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CLINICAL RESEARCH

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Repeatability of Fractional Flow Reserve Despite Variations in Systemic and Coronary Hemodynamics

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ABSTRACT

OBJECTIVES This study classified and quantified the variation in fractional flow reserve (FFR) due to fluctuations in systemic and coronary hemodynamics during intravenous adenosine infusion.

BACKGROUND Although FFR has become a key invasive tool to guide treatment, questions remain regarding its repeatability and stability during intravenous adenosine infusion because of systemic effects that can alter driving pressure and heart rate.

METHODS We reanalyzed data from the VERIFY (VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice) study, which enrolled consecutive patients who were infused with intravenous adenosine at 140 μg/kg/min and measured FFR twice. Raw phasic pressure tracings from the aorta (Pa) and distal coronary artery (Pd) were transformed into moving averages of Pd/Pa. Visual analysis grouped Pd/Pa curves into patterns of similar response. Quantitative analysis of the Pd/Pa curves identified the "smart minimum" FFR using a novel algorithm, which was compared with human core laboratory analysis.

RESULTS A total of 190 complete pairs came from 206 patients after exclusions. Visual analysis revealed 3 Pd/Pa patterns: "classic" (sigmoid) in 57%, "humped" (sigmoid with superimposed bumps of varying height) in 39%, and "unusual" (no pattern) in 4%. The Pd/Pa pattern repeated itself in 67% of patient pairs. Despite variability of Pd/Pa during the hyperemic period, the "smart minimum" FFR demonstrated excellent repeatability (bias −0.001, SD 0.018, paired $p = 0.93$, $r^2 = 98.2\%$, coefficient of variation = 2.5%). Our algorithm produced FFR values not significantly different from human core laboratory analysis (paired $p = 0.43$ vs. VERIFY; $p = 0.34$ vs. RESOLVE).

CONCLUSIONS Intravenous adenosine produced 3 general patterns of Pd/Pa response, with associated variability in aortic and coronary pressure and heart rate during the hyperemic period. Nevertheless, FFR – when chosen appropriately – proved to be a highly reproducible value. Therefore, operators can confidently select the "smart minimum" FFR for patient care. Our results suggest that this selection process can be automated, yet comparable to human core laboratory analysis. (J Am Coll Cardiol Intv 2015;8:1018–27) © 2015 by the American College of Cardiology Foundation.

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During the past 20 years, fractional flow reserve (FFR) has evolved from its first animal model and theoretical introduction (1) to an everyday clinical tool to guide coronary revascularization. As a result of 3 major randomized controlled trials (2–4) and a host of observational studies (5), both European (6) and American (7) guidelines recommend FFR when making treatment decisions for intermediate coronary lesions that lack definitive proof of ischemia, although the key randomized trials utilized FFR in lesions of at least 50% diameter stenosis, both intermediate and severe.

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A cornerstone of FFR since its inception has been the use of hyperemia. Because of autoregulation (8), only during hyperemia does a pressure ratio indicate the relative reduction in peak myocardial flow caused by a stenosis. Although the first FFR paper (1) used papaverine, the introduction of intravenous (IV) adenosine (9) allowed for sustained hyperemia with a superior safety profile, given the shorter duration and small risk of torsade de pointes with papaverine. The FAME trial used only IV adenosine (3) due to its reliability and ease of use. An opinion document on FFR for clinical trials specifically recommended IV adenosine over alternative agents such as intracoronary adenosine, papaverine, and nitroprusside (10).

However, some investigators have recently questioned the validity of FFR measurements made during IV adenosine infusion (11,12). Specifically, some investigators proposed that only the FFR measured during "stable hyperemia" should be used to guide treatment, even if lower values had been observed (11). Other investigators noted common FFR instability during IV adenosine infusion, but still recommended always using the lowest observed value (12). Given this controversy, we reanalyzed the tracings from the VERIFY (VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice) study (13) to answer 4 specific questions. First, what patterns of response occur during IV adenosine infusion? Second, how stable are aortic pressure (Pa), distal coronary pressure (Pd), heart rate, and FFR during the hyperemic period? Third, given these patterns of response and variable stability, can operators make repeatable FFR measurements? Fourth, can FFR selection be automated with comparable agreement to human choices from a physiology core laboratory?

ABBREVIATIONS AND ACRONYMS

FFR = fractional flow reserve
IV = intravenous
Pa = aortic pressure
PCI = percutaneous coronary intervention
Pd = distal coronary pressure

METHODS

The VERIFY study has already been published (13). We sought no further ethics board review for the current analysis, because each patient provided written informed consent for VERIFY, and the pressure tracings and clinical variables contained no confidential identifiers.

