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ORIGINAL RESEARCH

Coronary Flow Variations Following Percutaneous Coronary Intervention Affect Diastolic Nonhyperemic Pressure Ratios More Than the Whole Cycle Ratios

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BACKGROUND: Post–percutaneous coronary intervention (PCI) fractional flow reserve ≥0.90 is an accepted marker of procedural success, and a cutoff of ≥0.95 has recently been proposed for post-PCI instantaneous wave-free ratio. However, stability of nonhyperemic pressure ratios (NHPRs) post-PCI is not well characterized, and transient reactive submaximal hyperemia post-PCI may affect their precision. We performed this study to assess stability and reproducibility of NHPRs post-PCI.

METHODS AND RESULTS: Fifty-seven patients (age, 63.77±10.67 years; men, 71%) underwent hemodynamic assessment immediately post-PCI and then after a recovery period of 10, 20, and 30 minutes and repeated at 3 months. Manual offline analysis was performed to derive resting and hyperemic pressure indexes (Pd/Pa resting pressure gradient, mathematically derived instantaneous wave-free ratio, resting full cycle ratio, and fractional flow reserve) and microcirculatory resistances (basal microvascular resistance and index of microvascular resistance).

Transient submaximal hyperemia occurring post-PCI was demonstrated by longer thermodilution time at 30 minutes compared with immediately post-PCI; mean difference of thermodilution time was 0.17 seconds (95% CI, 0.07–0.26 seconds; P=0.04). Basal microcirculatory resistance was also higher at 30 minutes than immediately post-PCI; mean difference of basal microvascular resistance was 10.89 mm Hg.s (95% CI, 2.25–19.52 mm Hg.s; P=0.04). Despite this, group analysis confirmed no significant differences in the values of resting whole cycle pressure ratios (Pd/Pa and resting full cycle ratio) as well as diastolic pressure ratios (diastolic pressure ratio and mathematically derived instantaneous wave-free ratio). Whole cardiac cycle NHPRs demonstrated the best overall stability post-PCI, and 1 in 5 repeated diastolic NHPRs crossed the clinical decision threshold.

CONCLUSIONS: Whole cycle NHPRs demonstrate better reproducibility and clinical precision post-PCI than diastolic NHPRs, possibly because of less perturbation from predominantly diastolic reactive hyperemia and left ventricular stunning.

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Key Words: instantaneous wave-free ratio ■ nonhyperemic pressure ratios ■ post–percutaneous coronary intervention coronary physiology ■ post–percutaneous coronary intervention hyperemia ■ resting full cycle ratio

Physiological assessment of the hemodynamic significance of coronary artery stenoses with the pressure wire to guide revascularization decisions is well established and is recommended in both European and American guidelines.[1–5] Fractional flow reserve (FFR) documents the epicardial pressure

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CLINICAL PERSPECTIVE

What Is New?

- Whole cardiac cycle pressure ratios have better test-retest stability as well as clinical utility post–percutaneous coronary intervention (PCI).
- Diastolic nonhyperemic pressure ratios may be more affected by submaximal reactive hyperemia and PCI-induced left ventricular stunning post-PCI, resulting in inferior test-retest stability.

What Are the Clinical Implications?

- Post-PCI fractional flow reserve >90 is associated with better long-term outcomes.
- Although fractional flow reserve is well validated for reliability and reproducibility post-PCI, similar test-retest statistics are lacking for nonhyperemic pressure ratios.

Nonstandard Abbreviations and Acronyms

dPR	diastolic pressure ratio
FFR	fractional flow reserve
iFR	instantaneous wave-free ratio
IMR	index of microvascular resistance
NHPR	nonhyperemic pressure ratio
Pd/Pa	resting pressure gradient
RFR	resting full cycle ratio

gradient at hyperemia and is considered the gold standard invasive functional test; other nonhyperemic pressure ratios (NHPRs) have recently gained popularity given the absence of the need to use hyperemic agents.[6–8] Studies have confirmed that NHPRs have a similar diagnostic performance to FFR pre–percutaneous coronary intervention (PCI) to predict long-term outcome.[9] In addition to FFR, flow velocity by Doppler analysis or indirectly by saline transit time with thermodilution can also be measured at rest and hyperemia to derive coronary flow reserve and diagnose coronary microvascular disease via derangements of the index of microvascular resistance (IMR).

There has recently been an increased interest in the use of physiological measurements to ascertain procedural success after coronary artery stenting.[10–12] A significant number of patients continue to experience angina following PCI, and pressure wire assessment following PCI (post-PCI) can detect residual hemodynamically significant disease that may be missed otherwise.[13,14] A post-PCI FFR cutoff value of ≥0.90 has been accepted as a marker of procedural success given low subsequent events in patients achieving this target,[12] and similarly, recent data suggest that a post-PCI instantaneous wave-free ratio (iFR) value of ≥0.95 portends a good outcome.[10,15] In addition, IMR can also be measured post-PCI to quantify the degree of microvascular injury, and this too predicts outcome.[16]

Coronary stenting creates a complex microenvironment with multiple physiological changes; for reliable clinical utility of NHPRs as markers of procedural success, the stability and reliability of these resting indexes remain to be tested. Submaximal reactive hyperemia occurring immediately after successful stenting and caused by ischemia from intermittent coronary balloon occlusion during PCI has been observed, as well as left ventricular (LV) stunning, once reactive hyperemia has waned.[17] Coronary flow predominantly occurs in diastole, and LV stunning is also predominantly a diastolic phenomenon post-PCI, because of the earlier incidence of diastolic dysfunction in the ischemic cascade.[18]

We hypothesized that these post-PCI coronary and ventricular physiological changes may preferentially affect diastolic NHPRs (iFR and diastolic pressure ratio [dPR]), although the hyperemic indexes FFR and IMR would likely be unaffected and have previously been reported to be stable on repeated testing.[19] There are currently no reported data on the short- and medium-term stability and reproducibility of NHPRs following PCI.

In this study, we assessed and compared the stability and reproducibility of NHPRs post-PCI in the short- and medium-term, and related these findings to coronary flow velocity and microvascular resistance measured invasively by pressure wire, both at rest and during pharmacologically induced hyperemia.

METHODS

The authors declare that all supporting data are available within the article and its online Supplementary Files. This post hoc analysis was performed on prospectively recruited patients attending for invasive coronary assessment for stable angina from 2 clinical trials with similar inclusion criteria (see Supplementary Files).

Procedural Details

All patients abstained from nitrates, vasoactive medication, and caffeine for 24 hours before their PCI procedure and received preloading with 300 mg of aspirin and 300 mg of clopidogrel at least 2 hours before the PCI procedure, unless they were already established on these antiplatelet agents. Patients were anticoagulated with a bolus of unfractionated heparin (70–100 IU/kg) after arterial sheath insertion

(radial or femoral) to achieve an activated clotting time >250 seconds. Iopromide (Ultravist; Bayer HealthCare Pharmaceuticals, Leverkusen, Germany) was used as the contrast agent for all cases. Following successful stent implantation, the Pressure Wire X (Abbott Vascular, Santa Clara, CA), connected wirelessly to the Coroflow system (Coroventis, Uppsala, Sweden), was positioned and maintained in the distal third of the stented coronary artery. A 0.2-mg bolus of intracoronary glyceryl trinitrate was administered, and once steady-state coronary hemodynamics were achieved, the post-PCI baseline coronary pressures (aortic pressure [Pa] and distal wire pressure [Pd]) and flow velocity measurements were measured. The latter was derived from the reciprocal of mean transit time (Tmn) of an intracoronary injectate of room temperature saline (thermodilution technique) measured in triplicate.[20,21] These measurements were repeated following IV administration of adenosine at 140 µg/kg per minute. Coronary wedge pressure (Pw) was measured separately as resting Pd during the occlusive coronary balloon inflation at the time of coronary stent postdilatation. All hemodynamic measurements were repeated at rest and hyperemia at the following time points post-PCI: 10 minutes, 20 minutes, 30 minutes. and 3 months (for a subgroup of patients). At the end of the procedure, the pressure wire was withdrawn to the coronary ostium to enable pressure-drift correction of Pd, if necessary (Figure 1).

