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Impact of clinical and hemodynamic factors on coronary flow reserve and invasive coronary flow capacity in non-obstructed coronary arteries - *A patient level pooled analysis of the DEBATE and ILIAS studies*

Short title

Determinants of flow in non-obstructed coronaries

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Abstract

Aims Coronary Flow Reserve (CFR) is a physiological index for the assessment of myocardial flow impairment due to focal or microcirculatory coronary artery disease (CAD). Coronary flow capacity (CFC) is another flow-based concept in diagnosing ischemic heart disease, based on hyperemic average peak velocity (hAPV) and CFR. We evaluated clinical and hemodynamic factors which potentially influence CFR and CFC in non-obstructed coronary arteries.

Methods and results Intracoronary Doppler flow velocity measurements to obtain CFR and CFC were performed after inducing hyperemia in 390 non-obstructed vessels of patients who were scheduled for elective percutaneous coronary intervention (PCI) of another vessel. Akaike's Information Criterion (AIC) revealed age, female gender, history of myocardial infarction, hypercholesterolemia, diastolic blood pressure, oral nitrates and rate pressure product as independent predictors of CFR and CFC. After regression analysis, age and female gender were associated with lower CFR and age was associated with worse CFC in angiographically non-obstructed vessels.

Conclusions Age and female gender are associated with lower CFR, and age with worse CFC in an angiographically non-obstructed coronary artery. CFC seems to be less sensitive to variations in clinical and hemodynamic parameters than CFR, and therefore is a promising tool in contemporary clinical decision making in the cardiac catheterization laboratory.

Keywords: stable angina, other technique, clinical research, clinical trials

Condensed abstract

Coronary Flow Reserve (CFR) and coronary flow capacity (CFC) are important indices for the assessment of myocardial flow impairment due to coronary artery disease (CAD). We evaluated determinants of CFR and CFC in 390 non-obstructed coronary arteries of patients with stable CAD who were scheduled for elective percutaneous coronary intervention. Age and female gender are associated with lower CFR, and age with worse CFC in an angiographically non-obstructed coronary artery. CFC is less sensitive to variations in clinical and hemodynamic parameters than CFR and therefore a promising tool in contemporary clinical decision making in the cardiac catheterization laboratory.

Impact on daily practice

- Coronary flow is a critical determinant of myocardial ischemia, and plays an essential role in maintaining myocardial function
- Widespread implementation of coronary flow assessment in the catheterization laboratory is partially hampered due to presumed sensitivity of coronary flow assessment to clinical and hemodynamic parameters
- We demonstrate that age and female gender are weakly associated with coronary flow reserve and solely age is associated with worse coronary flow capacity in angiographically non-obstructed vessels, strengthening the role of a flow-based diagnostic approach towards ischemic heart disease (IHD) in contemporary clinical decision making in the cardiac catheterization laboratory

List of abbreviations

bAPV	baseline average peak flow velocity
CFC	coronary flow capacity
CFR	coronary flow reserve
FFR	fractional flow reserve
hAPV	hyperemic average peak flow velocity
IVUS	Intravascular ultrasound
MACE	major adverse cardiac events
MI	Myocardial infarction
RPP	rate pressure product

Introduction

Maximal coronary flow and coronary flow reserve (CFR), defined as the ratio of maximal to resting coronary flow, are the critical determinants of myocardial ischaemia and its clinical consequences[1, 2]. Such direct measurements of coronary flow may therefore be a valuable adjunct to coronary angiography, and coronary pressure measurements[3-5]. Particularly impaired CFR has been extensively documented to be associated with importantly increased risk for adverse clinical outcome, regardless of the technique used for its assessment[6]. Nonetheless, a potential influence of hemodynamic and clinical variables on CFR documented in small studies has historically been considered a limitation for the clinical application of CFR, but the magnitude and clinical relevance of such variables as encountered in clinical practice has not been evaluated in larger clinical studies[7-9]. Moreover, following these concerns regarding CFR, the concept of (invasive) coronary flow capacity (CFC) was introduced. By integrating both CFR and maximal flow, CFC aims to overcome the limitations of CFR related to its potential dependence on hemodynamic conditions[10, 11]. CFC is expected to be less dependent on systemic and coronary hemodynamics than CFR, but this has not been systematically evaluated. Assessment of invasive coronary flow velocity in coronary arteries in the absence of angiographical epicardial stenosis allows for the systematic evaluation of the impact of clinical and hemodynamic factors as encountered in routine clinical practice, on CFR and CFC[11, 12]. Therefore, the purpose of this analysis was to explore which clinical and hemodynamic parameters influence CFR and CFC in angiographically non-obstructed coronary arteries, and to determine the clinical relevance for the use of CFR and CFC in clinical decision-making.