DATA COLLECTION. In brief, the VERIFY study enrolled consecutive patients referred to 5 international centers for FFR-guided angiography or percutaneous coronary intervention (PCI). After its identification by the operator as a potential PCI target, 1 lesion/patient underwent standard FFR measurement using IV adenosine infusion at a dose of 140 μg/kg/min via a central or large antecubital vein, starting approximately 10 cardiac cycles into the recording. Pressure recordings started 2 min after the last contrast injection and continued for 2 min unless the patient did not tolerate the infusion. FFR measurement was then repeated after a 2-min rest period.

from St. Jude Medical (for NCT02184117) and Volcano Corporation (for NCT02328820), makers of intracoronary pressure and flow sensors. Dr. Kirkeeide has received internal funding from the Weatherhead PET Center for Preventing and Reversing Atherosclerosis; and has signed nonfinancial, nondisclosure agreements with St. Jude Medical and Volcano Corporation to discuss coronary physiology projects. Dr. Berry has received institutional research grant support and consultancy agreements from St. Jude Medical. Dr. De Bruyne has received institutional consultancy fees and research support from St. Jude Medical. Dr. Fearon has received institutional research support from St. Jude Medical; and has served as an advisor to HeartFlow Inc. Dr. Oldroyd has received speaker fees from St. Jude Medical, AstraZeneca, and Volcano Corporation. Dr. Pijls has received institutional grant support from St. Jude Medical; serves as a consultant for St. Jude Medical, HeartFlow Inc., and Boston Scientific; and possesses equity in Philips, ASML, and Heartflow. Dr. Gould has received internal funding from the Weatherhead PET Center for Preventing and Reversing Atherosclerosis; and he is the 510(k) applicant for cfrQuant, a software package for quantifying absolute flow using cardiac positron emission tomography. All royalties will go to a University of Texas scholarship fund. The University of Texas has a commercial, nonexclusive agreement with Positron Corporation to distribute and market cfrQuant in exchange for royalties. However, Dr. Gould retains the ability to distribute cost-free versions to selected collaborators for research. Dr. Daniel T. Johnson has reported that he has no relationships relevant to the contents of this paper to disclose.

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A handful of subjects had only 1 successful recording saved, and a few tracings were excluded due to loss of the Pd or Pa signal during the recording. We included only subjects with 2 valid, paired tracings to allow for repeatability analysis and comparison.

Operators used a coronary pressure wire and recording system (Certus and RadiAnalyzer Xpress, St. Jude Medical, St. Paul, Minnesota), storing anonymous tracings centrally for study analysis. Every 10 ms the recording system sampled aortic and coronary pressure to 0.1 mm Hg. Additionally, it provided a moving average for the pressure ratio of Pd/Pa at each sample point, computed as a retrospective average of uniform weight, of varying length depending on the heart rate, and without any error checking of the underlying pressure data (J. Svanerud, St. Jude Medical, personal communication, July 2014). This moving average served as an automated FFR selection to be confirmed or adjusted by the human operator.

"SMART MINIMUM" FFR ALGORITHM. Our algorithm first identified anacrotic limbs in the aortic pressure tracing to define the bounds of each cardiac cycle. The identification used high- and low-frequency filtering and a second derivative to select local minima followed by sharp upswings. To avoid well-known, high-frequency edge effects from a sharp, step-function average ("boxcar"), we instead used a Gaussian-weighted average of 1 s width. To align the phase of the weighted average with the underlying data, we centered a complete Gaussian at each sample point instead of using a retrospective average, which would lag the instantaneous change.

Each cardiac cycle then underwent quality control checks for both Pa and Pd to ensure physiologically plausible values for systolic and diastolic pressures, pulse pressure, and beat duration (see Online Appendix for further details). For those cardiac cycles of sufficient quality, the Gaussian-weighted average at midbeat summarized the Pa, Pd, and Pd/Pa, whereas the overall duration defined the heart rate.

The "smart minimum" FFR was selected as the lowest average of 5 consecutive cardiac cycles of sufficient quality within a run of 9 consecutive quality beats. The term "smart minimum" distinguishes its selection from a "simple minimum" that does not impose quality checks on the underlying pressure data. Automatic selection of rest Pd/Pa chose the highest average of 5 consecutive cardiac cycles of sufficient quality that occurred before the smart minimum FFR.

To compare our algorithm against other plausible FFR selections, we recorded the simple minimum FFR as the lowest average Pd/Pa value provided by the pressure recording system. We recorded the Pd/Pa value 1 and 2 min after the start of the tracing to mimic recommendations to wait a fixed period of time before measuring FFR. We also tried excluding 15 s after the transition to and start of hyperemia to investigate recommendations to avoid FFR measurements during adenosine onset. Finally, to study the sensitivity of our algorithm to the width of the Gaussian-weighted average, number of consecutive beats for selection, and type of moving average (Gaussian or boxcar), we varied these parameters.

MANUAL PARSING AND CLASSIFICATION OF Pd/Pa TRACINGS. After applying the "smart minimum" algorithm, we manually parsed each tracing into sequential components: rest period, transition to hyperemia, hyperemic period, and pullback during hyperemia or a final transition back to rest. Not all periods were present in every tracing. We excluded periods of the tracing with invalid data due to loss of Pa and/or Pd of sufficient quality. Note that the "smart minimum" algorithm did not use the manual parsing, which was only used for subsequent display and analysis.

On the basis of these components, we computed the percentage of the hyperemic period above 0.02 of the smart minimum FFR, because 0.02 represents approximately 1 SD of the difference between repeated measurements (13). We also computed the 25th, 50th (median), and 75th percentiles of Pa, Pd, Pd/Pa, and heart rate during the hyperemic period to quantify variability. We recorded the mean Pd/Pa during the entire hyperemic period.

