International Journal of Cardiology 279 (2019) 6–11

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Pressure-derived estimations of coronary flow reserve are inferior to flow-derived coronary flow reserve as diagnostic and risk stratification tools

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ARTICLE INFO

Article history:
Received 5 July 2018
Received in revised form 25 October 2018
Accepted 5 November 2018
Available online 7 November 2018

Keywords:
Pressure-derived coronary flow reserve
Pressure-bounded coronary flow reserve
Coronary flow reserve
Long-term clinical outcome

ABSTRACT

Background: Pressure-derived coronary flow reserve (CFR_{pres}) and pressure-bounded CFR (CFR_{pb}) enable simple estimation of CFR from routine pressure measurements, but have been inadequately validated. We sought to compare CFR_{pres} and CFR_{pb} against flow-derived CFR (CFR_{flow}) in terms of diagnostic accuracy, as well as regarding their comparative prognostic relevance.

Methods: We evaluated 453 intermediate coronary lesions with intracoronary pressure and flow measurements. CFR was defined as hyperemic flow/baseline flow. The lower bound (CFR_{pres}) and upper bound of CFR_{pb} were defined as $\sqrt{[(\Delta P_{hyperemia}) / (\Delta P_{rest})]}$ and $[(\Delta P_{hyperemia}) / (\Delta P_{rest})]$, respectively. Long-term follow-up (median: 11.8-years) was performed in 153 lesions deferred from treatment to document the occurrence of major adverse cardiac events (MACE) defined as a composite of cardiac death, myocardial infarction and target vessel revascularization. CFR < 2.0 was considered abnormal.

Results: CFR_{pb} was normal or abnormal in 56.7% of stenoses, and indeterminate in 43.3% of stenoses. There was a poor diagnostic agreement between CFR_{pres} and CFR_{pb} with CFR_{flow} (overall agreement: 45.5% and 71.6% of vessels, respectively). There was equivalent risk for long-term MACE for lesions with abnormal versus normal CFR_{pres} (Breslow $p = 0.562$), whereas vessels with abnormal CFR_{flow} were significantly associated with increased long-term MACE (Breslow $p < 0.001$). For vessels where CFR_{pb} was abnormal or normal, there was equivalent risk for long-term MACE for vessels with abnormal versus normal CFR_{pb} (Breslow $p = 0.194$), whereas vessels with abnormal CFR_{flow} were associated with increased MACE rates over time (Breslow $p < 0.001$).

Conclusions: Pressure-derived estimations of CFR poorly agree with flow-derived measurements of CFR, which may explain the inferior association with long-term MACE as compared to flow-derived CFR.

1. Introduction

Coronary flow reserve (CFR) is an established index that interrogates the functional status of both the epicardial and microcirculatory compartments of the coronary circulation [1]. Although CFR is among the most well-studied coronary physiology parameters in terms of ischemic heart disease prognosis, its invasive assessment can be technically challenging [2]. As a result, the pressure-derived fractional flow reserve (FFR) and instantaneous-wave free ratio (iFR) are now dominantly used to guide revascularization decision-making. Nonetheless, novel insights into the multi-level origin of IHD have fueled interest in the combined assessment of FFR and CFR, which allows specific separation between epicardial and microvascular involvement in IHD [3–6]. Following the technical difficulties of invasive coronary flow assessment, the calculation of CFR from routine coronary pressure measurements has been proposed as an alternative, simpler approach for CFR estimation [7]. Two concepts to estimate CFR from pressure measurements have been studied, the pressure-derived CFR (CFR_{pres}) [8,9], and the pressure-bounded CFR (CFR_{pb}) [10,11]. Nonetheless, both pressure-derived estimations of CFR have only been validated in small sample sizes, and their prognostic value was not compared to CFR_{flow}. The aim of the

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https://doi.org/10.1016/j.ijcard.2018.11.013
0167-5273/

present study was to compare CFR_{pres} and CFR_{pb} against CFR_{flow} in terms of diagnostic accuracy, as well as regarding their comparative prognostic relevance in a large cohort of patients with coronary stenoses of intermediate severity.

2. Methods

2.1. Data source

Between April-1997 and December-2014, we evaluated patients with coronary artery disease (CAD) referred for intracoronary evaluation of at least one intermediate coronary stenosis (40–70% diameter stenosis) in a series of consecutive study protocols [12–16]. Patient and procedural characteristics were entered into a dedicated database. All patients were evaluated in the Academic Medical Center, Amsterdam, The Netherlands (AMC), and Hospital Universitario Clinico San Carlos, Madrid, Spain (HUCSC). Patients with ostial stenoses, culprit vessels of acute coronary syndromes, serial stenoses, severe renal function impairment (MDRD calculated glomerular filtration rate < 30 mL/min/1.73 m^2), significant left main coronary artery stenosis, atrial fibrillation, recent myocardial infarction (<6 weeks before screening), prior coronary artery bypass graft surgery, or visible collateral development to the perfusion territory of interest were excluded. The institutional ethics committees approved the study protocols and all patients gave written informed consent.