Offline calculation were performed for: average resting pressure gradient Pd/Pa; fractional flow reserve (FFR=[Pd]/[Pa]$_{hyperemia}$), basal microvascular resistance (BMR=Pa×Tmn×[(Pd–Pw)/(Pa–Pw)]$_{baseline}$), and index of microvascular resistance (IMR=Pa×Tmn×[(Pd–Pw)/(Pa–Pw)]$_{hyperemia}$), both corrected for collaterals, as previously described and validated.[22,23] Further offline analysis was undertaken using the recorded pressure tracings on the Coroflow system to calculate resting full cycle ratio (RFR),[7] dPR,[24] and mathematically derived iFR (iFR$_{mat}$), measured by average Pd/Pa from 25% into the diastolic period until 5 ms before the end of diastole, as calculated and validated previously.[25] Clinical utility of NHPRs was assessed by the rate of crossover of patients resulting in change in diagnostic category of patients using a cutoff value of 0.95.

Statistical Analysis

Data are presented as mean (SD) or median (quartile 1–quartile 3) as appropriate unless otherwise stated. Comparisons were made for any significant differences by repeated-measure ANOVA or mixed model ANOVA and Friedman test, where appropriate, using GraphPad

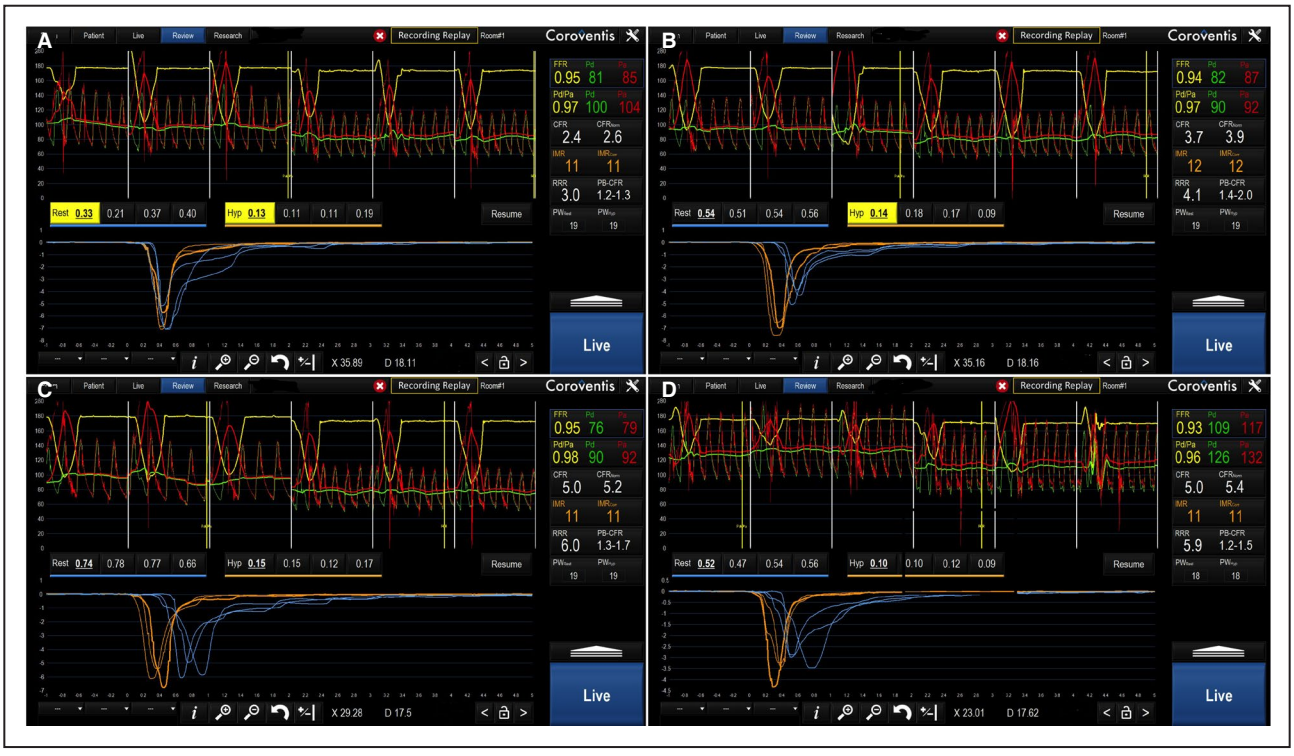

Figure 1. Serial post–percutaneous coronary intervention (PCI) hemodynamic raw data measured immediately post-PCI (A) and at +10 minutes (B), at +30 minutes (C), and at +3 months (D) post-PCI.
Resting pressure gradient (Pd/Pa) is measured at rest (nonhyperemia) - Pd/Pa and hyperemia - fractional flow reserve (FFR). Thermodilution transit time (Tmn) is measured at rest and hyperemia in triplicates to measure coronary flow reserved (CFR) and index of microvascular resistance (IMR).

Prism version 8.1.2 (227) (GraphPad Software, La Jolla, CA). Similarly, a simple linear regression and Bland-Altman test were performed between post-PCI indexes and the corresponding repeated measurements to assess correlation and bias with 95% limit of agreement.[26] Intraclass correlation coefficient was measured using IBM SPSS Statistics (Version 26). SEM and coefficient of repeatability were measured, as previously reported.[27] $P<0.05$ was deemed statistically significant, and a test-retest difference of >0.05 was deemed clinically significant in repeatability analysis. Authors had full access to the data and take full responsibility for their integrity.

The local research ethics committee approved the study: REC references 14/EE/0018 and 16/EE/0232. The study was performed according to institutional guidelines and registered under NCT03502083 and NCT03076476, respectively. The study conformed to the principles outlined in the Declaration of Helsinki, and all participants gave written informed consent.

RESULTS

Patient Study Flow

A total of 256 patients with stable angina awaiting elective angiography were screened, and 113 patients were eligible and recruited. Of these, 34 patients did not subsequently undergo PCI because of unobstructed coronary arteries, either angiographically or by invasive hemodynamic assessment, and were excluded. Twenty patients received IV glucagon-like peptide-1 infusion as part of another study, which is a coronary vasodilator, and therefore these patients were also excluded. Two further patients had complex coronary anatomy, one required left main bifurcation stenting, and the other underwent surgical revascularization, and were also excluded (Figure 2).

Fifty-seven patients were included in this study, who underwent invasive hemodynamic assessment by pressure wire immediately post-PCI, followed by repeated hemodynamic assessment in 36 patients at 10- and 30-minute intervals, and in 21 patients

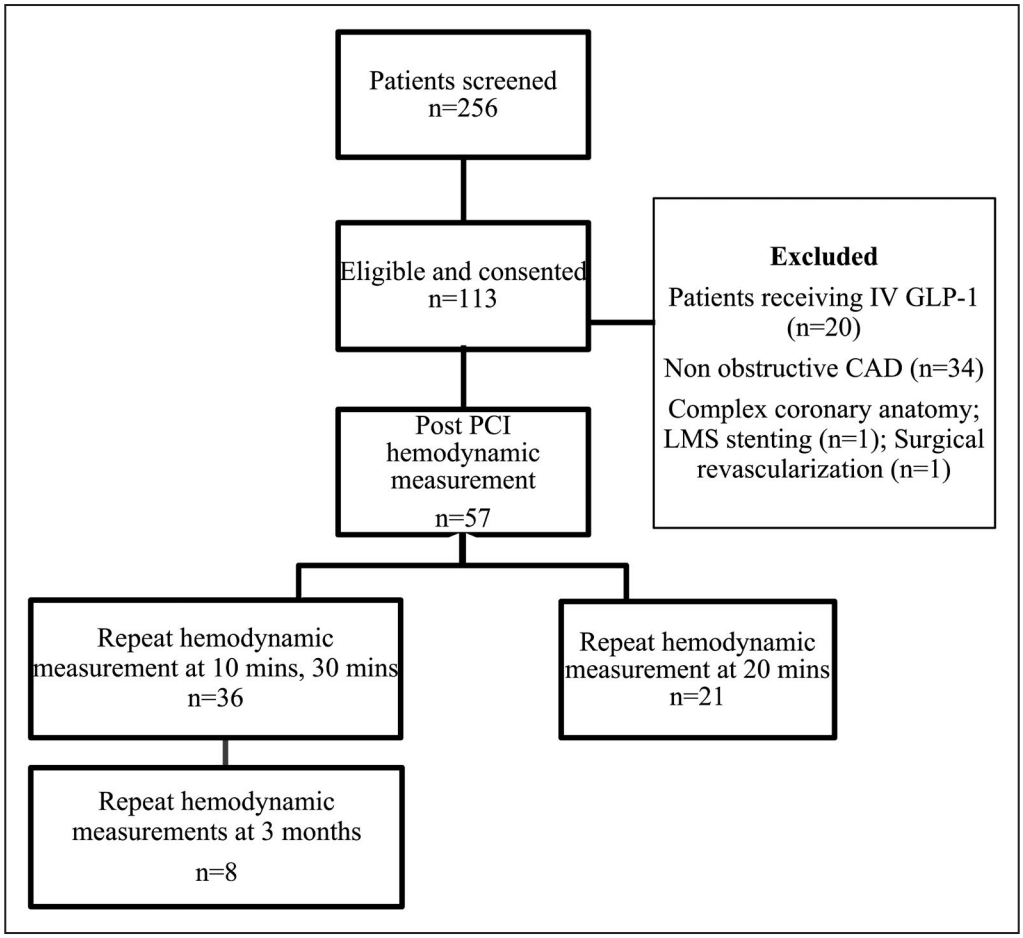

Figure 2. Schematic diagram of recruitment of patients.
CAD indicates coronary artery disease; GLP-1, glucagon-like peptide-1; LMS, left main stem; and PCI, percutaneous coronary intervention.

Table 1. Baseline Characteristics

Characteristic	Value (n=57)
Age, y	63.8±10.7
Men	41 (71.93)
Cardiovascular risk factors	
Current/ex-smoking	27 (47.37)
Hypertension	27 (47.37)
Diabetes	6 (10.53)
Hypercholesterolemia	18 (31.57)
Previous MI	19 (33.33)
Pharmacological therapy	
Aspirin	57 (100)
Statins	48 (84.21)
ACE inhibitors	24 (42.11)
β Blockers	33 (57.89)
Calcium channel blockers	12 (21.05)
Oral nitrates	19 (33.33)

Data are given as mean±SD or number (percentage). ACE indicates angiotensin-converting enzyme; and MI, myocardial infarction.

repeated physiological assessment was undertaken at 20 minutes. Eight patients had further hemodynamic assessment by pressure wire at 3 months.

Baseline Characteristics

Mean age for patients in this study was 63.8±10.7 years. Most of the patients were men, and almost half of the patients had history of hypertension and were either current or ex-smokers. Similarly, a quarter of patients in this study had a diagnosis of hypercholesterolemia, and 10% had diabetes. All patients were free from chest pain and had an isoelectric ST segment on their ECG monitor before post-PCI pressure wire assessment (Table 1).

Hemodynamic Indexes

Resting coronary flow velocity decreased between immediately post-PCI and 30 minutes post-PCI, demonstrated by mean difference Tmn of 0.17 seconds (95% CI, 0.07–0.26 seconds; *P*=0.04). There were corresponding increases in the mean difference of coronary flow reserve of 0.99 (95% CI, 0.24–1.75; *P*=0.03) and BMR of 10.89 mm Hg.s (95% CI, 2.25–19.52 mm Hg.s; *P*=0.04) from immediately post-PCI to 30 minutes post-PCI (Figure 3). There were no significant differences in the values of resting Pd/Pa, dPR, RFR, and iFR_{mat} between immediately post-PCI and 10, 20, or 30 minutes post-PCI (see Supplementary Files) (Table 2).

Reliability and Repeatability

Short-term reliability and repeatability in the resting pressure-derived indexes measured over the whole cardiac cycle (ie, Pd/Pa and RFR) were superior to those of indexes measured over diastole alone (dPR) and the wave-free period of diastole (iFR_{mat}). R values (95% CI) for Pd/Pa, RFR, dPR, iFR_{mat}, and FFR were 0.94 (0.88–0.97), 0.94 (0.87–0.97), 0.58 (0.31–0.77), 0.67 (0.41–0.82), and 0.79 (0.63–0.89), respectively, at

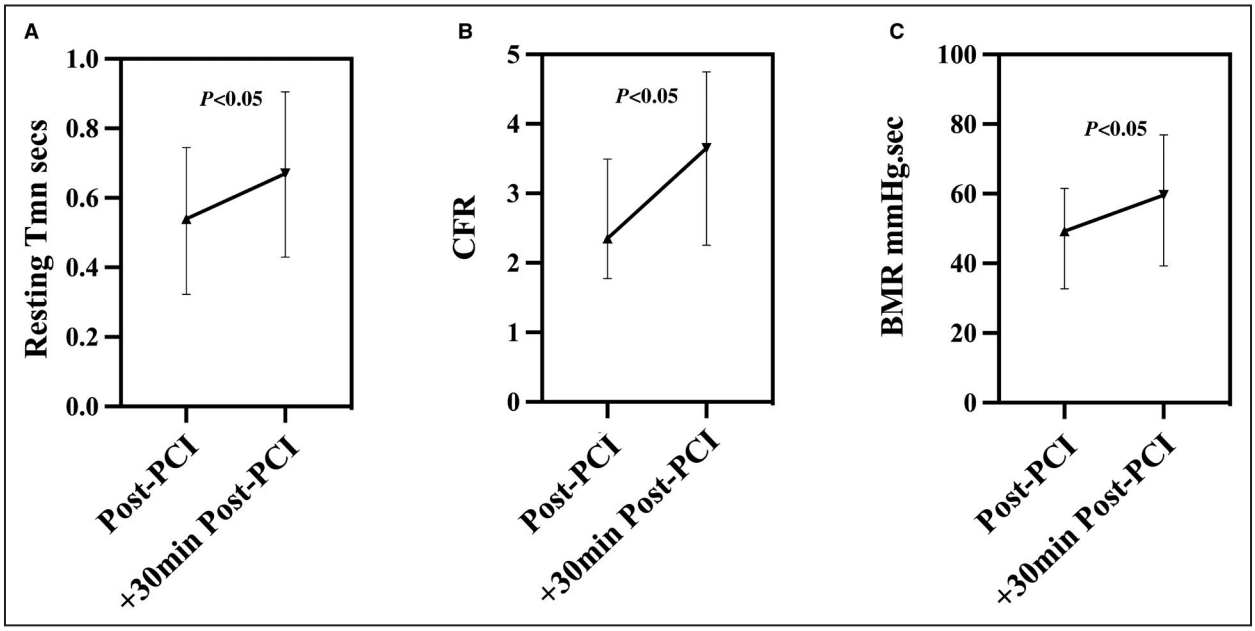

Figure 3. Post–percutaneous coronary intervention (PCI) coronary hemodynamic variation.
Post-PCI changes of coronary transit time (Tmn) (**A**), coronary flow reserve (CFR) (**B**), and basal microvascular resistance (BMR) (**C**) immediately post-PCI and at 30 minutes post-PCI. *P*<0.05 is given in bold.

Table 2. Comparison of Nonhyperemic and Hyperemic Indexes at Various Time Points Post-PCI

Parameter	Immediately post-PCI	+10 Min	+30 Min	*P* value
Nonhyperemia				
Systolic BP, mm Hg	137.20±28.46	145.40±25.98	143.30±25.61	0.20
Diastolic BP, mm Hg	68.70±12.29	72.19±13.32	71.78±11.97	0.63
Heart rate, bpm	69.47±16.68	66.92±12.27	65.92±12.27	0.31
Pd/Pa	0.94 (0.92–0.97)	0.95 (0.92–0.98)	0.95 (0.93–0.98)	0.43
dPR	0.95 (0.93–0.98)	0.95 (0.91–0.98)	0.96 (0.92–0.99)	0.40
iFR_{mat}	0.95 (0.93–0.98)	0.95 (0.91– 0.99)	0.96 (0.92–0.99)	0.88
RFR	0.92 (0.89–0.96)	0.92 (0.88–0.96)	0.93 (0.90–0.97)	0.43
BMR, mm Hg.s	49.25 (32.74–61.61)	55.14 (35.77–91.51)	59.60 (39.24–76.91)	0.04*
Tmn rest, s	0.54 (0.32–0.75)	0.62 (0.39–0.99)	0.67 (0.43–0.91)	0.04*
Hyperemia				
Tmn hyperemia, s	0.22 (0.13–0.28)	0.21 (0.15–0.30)	0.19 (0.15–0.25)	0.33
CFR	2.35 (1.78–3.50)	3.00 (2.38–4.15)	3.62 (2.25–4.75)	0.03*
FFR	0.90 (0.84–0.94)	0.89 (0.86–0.93)	0.89 (0.84–0.92)	0.98
IMR, mm Hg.s	14.70 (10.89–21.29)	16.08 (11.47–20.94)	13.77 (9.98–20.42)	0.30

Data are given as mean±SD or median (quartile 1–quartile 3). BMR indicates baseline microvascular resistance; BP, blood pressure; CFR, coronary flow reserve; dPR, average diastolic Pd/Pa; FFR, fractional flow reserve; iFR_{mat}, mathematically calculated instantaneous wave-free ratio; IMR, index of microvascular resistance; PCI, percutaneous coronary intervention; Pd/Pa, resting pressure gradient; RFR, resting full cycle ratio; and Tmn, coronary flow velocity (at rest and hyperemia).

*$P<0.05$ is deemed significant.

30 minutes. Similarly, intraclass correlation coefficient was also better for Pd/Pa and RFR, 0.89 and 0.91, compared with dPR and iFR_{mat}, 0.62 and 0.63. All repeatability indexes were poor for NHPRs at 3 months, with a clinically significant SEM of >0.10, compared with only 0.02 for FFR, making FFR a much more reliable index for determining procedural success (see Supplementary Files) (Table 3 and Figure 4).

Clinical Utility

NHPRs measured over the whole cardiac cycle showed better clinical precision with narrower variability than diastolic-only NHPRs. The proportion of patients with NHPR <0.95 immediately post-PCI, who crossed over to a value of >0.95 on repeated testing, was 3.90% for both Pd/Pa and RFR, compared with 12.99% and 11.69% for dPR and iFR_{mat}, respectively. Similarly, the proportions of patients with NHPR value >0.95 immediately post-PCI who crossed over to a value of <0.95 on repeated testing at 30 minutes were 6.49%, 2.60%, 11.60%, and 12.99% for Pd/Pa, RFR, dPR, and iFR_{mat}, respectively (Figure 5 and 6).

DISCUSSION

Our study confirms the phenomenon of post-PCI reactive hyperemia, which subsides within 30 minutes following the PCI procedure. Despite this variability in flow, the stability and repeatability of NHPRs within 30 minutes of PCI persisted when assessed at a cohort level. Nevertheless, NHPRs that sampled from the diastolic period alone (iFR_{mat} and dPR) had inferior reproducibility compared with whole cycle NHPRs (Pd/Pa and RFR), and at a patient level, had higher crossover rates to a

Table 3. Stability and Reproducibility of Pressure-Derived Indexes Immediately Post-PCI and 30 Minutes Post-PCI

Variable	SEM	R (95% CI)	Bias±SD	Limits of agreement, 95%	ICC	CR
Pd/Pa	0.00	0.94 (0.88 to 0.97)	−0.01±0.02	−0.04 to 0.04	0.89	0.01
RFR	0.00	0.94 (0.87 to 0.97)	−0.01±0.02	−0.05 to 0.03	0.91	0.01
dPR	0.01	0.58 (0.31 to 0.77)	−0.01±0.03	−0.08 to 0.06	0.62	0.01
iFR_{mat}	0.01	0.67 (0.41 to 0.82)	−0.01±0.04	−0.08 to 0.06	0.63	0.02
FFR	0.01	0.79 (0.63 to 0.89)	0.00±0.04	−0.07 to 0.08	0.88	0.02
BMR	5.02	0.68 (0.44 to 0.83)	−11.77±29.29	−69.16 to 45.63	0.82	13.91
IMR	2.11	0.41 (0.08 to 0.65)	2.32±12.70	−22.57 to 27.21	0.46	5.86

BMR indicates baseline microvascular resistance; CR, coefficient of repeatability; dPR, average diastolic Pd/Pa; FFR, fractional flow reserve; ICC, intraclass correlation coefficient; iFR_{mat}, mathematically calculated instantaneous wave-free ratio; IMR, index of microvascular resistance; PCI, percutaneous coronary intervention; Pd/Pa, resting pressure gradient; R, correlation coefficient; and RFR, resting full cycle ratio.

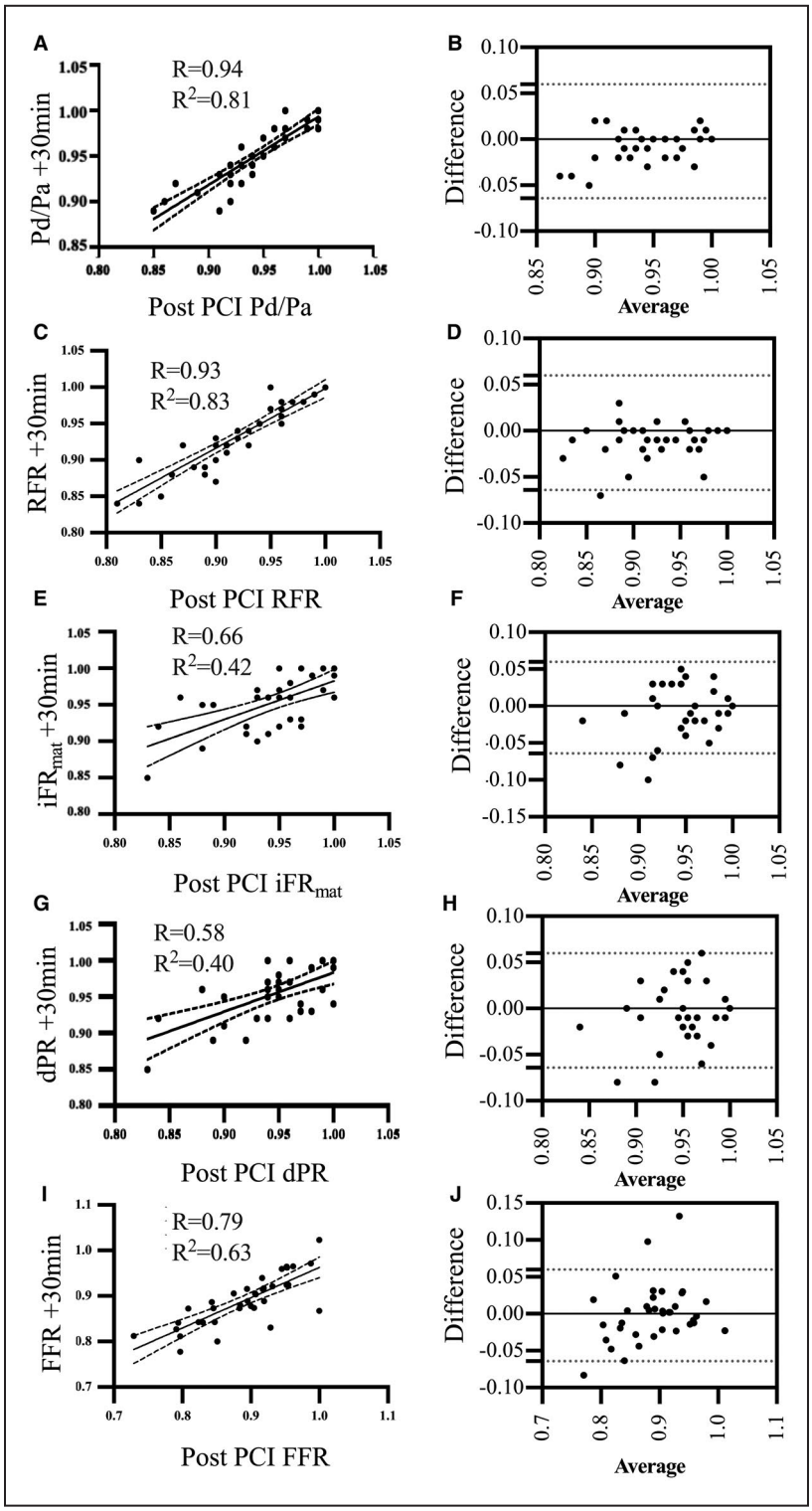

Figure 4. Stability of nonhyperemic pressure ratios.
Linear regression of post–percutaneous coronary intervention (PCI) pressure ratios compared with their respective retest value at 30 minutes. **A**, Resting pressure gradient (Pd/Pa). **C**, Resting full cycle ratio (RFR). **E**, Mathematically calculated instantaneous wave-free ratio (iFR_{mat}). **G**, Average diastolic Pd/Pa (dPR). **I**, Fractional flow reserve (FFR). R is derived from correlation matrix, whereas R^2 is calculated by simple linear regression. Bland-Altman charts are plotted opposite to report the degree of bias for post-PCI pressure ratio values vs repeated measurements at 30 minutes post-PCI for Pd/Pa (**B**), RFR (**D**), iFR_{mat} (**F**), dPR (**H**), and FFR (**J**).

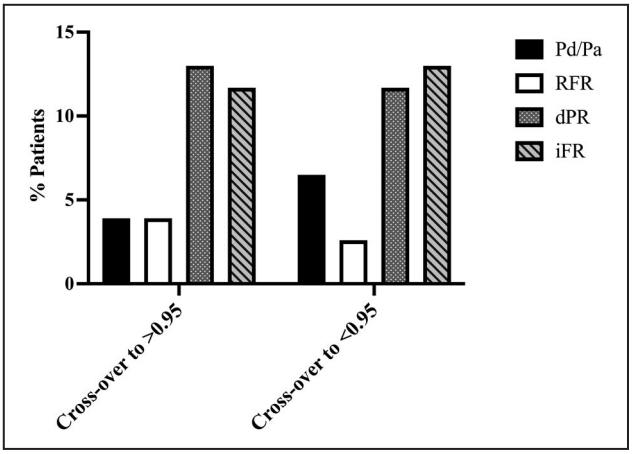

Figure 5. Clinical precision of nonhyperemic pressure ratios (NHPRs).
Change in diagnostic category with crossover to >0.95: patients with respective NHPR value <0.95 immediately post-PCI, which became >0.95 at 30 minutes, and crossover to <0.95: patients with respective NHPR value of >0.95 immediately post-PCI, which became <0.95 on repeated testing at 30 minutes. dPR indicates average diastolic Pd/Pa; iFR, instantaneous wave-free ratio; Pd/Pa, resting pressure gradient; and RFR, resting full cycle ratio.

different diagnostic category, when comparing NHPRs acquired immediately post-PCI with 30 minutes data.

A significant number of patients continue to have residual post-PCI ischemia with ongoing symptom burden, when coronary angiography alone is used to gauge procedural success.[13,14] This has led to a gradual uptake of use of pre-PCI invasive coronary physiology to guide management of coronary artery disease. But even patients treated with pre-PCI physiology-guided PCI continue to experience a noticeable long-term symptom burden as well as incidence of major adverse cardiac events.[28] Various recent studies have shown that repeating coronary physiological assessment post-PCI to confirm procedural success is independently associated with better long-term clinical outcomes after PCI.[13–15,29,30] Despite these encouraging data, a large, blinded, randomized controlled trial to confirm the utility of NHPR to guide post-PCI procedural success is needed. DEFINE GPS (Distal Evaluation of Functional Performance With Intravascular Sensors to Assess the Narrowing Effect: Guided Physiological Stenting) is likely to address this unmet need by investigating the utility of post-PCI iFR to predict long-term clinical outcomes of patients.

During PCI, invasive coronary instrumentation, particularly repeated balloon inflations, results in ischemia-driven reactive submaximal hyperemia.[17] This post-PCI reactive hyperemia is directly related to the duration of ischemic burden induced by balloon inflations[31] and is therefore likely to be more significant in complex PCI procedures that require multiple balloon inflations to prepare the lesion and optimize the stent result. Our study confirms post-PCI submaximal reactive hyperemia, as seen by a periprocedural increase in coronary flow velocity (see Supplementary Files), which continues to follow an upward trend when repeated at 10 minutes post-PCI and settles by 30 minutes post-PCI (Table 2 and Figure 3), demonstrating that the duration of post-PCI hyperemia is longer than previously reported.[31]

Once the initial phase of post-PCI submaximal hyperemia has waned, post-PCI LV stunning is apparent, which is known to have a more pronounced effect on the diastolic period of the cardiac cycle, with systole relatively spared.[17] LV stunning is masked initially by the reactive coronary hyperemia,[17,31] because of the cross talk between microvascular bed and the LV (stretch-activated cardiac myocyte calcium channels are activated because of the adjacent engorged microcirculation), a phenomenon known as the Gregg effect. The significant increase in the BMR at 30 minutes post-PCI compared with the immediate post-PCI value, which partially recovers at 3 months, is consistent with this. LV stunning, in turn, is known to reduce the backwards expansion wave amplitude through similar coronary-LV cross talk (cardiac myocyte relaxation fails to "pull open" the microcirculation and generate suction), which further impedes coronary flow at 30 minutes.[18,32] Because of the immediate post-PCI reactive hyperemia and late (30-minute) LV diastolic dysfunction effects on the backwards expansion wave, coronary flow and, in turn, NHPRs would be expected to be most divergent at these 2 time points.

Despite these dynamic changes in coronary physiology following PCI, NHPRs did not change significantly when compared as a cohort. However, at a patient level, NHPRs measured over the whole cardiac cycle (Pd/Pa and RFR) were more reproducible at test-retest than diastolic indexes of dPR and iFR_{mat}, calculated during the wave-free period.[7] This may be explained by the fact that coronary flow and, therefore, reactive hyperemia predominantly occurs in diastole, and post-PCI stunning affects diastolic function more than systolic as it occurs earlier in the ischemic cascade. Diastolic dysfunction would, in turn, reduce coronary flow via reduction in backwards expansion wave. Therefore, the post-PCI changes in coronary flow would be expected to particularly influence diastolic NHPRs.

Clinical utility of NHPRs to determine procedural success requires clinical reliability and repeatability/reproducibility of results with minimal crossover above or below the cutoff value of 0.95. Disappointingly, this occurred in ≈1 in 5 diastolic NHPR measurements, but disagreement was 3-fold lower for whole cycle NHPRs. A false-positive or false-negative post-PCI NHPR could potentially result in overtreatment or undertreatment.

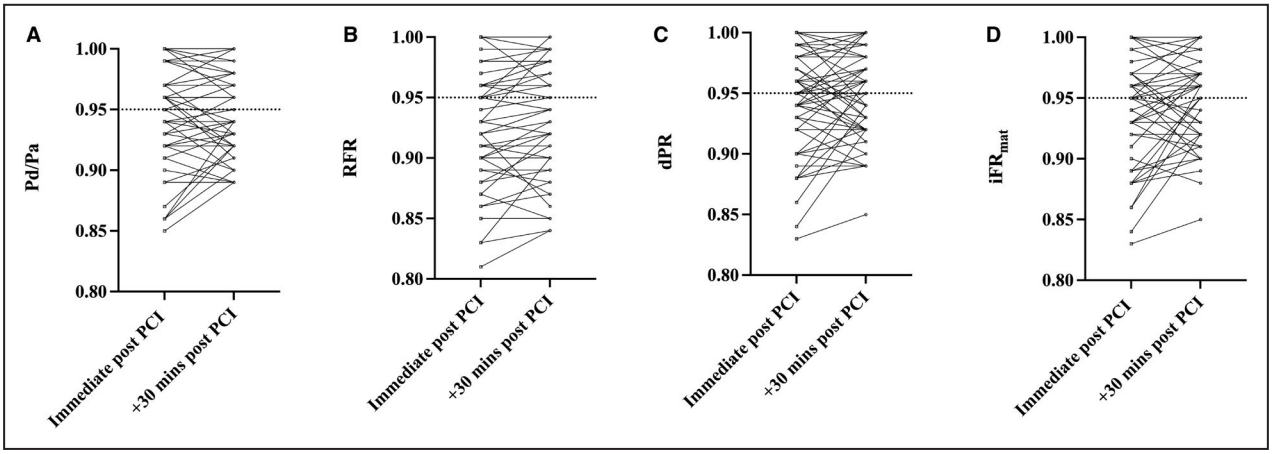

Figure 6. Reproducibility of resting pressure gradient (Pd/Pa) (A), resting full cycle ratio (RFR) (B), average diastolic Pd/Pa (dPR) (C), and mathematically calculated instantaneous wave-free ratio (iFR_{mat}) (D) immediately post–percutaneous coronary intervention (PCI) to 30 minutes post-PCI.

Whole cycle ratios: Pd/Pa, average ratio of Pd/Pa over whole cardiac cycle; RFR, lowest value of ratio of Pd/Pa over whole cardiac cycle. Diastolic ratios: dPR, average ratio of Pd/Pa over diastole; iFR, average Pd/Pa from 25% into diastole until 5 ms before the end of diastole.

Surprisingly, we did not see a greater proportion of diastolic NHPRs increase >0.95 at 30 minutes post-PCI, as might be expected as the post-PCI reactive hyperemia subsides and diastolic dysfunction is unmasked, impairing flow. However, this may simply reflect variable degrees of diastolic reactive hyperemia/LV stunning waning at different rates. NHPRs measured over whole cardiac cycle, and specifically RFR, had superior reliability and repeatability, and as a result, better clinical precision post-PCI.

FFR measurements during maximal hyperemia are not impacted by submaximal reactive hyperemic changes that occur post-PCI; hyperemic Tmn and IMR measures also remain stable post-PCI at various time points, and FFR and IMR have better test-retest repeatability than NHPRs.[33] As a result, FFR variability post-PCI is unlikely to change the categorization of patients post-PCI and may provide more reliable clinical decisions.[19]

Limitations

We performed a post hoc analysis on a relatively small number of patients, but we studied serial measurements in the same patient, which strengthens our data set, enabling test-retest analysis; and we believe our findings remain valid. The medium-term stability of NHPRs was assessed in fewer number of patients than planned because of the COVID-19 pandemic, and we cannot comment on NHPR stability beyond 3 months. We did not perform physiological assessment using the proprietary wire to measure iFR but instead calculated a mathematical iFR offline from the same raw data as the other NHPRs. Mathematical iFR has been validated against the proprietary wire-based iFR previously.[9] Moreover, using mathematical iFR in our study also ensured temporal sampling was consistent across all NHPR measurements, which facilitated as fair a comparison as could be obtained.

CONCLUSIONS

Whole cycle RFR has superior reproducibility and clinical precision among the nonhyperemic indexes, which may reflect less perturbation from predominantly diastolic reactive hyperemia and left ventricular stunning, that predominantly affects diastolic NHPRs.

ARTICLE INFORMATION

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Disclosures

There were no disclosures at the time of this study. Dr West has since become an employee of Abbott Vascular. All data collection and analysis were performed independent of any industry involvement.

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SUPPLEMENTAL MATERIAL

Data S1. Methods

Inclusion Criteria

Inclusion criteria for the study included patients undergoing elective PCI for stable angina (defined as at least Canadian Cardiovascular Society angina grade 2 despite the use/ intolerance to 2 antianginal medications), between the age of 18 and 75 years; listed for single vessel PCI with target vessel caliber >2.3mm and <3.8mm reference diameter, without significant tortuosity and calcification; lesion length ≤28mm; RFR <0.89 and/or FFR<0.80 prior to PCI and able to give informed consent for the study.

Exclusion criteria

Exclusion criteria included target lesion in left mainstem, saphenous vein or arterial grafts, chronic total occlusion and a patent coronary artery bypass graft (CABG) to the target vessel; any severe co-morbidity with expected life expectancy < 6 months; use of warfarin; pregnancy or women of child-bearing age; myocardial infarction within the previous 3 months; heart failure with ejection fraction <50%; deranged renal function; deranged liver function; active peptic ulcer disease confirmed on endoscopy; history of seizures; history of tachyarrhythmias; allergy or intolerance to aspirin, clopidogrel, prasugrel or ticagrelor or contraindication to 12 months' dual antiplatelet therapy; contraindication to use of adenosine (severe asthma/chronic lung disease with documented broncho reactivity); other comorbid condition that may affect microcirculatory function or troponin release (e.g. Seropositive inflammatory conditions).