Three authors (N.P.J., R.L.K., and K.L.G.) independently grouped the Pd/Pa responses into patterns, blinded to the enrolling center and paired tracing for each subject. Disagreements were resolved by consensus discussion. To facilitate visual analysis and comparison of Pd/Pa responses, we used sparklines: "data-intense, design-simple, word-sized graphics" (14).

HUMAN CORE LABORATORY ANALYSIS. As part of previous and separate publications, each tracing had already been analyzed centrally and independently at 2 different core laboratories as detailed in the Online Appendix. Each human analysis provided Pd/Pa and FFR values for accepted tracings, serving as reference standards for the "smart minimum" algorithm described in the previous text.

STATISTICAL METHODS. Statistical analyses were performed in R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria). Applicable tests were 2-tailed, and $p < 0.05$ was considered statistically significant. We used standard summary

statistical tests as detailed in the Online Appendix. All physiological data in this paper comes from our "smart minimum" algorithm except for a few human core laboratory and pressure recording system results that we explicitly identify as such in the text and in **Table 1**.

RESULTS

The VERIFY study enrolled 206 patients (13). Already 8 patients had only 1 tracing, and we excluded another 8 patients because of insufficient data in at least 1 tracing, leaving 190 patients with complete pairs. **Figure 1** depicts a sample tracing and its analysis, showing raw phasic pressure data, beat summaries, and the selected "smart minimum" FFR value with its associated pressures and heart rate during the hyperemic period. Online Figure F1 displays all Pd/Pa tracings (including excluded tracings), marking both the smart minimum FFR and rest Pd/Pa visually. Further results can be found in the Online Appendix.

PATTERNS OF PD/PA RESPONSE. Visual analysis of the Pd/Pa tracings revealed 3 major patterns of response as summarized in **Figure 2**: "classic" (sigmoid) in 215 of 380 (57%), "humped" (sigmoid with superimposed bumps of varying height) in 151 (40%), and "unusual" (no pattern) in 14 (4%). Online Figures F2 ("classic"), F3 ("humped"), and F4 ("unusual") all display Pd/Pa tracings as categorized into these 3 groups.

The pattern of Pd/Pa response remained unchanged in the majority of pairs, as summarized in **Figure 3**. Specifically, in 77 pairs (41% of 190) both responses were classic, in 46 pairs (24%) both responses were humped, and in 5 pairs (3%) both responses were unusual. Only in 33% of pairs did the response pattern differ: 37 pairs (20%) were first humped then classic, 21 pairs (11%) were first classic then humped, and 4 pairs (2%) were unusual once.

Online Table T1 summarizes the clinical characteristics for all pairs, as well as each response pattern. With the exception of the coronary vessel, no clinical or physiological characteristic differed significantly among the response patterns. Online Figures F5 to F10 and Table T2 detail the lack of repeatable hemodynamic responses to IV adenosine.

REPEATABILITY OF FFR DESPITE FLUCTUATING HEMODYNAMICS. **Figures 4 and 5** demonstrate that paired measurements of FFR remain highly repeatable, with an extremely linear relationship (r^2 = 98.2%, implying that the baseline FFR measurement explains over 98% of the population variation in the repeated FFR measurement), insignificant bias (Δ = −0.001, paired p = 0.93), and a small SD (0.018) especially compared with the mean (coefficient of variation 2.5%). By contrast, aortic pressure, distal coronary pressure, and heart rate at the time of FFR fluctuated greatly between paired measurements, with smaller correlation coefficients and larger SD compared with the mean, as detailed further in the Online Appendix.

Among Pd/Pa patterns, Bland-Altman analysis of paired FFR measurements revealed similar findings to the whole group but worse for the small minority with unusual responses: bias 0.001 and SD 0.017 when both were classic, bias −0.005 and SD 0.017 when both were humped, bias −0.002 and SD 0.019 when one was classic and the other was humped, and bias 0.001 and SD 0.024 when 1 or both were unusual.

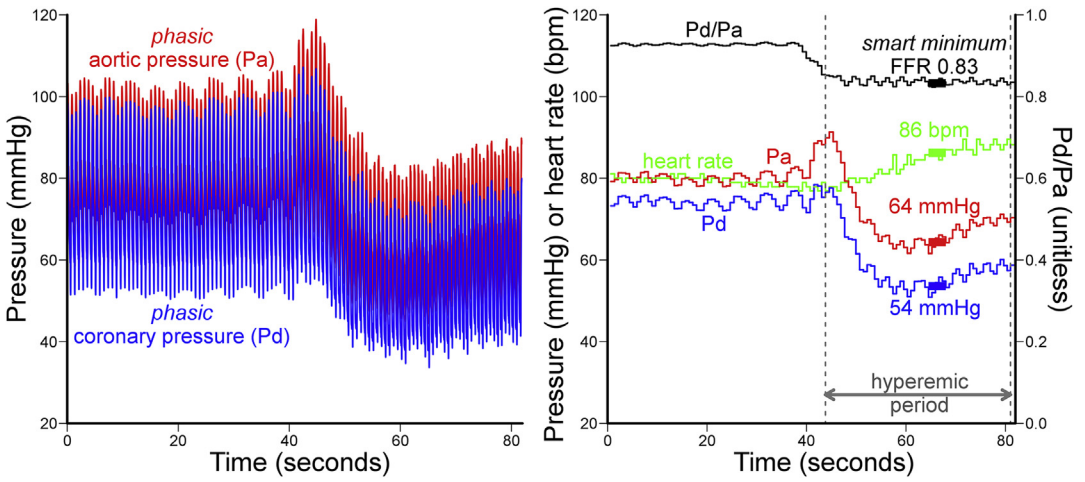
TABLE 1 Summary of FFR Algorithm Comparisons and Test/Retest Repeatability