2.2. Cardiac catheterization and hemodynamic measurements

Coronary angiography was performed in a manner suitable for quantitative coronary angiography-analysis (QCA). Intracoronary nitroglycerin (0.2 mg) was given before invasive measurements. In AMC, coronary flow and pressure was assessed sequential using Doppler sensor-equipped and pressure-sensor equipped guide-wires (Philips-Volcano, San Diego, CA). In HUCSC, coronary flow and pressure was assessed simultaneous by guide-wires equipped with temperature-sensitive pressure-sensors (Abbott-St. Jude Medical, St. Paul, MN) utilizing the thermodilution-technique. Pressure-sensors were equalized and normalized with aortic pressure, whereafter sensor-equipped guide-wires were positioned at least three vessel-diameters distal from the stenosis. At AMC, flow and pressure were determined during baseline and at peak hyperemia after intracoronary bolus injection of 20–40 μg adenosine for both the right and left coronary artery systems, and maximal values were averaged over three-heartbeats. At HUSCS, flow and pressure were determined during baseline and maximal stable hyperemia following two minutes of intravenous infusion of adenosine (140 μg/kg/min). After the procedure, sensor-equipped guide wires were pulled-back to the catheter to document pressure-drift. In the occurrence of clinical relevant pressure-drift (>2 mm Hg) measurements were repeated.

2.3. Data analysis

QCA was performed offline to determine percentage diameter stenosis with the use of validated automated contour detection algorithms. Doppler-derived CFR was defined as the ratio of hyperemic average peak velocity (hAPV) to baseline average peak velocity (bAPV), and thermodilution-derived CFR was defined as the ratio of the hyperemic average mean transit time (Tmn-hyp) to baseline average mean transit time (Tmn-bas) of three intracoronary bolus injections of saline. Distal coronary and aortic pressure was matched with Tmn for each baseline and hyperemic saline injections, and values were averaged. Doppler flow-derived and thermodilution-derived CFR datasets were merged and the term CFR_{flow} was used. CFR_{flow} < 2.0 was considered abnormal.

2.4. Theory and calculation of pressure-derived CFR and pressure-bounded CFR

The total pressure drop across a stenosis is the sum of viscous friction losses along the entrance and throat of the lesion that increase with flow linearly (Poiseuille's Law), and losses incurred by convective acceleration along the narrowed section (Bernoulli's Law) and increase with the square of flow. The relationship between the flow through a stenosis and the pressure drop over a stenosis is generally described as.

$$\Delta P = f \cdot Q + s \cdot Q^2$$

where ΔP is the pressure drop across the stenosis, Q is coronary flow across the stenoses, f is the coefficient of pressure loss due to viscous friction and s is the coefficient of pressure loss due to flow separation. The coefficients f and s are a function of stenosis geometry and rheological properties of blood [1].

The theory and calculation of pressure-derived estimations of CFR are explained in detail in the Supplementary materials. The concept of CFR_{pres} assumes that the stenosis pressure gradient is dominantly determined by separation losses, while the contribution of viscous friction losses is considered negligible [7]. CFR_{pres} can then be calculated as:

$$\text{CFRpres} = \sqrt{\left[\left(\Delta P_{hyperemia}\right)/\left(\Delta P_{rest}\right)\right]}$$

The concept of CFR_{pb} assumes that the stenosis pressure gradient may either be governed by friction losses alone on one end of the spectrum, or by separation losses on the other end. Thereby CFR_{pb} appraises the lower and upper extreme of CFR_{pb} to bound the range of actual CFR [10,11]. The lower bound of CFR_{pb} is reflected by the situation where pressure loss across a stenosis arises solely from separation losses and, therefore, equals CFR_{pres}.

$$\text{Lower bound } CFR_{pb} = \sqrt{\left[\left(\Delta P_{hyperemia}\right)/\left(\Delta P_{rest}\right)\right]}$$

The upper bound of CFR_{pb} is reflected by the situation where pressure loss across a stenosis arises solely from friction losses. Upper bound CFR_{pb} can then be calculated as:

$$\text{Upper bound } CFR_{pb} = \left(\Delta P_{hyperemia}\right)/\left(\Delta P_{rest}\right)$$

CFR_{pb} can then be bounded as:

$$\sqrt{\left[\left(\Delta P_{hyperemia}\right)/\left(\Delta P_{rest}\right)\right]} \le CFR \le \left[\left(\Delta P_{hyperemia}\right)/\left(\Delta P_{rest}\right)\right]$$

CFR_{pres} < 2.0 was considered abnormal. CFR_{pb} was determinate abnormal when both the upper and lower bounds of CFR_{pb} were < 2.0, whereas CFR_{pb} was determinate normal when both the upper and lower bound of CFR_{pb} were ≥ 2.0. In all other cases, CFR_{pb} was indeterminate.

