyperaemia in fractional flow reserve measurement. EuroIntervention 2015;11:905–13.

8. Sen S, Escaned J, Malik IS, et al. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. J Am Coll Cardiol 2012;59:1392–402.

9. Westerhof N, Segers P, Westerhof BE. Wave separation, wave intensity, the reservoir-wave concept, and the instantaneous wave-free ratio: novelty and significance. Hypertension 2015;66:93–8.

10. Hennigan B, Oldroyd KG, Berry C, et al. Discordance between resting and hyperemic indices of coronary stenosis severity: the VERIFY 2 study (A Comparative Study of Resting Coronary Pressure Gradient, Instantaneous Wave-Free Ratio and Fractional Flow Reserve in an Unselected Population Referred for Invasive Angiography). Circ Cardiovasc Interv 2016;9:e004016.

11. Berry C, van 't Veer M, Witt N, et al. VERIFY (VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice). J Am Coll Cardiol 2013;61:1421–7.

12. Johnson NP, Kirkeeide RL, Asrress KN, et al. Does the instantaneous wave-free ratio approximate the fractional flow reserve? J Am Coll Cardiol 2013;61:1428–35.

13. Nijjer SS, de Waard GA, Sen S, et al. Coronary pressure and flow relationships in humans: phasic analysis of normal and pathological vessels and the implications for stenosis assessment: a report from the Iberian-Dutch-English (IDEAL) collaborators. Eur Heart J 2016;37:2069–80.

14. Jeremias A, Maehara A, Généreux P, et al. Multicenter core laboratory comparison of the instantaneous wave-free ratio and resting Pd/Pa with fractional flow reserve. J Am Coll Cardiol 2014;63:1253–61.

15. Götberg M, Christiansen EH, Gudmundsdottir IJ, et al. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. N Engl J Med 2017;376:1813–23.

16. Davies JE, Sen S, Dehbi H-M, et al. Use of the instantaneous wave-free ratio or fractional flow reserve in PCI. N Engl J Med 2017;376:1824–34.

17. Kobayashi Y, Johnson NP, Zimmermann FM, et al. Agreement of the resting distal to aortic coronary pressure with the instantaneous wave-free ratio. J Am Coll Cardiol 2017;70:2105–13.

18. Kern MJ, Seto AH. Agreement and differences among resting coronary physiological indices. J Am Coll Cardiol 2017;70:2124–7.

19. Berry C, McClure JD, Oldroyd KG. Meta-analysis of death and myocardial infarction in the DEFINE-FLAIR and iFR-SWEDEHEART Trials. Circulation 2017 Sep 28 [E-pub ahead of print].

20. Petraco R, Escaned J, Davies J. Validation of iFR: clinical registries. In: Physiological Assessment of Coronary Stenoses and the Microcirculation. London: Springer London, 2017:225–31.

21. Kobayashi Y, Johnson NP, Berry C, et al. The influence of lesion location on the diagnostic accuracy of adenosine-free coronary pressure wire measurements. J Am Coll Cardiol Intv 2016;9:2390–9.

22. Piroth Z, Toth GG, Tonino PAL, et al. Prognostic value of fractional flow reserve measured immediately after drug-eluting stent implantation. Circ Cardiovasc Interv 2017;10:e005233.

23. Petraco R, Sen S, Nijjer S, et al. ECG-independent calculation of instantaneous wave-free ratio. J Am Coll Cardiol Intv 2015;8:2043–6.

24. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307–10.

KEY WORDS coronary physiology, coronary pressure measurements, FFR, iFR, resting indexes, wave-free period

APPENDIX For an expanded Methods section, as well as supplemental tables and figures, please see the online version of this article.