Comparison	FFR Bias	FFR SD	FFR p Value*	Comments
FFR Algorithms Proposed by Others Compared With Smart Minimum Algorithm				
vs. simple minimum†	−0.046	0.128	<0.001	Simple minimum *overestimates* severity
vs. hyperemic mean	0.022	0.020	0.008	Mean *underestimates* severity
vs. 1-min wait	−0.065	0.077	<0.001	1-min wait *overestimates* severity
vs. 2-min wait	−0.061	0.077	<0.001	2-min wait *overestimates* severity
vs. exclude 15 s after transition to hyperemia	−0.002	0.008	0.88	No improvement from waiting after onset of hyperemia
vs. exclude 15 s after start of hyperemia	−0.010	0.031	0.30	
Human Core Laboratory Comparisons With Smart Minimum Algorithm				
VERIFY vs. RESOLVE	0.019	0.013	0.13	No significant difference among smart minimum algorithm and human core laboratory selections
Smart minimum vs. RESOLVE	0.012	0.010	0.34	
Smart minimum vs. VERIFY	−0.006	0.007	0.43	
Test/Retest Repeatability				
VERIFY human core laboratory	<0.001	0.019	0.98	"Smart minimum" algorithm performs as well as human core laboratory
"Smart minimum" algorithm	−0.001	0.018	0.93	
Technical Components of Smart Minimum Algorithm				
vs. 1 beat	−0.003	0.008	0.74	No significant difference among various technical components in smart minimum algorithm
vs. 3 beats	−0.001	0.003	0.88	
vs. 7 beats	−0.001	0.002	0.88	
vs. 9 beats	−0.002	0.003	0.77	
vs. Gaussian 0.5-s width	<0.001	0.001	0.95	
vs. Gaussian 2-s width	−0.001	0.002	0.93	
vs. 5-beat boxcar	−0.002	0.018	0.90	

*p value from paired test. †Minimal Pd/Pa for entire tracing without error checking provided by the pressure recording system software (see Methods section).

FFR = fractional flow reserve; Pa = aortic pressure; Pd = distal coronary pressure; VERIFY = VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice.

FIGURE 1 Example Raw Tracing With Analysis



(Left) Phasic aortic pressure (Pa) **(red)** and distal coronary pressure (Pd) **(blue)** tracings. An intravenous infusion of adenosine at 140 μg/kg/min began after approximately 10 cardiac cycles and continued for the duration of the recording. **(Right)** Analysis of the phasic data shows the average Pa **(red)** and Pd **(blue)** pressures for each cardiac cycle, as well as derived heart rate **(green)** and Pd/Pa **(black)**. **Vertical dashed gray lines** denote the hyperemic period. **Horizontal bars** mark the smart minimum fractional flow reserve (FFR) and its associated pressures and heart rate. Note the stability of Pd/Pa during the hyperemic period (coefficient of dispersion [COD] 1.5%) compared with the much wider variations in aortic pressure (COD 7.6%), coronary pressure (COD 7.5%), and heart rate (COD 7.2%). Also, fine oscillations in the pressure tracings arise from the interplay of several peripheral and coronary control mechanisms as studied in animal models and addressed in the Online Appendix. bpm = beats/min.

NECESSARY DURATION OF IV ADENOSINE INFUSION. Figure 6 displays the cumulative distribution of the observed times from starting the baseline recording until reaching the smart minimum FFR. The population response to IV adenosine infusion displayed a sigmoid shape, with a sharp rise between about 50 and 100 s, indicating that 75% of patients achieved a minimum FFR value before or during this window.

ALGORITHM COMPARISONS. Table 1 summarizes the performance of the "smart minimum" FFR algorithm, with further details in Online Table T3. Its first section explored other potential algorithms for selecting FFR. Choosing the simple minimum without error checking or waiting 1 or 2 min overestimated lesion severity. Taking the mean FFR during the entire hyperemic period underestimated lesion severity. Excluding 15 s after the onset of hyperemia did not alter the results.

In the second section of Table 1, no significant difference existed when comparing our algorithm to existing results from previous publications by the VERIFY (13) and RESOLVE (15) core laboratories, especially considering the variation between the 2 core laboratories. In its third section, Table 1 quantifies the observation that our algorithm performed as well as the VERIFY core laboratory in terms of bias and SD during repeat measurements. The final section evaluated various technical components of the "smart minimum" algorithm. No significant differences were found for number of selected beats, Gaussian width, or a boxcar average.