Methods

Patients

The study population consisted of a total of 390 reference vessels (angiographic diameter stenosis (DS) <30%) of 390 patients with stable or unstable angina pectoris (class 1 to 3 according to the Canadian Cardiovascular Society; CCS or Braunwald's classification I or II) and with normal left ventricular function, who were scheduled for percutaneous coronary intervention in single vessel or multivessel disease. Patients were evaluated in the setting of two multicentre studies, the DEBATE II (Doppler Endpoints Balloon Angioplasty Trial Europe II)[13] and the ILIAS (Intermediate Lesions: Intracoronary Flow Assessment versus 99mTc-MIBI SPECT)[14]. Only patients for whom all relevant parameters were documented, were included in the analysis. Common exclusion criteria were acute myocardial infarction less than one week prior to angioplasty, chronic total occlusion, left ventricular hypertrophy or cardiomyopathy. All patients gave written informed consent.

Intracoronary flow velocity assessment

Flow measurements were performed in a reference coronary artery (DS<30% on visual estimation) using a 0.014 inch Doppler sensor tipped guidewire (FloWire, Endosonics, Rancho Cordova, California, currently: ComboWire XT, Philips Volcano, San Diego, California). Doppler flow velocity measurements were obtained during resting conditions (baseline average peak flow velocity; bAPV), as well as during hyperemia (hyperemic average peak flow velocity; hAPV) induced by an intracoronary bolus injection of adenosine (12-15 μg for the right coronary artery and 18-20 μg for the left coronary artery). Doppler flow velocity signals were used to calculate CFR, defined as the ratio of hAPV to bAPV. The definition of CFC was previously described elsewhere[11, 15, 16], in brief: normal CFC was defined as CFR≥2.8, as encountered in patients with risk factors for IHD without epicardial narrowing[15], with its

corresponding hAPV≥49.0 cm/s. Mildly reduced CFC was defined as CFR<2.8 but >2.1, which reflects the upper limit of reported CFR cut-off values for inducible ischemia, and the corresponding hAPV<49.0 and >33.0 cm/s, respectively. Moderately reduced CFC was defined as CFR≤2.1 and >1.7, analogous to the reported range of CFR cut-off values for inducible myocardial ischemia, and the corresponding hAPV≤33.0 and >26.0 cm/s, respectively. Finally, severely reduced CFC was defined as CFR≤1.7, and corresponding hAPV≤26.0 cm/s.

Statistical analysis

Variables are presented as mean±SD or frequency (percentage), where appropriate. The rate pressure product (RPP) was calculated by multiplying heart rate with systolic blood pressure. Akaike's Information Criterion (AIC) was used to determine the model with the best goodness of fit for predicting CFR or CFC, respectively, with candidate covariates including baseline characteristics, and angiographic and hemodynamic parameters (table 1, supplementary table 1 and supplementary table 2).The identified variables from the best model of fit according to AIC were entered in linear multivariable regression analysis to identify independent predictors of CFR and ordinal multivariable regression analysis for CFC. A p-value below the 2-sided α level of 0.1 for univariate and 0.05 for multivariate regression analysis was considered statistically significant. The STATA version 13.1 (StataCorp, College Station, Texas) software package was used for all statistical analyses.

