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# Continuum of Vasodilator Stress From Rest to Contrast Medium to Adenosine Hyperemia for Fractional Flow Reserve Assessment

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## ABSTRACT

**OBJECTIVES** This study compared the diagnostic performance with adenosine-derived fractional flow reserve (FFR) ≤0.8 of contrast-based FFR (cFFR), resting distal pressure (Pd)/aortic pressure (Pa), and the instantaneous wave-free ratio (iFR).

**BACKGROUND** FFR objectively identifies lesions that benefit from medical therapy versus revascularization. However, FFR requires maximal vasodilation, usually achieved with adenosine. Radiographic contrast injection causes submaximal coronary hyperemia. Therefore, intracoronary contrast could provide an easy and inexpensive tool for predicting FFR.

**METHODS** We recruited patients undergoing routine FFR assessment and made paired, repeated measurements of all physiology metrics (Pd/Pa, iFR, cFFR, and FFR). Contrast medium and dose were per local practice, as was the dose of intracoronary adenosine. Operators were encouraged to perform both intracoronary and intravenous adenosine assessments and a final drift check to assess wire calibration. A central core lab analyzed blinded pressure tracings in a standardized fashion.

**RESULTS** A total of 763 subjects were enrolled from 12 international centers. Contrast volume was 8 ± 2 ml per measurement, and 8 different contrast media were used. Repeated measurements of each metric showed a bias <0.005, but a lower SD (less variability) for cFFR than resting indexes. Although Pd/Pa and iFR demonstrated equivalent performance against FFR ≤0.8 (78.5% vs. 79.9% accuracy; $p = 0.78$; area under the receiver-operating characteristic curve: 0.875 vs. 0.881; $p = 0.35$), cFFR improved both metrics (85.8% accuracy and 0.930 area; $p < 0.001$ for each) with an optimal binary threshold of 0.83. A hybrid decision-making strategy using cFFR required adenosine less often than when based on either Pd/Pa or iFR.

**CONCLUSIONS** cFFR provides diagnostic performance superior to that of Pd/Pa or iFR for predicting FFR. For clinical scenarios or health care systems in which adenosine is contraindicated or prohibitively expensive, cFFR offers a universal technique to simplify invasive coronary physiological assessments. Yet FFR remains the reference standard for diagnostic certainty as even cFFR reached only ~85% agreement. (J Am Coll Cardiol Intv 2016;9:757–67)

**ABBREVIATIONS AND ACRONYMS**

**cFFR** = contrast-based fractional flow reserve

**FFR** = fractional flow reserve

**IC** = intracoronary

**iFR** = instantaneous wave-free ratio

**IQR** = interquartile range

**IV** = intravenous

**Pd/Pa** = resting ratio of distal coronary pressure to aortic pressure

**ROC** = receiver-operating characteristic curve

Diagnostic accuracy can be thought of as a pyramid (**Figure 1**). At the base of the pyramid, useless tests provide an accuracy of 50%, no better than an unbiased coin flip; at the pinnacle, a gold standard reaches 100% accuracy; and in between these extremes, we find the vast majority of our daily tools in medicine. Our general task is to rank-order new and existing tests so that we can make rational choices to reach a diagnosis and thereby improve patient outcomes by altering treatment (1).

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As a specific example, the diagnosis of significant coronary artery disease can pose a clinical challenge, especially in patients with ambiguous symptoms, intermediate or multiple angiographic stenoses, and absent, equivocal, or conflicting noninvasive testing. To assist with these dilemmas, fractional flow reserve (FFR) was uniquely validated 20 years ago against a multitest reference standard (2). However, FFR requires "maximally dilated conditions when all resistances are constant and the derivation of flow reserve from pressure is possible" (3). Inducing hyperemia carries some cost and risk, although the vast majority of effort and cost for any intracoronary (IC) physiology measurement remains fixed (IC nitroglycerin, systemic anticoagulation, pressure wire and its calibration, and instrumentation of the coronary vessel).

Two potential strategies modify this requirement, but with a reduction in diagnostic accuracy. First, resting physiology as used by Andreas Grüntzig et al. (4) in 1979 and revisited recently (5) avoids hyperemia completely. Second, an IC injection of contrast medium not only enables coronary angiography but also induces some degree of hyperemia, an observation dating back to 1959 in animals (6) and first used in 1974 for assessing human physiological stenosis severity (7). Because of its ubiquity in the catheterization laboratory, contrast medium could provide an easy and inexpensive tool for assessing FFR, so-called contrast FFR (cFFR).