2.5. Long-term follow-up

In AMC, 3-, 6-, 12-month, and long-term follow-up was performed by a clinical visit or by telephone contact to document the occurrence of major adverse cardiac events (MACE). MACE was defined as the composite of cardiac death, acute myocardial infarction not clearly attributable to a non-index vessel, and clinically driven (urgent) revascularization of the index vessel by means of coronary artery bypass graft surgery or PCI. All patient-reported adverse events were verified by evaluating hospital records or contacting the treating cardiologist or general practitioner.

2.6. Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or median + interquartile rangen and differences between groups were compared with one-way ANOVA or Kruskal-Wallis, as appropriate. Categorical variables are presented as counts (percentages), and were compared with Chi-square test. Correlation between CFR_{pres} and CFR_{flow} was tested by Spearman-Rho and continuous agreement was assessed by Bland-Altman and Passing-Bablok analyses. Classification agreement between CFR_{pres}/CFR_{pb} and CFR_{flow} ($CFR_{Doppler}$ and CFR_{thermo}) were tested by Cohen's kappa. Agreement between $CFR_{Doppler}$ or CFR_{thermo} and CRF_{pb}/CFR_{pres} are visualized in the Supplementary materials. Ten-year MACE-rates for normal and abnormal CFR_{pres}/CFR_{pb} and CFR_{flow} were estimated using the Kaplan Meier (KM)-method. Statistical significance of differences in event rates was assessed with the use of the Wilcoxon-Breslow-Gehan test of equality (Breslow p). The prognostic value of CFR_{pres}, CFR_{pb} and CFR_{flow} 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 criterion, where candidate covariates were clinical characteristics (Table 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 standardized-hazard ratios (sHRs) and their 95%-confidence intervals (CIs), which were estimated from the Cox-proportional hazard models by exponentiating the β-coefficient multiplied by the standard deviation (exp[β × SD]). A p-value below the 2-sided α-level of 0.05 was considered statistically significant. The Stata 13 (StataCorp LP, College Station, TX) software package was used for all calculations.

3. Results

3.1. Patients

Combined pressure and flow data were obtained in 362-patients (466-stenoses). We excluded 13-stenoses (2.8%) with a resting stenosis pressure drop <1 mmHg, leaving 354 patients (453-stenoses) for analysis; 298-vessels studied with Doppler flow velocity, and 155-vessels studied with thermodilution. Baseline demographic, procedural, and physiological characteristics of the patients are depicted in Table 1. Overall, coronary stenoses were of angiographic and physiologic intermediate severity (diameter stenosis: 53.0 ± 11.2%; FFR: 0.81 (Q1, Q3: 0.72, 0.88).

3.2. Relationship between CFR_{pres} and CFR_{flow}

The relationship between CFR_{pres} and CFR_{flow} is shown in Fig. 1. There was a modest correlation between CFR_{pres} and CFR_{flow} ($\rho = 0.44$,

Table 1
Baseline characteristic and physiologic outcome.

	Overall population	MACE analysis
Patients	N = 354	N = 153
Demographics		
Age, years	62 ± 11	61 ± 11
Male gender	264 (74.6)	109 (71.2)
Risk factors for coronary artery disease		
Hypertension	176 (49.7)	59 (38.6)
Hyperlipidemia	217 (61.3)	88 (57.5)
Positive family history	121 (34.2)	76 (49.7)
Cigarette smoking	103 (29.1)	48 (31.4)
Diabetes mellitus	70 (19.8)	24 (15.7)
Prior myocardial infarction	150 (42.4)	57 (37.3)
Prior PCI	113 (31.9)	33 (21.6)
Medication prior to admission		
Beta-blocker	273 (77.1)	119 (77.8)
Nitrates	225 (63.6)	109 (71.2)
Calcium antagonists	232 (65.5)	100 (65.4)
ACE-inhibitors	76 (21.5)	28 (18.3)
Statins	218 (61.6)	86 (56.2)
Aspirin	336 (94.9)	148 (96.7)
Lesions	N = 453	N = 153
Angiographic parameters		
Diameter stenosis (%)	53.0 ± 11.2	52.7 ± 8.3
Mean lumen diameter (mm)	1.30 ± 0.42	1.37 ± 0.39
Reference diameter (mm)	2.88 ± 0.0.66	2.90 ± 0.62
Physiologic outcome		
P_d/P_a	0.93 (0.88, 0.96)	0.94 (0.91, 0.97)
FFR	0.81 (0.72, 0.88)	0.82 (0.76, 0.88)
ΔP-hyperemia (mm Hg)	16.0 (10.0, 25.0)	17.0 (11.0, 23.0)
ΔP-baseline (mm Hg)	7.0 (3.0, 11.0)	6.0 (2.0, 9.0)
Δ-P_d/P_a	0.1 (0.06, 0.16)	0.12 (0.06, 0.16)
CFR_{flow}	2.2 (1.5, 2.7)	2.5 (2.1, 2.9)
$CFR_{pb\ upper\ bound}$	2.3 (1.6, 3.5)	2.9 (2.0, 4.7)
$CFR_{pb\ lower\ bound}$ (CFR_{pres})	1.5 (1.3, 1.9)	1.7 (1.4, 2.2)