Non hyperemic pressure ratios (Figure S1)

Non hyperemic ratios (NHPRs) used in this study are defined as below:

Whole cycle ratios

Pd/Pa- Average ratio of Pd to Pa over whole cardiac cycle.

RFR- Lowest value of ratio of Pd to Pa over whole cardiac cycle.

Diastolic ratios

dPR- Average ratio of Pd to Pa over diastole.

iFR_{mat}- Average Pd/Pa from 25% into diastole until 5ms before the end of diastole.

Data S2. Results

Comparison of hyperemic and non-hyperemic indices at various post-PCI time points with immediate post-PCI values are presented in **Table S1** and confirm significant changes in Tmn, BMR and CFR.

Results of short term (up to 30 minutes post PCI) and medium term (3 months post PCI) follow-up of coronary physiological indices are summarized in **Table S2** confirming the superior stability and reproducibility of whole cycle NHPR and FFR at all short-term time points.

Data S3. Submaximal Hyperemia and LV Stunning

Repeated balloon inflation results in LV stunning[17] which is consistent with our observations in this study; this contributes to the reduction in coronary transit times at +30 minutes, in association with a rise in BMR at 30 minutes. These indices when repeated at 3 months in a subgroup of 8 patients returned to baseline levels, consistent with LV stunning resolving (**Figure S2**).

Table S1: Comparison of hyperemic and non-hyperemic indices at various time points post-PCI to immediate post-PCI data. Mixed model data is given as mean difference from immediate post-PCI values (95% confidence interval of difference). P<0.05 is deemed significant**.**

Parameter	+10 mins	+20 mins	+30 mins	3 months	*p*
	Resting				
Systolic BP	-6.69 (-15.67 to 2.28)	1.85 (-9.27 to 12.91)	-4.66 (-13.64 to 4.31)	3.12 (-13.61 to 19.86)	0.20
Diastolic BP	-3.31 (-8.34 to 1.73)	0.52 (-5.6o 56.69)	-2.89 (-7.92 to 2.1)	1.25 (-8.11 to 10.60)	0.63
Heart Rate	2.71 (-1.45 to 6.86)	2.68 (-2.41 to 7.79)	3.96 (-0.20 to 8.11)	-0.42 (-8.08 to 7.23)	0.31
Pd/Pa	0.00 (-0.02 to 0.01)	-0.01(-0.02 to 0.01)	-0.01 (-0.02 to 0.01)	0.00 (-0.03 to 0.02)	0.43
dPR	0.00 (-0.02 to 0.01)	-0.01 (-0.03 to 0.01)	-0.01 (-0.02 to 0.01)	0.01 (-0.01 to 0.04)	0.40
iFR_{mat}	0.00 (-0.02 to 0.02)	-0.01 (-0.02 to 0.01)	-0.01 (-0.03 to 0.01)	-0.01 (-0.03 to 0.02)	0.88
RFR	-0.01 (-0.02 to 0.01)	-0.03 (-0.05 to 0.01)	-0.01 (-0.03 to 0.01)	-0.02 (-0.05 to 0.01)	0.43
BMR mmHg.secs	7.51 (-1.21 to 16.25)	3.62 (-4.50 to 11.74)	10.89 (2.25 to 19.52)	1.17 (-15.82 to 18.15)	**0.04**
Tmn rest, sec	0.14 (0.05 to 0.23)	0.11 (-0.10 to 0.31)	0.17 (0.07 to 0.26)	0.02 (-0.22 to 0.28	**0.04**

	Hyperemia				
Tmn hyperemia, sec	0.00 (-0.06 to 0.06)	-0.02 (-0.08 to 0.04)	0.03 (-0.03 to 0.09)	0.04 (-0.07 to 0.15)	0.33
CFR	0.38 (-0.37 to 1.14)	0.36 (-0.39 to 1.12)	0.99 (0.24 to 1.75)	0.52 (-0.82 to 1.86)	**0.03**
FFR	0.00 (-0.02 to 0.02)	-0.02 (-0.04 to 0.01)	0.00 (-0.02 to 0.02)	0.00 (-0.04 to 0.04)	0.98
IMR mmHg.sec	-0.18 (-4.73 to 4.37)	-2.18 (-6.73 to 2.37)	2.32 (-2.23 to 6.87)	3.32 (-4.94 to 11.59)	0.30

Pd/Pa_ average whole cycle distal coronary to aortic pressure; RFR_ resting full cycle ratio; dPR_ average diastolic Pd/Pa; iFR_{mat}_ mathematically calculated instantaneous wave free ratio; FFR_Fractional flow reserve; Tmn_ coronary flow velocity (at rest and hyperemia); BMR baseline microvascular resistance; IMR_ index of microvascular resistance.

Table S2. Comparison of the stability and reproducibility of pressure derived indices immediately post-PCI and at +10, +20, +30 minutes and 3 months follow-up post PCI.

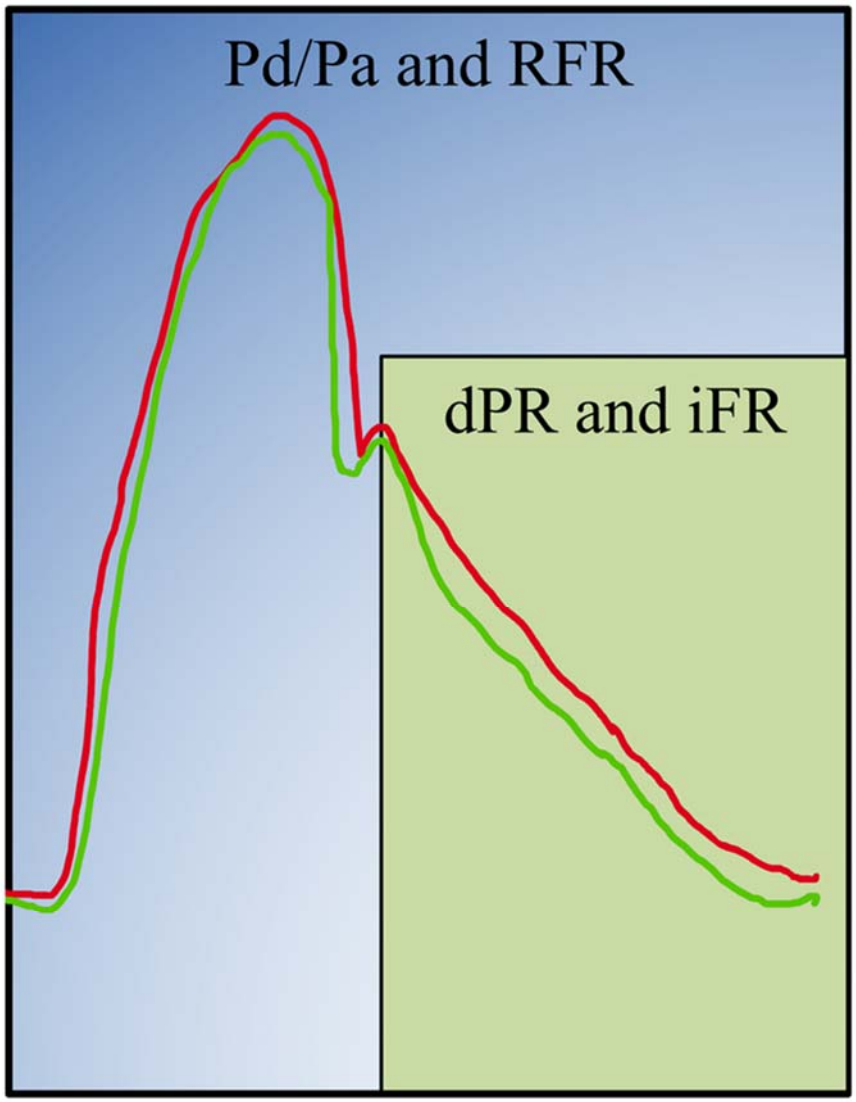
	SEM	R (95% C.I.)	Bias ± SD	Limits of Agreement (95%)	ICC	CR
10 minutes						
Pd/Pa	0.01	0.81 (0.65 to 0.90)	0.00 ± 0.03	-0.06 to 0.06	0.72	0.01
RFR	0.00	0.94 (0.88 to 0.97)	0.00 ± 0.02	-0.04 to 0.04	0.93	0.01
dPR	0.01	0.67 (0.42 to 0.82)	0.00 ± 0.03	-0.07 to 0.07	0.69	0.01
iFR	0.01	0.77 (0.59 to 0.88)	0.00 ± 0.03	-0.07 to 0.07	0.70	0.02
FFR	0.00	0.83 (0.69 to 0.91)	0.00 ± 0.04	-0.07 to 0.07	0.91	0.02
BMR	4.10	0.77 (0.57 to 0.88)	-8.38 ± 24.29	-55.99 to 39.23	0.89	11.37
IMR	1.48	0.74 (0.55 to 0.86)	-0.18 ± 8.89	-17.62 to 17.26	0.84	4.11
20 minutes						
Pd/Pa	0.01	0.76 (0.55 to 0.88)	0.00 ± 0.03	-0.05 to 0.05	0.72	0.02