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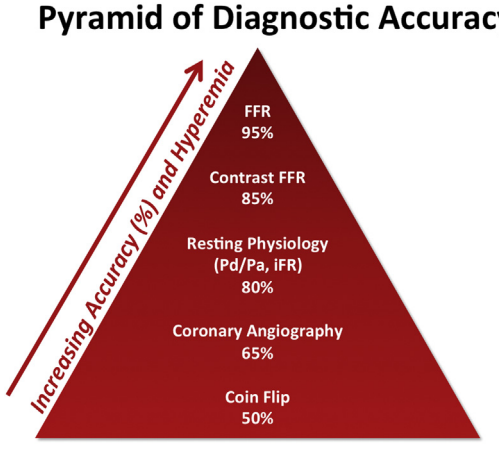
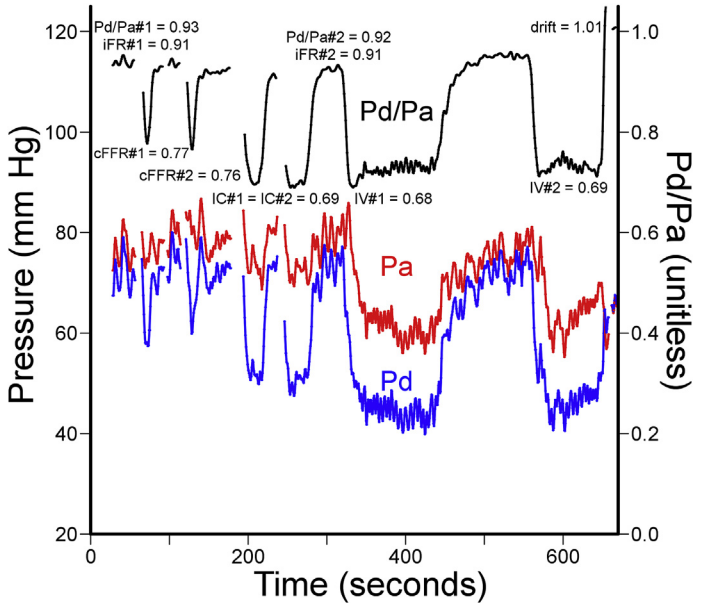
**FIGURE 1 Contrast Hyperemia Within the Pyramid of Diagnostic Accuracy**




Accuracy of any test must exist between 50% (equivalent to a coin flip) and 100% (the gold standard). By itself, the diagnostic angiogram has an accuracy of ~65% (18). Adding resting physiology increases the accuracy to ~80% (5,10). However, hyperemia uniquely increases the accuracy, first to 85% using contrast injection and then to at least 95% using potent vasodilators like adenosine (2).

**FIGURE 2 Example of Protocol**




Complete example from the study that demonstrates essentially no gradient at rest (high Pd/Pa and iFR) with a clearly positive result by cFFR then confirmed by both intracoronary and intravenous adenosine FFR. No significant drift was observed, and each metric was measured twice (#1 and #2). Aortic pressure (Pa) in **red**, distal coronary (Pd) in **blue**, and their ratio Pd/Pa in **black**. cFFR = contrast-based fractional flow reserve; IC = intracoronary; iFFR = instantaneous wave-free ratio; Pd/Pa = resting ratio of distal coronary pressure to aortic pressure.

Therefore, we compared the diagnostic performance and repeatability of cFFR and resting physiology (both resting ratio of distal coronary pressure to aortic pressure [Pd/Pa] and instantaneous wave-free ratio [iFR]) with FFR, ordering all metrics within the pyramid of diagnostic accuracy. Given the continuum between hyperemic physiological severity and clinical outcomes (8), quantifying the parallel continuum of vasodilator stress potency clarifies the trade off when using submaximal hyperemia to guide revascularization.

## METHODS

We performed an investigator-initiated, prospective diagnostic accuracy study that enrolled a multicenter, international cohort of patients undergoing routine FFR assessment for standard indications. Subsequent care proceeded as per routine from the clinical FFR measurement without further study-related follow-up. Each subject gave informed consent as approved by the local institutional review board of that participating center. Recruitment took place between June 2014 and April 2015.

We excluded subjects with previous coronary bypass surgery, known severe cardiomyopathy (left ventricular ejection fraction <30%) or left ventricular hypertrophy (septal wall thickness >13 mm), contraindication to adenosine, or renal insufficiency such that an additional 12 to 20 ml of contrast would, in the opinion of the operator, pose an unwarranted risk. In cases of multivessel disease, only the first lesion studied using FFR was included. Culprit lesions for an acute infarction were excluded, but nonculprit lesions were permitted. Standard demographic, clinical, and catheterization parameters were collected for each subject.

**PHYSIOLOGY PROTOCOL.** Figure 2 provides a graphical example of the complete physiology protocol. An initial period of at least 1 min provided a stable assessment of resting physiology without further contrast injection. Next, either a manual or injector-based IC bolus of contrast medium was given per local practice for diagnostic angiography. To remain pragmatic and reflect real-world conditions, the volume and type of IC contrast medium were not mandated but varied among sites and even among subjects at a single site but with a strong recommendation for 6 to 10 ml. After ~1 min when conditions

had returned to baseline, a second IC bolus of contrast medium was injected using the same technique as for the first injection.

Next, after the return of baseline conditions, a manual IC bolus of adenosine was administered. Based on local practice and patient features, operators selected the dose of IC adenosine, but with a strong recommendation for 100 to 200 μg, given emerging data regarding its dose/response curve (9). After ~1 min when conditions had returned to baseline, a second, identical bolus of IC adenosine was given.