Values are mean ± SD or N (%).
PCI = percutaneous coronary intervention, ACE = angiotensin converting enzyme, P_d/P_a = coronary distal-to-aortic pressure ratio, FFR = fractional flow reserve, $\Delta P = P_a$-P_d, Δ-P_d/P_a = (P_d/P_a-FFR), CFR_{flow} = flow-derived coronary flow reserve (CFR), CFR_{pb} = pressure-bounded CFR, CFR_{pres} = pressure-derived CFR.

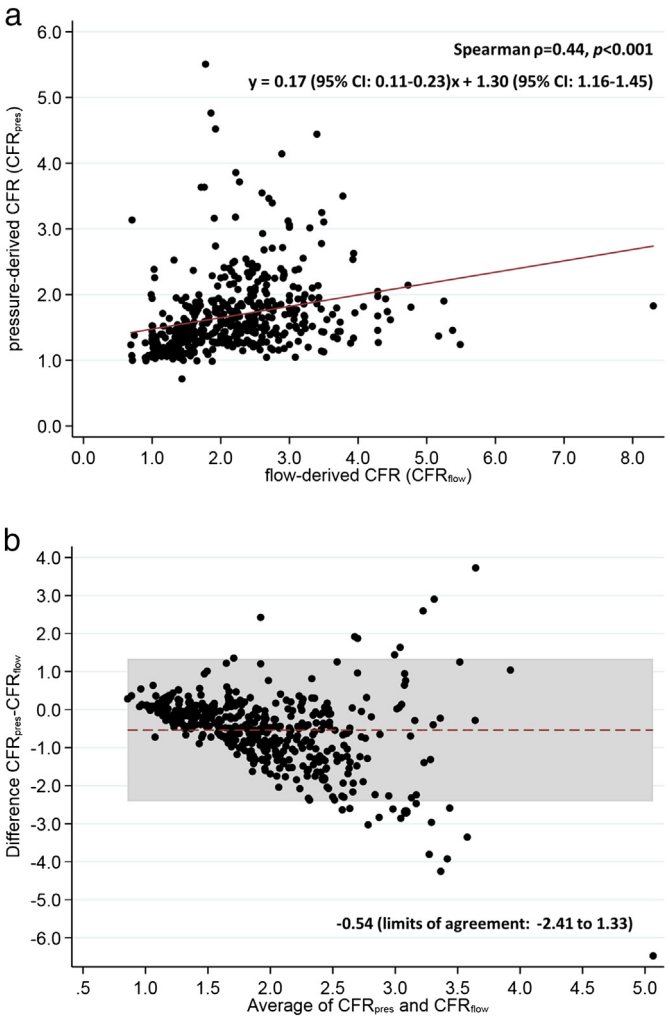

Fig. 1. Relationship between pressure-derived coronary flow reserve (CFR_{pres}) and flow-derived CFR ($CFR_{flow.}$); A) Scatterplot of CFR_{pres} and $CFR_{flow,}$ and B) Bland-Altman analysis of agreement for CFR_{pres} and CFR_{flow}.

p < 0.001) (Fig. 1A). Passing-Bablok analysis revealed a significant constant (Coefficient A: 0.66 (95%-CI: 0.55–0.78)) and proportional (Coefficient B: 0.43 (95%-CI: 0.36–0.50)) difference between the methods. Bland-Altman analyses revealed significant bias of −0.54 ± 0.95 (limits of agreement: −2.41, 1.33) (Fig. 1B).

CFR_{pres} was abnormal in 79.5% of stenoses (360 out of 453) and CFR_{flow} was abnormal in 41.5% of stenoses (188 out of 453). CFR_{pres} agreed with CFR_{flow} in 54.5% of stenoses (247 out of 453), of which CFR_{pres} and CFR_{flow} were concordant abnormal in 37.7% of stenosis (171 out of 453) and concordant normal in 16.8% of stenosis (76 out of 453). CFR_{pres} disagreed with CFR_{flow} in 45.5% of stenoses (206 out of 453), of which CFR_{pres} was abnormal and CFR_{flow} normal in 41.7% of stenosis (189 out of 453) and CFR_{pres} normal and CFR_{flow} abnormal in 3.8% of stenosis (17 out of 453). Accordingly, agreement between CFR_{pres} and CFR_{flow} was poor (Cohen's kappa coefficient: CFR_{flow} 0.173 ($CFR_{Doppler}$ 0.187; CFR_{thermo} 0.093)).

3.3. Relationship between CFR_{pb} and CFR_{flow}

CFR_{flow} was within the bounds of CFR_{pb} in 44.1% of stenoses (200 out of 453), CFR_{flow} was lower than the CFR_{pb} lower bound in 22.5% of stenoses (102 out of 453), and CFR_{flow} was higher than the CFR_{pb} upper bound in 33.3% of stenoses (151 out of 453) (Supplementary Table 1).

CFR_{pb} was determinate in 56.7% of stenosis (257 out of 453). Of these, CFR_{pb} was abnormal in 63.8% of stenoses (164 out of 257) and CFR_{flow} was abnormal in 48.6% of stenosis (125 out of 257). CFR_{pb} agreed with CFR_{flow} in 71.6% of stenoses (184 out of 257), of which CFR_{pb} and CFR_{flow} were concordant abnormal in 42.0% of stenosis (108 out of 257) and concordant normal in 29.6% of stenosis (76 out of 257). CFR_{pb} disagreed with CFR_{flow} in 28.4% of stenoses (73 out of 257), of which CFR_{pb} was abnormal and CFR_{flow} normal in 21.8% of stenosis (56 out of 257) and CFR_{pb} normal and CFR_{flow} abnormal in 6.6% of stenosis (17 out of 257) (Supplementary Table 2). Accordingly, agreement between CFR_{pb} and CFR_{flow} was poor (Cohen's kappa-coefficient: CFR_{flow} 0.436 ($CFR_{Doppler}$ 0.496; CFR_{thermo} 0.242)).

3.4. Clinical outcome after deferral of revascularization stratified by CFR_{pres}, CFR_{pb} and CFR_{flow}

Long-term clinical outcomes were available in 153 patients (182-stenoses) deferred from revascularization, which were enrolled at AMC. In patients with multiple stenoses, one was chosen at random for MACE-analyses, which consequently included 153-patients and 153-stenoses. Median follow-up was 11.8-years (Q1, Q3: 10.0, 13.3-years). Baseline characteristic for these patients are depicted in Table 1. CFR_{flow} was determined by Doppler flow velocity in all 153 patients.

CFR_{pres} was abnormal in 67% of stenoses (103 out of 153), and CFR_{flow} was abnormal in 20.3% of stenoses (31 out of 153). The KM-estimate of MACE for stenoses with abnormal CFR_{flow} was significantly higher than for stenoses with normal CFR_{flow} (CFR_{flow} < 2.0: 62.3% vs. CFR_{flow} ≥ 2.0: 32.8%, Breslow p < 0.001: Fig. 2B). Whereas, the KM-estimate of MACE was not significantly different for stenoses with