DISCUSSION

Our reanalysis of the VERIFY tracings answered 4 important questions regarding the use of IV adenosine to measure FFR. First, 3 general patterns of Pd/Pa response were seen during IV adenosine infusion, as summarized in Figures 2 and 3, with numerous specific examples detailed in Online Figures F1 to F4. Although an approximate 60% majority of tracings displayed a "classic" (sigmoid) response with a stable shelf, a substantial 40% minority did not. Therefore, operators must be prepared to observe fluctuations in Pd/Pa that never settle into a flat response despite a constant infusion of IV adenosine.

Second, during the hyperemic period, substantial changes occurred in the absolute aortic and coronary pressures and heart rate, with much smaller changes in the Pd/Pa ratio. Nevertheless, to answer the

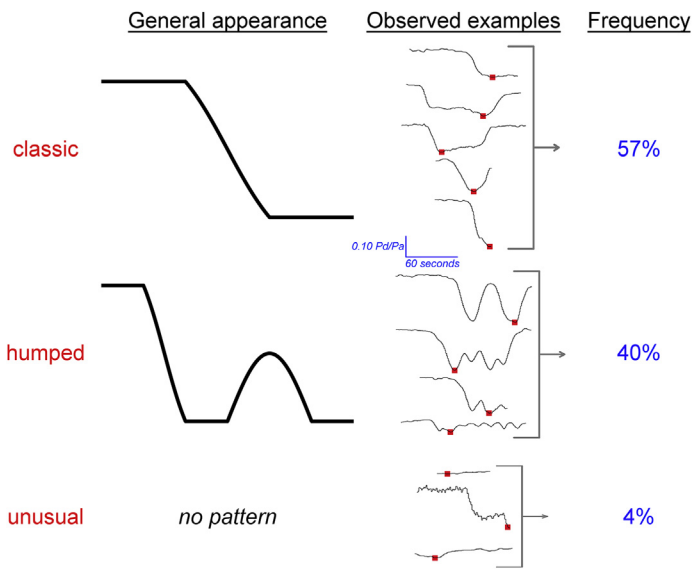
third question, the minimum FFR remains a highly repeatable measurement. Indeed, our **Figure 4** can be seen as the "natural history" version of previous work that specifically manipulated systemic pressure, heart rate, and contractility yet demonstrated that FFR remained insensitive to these parameters (16). Therefore, these findings together suggest that the primary focus during FFR measurement should remain on Pd/Pa, not its specific components or the associated heart rate. Although profound systemic hypotension during vasodilation can drop absolute coronary flow, thereby reducing the pressure loss and increasing the Pd/Pa value, such extremes occur infrequently and, in our experience, respond to a fluid challenge. As we have summarized previously (17), FFR stands apart among commonly used diagnostic tests in cardiology for being highly repeatable.

Fourth, our "smart minimum" algorithm demonstrated no significant differences from human choices made in a physiology core laboratory. As with every diagnostic test, the physician must understand its physiologic importance, measurement details including pitfalls, and clinical interpretation. However, many if not all tests benefit from automation, standardization, and transparency. If the FFR recording equipment could reliably and quickly select the correct FFR value in a vast majority of cases, then this improvement could facilitate and optimize decision making in clinical practice. Furthermore, a common, transparent algorithm among manufacturers of FFR recording devices would facilitate portability and comparability.

How can pressure wire recording systems help the operator separate the collection of massive elements of data (during which the operator must focus on avoiding pitfalls such as damping, whip, and signal loss) from their visualization and interpretation (during which the operator must focus on global pattern recognition and FFR selection)? Our work suggests that sparklines of Pd/Pa, as in our figures (14), could offer a superior method for visualizing intracoronary pressure measurements in the catheterization laboratory, medical record, and published scientific data. For example, the second tracing in **Figure 2** summarizes 14,285 data points collected over a 2.4-min period, but uses a visual area only 3 cm wide and 1 cm high although clearly marking the FFR value and revealing a classic (sigmoid) response pattern.

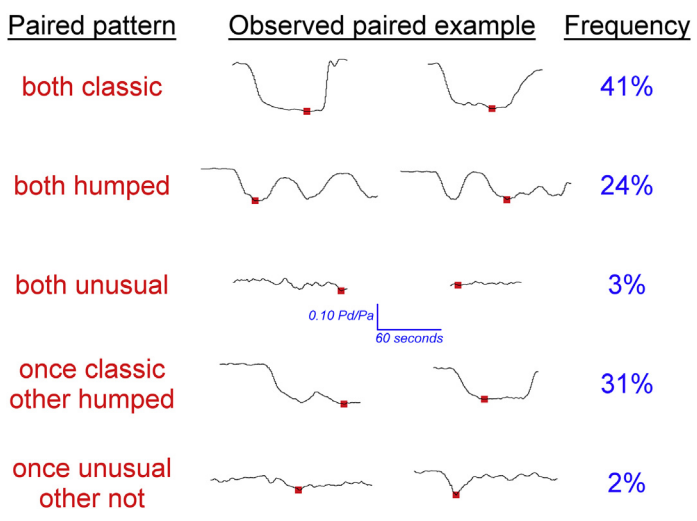
Our findings should not be misinterpreted as a radical change in how FFR should be analyzed. Rather, the "smart minimum" algorithm codifies the clinical practice of expert users, as exemplified by the lack of difference between its performance and human physiology core laboratories. The foundational trials