A subsequent period of at least 1 min provided a second assessment of resting physiology before starting an adenosine infusion at a standard rate of 140 μg/kg/min via either a central or wide-bore peripheral IV line. The duration of the infusion was ~2 min, but could be prolonged or abbreviated as necessary if a steady state had been reached or if the patient did not tolerate it. After stopping IV adenosine and waiting ~2 min for conditions to return to baseline, a second, identical IV adenosine infusion was performed.

At the end of the procedure, an optional but recommended drift check was performed by bringing the pressure sensor back to the guide catheter at the same location as equalization. Operators were encouraged to perform both IC and IV adenosine measurements in duplicate, but all 4 were not mandatory as long as at least one technique was repeated. In cases without IV adenosine, the second assessment of resting physiology occurred between the second IC contrast and first IC adenosine injections.

**CORE LAB ANALYSIS.** All pressure tracings were sent to the Cardiovascular Research Foundation physiology core lab for standardized and centralized review. Operators placed bookmarks denoting each section of the protocol, permitting objective separation of the entire pressure tracing into its anonymous components. Thus, the core lab carried out a post hoc analysis without knowledge of the locally determined Pd/Pa value, IC substance (contrast medium or adenosine), enrolling site, or subject/lesion characteristics. Because each section of the tracing was blinded and uncoupled from the rest, the core lab remained unbiased by knowledge of the other measurements for that subject.

The physiology core lab assessed tracing quality, including inspection for aortic and coronary pressure signal distortion or loss, aortic pressure damping, and limiting arrhythmia. Each submitted component tracing received a binary decision regarding adequate quality for inclusion and an associated Pd/Pa value (corresponding to resting Pd/Pa, cFFR, or FFR depending on the subsection of the overall recording). Additionally, the quality of the electrocardiogram was given a separate but analogous binary assessment. Drift check recordings were rejected if of suboptimal quality or else were given a Pd/Pa value (ideally 1.00 without drift).

Each component tracing apart from drift checks was analyzed separately and in automated fashion by the software package HARVEST version 1.0.0.127 (Volcano Corporation, San Diego, California) for iFR (under rest, contrast, or adenosine conditions). Because HARVEST requires an electrocardiographic signal and applies its own quality criteria to the tracing, some additional recordings were rejected despite being accepted by the core lab itself.

**STATISTICAL METHODS AND ENDPOINTS.** Analyses were performed using R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria). We used standard statistical techniques. Applicable tests were 2 tailed, and $p < 0.05$ was considered statistically significant. Additional details on the statistical analysis can be found in the Online Appendix.

The primary endpoint was accuracy against FFR ≤0.8 and compared using a McNemar test between metrics. Secondary endpoints included the area under the receiver-operating characteristic (ROC) curve (compared using the DeLong method), Bland-Altman analysis, sensitivity, and specificity. Because there could be as many as 4 FFR values for each subject (2 IC and 2 IV), a summary FFR value was computed by the following hierarchy: average of 2 IV values, a single IV value, the average of 2 IC values, or a single IC value. When both test and retest values were present, their average was used. Following previous work (5,10), we also explored a so-called hybrid strategy of selective adenosine administration for intermediate values between 2 thresholds ("gray zone") instead of no adenosine and a single threshold as for a binary strategy. A hybrid strategy can achieve an arbitrary accuracy with a variable proportion of lesions within the intermediate range, here presented with false positives equal to false negatives.

Existing binary thresholds of Pd/Pa <0.92 and iFR <0.90 (5) were selected. Because no accepted binary threshold existed for cFFR, we chose the value that maximized accuracy but performed a sensitivity analysis around this optimum.

Our sample size of at least 750 subjects was prospectively chosen as follows. Based on simulation work from a previous study (5), if contrast injection provides a conservative 20% of the hyperemia seen with adenosine, then ~300 subjects would be

necessary to detect the difference using a McNemar test. Given the 20% to 25% exclusions seen in recent physiology core labs (5,10), 300/(1 − 0.25) = 400 subjects would be necessary. Thus, we selected at least 750 subjects, assuming that just less than 50% would receive both IC and IV adenosine.

**ROLE OF ACADEMIC AUTHORS AND INDUSTRY.** Our investigator-initiated study was supported financially by St. Jude Medical. Volcano Corporation (subsequently acquired by Royal Philips) agreed to off-line and post hoc analysis for iFR values by the core lab using HARVEST software. The academic authors had full access to the data, carried out data analysis, and wrote the manuscript independent of industry. However, both companies reviewed the manuscript for confidential or proprietary information but requested no changes. The trial was prospectively registered with NCT02184117. Anonymous and unannotated pressure tracings for all subjects have been made publically available (11).

## RESULTS

A total of 763 subjects were enrolled from 12 centers. **Table 1** summarizes the demographic, clinical, and catheterization features, all typical for a cohort undergoing invasive assessment. The average IC contrast volume was 8 ± 2 ml, and 8 different contrast media were used, reflecting our pragmatic and real-world protocol.