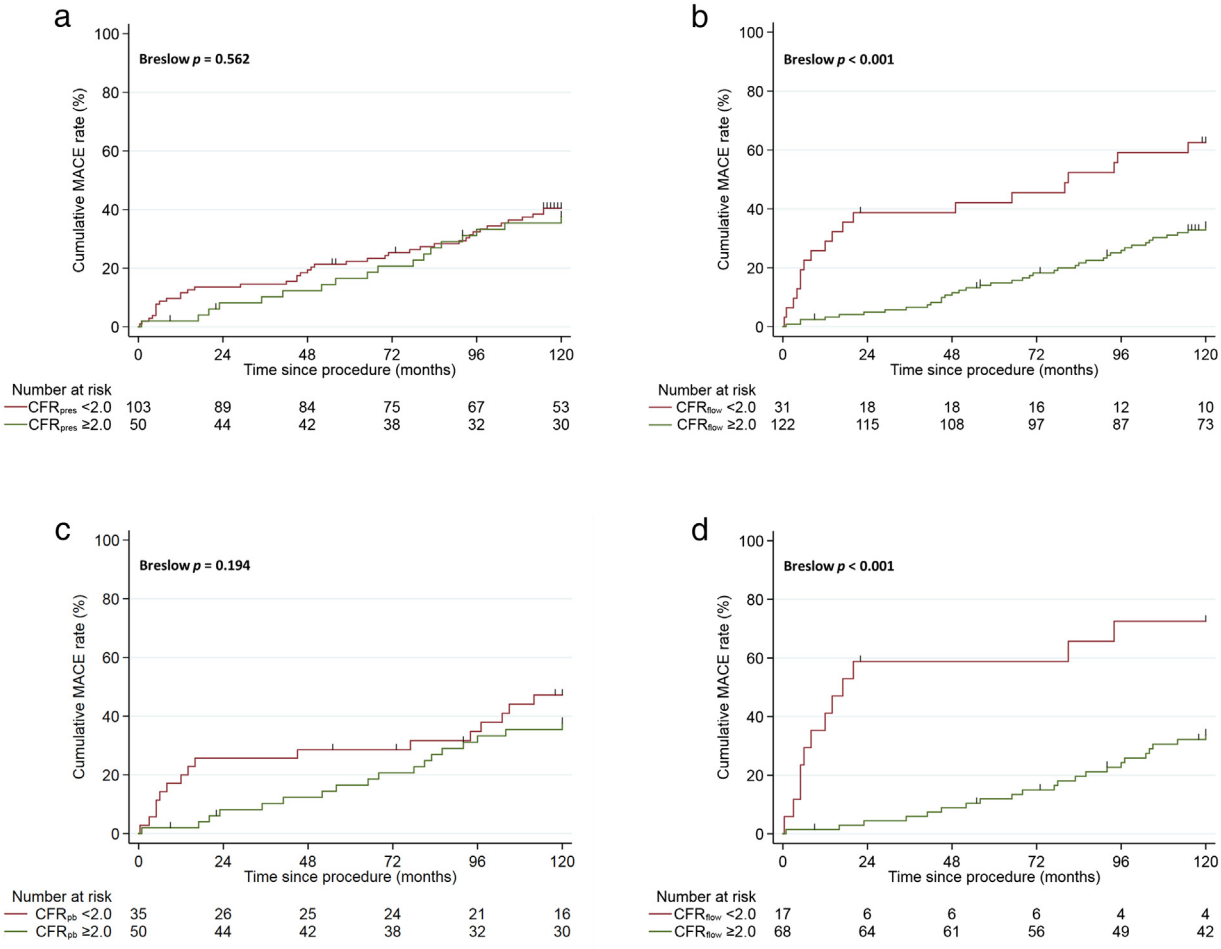

Fig. 2. Kaplan Meier estimates of major adverse cardiac event (MACE) rate during 10-years of follow-up, stratified by: A) pressure-derived coronary flow reserve (CFR_{pres}), CFR_{pres} < 2.0 was considered abnormal; B) flow-derived CFR (CFR_{flow}); C) pressure-bounded coronary flow reserve (CFR_{pb}); D) CFR_{flow} for vessels with abnormal or normal CFR_{pb}. CFR_{pres}, CFR_{pb} and CFR_{flow} < 2.0 was considered abnormal.

abnormal versus normal CFR_{pres} (CFR_{pres} < 2.0: 40.5% vs. CFR_{pres} ≥ 2.0: 37.6%; Breslow p = 0.562: Fig. 2A).

CFR_{pb} was determinate in 55.6% of stenosis (85 out of 153). Of these, CFR_{pb} was abnormal in 41.2% of stenoses (35 out of 86) and CFR_{flow} was abnormal in 20.0% of stenoses (17 out of 85). The KM-estimate of MACE for stenoses with abnormal CFR_{flow} was significantly higher than for stenoses with normal CFR_{flow} (CFR_{flow} < 2.0: 72.6% vs. CFR_{flow} ≥ 2.0: 33.8%, Breslow p < 0.001: Fig. 2D). Whereas, the KM-estimate of MACE was not significantly different for stenoses with abnormal versus normal CFR_{pb} (CFR_{pb} < 2.0: 47.2% vs. CFR_{pb} ≥ 2.0: 37.6%; Breslow p = 0.194: Fig. 2C).

The best-fit model for adjustment included angiotensin-converting-enzyme inhibitor use, the presence of diabetes mellitus, and age at the time of the index procedure. Cox-proportional hazards models adjusted for these variables demonstrated that, in the overall study population, CFR_{flow} was significantly associated with long-term MACE (CFR_{flow}-sHR: 0.63 (95%-CI: 0.46–0.86), p = 0.003), whereas lower (CFR_{pres}) and the upper bound of CFR_{pb} were not significantly associated with long-term MACE ($CFR_{pb\ lower\ bound}$ or CFR_{pres}-sHR: 0.83 (95%-CI: 0.60–1.15), p = 0.262); $CFR_{pb\ upper\ bound}$-sHR: 0.85 (95%-CI: 0.60–1.21), p = 0.367 (Table 2).

Table 2
Univariate and Adjusted logistic regression analyses for long-term MACE.