FIGURE 2 Patterns of Pd/Pa During Hyperemia



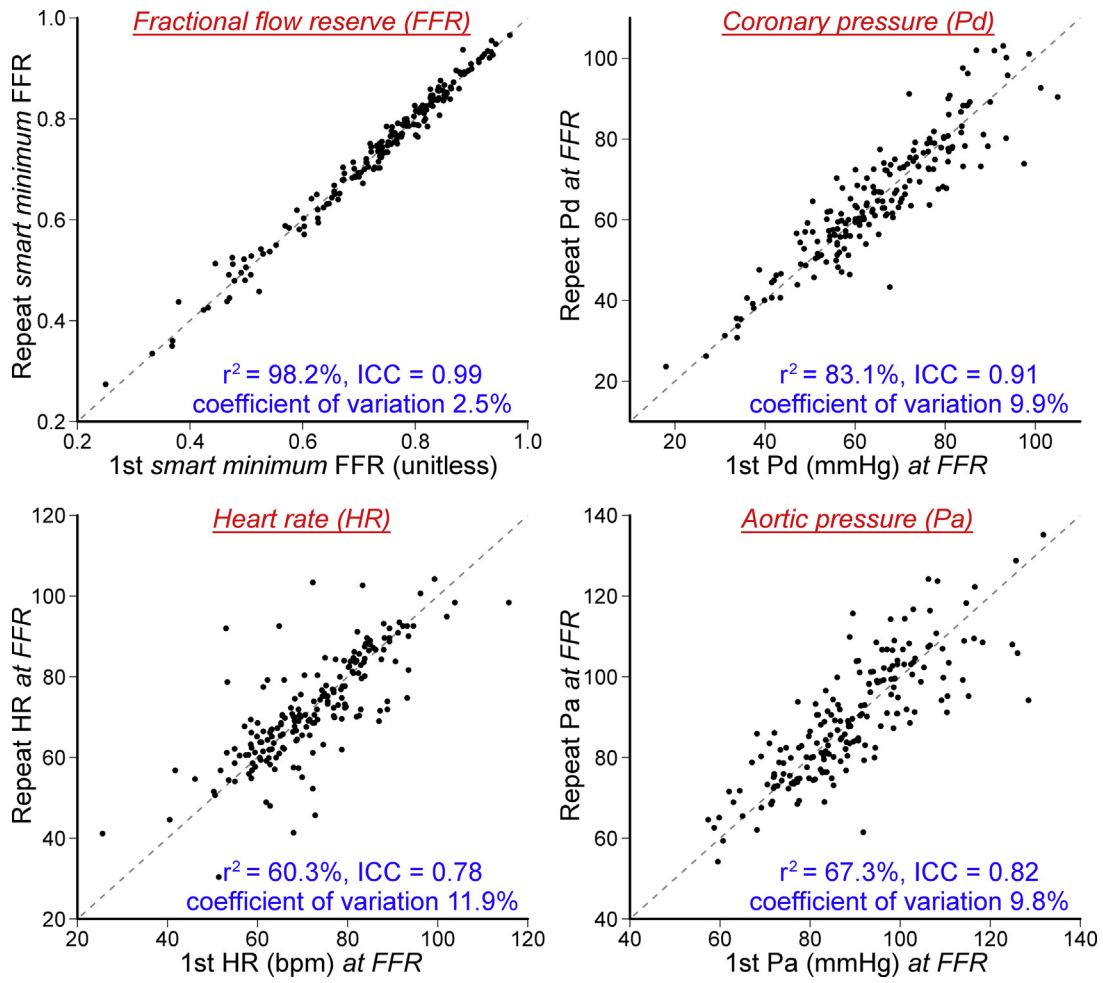
Three major Pd/Pa response patterns of varying frequency occurred during steady intravenous adenosine infusion: "classic" (sigmoid), "humped" (sigmoid with superimposed bumps of varying height), and "unusual" (no pattern). For each observed example, the **red dot** marks the smart minimum FFR. The **blue scale** for Pd/Pa and time applies to the example tracings. Abbreviations as in **Figure 1**.

FIGURE 3 Paired Patterns of Pd/Pa During Hyperemia



Each lesion underwent repeat study separated by 2 min of rest, producing 5 observed paired patterns of varying frequency. For each observed example, the **red dot** marks the smart minimum FFR. The **blue scale** for Pd/Pa and time applies to the example tracings. Abbreviations as in **Figure 1**.