Results

Patient characteristics

Patient characteristics are listed in table 1. Mean age was 59±11 years and 74% were male(n=289). A total of 390 unobstructed vessels were interrogated, with the majority in the ramus circumflex artery (RCx)(n=195) followed by the left anterior descending artery (LAD)(n=155) and the right coronary artery (RCA)(n=40). Detailed characteristics have been described elsewhere[13, 17].

CFR and CFC

Overall, mean CFR was 2.87±0.76 (Figure 1A). Men had higher mean CFR than women (2.96±0.04 versus 2.61±0.07, p=0.001). There was no significant difference in CFR between interrogated vessels: mean CFR was 2.83±0.79 for the RCx, 2.91±0.73 for the LAD and 2.90±0.75 for the RCA(p=0.16).

Overall CFC distribution is shown in Figure 1B. Mean CFR, bAPV, and hAPV across the CFC categories are shown in Table 2. Mean CFR was 3.14±0.70 for normal CFC(n=278), 2.28±0.30 for mildly reduced CFC(n=90), 1.80±0.27 for moderately reduced CFC(n=19) and 1.2±0.35 for severely reduced CFC(n=3). CFR and CFC distribution per vessel is shown in table 3.

Determinants of CFR in reference vessels

The best model for CFR identified by AIC included age, female gender, a history of MI, hypercholesterolemia, diastolic blood pressure, oral nitrates and RPP. Univariate linear regression analysis and subsequent multivariate linear regression analysis (table 4), revealed age(Slope=-0.014, 95%CI -0.021 to -0.007, p<0.001), female gender(Slope=-0.212, 95% CI -0.376 to -0.030, p=0.021) and oral nitrates(Slope=0.162, 95%CI 0.003 to 0.321, p=0.046) to be independently associated with CFR. The relationship between CFR and age is visualized in figure 2.

Resting and hyperemic flow in CFR calculation

The parameters associated with CFR in angiographically non-obstructed vessels listed above were subsequently evaluated for their association with bAPV and hAPV to determine whether their impact on CFR derived from an effect on resting or hyperemic flow(table 5 and 6). Increasing age was associated with a decrease in hAPV(Slope=-0.194, p=0.024), but not in bAPV(Slope=0.044, p=0.223)(Figure 2). Gender was associated with bAPV, where women had higher bAPV than men(mean bAPV 19.4±8.3 cm/s versus 17.3±7.5 cm/s, slope=2.129, p=0.017)(figure 3), but there was no association between gender and hAPV(Slope=-2.33; p=0.275). RPP was associated with bAPV(Slope=0.0007; p<0.001), but not with hAPV(Slope=0.0006; p=0.174). A history of MI, hypercholesterolemia and current or prior smoking were not associated with bAPV(p=0.710, p=0.231 and p=0.271, respectively) or hAPV(p=0.576, p=0.915 and p=0.063, respectively).

Determinants of CFC in reference vessels

Univariate ordinal logistic regression analysis revealed age, RPP and oral nitrates to be associated with CFC. Subsequent multivariate ordinal logistic regression analysis revealed that age(Slope=0.0397, 95% CI -0.411 to -0.060, p=<0.001) was independently associated with worse CFC, whereas oral nitrate use(Slope=-0.577, 95% CI -1.04 to -0.114 p=0.015) is associated with better CFC (Table 7).

Discussion

This analysis from a large patient cohort consisting of two multi-center trials, identified age and female gender as independent predictors of CFR in angiographically non-obstructed vessels. Age was the only independent predictor of a worse CFC in unobstructed coronary arteries. Oral nitrates are associated with both higher CFR and better CFC. This is therefore the first clinical study documenting that, CFC is more independent of clinical and hemodynamic parameters as encountered in routine clinical practice compared with CFR, enhancing the diagnostic value of CFC over CFR alone.