MACE study population (N = 153)				
Variable	Univariate analysis		Adjusted analysis[a]	
	sHR (95%CI)	p-Value	sHR (95%CI)	p-Value
CFR_{flow}	0.64 (0.46–0.88)	0.006	0.63 (0.46–0.86)	0.003
$CFR_{pb\ upper\ bound}$	0.85 (0.61–1.20)	0.364	0.85 (0.60–1.21)	0.367
$CFR_{pb\ lower\ bound}$ (CFR_{pres})	0.84 (0.62–1.15)	0.277	0.83 (0.60–1.15)	0.262

Data presented as standardized hazard ratio and its 95% confidence interval.
sHR = standardized hazard ratio; CFR_{flow} = flow-derived coronary flow reserve (CFR), CFR_{pb} = pressure-bounded CFR, CFR_{pres} = pressure-derived CFR.
[a] Adjusted for angiotensin converting enzyme inhibitor use, the presence of diabetes mellitus, and age at the time of physiological assessment.

4. Discussion

The present study demonstrates that pressure-derived estimations of CFR show a poor agreement with actual flow-derived CFR. In addition, both pressure-derived estimates of CFR show no association with long-term MACE, whereas actual CFR_{flow} has a potent association with long-term MACE in the same patient population.

4.1. Pressure-derived estimations of CFR: physiological basis of its unreliability

The inaccuracy of pressure-derived estimation of CFR is likely explained by basic physiology. Most importantly, both concepts of pressure-derived estimation of CFR assume that the pressure drop across a stenosis fully explains the impairment in CFR. However, coronary hemodynamics are characterized by an interplay between epicardial conduit arteries and the coronary microcirculation [4,17]. Such interplay determines that changes in coronary pressure gradients

from baseline to hyperemic conditions may be induced by opposing changes in coronary flow. Taken into consideration Poiseuille's and Bernoulli's Law ($\Delta P = f \cdot Q + s \cdot Q^2$), a small increase in ΔP from baseline to hyperemic conditions may be governed by dominant microvascular dysfunction precluding an increase in coronary flow in the presence of a moderate coronary stenosis (moderate *f* and *s*; low *Q*) or by a mild stenosis with high coronary flow when microvascular function is normal (low *f* and *s*; high *Q*). Vice versa, a large increase in ΔP from baseline to hyperemic conditions may result from a large increase in coronary flow in the setting of moderate non-flow-limiting coronary stenosis with normal microvascular function (moderate *f* and *s*; high *Q*) or by a severe flow-limiting stenosis (high *f* and *s*; low *Q*). These pathophysiological mechanisms may induce similar changes in ΔP, but have opposing prognostic implications [6,18], which are not reflected in pressure-derived estimations of CFR.

Secondly, the concept of CFR_{pres} ($CFR_{pb\ lower\ bound}$) neglects energy losses due to viscous friction, which actually pose an important factor in the occurrence of a pressure drop across a coronary stenosis. Friction losses increase linearly with flow, and depend critically on stenosis diameter and length. Therefore, they play an important role particularly for tight and longer stenoses, and can easily exceed separation losses for severe lesions at low (baseline) flow rates. The theoretical derivation of CFR_{pres} is likely incorrect in such stenoses. Additionally, for mild diffuse stenoses, the baseline pressure gradient may be significant on the basis of significant friction losses, whereas the increase in pressure gradient from baseline to hyperemia may only be small due to low flow separation losses. According to the methodology of CFR_{pb}, the bounds of CFR_{pb} are assumed to be abnormal in such stenoses, while CFR_{flow} actually may be normal. Indeed, our data showed that in stenoses with abnormal CFR_{pb} and normal CFR_{flow} the baseline pressure-gradient was routinely large, whereas the increase in ΔP from baseline to hyperemia was only modest (Supplementary Table 2). Vice versa, for short severe stenoses, the baseline pressure gradient may not be significant due to mild friction losses, whereas the increase from baseline to hyperemic pressure gradient may be large due to high flow separation losses. The bounds of CFR_{pb} are assumed to be normal in such stenoses, while CFR_{flow} actually may be abnormal. Accordingly, our data showed that in stenoses with normal CFR_{pb} and abnormal CFR_{flow}, the baseline pressure-gradient was routinely small, whereas the increase in ΔP from baseline to hyperemia was large (Supplementary Table 2) [8]. The relative contribution of viscous friction and flow separation losses on the pressure gradient and coronary flow as well as their prognostic implications warrant further studying.

Third, the poor diagnostic accuracy between $CFR_{pres,}$ CFR_{pb} and CFR_{flow} could partly be explained by changes in stenosis geometry between baseline and hyperemic conditions, as pressure-derived estimations of CFR assume that the *f* and *s* coefficients remain equal in resting and hyperemic conditions [19]. This hypothesis supports the fact that pressure-derived CFR provided a substantially better estimation of CFR_{flow} in fluid dynamic modeling with fixed stenoses than in animal studies. Changes in geometry have been attributed to paradoxical vasoconstriction distal to the stenosis [20], or the presence of collapsible stenoses [21]. Yet, although potentially clinically relevant, it remains unclear to what extent alterations in stenosis geometry affect hemodynamic indices.

4.2. Comparison with previous studies

CFR_{pres} was initially validated by computational fluid-dynamics modeling and in an in-vitro bench study, which yielded favorable relationships between CFR_{pres} and CFR_{flow} [7]. Subsequent in-vivo validation in an animal model (29-stenoses) and humans (34-stenoses) using Doppler flow velocity-derived CFR revealed a significant correlation between both methods [9]. However, an additional validation in humans (38-stenoses) using coronary thermodilution-derived CFR, revealed that CFR_{pres} systemically underestimated CFR [8]. Zimmermann and colleagues validated the concept of CFR_{pb} and studied the prognostic value of CFR_{pb} in lesions with normal FFR (FFR ≥ 0.75) included in the Fractional Flow Reserve to Determine the Appropriateness of Angioplasty in Moderate Coronary Stenosis (DEFER) trial. In a small patient subset of 64 stenoses, the authors demonstrated a diagnostic agreement with CFR_{flow} of 84% with thermodilution-derived CFR, but documented no significant differences in MACE or angina burden between lesions with normal or abnormal CFR_{pb} [10]. Ahn and colleagues studied the prognostic implications of CFR_{pb} in 5029 lesions, and documented that CFR_{pb} yields no incremental prognostic value over FFR. Hence, the authors conclude that CFR fails to independently predict the risk of cardiac events [11]. However, these conclusions focusing on prognostic value of CFR_{pb} and extrapolating these results to overall CFR_{flow} have followed before a proper validation of CFR_{pb} with CFR_{flow} was performed. We documented poor diagnostic agreement between CFR_{pres} or CFR_{pb} and CFR_{flow}. Following the poor diagnostic agreement, we documented a poor association between CFR_{pres} or CFR_{pb} and long-term MACE, whereas CFR_{flow} provided substantial prognostic information in the same patient cohort.

4.3. Clinical implications

Simultaneous FFR and CFR measurements have been shown to provide incremental prognostic value over sole FFR measurements [22–25], and may augment identification of stenoses most-likely to benefit from PCI. The present study, representing the largest cohort of patients with intermediate CAD to study the relationship between CFR_{pres}, CFR_{pb} and $CFR_{flow,}$ unequivocally documents a poor diagnostic agreement between CFR_{flow} with CFR_{pb}, which translates in the absence of prognostic value of $CFR_{pb,}$ whereas CFR_{flow} provides substantial prognostic value in the same patient cohort.

4.4. Limitations

First, the relatively small-sample size limits the statistical power of the MACE-analyses. Secondly, the assessment of adverse-events was 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 previously. Thirdly, the present study compromises pooled-data from Doppler flow and thermodilution-derived CFR, and it should be noted that there is only modest agreement between CFR derived from both techniques [26]. This is also reflected by a different, yet overall poor, agreement of CFR_{pres}/CFR_{pb} with the two techniques, of which $CFR_{Doppler}$ shows superior agreement (CFR_{pres} vs $CFR_{Doppler}$ 0.187; CFR_{pres} vs. CFR_{thermo} 0.093; CFR_{pb} vs. $CFR_{Doppler}$ 0.496; CFR_{pb} vs CFR_{thermo} 0.242). Nonetheless, based on the theoretical limitations as outlined in this manuscript, neither CFR_{pres} nor CFR_{pb} should be used as a reference standard to compare $CFR_{Doppler}$ with CFR_{thermo}. Fourthly, in the present study we excluded lesions with P_d/P_a of 1.00. However, CFR_{pb} may inherently be less accurate in cases of small resting pressure gradients where effects of pressure drift are most pronounced. Finally, potential unrecognized biological variation when matching pressure and flow data may induce disagreements between CFR_{flow} and CFR_{pres}/CFR_{pb}, which applies to the Doppler-cohort, where pressure and flow velocity were obtained by sequential measurements, and thermodilution-cohort, where extended measurement periods are required throughout a variable hyperemic plateau phase. Yet, the comparable poor agreement in both cohorts supports the understanding that such variability does not drive the outcomes of the present study.

5. Conclusion

Pressure-derived estimations of CFR agree poorly with flow-derived measurements of CFR, which may explain the inferior association with

clinical outcomes as compared to flow-derived CFR. The inaccuracy of pressure-derived estimations of CFR means that there is no place for these indices in contemporary diagnostic strategies or scientific efforts towards multimodality assessment of the coronary circulation.

Disclosures

G.W. is partly supported by a research fellowship grant by Philips-Volcano Corporation. T.H., M.L., M.M., M.E.P., J.E. and J.P. have served as speaker at educational events organized by St Jude Medical, Boston Scientific, or Volcano Corporation. The remaining authors have no conflict of interest to declare.

Funding

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.11.013.

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