



Prognostic implications of resting distal coronary-to-aortic pressure ratio compared with fractional flow reserve: a 10-year follow-up study after deferral of revascularisation

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Abstract

Introduction The distal coronary-to-aortic pressure ratio (P_d/P_a) is a non-hyperaemic physiological index to assess the functional severity of coronary stenoses. Studies comparing P_d/P_a with fractional flow reserve (FFR) show superior diagnostic efficiency for myocardial ischaemia. Nevertheless, a direct comparison regarding long-term clinical outcomes is still not available. The present observational study compared the prognostic value of P_d/P_a and FFR for major adverse cardiac events (MACE) during a 10-year follow-up period after deferral of revascularisation.

Methods Between April 1997 and September 2006, we evaluated 154 coronary stenoses (154 patients) in which revascularisation was deferred with intracoronary pressure and flow measurements during the rest-

ing and hyperaemic state. Long-term follow-up (median: 11.8 years) was performed to document the occurrence of MACE, defined as a composite of cardiac death, myocardial infarction and target vessel revascularisation.

Results The study population comprised angiographically intermediate coronary stenoses, with a mean diameter stenosis of $53 \pm 8\%$, and intermediate physiological severity with a median FFR of 0.82 (Q1, Q3: 0.76, 0.88). The association of P_d/P_a with long-term MACE was similar to that of FFR [FFR-standardised hazard ratio (sHR): 0.77, 95% confidence interval (CI): 0.61–0.98; P_d/P_a -sHR: 0.80, 95% CI: 0.67–0.96]. In the presence of disagreement between P_d/P_a and FFR, normal P_d/P_a was generally associated with high coronary flow reserve (CFR) and a favourable clinical outcome, whereas abnormal P_d/P_a was generally associated with CFR around the ischaemic cut-point and an impaired clinical outcome, regardless of the accompanying FFR value.

Conclusion The present study suggests that P_d/P_a provides at least equivalent prognostic value compared with FFR. When P_d/P_a disagreed with FFR, the base-

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What's new?

- The distal coronary-to-aortic pressure ratio (P_d/P_a) demonstrates a continuous and independent relationship with subsequent long-term clinical outcomes.
- The prognostic value of P_d/P_a is at least equivalent to that of fractional flow reserve (FFR), but exceeds FFR as a risk stratification tool at their contemporary clinical cut-off values.
- When P_d/P_a disagreed with FFR, P_d/P_a conferred superior prognostic value in this study population.



line index conferred superior prognostic value in this study population.

Keywords Coronary artery disease · Fractional flow reserve · Resting distal-to-aortic pressure ratio · Major adverse cardiac events

Introduction

Guidelines on coronary revascularisation recommend the hyperaemia-dependent fractional flow reserve (FFR) for clinical decision-making, yet its clinical adoption has remained limited. As a corollary, the resting distal coronary-to-aortic pressure ratio (P_d/P_a) and the instantaneous wave-free ratio (iFR) were (re-)introduced with the aim of simplifying the use of coronary physiology in daily clinical practice by enabling its assessment during resting conditions [1–3]. Although baseline indices and FFR show equal diagnostic accuracy for positron emission tomography-derived flow abnormalities [4, 5], studies using invasive Doppler-derived coronary flow reserve (CFR) as the reference standard documented superior identification of flow abnormalities by P_d/P_a and iFR over FFR [3, 6, 7]. Doppler-derived CFR is considered a critical determinant of myocardial ischaemia and has relevant prognostic value in the setting of stable ischaemic heart disease [8, 9]. Accordingly, two landmark randomised clinical trials demonstrated that an iFR-guided revascularisation strategy is non-inferior to a FFR-guided revascularisation strategy in terms of clinical outcome at 1-year follow-up [10, 11]. However, the long-term prognostic value of P_d/P_a has yet not been compared to that of FFR. Therefore, the aim of the present study was to compare the prognostic value of P_d/P_a , with that of FFR for major adverse cardiac events (MACE) during a 10-year follow-up period after deferral of revascularisation.