FIGURE 4 Repeatability Between Pairs



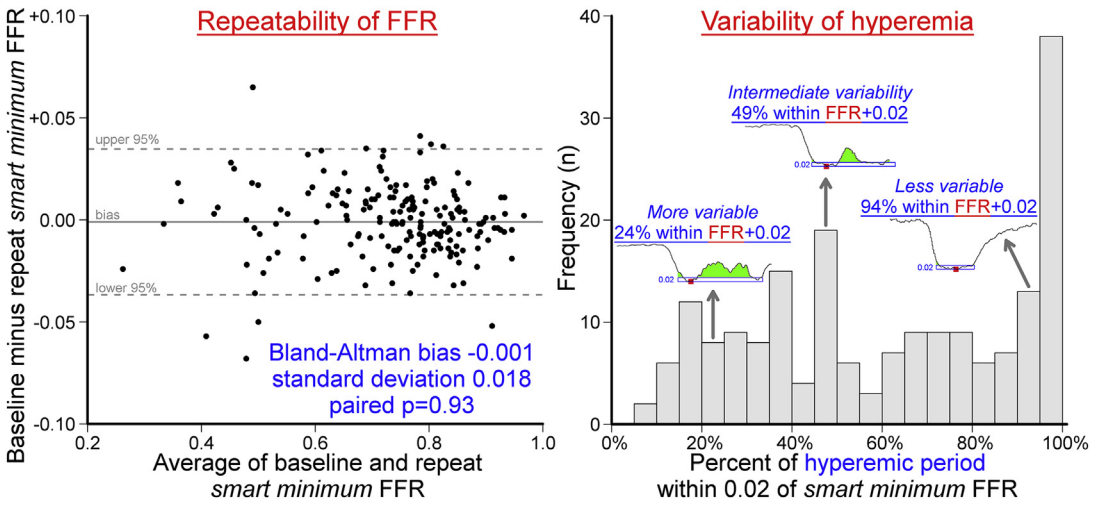
Each panel displays paired measurements at the smart minimum FFR as depicted in the right panel of Figure 1: FFR **(upper left),** Pd **(upper right),** Pa **(lower right)**, and heart rate (HR) **(lower left panel)**. As quantified by various statistical measures (Pearson [r] and intraclass correlation coefficient [ICC]), FFR demonstrates the highest repeatability. Abbreviations as in Figure 1.

supporting FFR (2–4) did not use centralized physiology core laboratories, meaning their results generalize to cardiologists in daily practice. Instead, this algorithm has the potential to improve the quality of FFR information, thereby reducing unwanted variability and uncertainty in clinical decision making.

Because FFR has become a standard measure of physiological stenosis severity, understanding the mechanisms behind our observations carries clinical and physiological relevance. The VERIFY study was not designed to address this separate question. Subsequent studies could measure pressure and flow together, titrate the adenosine infusion dose, compare patterns of response among various hyperemic drugs, measure serum caffeine levels, and add alpha- and beta-receptor modulators (agonists and antagonists) to distinguish among potential mechanisms. Although we await these future mechanistic insights, our present results have demonstrated that the minimum FFR value remains robustly repeatable for clinical application.

COMPARISON TO EXISTING PUBLISHED DATA. Almost 25 years ago, IV adenosine infusion for hyperemia was introduced by comparison to papaverine and was evaluated using an intracoronary 3-F Doppler catheter (9). Those authors also observed flow variations consistent with the "humped" response in our Figure 2: "At the lower infusion rates…coronary blood flow velocity often rose and fell in a cyclic pattern

FIGURE 5 Repeatability of FFR Despite Variability of Hyperemia

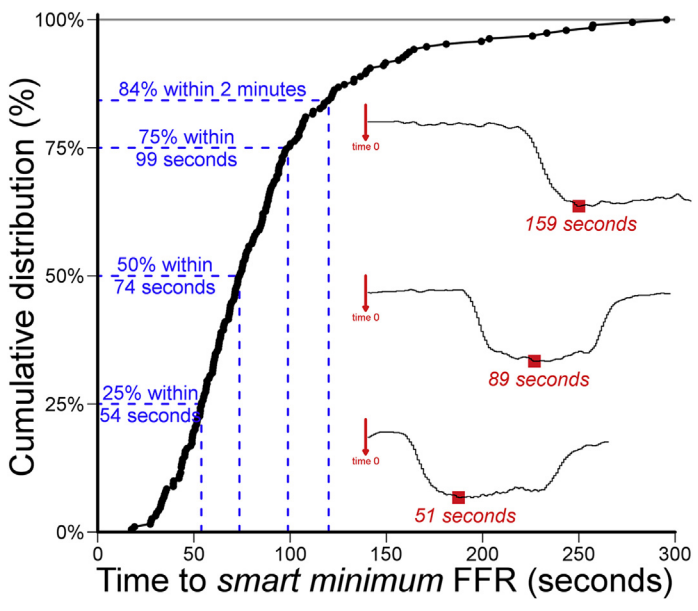


(Left) Bland-Altman analysis of repeated smart FFR measurements demonstrates no significant bias ($\Delta = -0.001$, paired $p = 0.93$) with an SD of approximately ±0.02. However, the variability of Pd/Pa during the hyperemic period **(right)** reveals a wide range. Three example tracings depict progressive differences in the stability of Pd/Pa during the hyperemic period, marked in each tracing as a **blue box** with height 0.02 (roughly the SD for repeated FFR measurements). For each example, the **red dot** locates the smart minimum FFR and the **colored green area** denotes the portion of the hyperemic period outside of the stable **blue box**. Abbreviations as in Figure 1.

with a cycle length of about 30 seconds…when the coronary infusion rate was increased, hyperemia became sustained at the maximal level." Indeed, the case shown in their Figure 5 displays a "humped" response in flow levels, albeit at lower IV infusion rates than in our VERIFY reanalysis, but with similar periodicity. Their Table 4 describes "cyclic variation" in 3 of 30 arteries (10%) even at a rate of 140 μg/kg/min, compared to 39% in our Figure 2.