Origin of association between clinical and hemodynamic parameters and flow abnormalities

CFR is a physiological parameter that has been extensively validated and is associated with improved risk stratification regarding MACE, regardless of the methodology used for its assessment[6, 18-20]. However, in part due to its presumed sensitivity to variations in resting hemodynamics, its implementation in larger clinical practice has been limited. In the present study, age, female gender and oral nitrates significantly influenced CFR in a reference vessel. Interestingly, ageing was associated with lower CFR mainly driven by a decrease in hAPV, as documented previously[21, 22]. Female gender, in contrast, was associated with lower CFR, potentially due to a lower vascular tone and subsequently higher bAPV[23]. Cardiac work load estimated by RPP has generally been associated with an increase in both bAPV and hAPV[24, 25]. Although a decrease in CFR is generally assumed with increases in cardiac workload, a simultaneous increase in maximal hyperemic flow together with a proportional increase of baseline flow, can result in a normal CFR[26]. Furthermore, de Bruyne et al.[27] found a significant association between CFR and hemodynamic changes in heart rate, blood pressure and contractility, but measured CFR under clinically challenging hemodynamic situations in which physiological assessment is usually not applied, since vasodilatory capacity is naturally impaired in these situations.

Oral nitrates induce vasodilation and subsequent increase coronary blood flow to the myocardium, resulting in higher CFR and CFC[28].

Diabetes mellitus was not associated with lower CFR values in the present cohort. However, we found that diabetic patients had higher bAPV compared with non-diabetic patients (20.5±10.4 cm/s versus 17.6±7.5 cm/s, for diabetics and non-diabetics, respectively; p=0.046) but similar hAPV (52.6±18.4 cm/s versus 48.2±18.4 cm/s, for diabetics and non-diabetics, respectively; p=0.182). Higher bAPV in diabetics has been previously documented, and has been attributed to malfunctioning of the myocardial metabolism[29, 30], as well as impaired endothelial function, or even structural anatomical changes of the microcirculatory vasculature[9, 31]. Although mean CFR values were not different between diabetics and non-diabetics in this study, higher resting flows evidently lead to lower CFR values in the individual patient and may impact clinical decision-making. Such impact of diabetes on resting flow would be vanquished by using CFC.

Despite these considerations, the prognostic value of CFR in angiographically non-obstructed coronary arteries remains undisputed. Several studies have documented that lower CFR is associated with an increased risk of MACE, both in vessels with[6, 32] and without[33] obstructive CAD.

The concept of CFC: hAPV complementing CFR

The concept of CFC has been originally validated using PET imaging[12], and has been extrapolated to invasive coronary flow measurements[11]. These studies have suggested an improved risk-stratification by using CFC over the application of CFR alone, although more definitive data is required for confirmation of these findings. In the present study, we found that CFC is mostly independent of clinical and hemodynamic factors except for age, overcoming most of the potential limitations of using CFR alone. By integrating both CFR and hAPV, CFC is less prone to variations in baseline flow compared with CFR. As documented in the present

study, this applies to alterations in flow in diabetics, female patients, and increases in cardiac work load. In the present study, age was the only parameter associated with lower CFC, which is anticipated since age impacts CFR through a solitary decrease in hAPV, leading to a decrease in CFC through impairment of both CFR and hyperemic flow.

Clinical implications

It is increasingly recognized that IHD has a multilevel origin, and that a stenosis-centered approach seem insufficient for optimal treatment of this complex syndrome. Current pressure-derived indices such as Fractional Flow Reserve (FFR) and instantaneous wave-free ratio (iFR) are frequently used in contemporary clinical practice to estimate flow impairment of a stenosis, but remain an imperfect reference standard for inducible myocardial ischemia[34]. In the FAME II study (Fractional Flow Reserve versus Angiography for Multivessel Evaluation), comparing FFR-guided PCI with angiography guided PCI, 50% of patients with FFR≤0.80 treated with optimal medical therapy did not require revascularization nor did 70% suffer from major adverse cardiac events during five years of follow-up[35]. Subsequently, it has been well-documented that coronary flow is fundamentally more important than coronary pressure in maintaining coronary function[34, 36], leading to a clear need for a robust flow-based approach to diagnosis and treatment of IHD. CFR, although a robust risk-stratification tool at the population-level[3, 37], has been documented to be influenced by clinical and hemodynamic parameters unrelated to the extent of coronary artery disease that might lead to inadvertent alterations of CFR, that can impact clinical decision-making in the individual patient. Furthermore, we found that CFC is largely independent of these variables that occur in clinical practice, and has been documented to enhance risk-stratification provided by CFR[11, 12]. The latter, in corroboration with the findings in the present study support further research towards the implementation of CFC as a coronary flow-based index of coronary artery disease severity in contemporary clinical practice.