Methods

Data source

Between April 1997 and September 2006, we prospectively enrolled patients with angina referred for evaluation of ≥ 1 intermediate coronary stenosis (40%–70% diameter stenosis at visual assessment) in a series of study protocols [12–14] that included intracoronary pressure and flow measurements during resting and hyperaemic conditions. We excluded patients with ostial stenoses, serial stenoses, severe renal function impairment, significant left main stenosis, atrial fibrillation, myocardial infarction <6 weeks before screening, prior coronary artery bypass surgery (CABG), or visible collateral development to the perfusion territory of interest. The study protocols complied with the Declaration of Helsinki and were approved by the institutional ethics committee. All patients gave written informed consent.

Study procedures and subsequent treatment

Coronary angiography was performed according to standard practice. Quantitative coronary angiography analyses were performed offline using validated software (QCA-CMS version 3.32, MEDIS, Leiden, The Netherlands). Intracoronary nitroglycerin (0.1 μg) was given prior to invasive measurements. Intracoronary pressure and flow was measured with 0.014" pressure and Doppler sensor-equipped guide wires (Philips-Volcano, San Diego, CA, USA) during resting and hyperaemic conditions. Hyperaemia was induced by an intracoronary bolus of adenosine (20–40 μg). Revascularisation was performed at the operator's discretion, and decisions on further treatment and medication during follow-up were entirely left to the discretion of the treating cardiologist [8, 15].

Long-term follow-up

Three-, 6-, 12-month and long-term follow-up was performed by clinical visit or telephone contact to document the occurrence of MACE, defined as the composite of cardiac death, acute myocardial infarction attributable to the target vessel, and clinically driven revascularisation of the target-vessel by CABG or percutaneous coronary intervention (PCI). All patient-reported events were verified and adjudicated after evaluating hospital records or contacting the treating physicians.

Haemodynamic data analysis

The physiological indices were defined as:

- FFR = mean P_d /mean P_a (hyperaemia)
- P_d/P_a = mean P_d /mean P_a (resting conditions)
- CFR = hyperaemic average peak flow velocity (APV)/baseline APV

For dichotomous evaluations, FFR ≤ 0.80 [16], and $P_d/P_a \leq 0.92$ [2] were considered abnormal (Fig. 1).

Statistical analysis

In the presence of multiple stenoses of intermediate severity, one was randomly marked the index stenosis and used for subsequent analyses. Normality of the distribution and homogeneity of variances were tested with the Shapiro-Wilk statistic and Levene's test, respectively. Continuous variables are presented as mean \pm standard deviation or median [1st, 3rd quartile (Q1, Q3)], and compared with Student *t*-test or Mann-Whitney U-test. Categorical variables are presented as frequency (percentage) and compared with Fisher exact test. The prognostic value of FFR and P_d/P_a for 10-year MACE was assessed using Cox regression analyses, adjusted for the effect of relevant clinical characteristics. The best-fit model for adjustment was identified using Akaike's information