Because they focused on flow changes and FFR had not yet been introduced, their data only indirectly supports a common mechanism between their Doppler flow velocity cycles and the humps in our Pd/Pa tracings. However, their finding that these cycles diminished at higher rates of IV adenosine infusion suggests that future work could determine whether the incidence of Pd/Pa "humps" falls at rates of 180 or 210 μg/kg/min or with direct right atrial or intracoronary infusion. We found significant variation in Pd/Pa patterns among coronary vessels. Although the adenosine dose is weight-adjusted for the entire subject, it might be necessary to adjust the dose for the unmeasurable distal myocardial mass to achieve stable receptor saturation. The shorter duration until the transition to hyperemia observed during the repeat measurement (43 s vs. 35 s), and the larger conversion from humped then classic compared to classic then humped (37 pairs vs. 21 pairs, respectively) both

FIGURE 6 Distribution of Times to FFR



A cumulative distribution of times from the start of the first recording until the smart minimum FFR demonstrates that 50% of cases occur within 74 s, whereas only 16% occur after 2 min. Intravenous adenosine at 140 μg/kg/min began approximately 10 cardiac cycles into the recording. Three example Pd/Pa tracings depict progressive differences in the waiting period for FFR during a steady intravenous adenosine infusion. Abbreviations as in Figure 1.

suggest residual effects or a "priming" from IV adenosine even after a 2-min rest period.

Recent work proposed 7 patterns of response to IV adenosine infusion, but with an emphasis on Pa and Pd separately and without repeated, paired tracings for the same lesion (11). However, as clarified in our **Figure 4**, Pa and Pd responses vary markedly even for the same patient when repeating an FFR measurement. Rather, only the Pd/Pa ratio displays a highly repeatable response. Furthermore, as summarized in our **Figure 2**, approximately 40% of tracings do not reach a stable state, thereby invalidating their proposed 3 classification stages of "base," "peak," and "stable." In contradistinction to their recommendation that "ideally, measurements should only be made when stable hyperemia is achieved after ≥60 s of stable intravenous adenosine infusion" (11), our **Table 1** demonstrates that waiting 1 or even 2 min in hopes of achieving a "stable" period performs worse than always selecting the "smart minimum" FFR. Indeed, our results in **Figure 6** make it unlikely that any "1 size fits all" solution exists for timing.

Other recent work proposed 3 patterns of response to IV adenosine infusion, but again with an emphasis on Pa and Pd separately and without repeated, paired tracings for the same lesion (12). Although noting similar remarks as we previously mentioned regarding paired measurements and highly repeatable "smart minimum" FFR values, we do agree with these authors that FFR pullback curves could be affected by the "humped" response pattern that occurs in roughly 40% of cases. We suggest 3 solutions: rapid pullback during the nadir phase, increased IV adenosine rate that might convert to a "classic" pattern, or serial stationary measurements along the artery of sufficient duration to obtain a "smart minimum" FFR.

STUDY LIMITATIONS. The VERIFY study only recorded intracoronary pressure. Measuring pressure and flow simultaneously might allow distinction between mechanisms responsible for the observed "humps" in Pd/Pa tracings. Geometric changes in stenosis geometry due to flow-mediated vasodilation should change the pressure loss versus flow relationship, whereas oscillations in microvascular resistance due to incomplete adenosine saturation should follow the same quadratic curve. Future work could repeat the VERIFY design but measure both pressure and flow.

Our study used test/retest repeatability and agreement with human physiology core laboratories as its benchmarks. We, therefore, cannot comment on its effect on clinical events, although repeatability is generally considered an advantage in patient management guided by threshold criteria.

CONCLUSIONS

Our results can be summarized simply for clinical application: within reason, always take the minimum FFR value. Although the Pd/Pa curve will not always reach a stable shelf, and various patterns of response exist to IV adenosine infusion, the minimum FFR value remains a highly repeatable measurement. In the future, automatic software will likely be able to select the correct FFR value with similar performance to a human physiology core laboratory. Sparkline displays of Pd/Pa provide a concise visualization of intracoronary pressure data.

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PERSPECTIVES

WHAT IS KNOWN? FFR improves clinical outcomes and requires hyperemia, often achieved with an IV adenosine infusion. However, uncertainly exists regarding FFR repeatability and stability during IV adenosine infusion because of systemic effects that can alter driving pressure and heart rate.

WHAT IS NEW? Although various patterns of coronary pressure and systemic hemodynamic response exist during IV adenosine infusion, the minimum FFR value remains highly repeatable and its selection can be successfully automated.

WHAT IS NEXT? Future studies could explore the mechanisms behind response patterns during IV adenosine infusion and determine if similar effects exist with other systemic vasodilators like regadenoson.

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KEY WORDS adenosine, algorithm, fractional flow reserve, repeatability

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