The physiology core lab analyzed 4,946 recordings (100%) and accepted 4,453 (90.0%), with exclusions mainly due to damping or distortion of the aortic pressure waveform. A total of 3,802 tracings (76.9%) also had a sufficient electrocardiogram, and HARVEST produced an iFR value for 3,764 (76.1%). Additionally, the core lab analyzed 616 drift checks (80.7% of cohort) and accepted 604 (98.1% of submitted) as technically adequate, irrespective of the amount of drift. Median physiological metrics for the cohort were a Pd/Pa of 0.92 (interquartile range [IQR]: 0.88 to 0.95), an iFR 0.90 (IQR: 0.84 to 0.94), cFFR 0.85 (IQR: 0.79 to 0.91), and FFR 0.81 (IQR: 0.73 to 0.86). Among subjects with all 3 measurements, 9.4% had a Pd/Pa ≤0.8, 28.8% had either a Pd/Pa or cFFR ≤0.8, and 49.2% had FFR ≤0.8.

**TEST/RETEST REPEATABILITY.** **Figure 3** displays the repeatability of physiological indexes, with a visual impression of more scatter for resting physiology than either contrast or adenosine hyperemia. Quantitative analysis supports the visual impression, with the largest SD between repeated measurements for iFR (0.033), intermediate for Pd/Pa (0.023), and

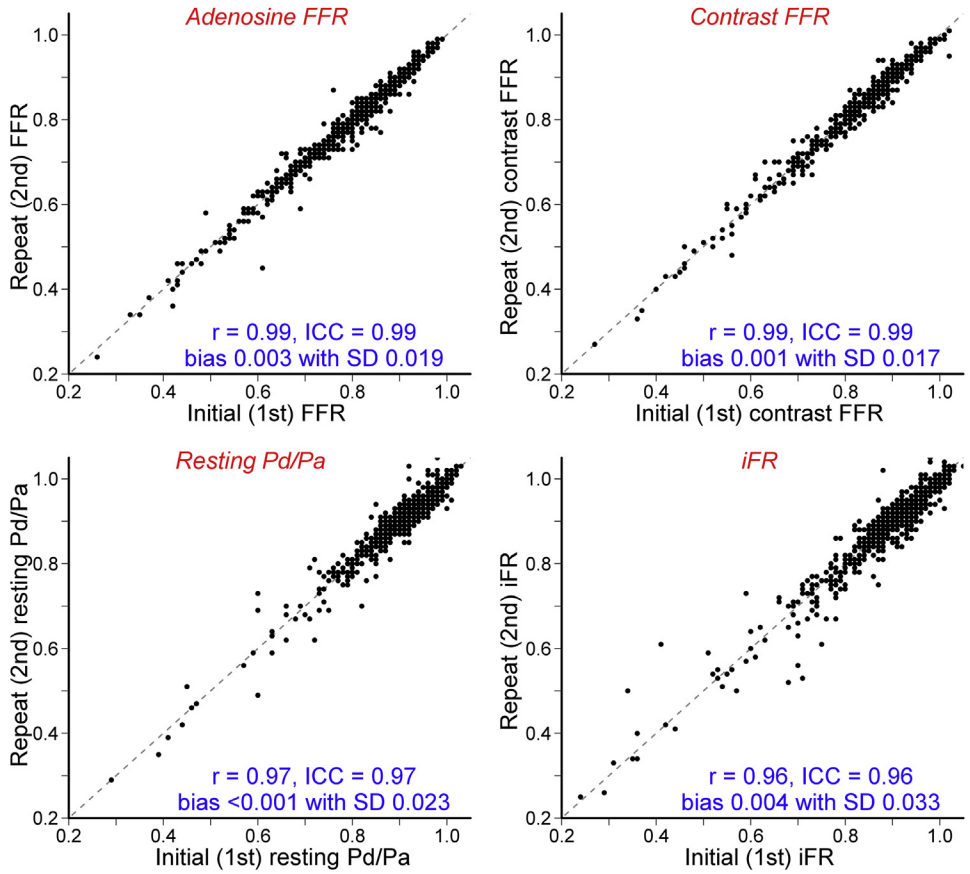
**TABLE 1 Baseline Characteristics (N = 763)**

| | |
|---|---|
| Clinical | |
| Age, yrs | 66 ± 10 |
| Male | 547 (72) |
| Body mass index, kg/m$^2$ | 27.3 ± 4.7 |
| Smoking (current or past) | 363 (48) |
| Hypertension | 545 (71) |
| Dyslipidemia | 508 (67) |
| Diabetes mellitus | 219 (29) |
| Family history of premature CAD | 191 (25) |
| Renal insufficiency (GFR <60) | 74 (10) |
| Previous MI | 198 (26) |
| Previous PCI | 114 (15) |
| Presentation | |
| Stable | 598 (78) |
| Unstable angina | 84 (11) |
| NSTEMI | 73 (10) |
| STEMI | 8 (1) |
| Catheterization | |
| Coronary vessel | |
| Left main | 25 (3) |
| LAD | 460 (60) |
| LCx | 138 (18) |
| RCA | 140 (18) |
| Contrast medium | |
| Iobitridol | 40 (5) |
| Iodixanol | 189 (25) |
| Iohexol | 106 (14) |
| Iomeprol | 227 (30) |
| Iopamidol | 8 (1) |
| Iopromide | 69 (9) |
| Ioversol | 68 (9) |
| Ioxaglate | 56 (7) |
| Volume of IC contrast, ml | 8 ± 2 |
| 5 | 17 (2) |
| 6 or 7 | 324 (42) |
| 8 or 9 | 210 (28) |
| 10 | 211 (28) |
| 12 | 1 (<1) |
| Dose of IC adenosine, μg* | 168 ± 46 |
| <80 | 11 (2) |
| 80 or 90 | 39 (7) |
| 100–150 | 157 (29) |
| 160–200 | 261 (48) |
| >200 | 81 (15) |
| Route of IV adenosine* | |
| Central | 124 (28) |
| Peripheral | 315 (72) |

Values are mean ± SD or n (%). *Only 549 patients received IC adenosine and 439 received IV adenosine, whereas data in all other rows are based on N = 763 total.

CAD = coronary artery disease; GFR = glomerular filtration rate; IC = intracoronary; IV = intravenous; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery; STEMI = ST-segment elevation myocardial infarction.

**FIGURE 3 Repeatability**



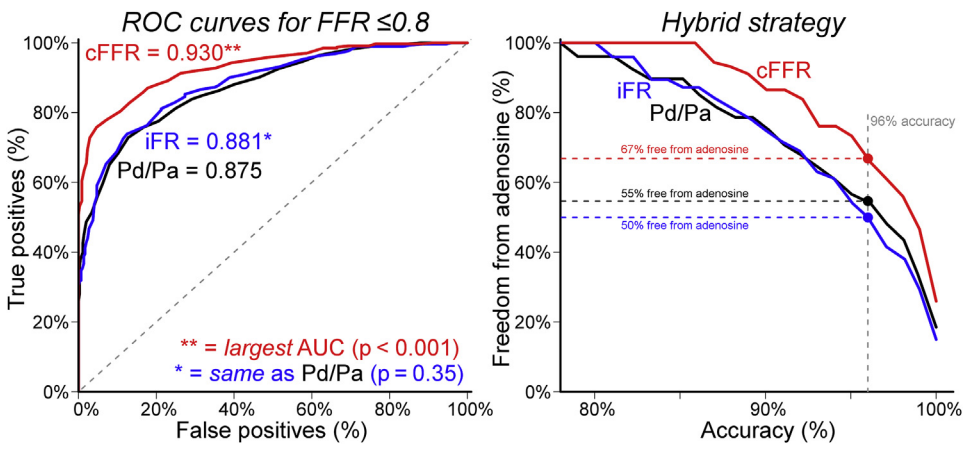

All metrics demonstrate minimal average difference when measured twice, with a bias <0.01 essentially superimposed on the **thin, dashed gray line** of identity. However, hyperemic metrics of contrast FFR and FFR provide superior repeatability compared with resting metrics of Pd/Pa and iFR, as shown visually by the raw data (**black dots**, many of which are superimposed) and quantified by correlation coefficients (r from Pearson, ICC from intraclass correlation) and SD of the difference. ICC = intraclass correlation coefficient; other abbreviations as in Figure 2.

smallest and similar for cFFR and FFR (0.017 and 0.019, respectively). Comparisons of variance confirmed the trend with $p < 0.001$ for all pairs except cFFR and FFR, with $p = 0.51$ demonstrating equivalence. The average difference between repeated measurements was <0.005 for all metrics and thus clinically insignificant.

**DIAGNOSTIC PERFORMANCE.** A binary threshold of cFFR ≤0.83 produced an accuracy of 85.8%, superior to both Pd/Pa (78.5%) and iFR (79.9%) (McNemar $p < 0.001$ vs. both resting metrics), when compared with FFR ≤0.8. The diagnostic accuracy of Pd/Pa and iFR did not differ significantly ($p = 0.78$). Notably cFFR accuracy remained >84% for thresholds 0.83 to 0.85. Sensitivity remained similar among all metrics (75.8% cFFR, 77.9% Pd/Pa, 81.1% iFR), but cFFR improved specificity (95.3% cFFR, 79.0% Pd/Pa, 78.7% iFR). The area under the ROC curve was largest for cFFR at 0.930 (DeLong $p < 0.001$ vs. both resting metrics) and equivalent between Pd/Pa at 0.875 and iFR at 0.881 ($p = 0.35$) as displayed in the left panel of Figure 4.

The right panel of Figure 4 compares hybrid strategies, visually showing the greater freedom from adenosine when using cFFR compared with Pd/Pa and iFR, which were similar. A specific example at 96% accuracy can be seen in Figure 4 with further details in Table 2 for a range of potential accuracies. As a physiological explanation for the superior

**FIGURE 4** Diagnostic Performance




Using a single cutoff as shown by the ROC curves on the **left**, contrast FFR **(red line)** has the largest area under the ROC curve ($p < 0.001$), whereas iFR **(blue line)** and Pd/Pa **(black line)** have equivalent areas ($p = 0.35$). Using a hybrid strategy as shown on the right, contrast FFR avoids adenosine most often for any desired accuracy, whereas no clinical difference exists between iFR and Pd/Pa. For example, although a 96% accuracy can be achieved with all 3 metrics, cFFR avoids adenosine in approximately two-thirds of the population, whereas Pd/Pa and iFR avoid adenosine in only about one-half (see the 96% row in Table 2 for values and gray zone ranges but using 2 decimal places for thresholds). AUC = area under the curve; ROC = receiver-operating characteristic; other abbreviations as in Figures 1 and 2.

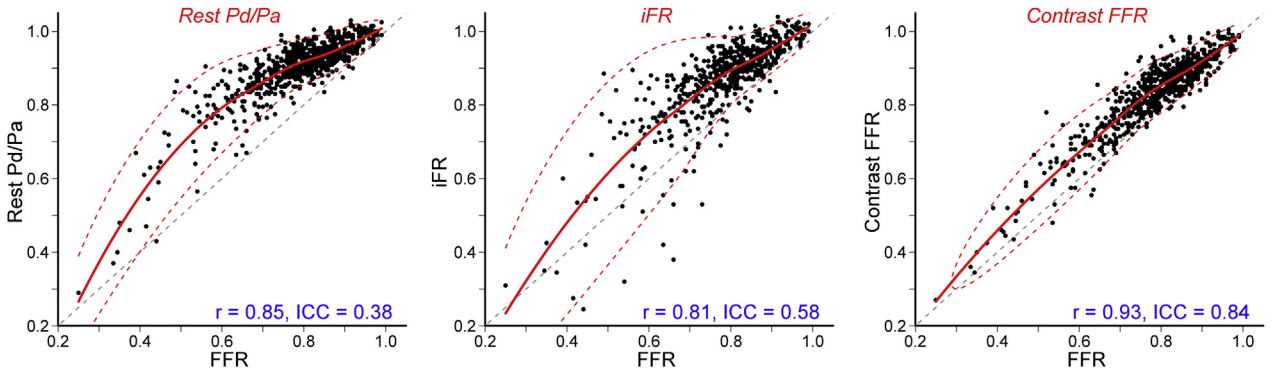
diagnostic performance of cFFR, Figure 5 depicts the increasingly linear relationship with decreasing scatter versus FFR when hyperemia increases with contrast. The equivalent diagnostic performance of Pd/Pa and iFR can be explained through their extremely linear relationship. Correlation between the 2 resting metrics was $r = 0.964$ such that Pd/Pa explained 93% of the iFR variation; best-fit regression of $iFR = 1.314 \times Pd/Pa - 0.313$ had an average difference <0.001 with an SD of 0.031, equivalent to the SD of 0.033 for a repeated iFR measurement itself.

**TABLE 2** Selective Adenosine ("Hybrid") Performance Versus FFR ≤0.8 for Balanced False Positives and Negatives

| | Pd/Pa | | | iFR | | | cFFR | | |
|---|---|---|---|---|---|---|---|---|---|
| Rounded Accuracy, % | Gray Zone | Need Adenosine, % | Accuracy, % | Gray Zone | Need Adenosine, % | Accuracy, % | Gray Zone | Need Adenosine, % | Accuracy, % |
| 100 | 0.83-0.99 | 81.5 | 100 | 0.78-1.01 | 84.0 | 100 | 0.78-0.96 | 74.0 | 100 |
| 99 | 0.86-0.97 | 67.4 | 98.8 | 0.80-0.97 | 71.2 | 99.1 | 0.80-0.92 | 56.7 | 99.1 |
| 98 | 0.87-0.96 | 59.8 | 98.0 | 0.83-0.96 | 63.9 | 98.5 | 0.82-0.91 | 47.2 | 98.1 |
| 97 | 0.88-0.96 | 56.5 | 96.9 | 0.84-0.95 | 58.4 | 97.1 | 0.82-0.90 | 41.2 | 97.0 |
| 96 | 0.88-0.95 | 50.9 | 95.6 | 0.85-0.94 | 49.9 | 95.6 | 0.83-0.90 | 37.2 | 95.8 |
| 95 | | | | 0.86-0.94 | 46.0 | 95.2 | 0.83-0.89 | 32.3 | 95.3 |
| 94 | 0.89-0.95 | 46.0 | 94.2 | 0.87-0.94 | 42.8 | 94.0 | 0.83-0.88 | 26.3 | 94.1 |
| 93 | | | | 0.87-0.93 | 37.0 | 92.7 | 0.83-0.87 | 20.9 | 93.3 |
| 92 | 0.89-0.94 | 38.1 | 92.0 | 0.87-0.92 | 30.8 | 91.5 | | | |
| 90 | 0.90-0.94 | 32.0 | 90.0 | | | | 0.84-0.87 | 16.2 | 90.2 |
| 89 | | | | 0.88-0.92 | 25.2 | 89.3 | 0.84-0.86 | 11.9 | 88.7 |
| 88 | 0.90-0.93 | 24.7 | 88.1 | 0.88-0.91 | 19.8 | 87.6 | 0.84-0.85 | 8.6 | 87.5 |
| 85 | 0.91-0.93 | 18.5 | 84.7 | 0.89-0.91 | 15.8 | 84.5 | | | |
| 83 | | | | 0.89-0.90 | 10.6 | 82.6 | | | |
| 82 | 0.91-0.92 | 10.3 | 82.2 | | | | | | |

cFFR = contrast-based fractional flow reserve; FFR = fractional flow reserve; iFFR = instantaneous wave-free ratio; Pd/Pa = resting ratio of distal coronary pressure to aortic pressure.

**FIGURE 5 Scatterplots of Each Metric With FFR**




Resting physiology (either Pd/Pa or iFR) displays a less linear and more scattered relationship with FFR than does modest hyperemia (contrast FFR), as shown visually by the raw data **(black dots)** and its local regression (**thick red line** with **dashed lines** as 95% confidence intervals) and quantified by correlation coefficients (r from Pearson, ICC from intraclass correlation). The **thin dashed gray line** represents identity. Abbreviations as in Figures 1 through 3.

## DISCUSSION

Our study clarified the continuum of vasodilator stress for IC pressure measurements as a fundamental physiological insight linking the magnitude of hyperemia to diagnostic accuracy (Figure 1). We demonstrated 3 clinically important physiological properties of the hyperemic continuum. First, hyperemia improves repeatability, as shown in Figure 3, such that resting measurements carry lower precision than those made using contrast or adenosine. Second, contrast hyperemia outperforms resting physiology for predicting FFR, as shown in Figure 4 and Table 2. Third, intermediate hyperemia induced by contrast reduces scatter and promotes a more linear relationship with FFR, distinct from the wider scatter and curvilinear relationship provided by resting physiology, as shown in Figure 5.

The pyramid of diagnostic accuracy (Figure 1) places FFR very close to its apex based on several lines of evidence. First, FFR was validated 20 years ago in a clinically relevant population with chest pain of uncertain origin and a moderate stenosis in a major coronary vessel (2). For its composite reference standard, the study used a triad of noninvasive tests covering electrical (bicycle electrocardiogram), perfusion (stress single-photon emission computed tomography), and contractile (dobutamine echocardiography) aspects both before and after revascularization. Notably, "composite information from sequentially performed noninvasive tests has a diagnostic accuracy of almost 100%," and FFR achieved a 93% accuracy using a threshold of 0.75 (2). Second, FFR-guided revascularization improved a variety of outcomes in 3 major randomized outcomes trials (12–14) when added to clinical symptoms, noninvasive testing, and invasive angiography. Third, FFR has been shown to be cost saving versus angiography to guide percutaneous coronary intervention (15) and cost-effective to select PCI instead of medical therapy (16). These aspects of excellent repeatability (17), high diagnostic accuracy, improved patient outcomes in randomized trials, and proven cost-effectiveness together form the key criteria when evaluating any diagnostic test (1), including FFR.

Angiographic evaluation alone achieved an accuracy of 66% compared with FFR in a study of >1,000 lesions analyzed by quantitative coronary angiography (18). Resting physiology without hyperemia achieved an accuracy of ~80% compared with FFR, both retrospectively (80.4% for iFR; 81.5% for Pd/Pa) (5) and prospectively (82.5% for iFR; 83.2% for Pd/Pa) (10) from a total of >2,200 lesions. In the current study, resting physiology similarly achieved an accuracy of ~80% (79.9% for iFR; 78.5% for Pd/Pa), which contrast hyperemia significantly improved to 85.8%.

Thus, a pyramid of diagnostic accuracy arises from thousands of patients in multiple studies: no accuracy (50%), angiography (65%), resting physiology (80%), contrast hyperemia (85%), FFR (95%). Clear improvements in diagnostic performance can be achieved by adding angiography, then physiology, and finally the hyperemic continuum. As a parallel, the numeric value of FFR displays a continuous relationship with clinical outcomes both before and

**TABLE 3 Review of Existing Literature on Contrast FFR**

| Lesions | Country | Reference | Contrast | Dose | Repeatability | Core Lab | iFR | Cutoff | Accuracy, % | AUC |
|---|---|---|---|---|---|---|---|---|---|---|
| 763 | International | This paper | 8 different | Pragmatic | Yes | Yes | Yes | 0.83 | 85.8 | 0.930 |
| 328 | Spain | (19) | NR | 6 ml | No | No | No | 0.90 | NR | 0.92 |
| 108 | France | (20) | Iodinaxol or iomperol | RCA = 6 ml, LCA = 10 ml | No | No | No | 0.85 | 86 | 0.94-0.98 |
| 104 | Italy | (21) | Iomeprol | 6 ml | Yes | No | No | 0.83 | 85 | 0.98 |
| 98 | Portugal | (22) | Iodinaxol or iopromide | 10 ml | 10% subset | No | No | 0.84 | 89.9 | 0.965 |
| 80 | Japan | (23) | Iomeprol | 6 ml | Subset | Yes | No | 0.84 | 87.5 | 0.93 |
| 37 | United States | (24) | Iodixanol | 6 ml | No | No | No | NR | NR | NR |
| 21 | Belgium | (25) | Iohexol | 6 ml | No | No | No | NR | NR | NR |

AUC = area under the receiver-operating characteristic curve; LCA = left coronary artery; NR = not reported; RCA = right coronary artery; other abbreviations as in Table 2.

after revascularization (8). The 2 related continua thereby link the degree of hyperemia with subsequent risk, implying that strong vasodilators yield optimal and personalized selection for revascularization. As such, our study provides a fundamental physiological and mechanistic link between pharmacological stress and patient care.

**COMPARISON WITH EXISTING LITERATURE.** Table 3 compares our results with those of others studies that have looked at cFFR specifically (19-25). Notable features of the current study include its larger sample size, international patient population, pragmatic choice of contrast medium and dose, uniform test/retest repeatability, central and blinded core lab, and iFR measurement. Nevertheless, our cFFR threshold and its diagnostic performance broadly agree with those reported by others.

Several studies have compared resting physiology with FFR, and our results provide an independent validation of these existing findings. Our Pd/Pa accuracy of 78.5% approximates other results (81.5% [5] and 83.2% [10]), as does the 0.875 area under the ROC curve (0.880 [26], 0.82 [5], and 0.90 [10]). Similarly, our iFR accuracy of 79.9% agrees with other results (80.4% (5) and 82.5% [10]) as does the 0.881 area under the ROC curve (0.871 [26], 0.81 [5], and 0.90 [10]). In agreement with our results, all previous work has also found an equivalent accuracy and/or ROC area between Pd/Pa and iFR (5,10,26) due to their highly linear relationship (5). Finally, our results confirm previous reports that the value during the iFR period decreases from rest to hyperemia and that FFR has a superior test/retest repeatability (26).

**STUDY LIMITATIONS.** Contrast medium produces a shorter period of hyperemia than an IC bolus of adenosine, as displayed visually in **Figure 2** and quantified in earlier work (25). Therefore, neither agent can be used to produce a pull-back tracing to distinguish diffuse from focal disease. However, both techniques permit rapid serial measurements along the artery. Alternatively, after observing a low, distal cFFR value, operators could switch to a longer acting drug like IV adenosine or regadenoson for a pullback.

In order to make our results generally applicable, we specifically designed a pragmatic protocol with respect to contrast medium and volume. A post hoc exploration suggested heterogeneity among contrast media, although our protocol was not designed to answer this separate question. Our results did not support a significant effect of contrast volume within the 6 to 10 ml used in almost 98% of cases, but smaller or larger contrast volumes might produce a different degree of hyperemia. A paired study using several contrast media or volumes in random order for the same lesion could be performed. However, typically hospitals choose their contrast medium and operators choose their contrast volume for many reasons distinct from its coronary hyperemic potential. Possibly cFFR measured using a specific contrast medium and volume could reach an accuracy of ~90% compared with adenosine FFR.

We did not collect data on contrast-induced nephropathy. The average IC contrast dose was $8 \pm 2$ ml per measurement, and some operators document wire position using contrast as part of the clinical procedure. A validated risk score for contrast-induced nephropathy assigns 1 point per 100 ml of contrast volume, such that an extra 10 ml would have an odds ratio of ~1.025 (27). Thus, we believe that the impact of this small amount of extra contrast has negligible clinical significance for the vast majority of patients. We did not mandate flushing catheters after an IC injection (contrast or adenosine), potentially producing dampened aortic curves that would have been excluded during core lab review. However, only 10% of tracings were rejected for any reason, implying at most a small effect in the entire cohort.

## CLINICAL RELEVANCE AND CONCLUSIONS

Some operators prefer to avoid adenosine when performing physiological lesion assessment due to rare side effects and minimal but nonzero added time and expense. Additionally, adenosine remains expensive or unavailable in some areas of the world, and occasional patients have contraindications. Our results demonstrate that for these operators, health care systems, and clinical scenarios, cFFR predicts FFR better than Pd/Pa or iFR using either a binary or hybrid approach. Additionally, measuring cFFR is more repeatable and more linear with respect to FFR. Further advantages of cFFR include its universal and immediate availability independent of special software or a valid electrocardiogram tracing, unlike iFR. However, FFR with strong hyperemia like adenosine remains the reference standard in the pyramid of diagnostic accuracy.

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### PERSPECTIVES

**WHAT IS KNOWN?** FFR requires maximal vasodilation, usually achieved with adenosine. Because radiographic contrast injection causes submaximal coronary hyperemia, it could provide an easy and inexpensive tool for predicting FFR.

**WHAT IS NEW?** cFFR achieves an accuracy of ~85% compared with adenosine-based FFR. It offers superior diagnostic performance and repeatability compared with Pd/Pa and iFR.

**WHAT IS NEXT?** Future studies evaluating adenosine-free indexes should include cFFR in their protocols.

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**KEY WORDS** adenosine, contrast medium, fractional flow reserve, hyperemia, instantaneous wave-free ratio

**APPENDIX** For supplemental material, please see the online version of this article.