RFR	0.01	0.87 (0.68 to 0.95)	0.00 ± 0.02	-0.05 to 0.05	0.87	0.01
dPR	0.01	0.83 (0.67 to 0.92)	0.00 ± 0.03	-0.05 to 0.05	0.79	0.01
iFR	0.01	0.80 (0.61 to 0.90)	0.00 ± 0.03	-0.06 to 0.06	0.77	0.02
FFR	0.01	0.87 (0.76 to 0.93)	-0.01 ± 0.03	-0.08 to 0.05	0.93	0.01
BMR	4.56	0.71 (0.51 to 0.84)	4.39 ± 29.18	-52.81 to 61.59	0.88	12.63
IMR	1.57	0.55 (0.30 to 0.74)	-2.13 ± 10.06	-21.85 to 17.60	0.71	4.35
30 minutes						
Pd/Pa	0.00	0.94 (0.88 to 0.97)	-0.01 ± 0.02	-0.04 to 0.04	0.89	0.01
RFR	0.00	0.94 (0.87 to 0.97)	-0.01 ± 0.02	-0.05 to 0.03	0.91	0.01
dPR	0.01	0.58 (0.31 to 0.77)	-0.01 ± 0.03	-0.08 to 0.06	0.62	0.01
iFR	0.01	0.67 (0.41 to 0.82)	-0.01 ± 0.04	-0.08 to 0.06	0.63	0.02
FFR	0.01	0.79 (0.63 to 0.89)	0.00 ± 0.04	-0.07 to 0.08	0.88	0.02
BMR	5.02	0.68 (0.44 to 0.83)	-11.77 ± 29.29	-69.16 to 45.63	0.82	13.91

IMR	2.11	0.41 (0.08 to 0.65)	2.32 ± 12.70	-22.57 to 27.21	0.46	5.86
			3 months			
Pd/Pa	0.02	0.63 (-0.14 to 0.92)	-0.01 ± 0.04	-0.09 to 0.08	0.51	0.04
RFR	0.11	0.56 (-0.20 to 0.91)	-0.02 ± 0.05	-0.12 to 0.08	0.43	0.31
dPR	0.11	0.51 (-0.33 to 0.88)	0.00 ± 0.05	-0.11 to 0.11	0.43	0.31
iFR	0.11	0.46 (-0.48 to 0.84)	-0.02 ± 0.06	-0.14 to 0.11	0.29	0.32
FFR	0.02	0.56 (-0.23 to 0.91)	0.00 ± 0.06	-0.12 to 0.12	0.59	0.07
BMR	12.66	0.46 (-0.44 to 0.90)	-0.45 ± 33.49	-66.10 to 65.19	0.62	35.07
IMR	5.63	-0.34 (-0.87 to 0.55)	5.36 ± 14.89	-23.84 to 34.55	-0.94	15.59

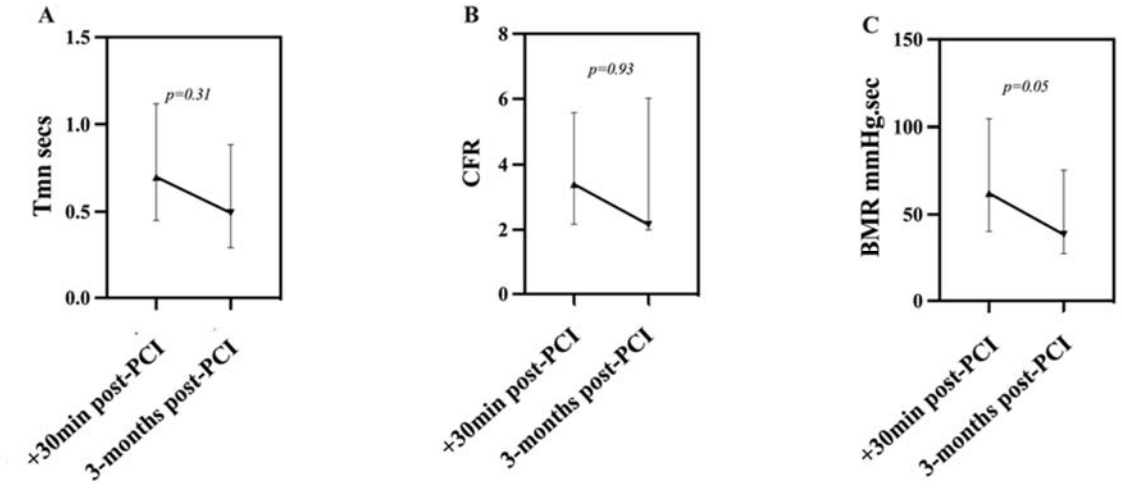
SEM_Standard error of mean; R_correlation coefficient; ICC_ intraclass correlation coefficient; CR_ coefficient of repeatability; Pd/Pa_ average whole cycle distal coronary to aortic pressure; RFR_ resting full cycle ratio; dPR_ average diastolic Pd/Pa; iFR_{mat}_ mathematically calculated instantaneous wave free ratio; FFR_Fractional flow reserve; BMR baseline microvascular resistance; IMR_ index of microvascular resistance.

Figure S1. Schematic representation of NHPRs measured over different parts of the cardiac cycle.



Whole cycle ratios: Pd/Pa- average ratio of Pd to Pa over whole cardiac cycle; RFR- Lowest value of ratio of Pd to Pa over whole cardiac cycle. Diastolic ratios: dPR- average ratio of Pd to Pa over diastole; iFR-average Pd/Pa from 25% into diastole until 5ms before the end of diastole. Pd- distal coronary pressure; Pa- proximal aortic pressure.

Figure S2. **Post PCI hemodynamic changes at 3 months.** Changes in Tmn (A), CFR (B) and BMR (C) from +30 minutes post PCI to 3 months post PCI (n=8).



Tmn_ thermodilution time; CFR_ coronary flow reserve and BMR_baseline microvascular resistance.