Limitations

This study is based on a post-hoc analysis consisting of two multi-center studies[13, 17], in which all coronary flow measurements were performed by interventional cardiologists with ample experience in coronary flow velocity assessment. Only patients for whom all baseline clinical and hemodynamic variables were available, were included in this analysis, leading to a limited number of analysed variables and patients. Administered adenosine doses were recommended for inducing hyperemia in the two included studies, but these dosages induce sufficient vasodilation for physiological assessment[38]. Furthermore, these measurements have been performed in vessels with DS<30% by visual estimation, which does not exclude the presence of subclinical atherosclerosis that may impact coronary flow values[39, 40]. Intravascular ultrasound (IVUS) was not routinely performed to improve the selection of patients. Oral nitrates were not discontinued before intracoronary flow assessment, potentially increasing CFR and CFC due to permanent vasodilation.

Conclusion

Age and female gender are independent predictors of lower CFR in an angiographically non-obstructed vessel. Age is associated with worse CFC, thus CFC seems to be more independent of clinical and hemodynamic parameters compared with CFR. Therefore, the present findings may strengthen the value of invasive coronary flow assessment in contemporary clinical decision making in the cardiac catheterization laboratory.

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Figure legends

Figure 1. Overall CFR (A) and CFC (B) distribution. (A) CFR mean±SD was 2.87±0.76. (B) Overall CFC distribution based on CFR and hAPV. The coloured dots represent the corresponding CFC category. Blue = normal CFC, green = mildly reduced CFC, orange = moderately reduced CFC, red = severely reduced CFC.

Figure 2. Inverse correlation between CFR and (A) age ($p<0.001$, $R^2=0.0619$), (B) CFR and bAPV ($p=0.244$, $R^2=0.0035$) and (C) CFR and hAPV ($p=0.016$, $R^2=0.0149$).

Figure 3. Correlation between CFR and bAPV in men ($R^2=0.3576$) (A) and women ($R^2=0.1416$) (B).

Table 1. Patient characteristics for the two merged patient cohorts (n=390).

	Mean±SD or n (%)
Age	59.2±10.8
Male	289 (74.1)
Previous MI	126 (32.3)
Hypertension	152 (40)
Diabetes mellitus	31 (8)
Hypercholesterolemia	216 (55.4)
Current or previous smoker	167 (42.8)
Positive family history	167 (42.8)
Acetylsalicylic acid	355 (91)
Beta blocker	269 (67.9)
Calcium antagonist	200 (51.3)
Oral nitrates	255 (65.4)
Interrogated vessel	390
RCx	195 (50)
LAD	155 (39.7)
RCA	40 (10.3)

Table 2. Distribution of CFR and interrogated vessels per CFC category.

CFC category	CFR	bAPV	hAPV
Normal (n=278)	3.14±0.70	18.41±8.8	53.67±18.6
Mildly reduced (n=90)	2.28±0.30	16.53±3.9	36.9±7.0
Moderately reduced (n=19)	1.80±0.27	16.68±4.8	26.95±5.2
Severely reduced (n=3)	1.2±0.35	15.3±9.3	17.7±8.5

Table 3. CFC distribution subdivided per interrogated vessel, with corresponding CFR (shown as mean±SD).