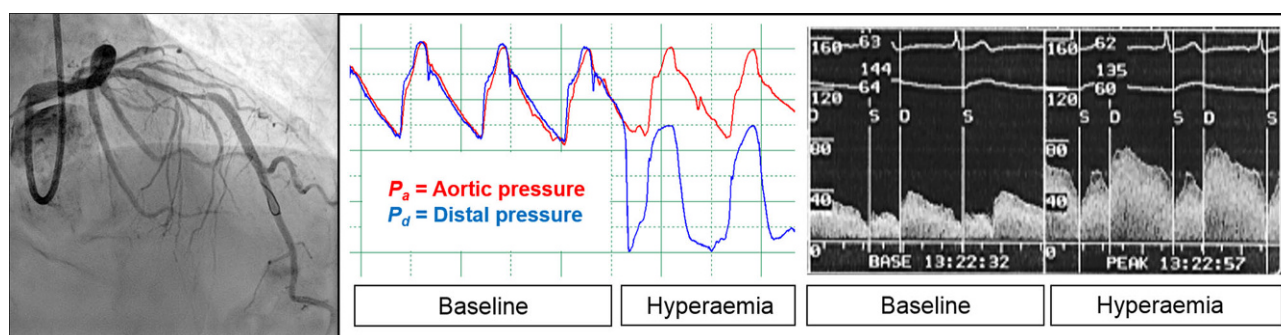


Fig. 1 Example of intracoronary pressure and flow measurements. Resting distal-to-aortic pressure ratio (P_d/P_a) is defined as the distal coronary pressure to aortic pressure ratio during baseline conditions. Fractional flow reserve is defined as the distal coronary pressure to aortic pressure ratio during hyper-

aemic conditions induced by hyperaemic agents. Coronary flow reserve is defined as the coronary flow velocity during hyperaemia to coronary flow velocity during baseline ratio measured distal from the stenosis of interest

Table 1 Demographic, angiographic and physiological characteristics

Number	<i>n</i> = 154
<i>Demographics</i>	
Age, years	61 ± 11
Male	110 (71)
<i>Risk factors for coronary artery disease</i>	
Hypertension	60 (39)
Hyperlipidaemia	89 (58)
Positive family history	76 (49)
Cigarette smoking	48 (31)
Diabetes mellitus	24 (16)
Prior myocardial infarction	57 (37)
Prior PCI	34 (22)
<i>Medication at hospital admission</i>	
Beta-blocker	120 (78)
Nitrates	110 (71)
Calcium antagonists	101 (66)
ACE inhibitors	28 (18)
Statins	87 (56)
Acetylsalicylic acid	149 (97)
<i>Angiographic characteristics</i>	
Reference vessel diameter, mm	2.9 ± 0.6
Diameter stenosis, %	53 ± 8
Minimal lumen diameter	1.4 ± 0.4
<i>Physiological characteristics</i>	
FFR	0.82 (0.76, 0.88)
FFR when FFR ≤ 0.80 (<i>n</i> = 67)	0.74 (0.70, 0.78)
FFR when FFR > 0.80 (<i>n</i> = 87)	0.88 (0.84, 0.92)
P_d/P_a	0.94 (0.91, 0.97)
P_d/P_a when P_d/P_a ≤ 0.92 (<i>n</i> = 53)	0.90 (0.86, 0.91)
P_d/P_a when P_d/P_a > 0.92 (<i>n</i> = 101)	0.97 (0.94, 0.98)
CFR	2.5 (2.1, 2.9)
CFR when CFR < 2.0 (<i>n</i> = 31)	1.8 (1.5, 1.9)
CFR when CFR ≥ 2.0 (<i>n</i> = 123)	2.6 (2.3, 3.1)
Values are number (%), mean ± standard deviation, median (1st, 3rd quartile)	
FFR fractional flow reserve; P_d/P_a resting distal coronary-to-aortic pressure ratio; CFR coronary flow reserve; PCI percutaneous coronary intervention; ACE angiotensin-converting-enzyme	

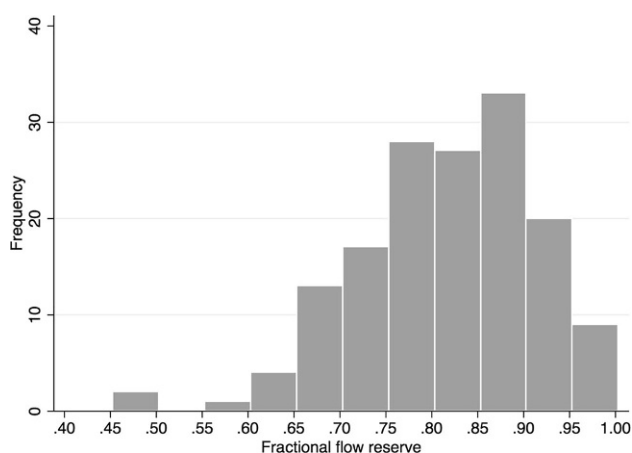


Fig. 2 Distribution of fractional flow reserve values across the study population