Vessel	Normal CFC	Mildly reduced CFC	Moderately reduced CFC	Severely reduced CFC
RCx	3.14±0.71 (n=136)	2.30±0.28 (n=42)	1.75±0.29 (n=14)	1.2±0.35 (n=3)
LAD	3.16±0.69 (n=112)	2.29±0.31 (n=40)	1.9 (n=3)	-
RCA	3.15±0.70(n=30)	2.16±0.35 (n=8)	2.0 (n=2)	-
Total (n=390)	278	90	19	3

Table 4. **Univariate and multivariate regression analysis for CFR.**

	Univariate regression analysis			Multivariate regression analysis		
	Slope	95% CI	p-value	Slope	95% CI	p-value
Age	-0.018	-0.024 to -0.011	<0.001	-0.014	-0.021 to -0.007	<0.001
Female gender	-0.348	-0.512 to -0.178	<0.001	-0.212	-0.376 to -0.030	0.021
RPP	-0.00007	-0.0001 to 0.00004	<0.001			
Hypercholesterolemia	0.19445	0.0429 to 0.346	0.012			
Oral nitrates	0.1617	0.0028 to 0.3205	0.046	0.2202	0.031 to 0.409	0.023

Table 5. **Univariate and multivariate regression analysis of bAPV.**

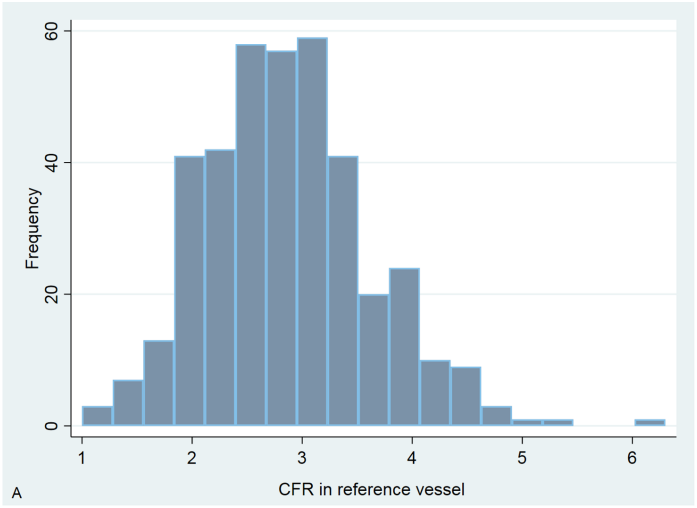
	Univariate regression analysis			Multivariate regression analysis		
	Slope	95% CI	p-value	Slope	95% CI	p-value
Female gender	2.11	0.353 to 3.871	0.019	-	-	-
RPP	0.0007	0.0003 to 0.001	<0.001	0.0005	0.0002 to 0.0009	0.002
Diabetes mellitus	2.87	0.013 to 5.723	0.049	-	-	-

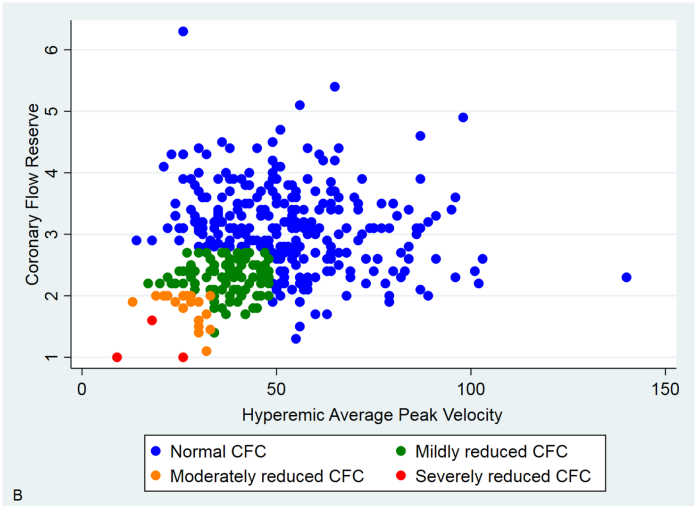
Table 6. Univariate and multivariate regression analysis for hAPV.

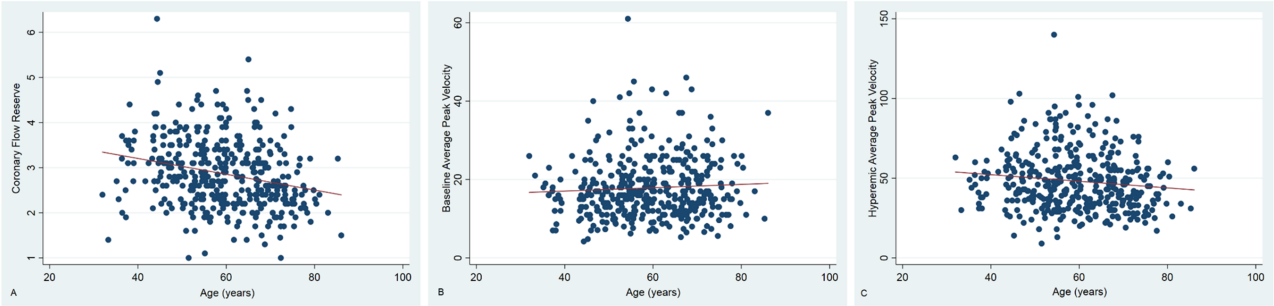
	Univariate regression analysis			Multivariate regression analysis		
	Slope	95% CI	p-value	Slope	95% CI	p-value
Age	-0.208	-0.376 to -0.039	0.016	-0.246	-0.421 to -0.071	0.006
Current or prior smoking	3.883	-0.189 to 7.173	0.039	-	-	-
Acetylsalicylic acid	6.052	-0.334 to 12.44	0.063	-	-	-

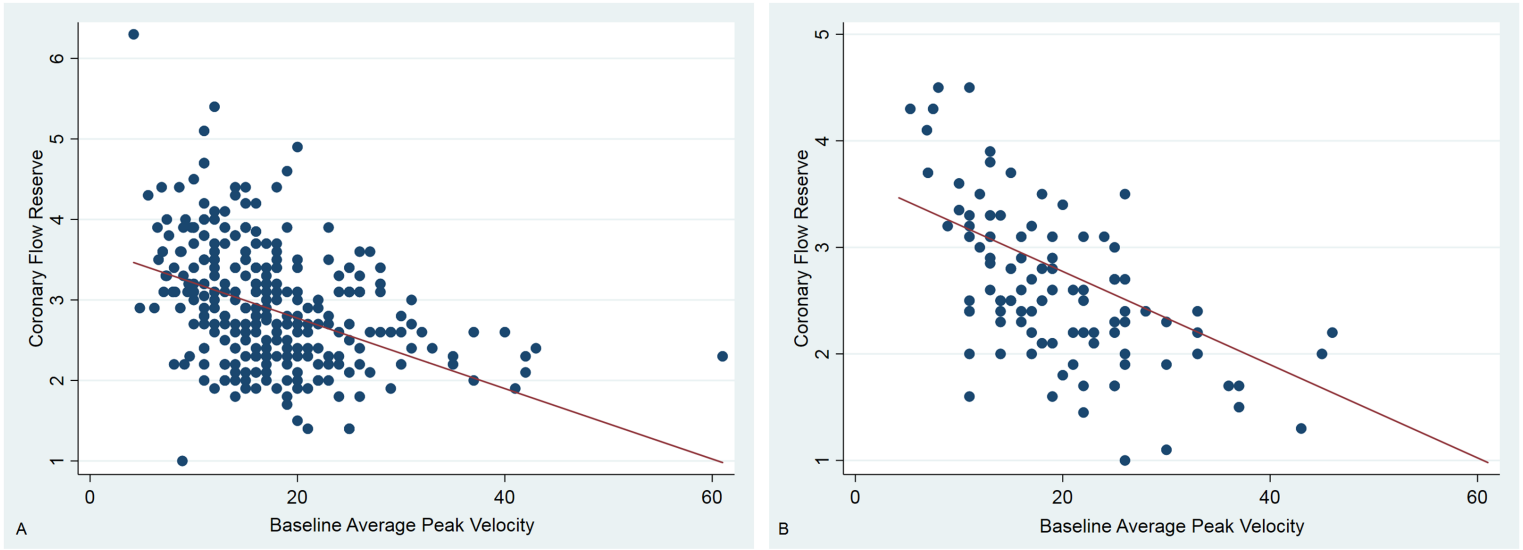
Table 7. Univariate and multivariate ordered logistic regression analysis of CFC.