criterion, where candidate covariates were: clinical characteristics (Tab. 1) and the interrogated vessel. All Cox proportional-hazards models were preceded by verification of the proportional hazard assumption using Schoenfeld's residuals. Results are presented as standardised hazard ratios (sHRs) and their 95% confidence intervals (CIs), estimated from the Cox proportional-hazard models by exponentiating the β -coefficient multiplied by the $SD[\exp(\beta \times SD)]$. Next, according to their clinical cut-off values, 10-year MACE rates for normal and abnormal FFR and P_d/P_a were estimated using the Kaplan-Meier (KM) method, and differences were tested with the Wilcoxon-Breslow-Gehan test of equality (Breslow p). Finally, KM estimates of 10-year MACE were evaluated across the four quadrants of P_d/P_a and FFR (dis)agreement, where differences were evaluated with Breslow p . A p -value below the 2-sided α -level of 0.05 was considered statistically significant. The STATA 13.1 statistical software package (StataCorp, College Station, TX, USA) was used for all calculations.

Results

Patient population

A total of 228 patients (299 stenoses) were included. Revascularisation was deferred in 159 patients, in 154 of whom (183 stenoses) resting and hyperaemic coronary pressure and flow velocity data and long-term

follow-up were available. In patients with multiple stenoses, one was chosen at random for MACE analyses, which consequently included 154-patients with 154 stenoses. Median follow-up in these patients was 11.8 years (Q1, Q3: 10.0, 13.3 years). Mean age was 60 ± 11 years and 71% of patients were male. Additional baseline characteristics are depicted in Tab. 1.

Angiographic and physiological measurements

The study population comprised angiographically intermediate stenoses, with a mean diameter stenosis of $53 \pm 8\%$, and intermediate physiological severity with a median FFR of 0.82 (Q1, Q3: 0.76, 0.88) (Fig. 2), median P_d/P_a of 0.94 (Q1, Q3: 0.91, 0.97) and median CFR of 2.5 (Q1, Q3: 2.1, 2.9). Stenoses were haemodynamically significant in 43.5% and 34.4% of cases according to FFR and P_d/P_a , respectively. Angiographic and physiological characteristics are depicted in Tab. 1.

Clinical outcome after deferral of revascularisation stratified by FFR and P_d/P_a

The best-fit model for adjustment included angiotensin-converting-enzyme inhibitor use, the presence of diabetes mellitus and age. Cox regression analysis adjusted for these variables demonstrated that FFR and P_d/P_a were both significantly and equivalently associated with long-term MACE [FFR-sHR: 0.77 (95% CI: 0.61–0.98), $p=0.033$; P_d/P_a -sHR: 0.80 (95% CI: 0.67–0.96), $p=0.014$] (Tab. 2). Fig. 3 shows the KM curves for cumulative MACE up to 10 years of follow-up according to normal or abnormal results for FFR and P_d/P_a . At 10-year follow-up, the KM estimate of MACE was not significantly different for stenoses with abnormal versus normal FFR (FFR ≤ 0.80 : 45.8% vs FFR > 0.80 : 34.4%; Breslow $p=0.17$; Fig. 3a). In contrast, the KM estimate of MACE at 10-year follow-up for stenoses with abnormal P_d/P_a was significantly higher than for stenoses with normal P_d/P_a ($P_d/P_a \leq 0.92$: 52.0% vs $P_d/P_a > 0.92$: 32.7%; Breslow $p=0.006$; Fig. 3b).

Clinical outcome according to discordance between FFR and P_d/P_a

P_d/P_a agreed with FFR in 71% of stenoses (110 out of 154), of which 25% of the stenoses (38 out of 154)

Table 2 Univariate and adjusted Cox regression analyses for long-term major adverse cardiac events

Overall study population ($n=154$)					
Univariate analysis			Adjusted analysis ^a		
Variable	sHR (95%CI)	p -value	Variable	sHR (95%CI)	p -value
P_d/P_a	0.76 (0.63–0.91)	0.003	P_d/P_a	0.80 (0.67–0.96)	0.014
FFR	0.76 (0.59–0.98)	0.034	FFR	0.77 (0.61–0.98)	0.033

Data presented as standardised hazard ratio and its 95% confidence interval
^aAdjusted for angiotensin-converting enzyme inhibitor, the presence of diabetes mellitus and age
sHR standardised hazard ratio; P_d/P_a resting distal coronary-to-aortic pressure ratio; FFR fractional flow reserve

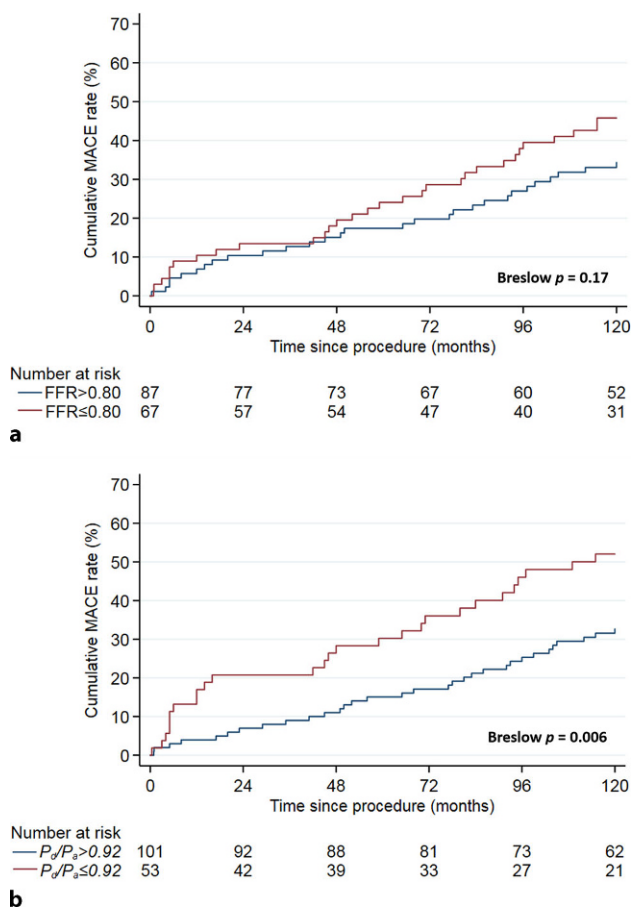


Fig. 3 Kaplan-Meier estimates of major adverse cardiac event (MACE) rate during 10 years of follow-up, stratified by: **a** fractional flow reserve (FFR); FFR ≤ 0.80 was considered abnormal. **b** Resting distal coronary-to-aortic pressure ratio (P_d/P_a). $P_d/P_a \leq 0.92$ was considered abnormal

were concordant abnormal, and 47% of stenoses (72 out of 154) were concordant normal. P_d/P_a disagreed with FFR in 29% of stenoses (44 out of 154), and was characterised by abnormal FFR and normal P_d/P_a in 19% of stenoses (29 out of 154) and by normal FFR and abnormal P_d/P_a in 10% of stenoses (15 out of 154) (Fig. 4a). Fig. 4b depicts the KM curves for cumulative MACE up to 10-year follow-up stratified by P_d/P_a and FFR agreement. A normal P_d/P_a was generally associated with a favourable clinical outcome, regardless of the accompanying FFR value, whereas abnormal P_d/P_a was generally associated with an impaired clinical outcome, regardless of the accompanying FFR value (overall Breslow $p = 0.04$).

Agreement with CFR

CFR was significantly different across the four quadrants of P_d/P_a and FFR (dis)agreement (Tab. 3). A normal P_d/P_a was generally associated with high CFR and an abnormal P_d/P_a was generally associated with CFR values around the ischaemic cut-off, regardless of the accompanying FFR value (overall $p = 0.006$).

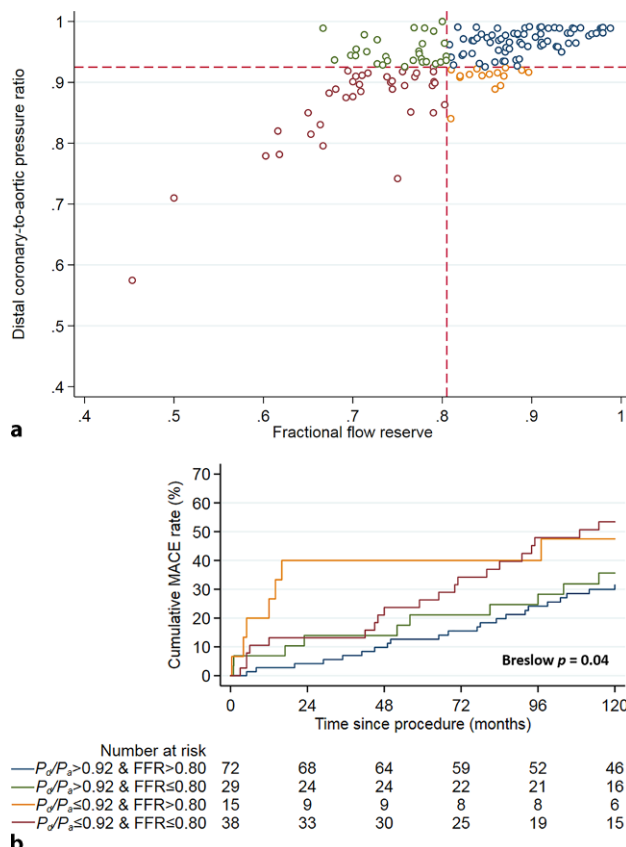


Fig. 4 **a, b** Discordance between resting distal coronary to aortic pressure ratio (P_d/P_a) and fractional flow reserve (FFR). **a** Scatterplot of P_d/P_a and FFR. The dotted lines represent the respective cut-off values for P_d/P_a (0.92), and FFR (0.80). **b** Kaplan-Meier estimates of major adverse cardiac event (MACE) rate during 10 years of follow-up, stratified by P_d/P_a -FFR discordance

Discussion

The current article is the first to document that P_d/P_a demonstrates a continuous and independent relationship with subsequent long-term clinical outcomes which is at least equivalent to that of FFR, and that P_d/P_a exceeds FFR as a risk stratification tool at the contemporary clinical cut-off values. When discordance with FFR occurs, P_d/P_a may therefore confer superior clinical value.

Prognostic relevance of resting versus hyperaemic stenosis pressure drops

The superior prognostic relevance of resting P_d/P_a over FFR at contemporary cut-offs may be explained by a better agreement of P_d/P_a with coronary flow. Our observations support those of previous studies that demonstrated a better relationship between resting indices and Doppler-derived CFR than for FFR and Doppler-derived CFR [3, 6, 7]. It has been documented that, when FFR disagrees with CFR, CFR has superior prognostic value over FFR for long-term

Table 3 Study population characteristics according to FFR— P_d/P_a disagreement

	FFR > 0.80 and $P_d/P_a > 0.92$	FFR ≤ 0.80 and $P_d/P_a > 0.92$	FFR > 0.80 and $P_d/P_a ≤ 0.92$	FFR ≤ 0.80 and $P_d/P_a ≤ 0.92$	Overall p -value
Number of patients	72	29	15	38	
<i>Demographics</i>					
Age, years	61 ± 11	57 ± 11	66 ± 8	60 ± 11	0.09
Male gender, n (%)	51 (71)	22 (76)	7 (47)	30 (78)	0.14
<i>Coronary risk factors</i>					
Hypertension, n (%)	43 (60)	8 (28)	9 (60)	14 (37)	0.22
Hyperlipidaemia, n (%)	41 (57)	17 (59)	8 (53)	23 (61)	0.97
Positive family history, n (%)	33 (46)	14 (48)	9 (60)	20 (53)	0.76
Cigarette smoking, n (%)	20 (28)	9 (31)	2 (13)	17 (45)	0.13
Diabetes mellitus, n (%)	9 (13)	8 (28)	3 (20)	4 (11)	0.2
Prior myocardial infarction, n (%)	33 (46)	8 (28)	3 (20)	13 (34)	0.15
Prior PCI, n (%)	20 (28)	8 (28)	2 (13)	4 (11)	0.14
<i>Medication at hospital admission</i>					
Beta-blocker, n (%)	57 (79)	24 (83)	10 (67)	29 (76)	0.63
Nitrates, n (%)	51 (71)	19 (66)	12 (80)	28 (74)	0.8
Calcium antagonists, n (%)	44 (61)	17 (59)	11 (73)	29 (76)	0.31
ACE inhibitors, n (%)	15 (21)	2 (7)	2 (13)	9 (24)	0.28
Lipid-lowering drugs, n (%)	39 (54)	15 (52)	9 (60)	24 (63)	0.77
Acetylsalicylic acid, n (%)	69 (96)	29 (100)	15 (100)	36 (95)	0.76
<i>Angiographic characteristics</i>					
Diameter stenosis, %	53 (44–57)	55 (50–62)	51 (47–56)	55 (50–58)	0.46
Reference diameter, mm	3.0 (2.6–3.5)	2.7 (2.5–3.3)	2.8 (2.5–3.0)	2.6 (2.3–3.1)	0.09
Minimal lumen diameter, mm	1.5 (1.1–1.7)	1.2 (1.1–1.6)	1.3 (1.1–1.5)	1.2 (1.1–1.3)	0.03
<i>Physiological characteristics</i>					
APV basal, cm/s	15 (12–18)	18 (13–24)	16 (13–24)	17 (11–21)	0.19
APV hyperaemia, cm/s	38 (31–48)	38 (31–55)	38 (29–54)	36 (30–45)	0.68
CFR	2.6 (2.2–3.0)	2.5 (1.9–2.9)	2.2 (1.8–2.8)	2.2 (1.8–2.7)	0.006
FFR	0.89 (0.85–0.93)	0.78 (0.73–0.78)	0.85 (0.82–0.87)	0.71 (0.67–0.76)	0.001
P_d/P_a	0.97 (0.96–0.98)	0.94 (0.94–0.96)	0.91 (0.91–0.92)	0.89 (0.85–0.91)	0.001

Values are number (%), mean ± standard deviation, median (1st, 3rd quartile)

FFR fractional flow reserve; P_d/P_a resting distal coronary-to-aortic pressure ratio; PCI percutaneous coronary intervention; ACE angiotensin converting enzyme; APV average peak flow velocity; CFR coronary flow reserve

clinical outcomes [8, 9, 15]. This is likely due to the fact that FFR and CFR move in opposite directions from resting conditions to hyperaemia: FFR decreases and becomes more abnormal, while CFR increases and becomes more normal. Hence, the combination of an abnormal FFR and normal P_d/P_a may occur on the basis of a normal P_d/P_a value that decreases to abnormal FFR values at hyperaemia due to a large increase in coronary flow with a normal CFR. Such stenoses are considered non-flow-limiting, and likely have excellent clinical outcomes when managed medically [8, 9, 15, 17, 18]. On the other hand, an abnormal P_d/P_a may occur in combination with a normal FFR when a stenosis may coexist

with an exhausted CFR as a result of compensatory vasodilation during resting conditions to maintain resting perfusion. The abnormal P_d/P_a may only decrease to normal FFR values due to the limited increase in coronary flow from baseline to hyperaemia. The optimal management of vessels exhibiting this haemodynamic pattern remains a matter of debate [19]. Since myocardial function thrives on coronary flow and not on perfusion pressure, reductions in distal coronary perfusion, however, should not be associated with impaired myocardial function as long as adequate coronary flow is present [20]. This is supported by a recent randomised study documenting excellent clinical outcomes when magnetic resonance

imaging-defined perfusion deficits were used to guide coronary intervention [18]. Since myocardial function and clinical outcomes are determined by coronary flow independent of coronary pressure [8, 9, 15, 20], and P_d/P_a has better agreement with invasively measured coronary flow than FFR [3], this may provide an explanation why P_d/P_a has superior prognostic value when there is disagreement with FFR.

Comparison with previous FFR studies

Importantly, our observation that there was no difference in clinical outcomes between FFR-positive and FFR-negative cases might wrongly be interpreted to be in contrast with the findings from FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) and FAME II [16, 21]. FAME compared FFR versus angiography for guidance of revascularisation and documented superior clinical outcome using a FFR-guided revascularisation strategy. FAME II compared PCI+optimal medical therapy (OMT) versus OMT for treatment of FFR-positive lesions and documented superior clinical outcome for lesions treated with PCI+OMT. It is important to note that the average FFR in FFR-positive stenosis in FAME was 0.60 ± 0.14 [21]. In FAME II, the average FFR in FFR-positive stenoses amounted to 0.68 ± 0.10 in the medical therapy group and 0.68 ± 0.15 in the PCI group [16]. Hence, the stenoses included in the FAME studies were physiologically much more severe than those encountered typically in contemporary daily practice. Most importantly, among these severe stenoses in the FAME II study, around 60% of lesions in the medical therapy group did not require any coronary intervention within 2 years after initial deferral from revascularisation—a result that is consistent up to 5-year follow-up. The present study involves true physiologically intermediate stenoses as typically encountered in daily practice (Tab. 1; [2, 10, 11, 18]). This is relevant for the observed differences in clinical outcomes compared with the FAME studies: FFR reflects a risk continuum, where risk for adverse events becomes higher with decreasing FFR [22]. This risk continuum for FFR was also noted in the Cox regression analysis for FFR in the present study. However, the FAME II trial showed that the benefit of revascularisation was supreme in vessels with $FFR < 0.65$. Similarly, a recent patient-level meta-analysis on the prognostic value of FFR identified an optimal 0.67 FFR threshold for clinical outcomes [22]. These findings support the lack of a difference in MACE between $FFR \leq 0.80$ and > 0.80 in the present study, where, similar to daily clinical practice, most FFR values in FFR-positive stenoses were > 0.70 and therefore above the FFR thresholds associated with impaired clinical outcomes.

Limitations

The relatively small sample size limits the statistical power and the strength of the conclusions, especially for the discordant groups. We used intracoronary administration of 20–40 μg of adenosine, which remains a subject for debate. However, it has been documented that the observed FFR is already within 0.02 of its minimal value at intracoronary adenosine dosages above 23 μg [23]. Since the test/retest repeatability of FFR itself has a standard deviation of 0.02 [24], FFR differences < 0.02 are smaller than the variability of the FFR measurement itself and, therefore, are considered clinically irrelevant [23]. It is therefore unlikely that the dose of adenosine has interfered with the results in the present study. This is supported by the limited differences in FFR values derived from low-dose intracoronary versus intravenous adenosine administration [25], and by the fact that such small differences in FFR between intravenous and intracoronary adenosine were documented to be clinically irrelevant in the DEFER trial [26]. Additionally, this study is limited by the assessment of adverse events at long-term follow-up partly performed by telephone contact. Such an approach is sensitive towards patient recall bias, which may result in under-reporting of adverse events. Nonetheless, the long-term MACE rates reported in the present study are comparable with those reported in contemporary studies using FFR guidance [26, 27].

Conclusion

The present study documents that P_d/P_a demonstrates a continuous and independent relationship with subsequent long-term clinical outcomes which is at least equivalent to that of FFR, and suggests that P_d/P_a exceeds FFR as a risk stratification tool at its contemporary cut-off value.

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M. Voskuil, R.J. de Winter and J.G.P. Tijssen declare that they have no competing interests.

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