	Univariate regression analysis			Multivariate regression analysis		
	Slope	95% CI	p-value	Slope	95% CI	p-value
Age	0.037	0.015 to 0.057	0.001	0.0397	0.013 to 0.055	0.001
RPP	0.0001	0.00001 to 0.00019	0.034	-	-	-
Oral nitrates	-0.453	-0.902 to -0.0031	0.048	-0.5766	-1.04 to -0.114	0.015









Appendix to manuscript

"Impact of clinical and hemodynamic factors on coronary flow reserve and invasive coronary flow capacity in non-obstructed coronary arteries - *A patient level pooled analysis of the DEBATE and ILIAS studies"*

Supplementary file 1. Table 1. Akaike's Information Criterion selection process for CFR

Number of variables	Included variables	Cp	R2Adj	AIC	BIC	R2
6	Age, female gender, history of MI, diastolic blood pressure, RPP, hypercholesterolemia	3.53	0.116	870.2	898.1	0.129
5	Age, female gender, history of MI, diastolic blood pressure, RPP	3.58	0.113	870.3	894.2	0.124
6	Age, female gender, history of MI, diastolic blood pressure, RPP, statin use	3.62	0.115	870.3	898.2	0.129
7	Age, female gender, history of MI, diastolic blood pressure, RPP, statin use, smoking	3.82	0.117	870.5	902.3	0.133
7	Age, female gender, history of MI, diastolic blood pressure, RPP, statin use, smoking, hypercholesterolemia	3.91	0.117	870.6	902.4	0.133
5	Age, female gender, history of MI, RPP, hypercholesterolemia	3.95	0.112	870.7	894.6	0.124
4	Age, female gender, history of MI, RPP	4.02	0.110	870.8	890.7	0.119
6	Age, female gender, history of MI, diastolic blood pressure, RPP, smoking	4.09	0.114	870.8	898.7	0.128
6	Age, female gender, history of MI, RPP, smoking, hypercholesterolemia	4.16	0.114	870.9	898.8	0.128
5	Age, female gender, diastolic blood pressure, RPP, hypercholesterolemia	4.24	0.112	871.0	894.9	0.123

Abbreviations: CFR, coronary flow reserve; Cp, Mallow's Cp; R2Adj, Adjusted R2; AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion

Supplementary file 2. Table 2. Akaike's Information Criterion selection process for CFC

Number of variables	Included variables	Cp	R2Adj	AIC	BIC	R2
8	Age, female gender, history of MI, diabetes, hypertension, RPP, statin use, calcium antagonist use	5.53	0.051	717.7	753.5	0.070
7	Age, female gender, history of MI, diabetes, hypertension, RPP, calcium antagonist use	5.88	0.047	718.1	750.0	0.064
6	Age, history of MI, diabetes, hypertension, RPP, calcium antagonist use	6.34	0.044	718.6	746.5	0.058
5	Age, diabetes, hypertension, RPP, calcium antagonist use	6.44	0.041	718.8	742.7	0.053
7	Age, history of MI, diabetes, hypertension, RPP, statin use, calcium antagonist use	6.45	0.046	718.7	750.5	0.063
9	Age, female gender, history of MI, diabetes, hypertension, RPP, aspirin use, statin use, calcium antagonist use	6.49	0.051	718.6	758.4	0.072
8	Age, female gender, history of MI, diabetes, hypertension, RPP, aspirin use, statin use, calcium antagonist use	6.61	0.048	718.8	754.6	0.067
6	Age, female gender, diabetes, hypertension, RPP, calcium antagonist use	6.61	0.043	718.9	746.8	0.058
7	Age, female gender, history of MI, diabetes, hypertension, statin use, calcium antagonist use	6.76	0.045	719.0	750.9	0.062
6	Age, female gender, history of MI, diabetes, statin use, calcium antagonist use	6.78	0.043	719.1	747.0	0.057

Abbreviations: CFC, coronary flow capacity; Cp, Mallow's Cp; R2Adj, Adjusted R2; AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion