Disturbed Coronary Hemodynamics in Vessels with Intermediate Stenoses Evaluated with Fractional Flow Reserve: A Combined Analysis of Epicardial and Microcirculatory Involvement in Ischemic Heart Disease

Running title: Echavarria-Pinto et al.; Abnormal hemodynamics in FFR interrogated vessels

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Abstract

Background—In chronic ischemic heart disease (IHD), focal stenosis, diffuse atherosclerotic narrowings (DAN) and microcirculatory dysfunction (MCD) contribute to limit myocardial flow. The prevalence of these IHD levels in fractional flow reserve (FFR) interrogated vessels remains largely unknown.

Methods and Results—Using intracoronary measurements, 91 coronaries (78 patients) with intermediate stenoses were classified in four FFR and coronary flow reserve (CFR) agreement groups, using FFR>0.80 and CFR<2 as cutoffs. Microcirculatory resistance (IMR) and atherosclerotic burden (Gensini score) were also assessed. MCD was assumed when IMR≥29.1 (75th percentile). Fifty-four (59.3%) vessels had normal FFR, from which only 20 (37%) presented both normal CFR and IMR. Among vessels with FFR>0.80, most (63%) presented disturbed haemodynamics: abnormal CFR in 28 (52%) and MCD in 18 (33%). Vessels with FFR>0.80 presented higher IMR [adjusted mean 27.6 (95% CI: 23.4 to 31.8)] than those with FFR≤0.80 [17.3 (95% CI: 13.0 to 21.7), p=0.001]. Atherosclerotic burden was inversely correlated with CFR (r=-0.207, p=0.055), and in vessels with FFR>0.80 and CFR<2 (n=28, 39%), IMR had a wide dispersion (7-72.7 U), suggesting a combination of DAN and MCD. Vessels with FFR≤0.80 and normal CFR presented the lowest IMR, suggesting a preserved microcirculation.

Conclusions—A substantial number of coronary arteries with stenoses showing an FFR>0.80 present disturbed haemodynamics. Integration of FFR, CFR and IMR supports the existence of differentiated patterns of IHD that combine focal and diffuse coronary narrowings with variable degrees of MCD.

Key words: coronary disease, physiology, microcirculation
Introduction

Chronic ischemic heart disease (IHD) is a multifactorial entity that occurs both in the presence or absence of obstructive coronary artery disease (CAD). Fractional flow reserve (FFR) has become a standard method to assess obstructive CAD in the catheterization laboratory following the demonstration that decision-making based on FFR results in better patients outcomes than angiography-guided revascularisation. However, identification of other factors contributing to IHD, such as diffuse atherosclerotic narrowing (DAN) and microcirculatory dysfunction (MCD), remains largely elusive to the simplified model of physiological assessment provided by the FFR. This diagnostic gap is important because it remains plausible that patients with normal FFR values and MCD might have a worse prognosis. The same applies to the presence of DAN, frequently overlooked during angiography, which may cause myocardial ischemia and influence long-term outcome.

When combined with FFR, coronary flow reserve (CFR) and microcirculatory resistance could provide additional insights on the contribution of obstructive CAD, DAN and MCD to IHD. In this study, we performed a comprehensive assessment of coronary haemodynamics in vessels with intermediate stenoses, using FFR, CFR and the index of microcirculatory resistance (IMR). In addition, the Gensini score was recalled as a surrogate of atherosclerotic burden. The obtained data was combined to outline three separate patterns of atherosclerotic involvement in IHD: focal epicardial stenoses, DAN and MCD.

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Methods

Study Population

Patients with a clinical indication for FFR interrogation of 1 or more intermediate coronary stenoses (40% to 70% diameter stenosis by quantitative coronary angiography [QCA]), investigated at Hospital Clinico San Carlos, Madrid, Spain, were prospectively studied. Culprit vessels of acute coronary syndromes, serial stenoses and marked diffuse narrowings were excluded. Very distal narrowings, not amenable for revascularisation (vessel diameter <1 mm), were allowed. Other exclusion criteria were left main stenosis, surgical grafts, contraindications to adenosine, hemodynamic instability and severe vessel tortuosity or calcification. All patients gave informed consent and Institutional Review Board approval was obtained according to current regulations.

Angiographic Analysis

Angiographic data was collected by two experienced reviewers blinded to physiology data. Angiographic views were obtained following intracoronary nitrates (0.2 mg) administration. Offline QCA was performed in optimal projections using validated software (CASS II, Pie Medical, Maastricht, The Netherlands). Minimum lumen diameter [MLD], percent diameter stenosis (DS), lesion length and reference lumen diameter were measured. Atherosclerotic burden was assessed using the Gensini score. This score limited to the vessel interrogated with the guidewire (arterial-Gensini score) was also recalled.

Intracoronary Physiological Indices

Coronary guidewires with pressure and temperature sensors (St. Jude Medical, St. Paul, Minnesota) were used according to described methodology. FFR was calculated as the ratio of distal coronary pressure (Pd) to proximal coronary pressure (Pa) at stable
hyperemia induced by intravenous adenosine (140µg/kg/min through a central vein).
Persistence of calibration was checked. CFR was measured simultaneously with FFR using
the thermodilution method, as described elsewhere.\textsuperscript{11} Resting and hyperaemic
thermodilution curves (in triplicate) were obtained, and CFR was calculated as the ratio of
mean transit time ($T_{mn_{bas}}$) divided by mean hyperemic transit time ($T_{mn_{hyp}}$). IMR was
calculated as the product of mean distal coronary pressure during maximal hyperemia and
$T_{mn_{hyp}}$.\textsuperscript{7} In arteries with FFR<0.75, IMR was corrected for coronary wedge pressure using
the method proposed by Yong et al.\textsuperscript{12} A meticulous technique was followed to avoid
potential pitfalls affecting these indices.

**Cut-off Values for Physiological Indices**

\[
\text{FFR} \leq 0.80 \quad (\text{low-FFR}) \quad \text{and} \quad \text{CFR} < 2 \quad (\text{low-CFR})\]

Based on the reported variability of IMR in patients with and without CAD,\textsuperscript{14} values ≥75
percentile of IMR in the overall study population were assumed abnormal (high-IMR) and
suggestive of MCD.

**Classification of Focal, Diffuse Epicardial and Microcirculatory Compartments**

In identifying relative contributions of epicardial conductance (focal or DAN) and
microcirculatory resistance to myocardial flow impairment, we used the four-quadrant
distribution of the agreement between FFR and CFR proposed by Johnson et al.:\textsuperscript{8} (A)
predominantly focal epicardial involvement (low-FFR and high-CFR); (B) adequate and
concordant (high-FFR and high-CFR); (C) reduced and concordant quadrant (low-FFR and
low-CFR) and (D) predominantly diffuse epicardial involvement (high-FFR and low-CFR).
In the latter quadrant, those with CFR<2 and FFR near 1.0 (pressure loss less than 5mm)
were labeled as lone-MCD\textsuperscript{8} (Figure 1).
Statistical Analysis

All continuous variables are presented as mean ± SD or median (interquartile range), according to their normal or non-normal distribution. Categorical variables are presented as numbers or percentages. Normalcy and homogeneity of the variances were tested using the Kolmogorov-Smirnov and Levene tests. Data was analyzed on per-patient basis for clinical characteristics, and on per-vessel basis for the rest of calculations. From per-patient analyses, those with more than 1 interrogated vessel showing differences in quadrant classification between vessels were excluded. Continuous variables were compared with t test or Mann-Whitney U test, as appropriate. Categorical variables were compared by the maximum likelihood χ² test. Linear regression analyses were used to determine correlation coefficients (Pearson or Spearman, as appropriate) between quantitative variables. At patient-level, overall differences between quadrants were compared with maximum likelihood χ² tests. At vessel-level, mixed effect regression models were used to correct for additional variability of arteries from the same subject. From these models, adjusted means (adjmean) and 95% confidence intervals are presented. If significant, between-quadrants differences were compared with maximum likelihood χ² tests or mixed effect regression models, as appropriate. No post-hoc corrections were performed. A p value <0.05 was considered significant. The SPSS 20.0 (IBM Corp, Armonk, New York) statistical software package was used for all calculations.

Results

Baseline Characteristics

Clinical, angiographical, and physiological characteristics of the study population (91 arteries studied in 78 patients) are shown in Tables 1 and 2. Mean FFR value was 0.81±0.12 (min 0.4-max 1.0). FFR was ≥0.75 in 70 (76.9%) cases, >0.80 in 54 (59.3%),
between 0.7-0.9 in 62 (68.1%), and <0.70 in only 12 (13.1%). Mean CFR was 2.0 ± 0.85 (min 1.0-max 4.74). A CFR <2 was documented in 53 (58.2%) cases; 9 (10.9%) had a CFR >3 and only 2 (2.2%) >4. IMR mean and median values were 26.3±16 and 18.1 (12.1-29.1), respectively (min 3.7-max 72.7). A 75th IMR percentile value of 29.1 U was documented and used as cutoff for high-IMR cases (MCD).

FFR, CFR and IMR values were similar among patients with and without hypertension, diabetes, obesity, current smoking or history of prior myocardial infarction; findings that could be limited by our small sample size (Supplemental Table 1). Also, FFR, CFR and IMR values were not significantly different between clinical presentations, either as acute coronary syndromes or as stable angina (adj means, p for overall comparisons: FFR=0.359, CFR=0.995 and IMR=0.540).

Angiographic Analysis

Table 2 shows relevant QCA data. Stenosis severity correlated with FFR [positively with MLD (r=0.258; p=0.024) and negatively with DS (%) (r=-0.331; p=0.003)], but not with CFR (MLD: r=-0.056, p=0.631; DS: r=-0.124, p=0.287) or IMR (MLD: r=-0.064, p=0.585; DS: r=-0.025, p=0.829).

Correlations between FFR, CFR and IMR

FFR was not significantly correlated with CFR (r=0.171; p=0.105). A significant and positive correlation between FFR and IMR was found (r=0.451; p<0.001), illustrating the haemodynamic dependence of FFR on microcirculatory status (Figure 1). However, in arteries with FFR>0.80 (n=54), this correlation became non-significant (r=0.128; p=0.358). CFR and IMR were not correlated in the overall vessel population (r=0.112; p=0.293) nor in only those with FFR>0.80 (r=-0.040; p=0.774).
Findings in Non-significant Coronary Stenoses (FFR >0.80)

In total, 54 arteries (59.3%) had a FFR >0.80. When compared with arteries with FFR ≤0.80, vessels with FFR >0.80 presented higher IMR [27.6 (95% CI: 23.4 to 31.8) vs 17.3 (95% CI: 13.0 to 21.7); p=0.001] and CFR values [2.1 (95% CI: 1.8 to 2.3) vs 1.8 (95% CI: 1.5 to 2.0); p=0.035] (adj.means). Remarkably, when CFR and IMR were used as dichotomous variables, a high number of vessels with normal FFR presented abnormal CFR or IMR: 28 (51.9%) had low-CFR and 18 (33.3%) high-IMR. Consequently, only 20 (37%) vessels with FFR >0.80 had concordant normal values of all three indexes.

Finally, within the normal FFR group, classification agreement between dichotomized values of CFR and IMR was low (kappa of -0.098; p=0.441). They were concordant only in 24 (44.44%); and in 30 (55.6%) arteries a classification disagreement was observed: CFR<2 but normal-IMR (<75th percentile) in 20 (37%) and CFR≥2 with high-IMR in 10 (18.5%) arteries.

Construction of the Four-quadrant Model of IHD Based on the FFR/CFR Relationship

Further assessment of the FFR/CFR relationship was performed in a four-quadrant scatterplot (Figure 1). Categorical agreement between FFR and CFR was low (kappa of 0.147, p=0.135). FFR and CFR were concordant in 51 (56.1%) cases: B in 26 (28.6%) and C in 25 (27.5%). Classification disagreement occurred in 40 vessels (44.0%): A in 12 (13.2%) and D in 28 (30.9%). Within D, 6 vessels (representing 6.6% of overall, and 21.4% of vessels in D) met the definition of lone-MCD. Table 3 reports clinical and physiological differences among the four quadrants. Patients in D were older and had less diabetes and obesity than those in B and C.
Microcirculatory Resistance and FFR/CFR Relationship

Subsequently, the microcirculatory resistance was investigated among the four-quadrant distribution of the FFR/CFR relationship. This revealed a significant difference in IMR values between groups (adjmean, p for overall comparison=0.007) (Figure 2A, Table 3). The highest microcirculatory resistance was observed in D [29.1 (95% CI: 22.9 to 35.4)] and the lowest in A [15.8 (95% CI: 9.9 to 21.8)]. IMR values in D were significantly higher than those in C [29.1 (95% CI: 22.9 to 35.4) vs 18.0 (95% CI: 12.3 to 23.8); p=0.010] and A [vs 15.8 (95% CI: 9.9 to 21.8); p=0.003]. The second quadrant ranking in IMR values was B [25.9 (95% CI: 20.8 to 31.0)]. These values were significantly higher than those in C [vs 18.0 (95% CI: 12.3 to 23.8); p=0.045] and A [vs 15.8 (95% CI: 9.9 to 21.8; p=0.013]. No significant differences in microcirculatory resistance were found between D and B (p=0.412)(all, adjmeans). Figure 2B shows the prevalence of vessels with IMR values suggestive of MCD. Importantly, 78% (18/23) of vessels with MCD had an associated FFR>0.80.

Inclusion of the “Lone-microcirculatory Dysfunction” Region in the Conceptual Plot of the FFR/CFR Relationship

Six arteries of D (representing 6.6% of total and 21.4% of D vessels) met the definition of lone-MCD. These analyses rendered the results visually represented in Figure 2 (adjmean, p for overall comparison=0.016). It can be acknowledged that these arteries had the highest microcirculatory resistance [38.6 (95% CI: 21.1 to 56.1)] in the study population and this was significantly higher than that in A [vs 15.8 (95% CI: 9.9 to 21.8); p=0.021] and C [vs 18.0 (95% CI: 12.6 to 23.8); p=0.028] (all, adjmeans).
Gensini Score as a Surrogate of Atherosclerotic Burden

In univariate analysis, the Gensini score revealed more diffuse atherosclerotic burden in patients with diabetes [52.5(28.5-86) vs 32.3(23.5-51); p=0.018], prior MI [48(29.5-65.5) vs 28.8(19-44); p<0.001] and a statistical trend was also observed in patients with dyslipidemia [43(28-57.3) vs 29.5(21.5-51); p=0.056]. No significant correlation between age and Gensini score was found (r=-0.050; p=0.670) (Table 3). Overall, this score was not significantly different between the four quadrants of the FFR/CFR relationship (adjmean p=0.097). However, when diffuse atherosclerosis was analyzed at a per-vessel level (arterial-Gensini score), trends towards higher degree of this index in A and C vessels were observed. No significant associations between arterial-Gensini score and FFR (r=-0.171, p=0.113) or IMR (r=-0.015, p=0.889) were documented. However, a marginal, negative association between the latter and CFR was found (r=-0.207, p=0.055).

Discussion

The main conclusions of this study are: 1) more than half (59%) of the coronary vessels with intermediate stenoses and an associated normal FFR (FFR>0.80) present data suggestive of abnormal haemodynamics associated with IHD (CFR<2 in 52%; high IMR in 33%); 2) abnormal FFR values (FFR<0.80) are highly unlikely when MCD is present and 3) integration of FFR, CFR and IMR supports the existence of differentiated patterns of atherosclerotic disease that combine focal and DAN with variable degrees of MCD. In the following paragraphs these aspects are discussed in detail.

Fractional flow reserve and myocardial flow impairment in ischemic heart disease.

Obstructive CAD in angiography has been customarily taken as indicative of IHD. However, impairment of myocardial blood supply in IHD has a multilevel origin. In epicardial vessels, both focal and diffuse atheromatous narrowings increase vascular
 resistance, with an added component of vasoconstriction triggered by endothelial dysfunction. At a microcirculatory level, increased resistance may result from structural remodelling (arteriolar obliteration and capillary rarefaction), vasoconstriction of large arteriole resulting from endothelial dysfunction or alpha-adrenergic stimulation, and extravascular compression of capillaries and venules. Despite that, assessment of IHD in clinical practice largely focuses on the identification of ischemia-generating epicardial stenoses that can be targeted with revascularisation. Gaining insights on other levels of IHD is important from the two-fold perspective that abnormal microcirculatory haemodynamics have been identified as predictive of cardiac events in patients without epicardial stenoses, and that patients allocated to the revascularisation deferral arm in pivotal FFR randomized trials were not free from long-term cardiac events (21% major adverse cardiovascular event (MACE) rate in DEFER trial, 33% and 20% long-term angina at 5 and 2 years follow-up in the DEFER and FAME trials, respectively).

**Dual Assessment of the Coronary Circulation with FFR and CFR**

In this research we focus on the information encoded in the classification agreement between FFR and CFR. This approach provides a richer perspective of coronary haemodynamics and might help to identify patients that, despite a normal FFR, have impaired myocardial blood supply and, potentially, poorer prognosis (Figure 3). Both CFR and FFR were originally used to assess functional stenotic significance; however, beyond the close concordance initially reported, a significant disagreement between both methods has been consistently found, like in our study. Recently, a new interpretation of the classification agreement between FFR and CFR was proposed by Johnson et al on the grounds of published studies and original findings with CFR derived from non-invasive positron emission tomography (PET) (Figure 1A). A fluid dynamic
Model fitting their observations suggests that the distribution of values in the four quadrants of the FFR/CFR relationship obeys to the relative contributions of focal stenosis, DAN and MCD.8

We applied this concept to patients with intermediate coronary stenoses, which constitute the current recommendation for FFR in clinical practice guidelines. Microcirculatory resistance was measured to obtain additional information on vessels included in the four quadrants of the FFR/CFR classification agreement. In the absence of well-defined cutoffs to identify MCD, the 75th quartile of overall IMR was used as a threshold for identification of MCD. This IMR threshold (29.1 U) seems reasonable because it is very similar to the highest “limit of IMR normality“ (<30 U) reported by Melikian et al. in patients without clinical evidence of atherosclerosis.14

Impact of Microcirculatory Dysfunction (MCD) on FFR Interrogation

Fractional flow reserve has greatly contributed to make decisions on coronary revascularisation by applying a restricted model of coronary physiology.3, 27 Being a translesional hyperemic pressure ratio, FFR is a relative index of epicardial conductance, and therefore it is influenced by the limits to maximal achievable blood flow caused by MCD and/or distal epicardial stenoses. It has been proposed that the presence of MCD is not an obstacle to take decisions based on FFR, provided that MCD is deemed to be non-reversible.28 Yet, the actual prevalence of MCD in cases in which revascularisation is deferred based on FFR is largely unknown.

In our study, microcirculatory resistance was significantly higher in vessels with non-severe stenoses (FFR>0.80). As a matter of fact, 33.3% of FFR non-severe stenoses had high IMR values suggestive of MCD. As shown in a separate analysis (Figure 2), this was particularly pronounced in stenoses meeting the “lone-MCD“ (high FFR, low CFR and
pressure loss <5 mmHg), providing support to the model of Johnson et al.\textsuperscript{8} An important message of our research is that, in intermediate stenoses, an FFR >0.80 does not identify only “healthy” vessels, but rather a mix of vessels with impaired and non-impaired myocardial circulation. As a corollary, an important proportion of patients in whom revascularisation is deferred on the grounds of FFR>0.80, have abnormal coronary haemodynamics.

Alternatively, vessels with FFR<0.75 stenoses frequently presented low or normal IMR values (IMR quartiles 1 to 3). This suggests that FFR classifies as hemodynamically severe only those stenoses located in vessels without MCD. In vessels with FFR<0.75, low microcirculatory resistance aimed to compensate high epicardial resistance, was found. Finally, the high microcirculatory resistance found among vessels in B is unclear. Whether this represents an incipient state of MCD (in which CFR is still preserved) or a heterogeneous response to hyperemic stimuli remains to be addressed by future research.

**Relationship between Angiography and Intracoronary Physiological Indexes**

Angiographic and physiological indices correlated poorly, reinforcing the well-known limitations of angiography in depicting functional severity of intermediate stenoses. Despite being also an angiographic index, the Gensini score is widely used\textsuperscript{29, 30} and has demonstrated to provide relevant prognostic information.\textsuperscript{29} Interestingly, the documented trend towards a negative, significant association between arterial-Gensini score and CFR (r=-0.207, p=0.055) is in agreement with the proposal made by Johnson et al\textsuperscript{8} regarding the effect of DAN on CFR. It has to be kept in mind that, being a pre-requisite for FFR interrogation, patients with distal coronary stenoses that might interfere with FFR measurements were excluded from our study, and that therefore the effect of DAN on CFR may have been more evident in the study of Johnson et al based on PET.\textsuperscript{8}
**Classification Disagreement between FFR and CFR**

In the discordant A group (FFR≤0.80 and CFR≥2), the expected physiological substrate would be the presence of a focal epicardial narrowing with normal distal epicardial conductance and functionally preserved microcirculation. A CFR>2.0 would therefore reflect that diffuse disease and microcirculatory impairment are minimal. At a difference with FFR, CFR has a large inter-individual variability, influenced by age, gender and physical training among other factors. IMR measurements suggest that MCD was absent in group A vessels, supporting previous observations based on Doppler-derived microcirculatory resistance in the same FFR/CFR classification quadrant. Since normal CFR values in group A vessels suggests adequate myocardial blood supply, the benefit of revascularisation of epicardial stenoses, despite abnormal FFR, might be challenged. Further investigation on this hypothesis is required.

DAN causes pressure losses and influences FFR values. Vessels without focal stenoses but with angiographic signs of atherosclerosis present lower FFR values, compared with angiographically normal coronaries. DAN has also been proposed as the dominant cause for group D discrepancy (FFR>0.80 and CFR<2.0). In theory, MCD could also account for group D vessel classification. In support of this, we documented significantly higher microcirculatory resistances in D than in C or A vessels. However, within this quadrant, IMR had a wide dispersion of values (from 7 to 72.7 units), supporting the concept that discrepancies in group D have a dual origin in DAN and MCD. (Figures 4 and 5).
Implications for Prognosis and Future Directions

Do these haemodynamic patterns convey prognostic information? As already mentioned, the rates of MACE and persistent angina at follow up in landmark FFR studies suggests that the invasive diagnosis of IHD can be still potentially improved. In this regard, for example, other authors have reported a worse prognosis in patients with D group vessels. Among 159 patients with FFR≥0.75, Meuwissen et al. found that those (n=28) with abnormal Doppler-derived CFR presented a significantly higher MACE rate (17%) at 1-year follow-up than those (n=129) with normal CFR (5% MACE rate).

Similar conclusions come from non-invasive studies. In 103 patients with normal myocardial perfusion by single-photon emission computerized tomography (a surrogate of stenoses with FFR>0.75), Herzog et al found that abnormal PET-derived CFR (n=32) was associated with a significantly higher MACE (6.25% vs. 1.4% per year; p <0.05) and cardiac death rates (3.1% vs. 0.5% per year; p <0.05) during follow-up, compared with normal CFR patients (n=71). Recently, Murthy et al reported in a large population an adjusted 3.2 and 4.9-fold increase in cardiac death rate for diabetics and non-diabetics patients, respectively, showing impaired PET-derived CFR (p=0.0004). Finally, DAN in the absence of focal stenosis has been associated with an increased risk of MACE [HR of 1.85 (1.51-2.28)]. Overall, this evidence suggests that both, DAN and MCD may have prognostic implications that could, in addition to obstructive CAD, improve IHD risk stratification.

Limitations

Our study can be envisaged as hypothesis generating due to our relatively small sample size. Our study reflects the recommended use of FFR-guided revascularization. Patients with intermediate stenoses may have a lower risk than those with more severe
stenoses included in other studies. Coronary wedge pressure was not measured. This might lead to overestimation of IMR\textsuperscript{36} in tight stenoses with significant collateral support. Even when overestimation should be minimal in intermediate severity stenoses, corrected IMR values as proposed by Yong et al\textsuperscript{12} were used to minimize that effect. A separate analysis of our dataset using uncorrected IMR revealed similar results to those reported in the manuscript. Finally, a comparative survival analysis of patients with vessels belonging to the different categories contemplated in our study (A, B, C and D) was not performed due to limited sample size.

**Conflict of Interest Disclosures:** J Escaned has served as speaker in educational events organized by St Jude Medical and Volcano Corporation. JE Davies is a consultant for Volcano Corporation.
References:


Table 1

General Characteristics of Study Population

n = 78

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>65.8±10.5</td>
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<td>Men</td>
<td>64 (82.1)</td>
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<td>Cardiovascular risk factors.</td>
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<tr>
<td>Hypertension</td>
<td>57 (73.1)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>20 (25.6)</td>
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<tr>
<td>Dyslipidemia</td>
<td>54 (69.2)</td>
</tr>
<tr>
<td>Smoker</td>
<td>20 (25.6)</td>
</tr>
<tr>
<td>Obesity</td>
<td>31 (39.7)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>42 (53.8)</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>37 (47.4)</td>
</tr>
<tr>
<td>Gensini score</td>
<td>34 (24-57)</td>
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<tr>
<td>Clinical presentation.</td>
<td></td>
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<tr>
<td>Stable angina</td>
<td>40 (51.3)</td>
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<tr>
<td>Post-MI</td>
<td>24 (30.8)</td>
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<tr>
<td>Unstable angina II B</td>
<td>11 (14.1)</td>
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<tr>
<td>Unstable angina III B</td>
<td>3 (3.8)</td>
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Values are mean ± S.D, median (25th-75th) or n (%).

MI: myocardial infarction; II B: primary angina, at rest, within past month but not within preceding 48 hr; III B: primary angina, at rest, within preceding 48 hr.
Table 2

General Characteristics of Epicardial Stenoses Included in Study

n=91

<table>
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<th>Stenosis location</th>
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<tr>
<td>Left anterior descending artery</td>
<td>39 (42.9)</td>
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<tr>
<td>Circumflex coronary artery</td>
<td>21 (23.1)</td>
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<td>Right coronary artery</td>
<td>31 (34.1)</td>
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Quantitative coronary angiography.

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<tr>
<td>Reference diameter, mm</td>
<td>3.05 ± 0.64</td>
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<tr>
<td>Minimum lumen diameter, mm</td>
<td>1.31 ± 0.43</td>
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<tr>
<td>Diameter stenosis, %</td>
<td>46.99 ± 12.25</td>
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<td>Lesion length, mm</td>
<td>7.80 ± 3.56</td>
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Coronary physiological parameters.

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<tr>
<td>P_a, mmHg*</td>
<td>79.4 ± 20.7</td>
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<tr>
<td>P_d, mmHg*</td>
<td>64.7 ± 20.8</td>
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<tr>
<td>FFR</td>
<td>0.81 ± 0.12</td>
</tr>
<tr>
<td>CFR</td>
<td>1.94 ± 0.80</td>
</tr>
<tr>
<td>IMR, U</td>
<td>18 (12.1-29.1)</td>
</tr>
<tr>
<td>Tmn_{bas}, seg</td>
<td>0.73 ± 0.48</td>
</tr>
<tr>
<td>Tmn_{hyp}, seg*</td>
<td>0.37 ± 0.21</td>
</tr>
</tbody>
</table>

Values are mean ± S.D, median (25th-75th) or n (%).
P_a: aortic pressure; P_d: distal pressure; FFR: fractional flow reserve; CFR: coronary flow reserve; IMR: index of microcirculatory resistance; Tmn_{bas}: basal mean transit time; Tmn_{hyp}: hyperemic mean transit time. *During stable hyperemia
### Table 3
Clinical and Physiological Differences Among the Four-quadrant Distribution of the FFR/CFR Relationship

<table>
<thead>
<tr>
<th>Predominantly focal (FFR ≤0.80 and CFR ≥2)</th>
<th>Adequate and concordant (CFR ≥2 and FFR &gt; 0.80)</th>
<th>Reduced and concordant (CFR &lt; 2 and FFR ≤0.80)</th>
<th>Predominantly diffuse (CFR &lt; 2 and FFR &gt; 0.80)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Per-patient analyses</strong> (n=73)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>68±9</td>
<td>62±9</td>
<td>63±11</td>
<td>70±11^b,c</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8(88.9)</td>
<td>14(66.7)</td>
<td>15(68.2)</td>
<td>16(76.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3(33.3)</td>
<td>8(38.1)</td>
<td>9(40.9)</td>
<td>1(4.8)^a,b,c</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>7(77.8)</td>
<td>16(76.2)</td>
<td>15(68.2)</td>
<td>13(61.9)</td>
</tr>
<tr>
<td>Obesity</td>
<td>1(11.1)</td>
<td>11(52.4)^a</td>
<td>12(54.5)^a</td>
<td>5(23.8)^b,c</td>
</tr>
<tr>
<td>Smoker</td>
<td>3(33.3)</td>
<td>4(19.0)</td>
<td>5(22.7)</td>
<td>6(28.7)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>7(77.8)</td>
<td>9(42.9)</td>
<td>12(54.5)</td>
<td>12(57.1)</td>
</tr>
</tbody>
</table>

| **Per-artery analyses** (n=91)            |                                               |                                               |                                               |         |
| Physiological parameters                 |                                               |                                               |                                               |         |
| FFR                                       | 0.73(0.70 to 0.77)                            | 0.88(0.86 to 0.90)^a,c                       | 0.68(0.63 to 0.73)                            | 0.90(0.88 to 0.92)^a,c | <0.001 |
| CFR                                       | 2.56(2.29 to 2.83)                            | 2.76(2.50 to 3.02)^c                         | 1.39(1.25 to 1.52)^a                         | 1.43(1.33 to 1.54)^a,b,c | <0.001 |
| IMR, U                                    | 15.8(9.8 to 23.10)                           | 25.9(20.8 to 31.0)^a,c                      | 18.0(12.3 to 23.8)                           | 29.1(22.9 to 35.4)^a,c | 0.007 |
| High-IMR                                  | 2(16.7)                                      | 10(38.5)                                      | 3(12.0)                                       | 8(28.6) | 0.123 |
| P_a, mmHg®                                | 70(57 to 83)                                 | 81(74 to 89)                                 | 75(66 to 84)                                 | 85(78 to 92) | 0.154 |
| P_b, mmHg®                                | 52(42 to 63)                                 | 72(64 to 78)^a,c                             | 51(44 to 57)                                 | 77(69 to 84)^a,c | <0.001 |
| Tmn_hyp, seg                               | 0.83(0.53 to 1.13)                           | 1.01(0.80 to 1.2)^a,c                       | 0.56(0.41 to 0.70)                           | 0.57(0.44 to 0.70)^a,c | 0.001 |
| Tmn_hyp, seg°                              | 0.31(0.22 to 0.40)                           | 0.36(0.30 to 0.43)                           | 0.40(0.29 to 0.50)                           | 0.39(0.31 to 0.46) | 0.599 |
| Angiographic analyses                     |                                               |                                               |                                               |         |
| Gensini score                              | 70.5(37.2 to 103.7)                          | 34.8(28.4 to 41.2)                           | 46.3(32.6 to 59.9)                           | 41.4(31.9 to 51.0) | 0.097 |
| Vessel only-Gensini score                  | 18.7(11.2 to 26.3)                           | 10.1(7.7 to 12.4)                            | 17(10 to 23)                                 | 15(10 to 20) | 0.063 |

* p value
Values are mean ± S.D, adjmean (95% CI) or n (%).

*Patients with stenosed vessels in discordant quadrants were excluded

MI: myocardial infarction; Pa: aortic pressure; Pd: distal pressure; FFR: fractional flow reserve; CFR: coronary flow reserve; IMR: index of microcirculatory resistance; Tmnbas: basal mean transit time; Tmnhyp: hyperemic mean transit time.

°During stable hyperemia

¹P<0.05 compared to group A

²P<0.05 compared to group B

³P<0.05 compared to group C

•Mixed effect regression models or maximum likelihood χ² tests were used for overall and between groups’ comparisons.
**Figure Legends:**

**Figure 1.** Conceptual and documented plots of the FFR/CFR relationship. Panel A: Conceptual plot of the FFR/CFR relationship showing the four different quadrants (modified from reference 8). Panel B: Scatterplot of FFR and CFR values in our study with high-IMR values (>29.1 U) highlighted.

**Figure 2.** Coronary microcirculatory resistance within the FFR/CFR relationship. Upper panel: Microcirculatory resistance among quadrants of the FFR/CFR relationship. Only p<0.05 values are shown. Lower panel: Prevalence of arteries with high-IMR. Numbers within columns represent n/total within each quadrant of the FFR/CFR relationship. Please also note that arteries meeting the “lone-MCD” definition were subtracted from quadrant D. All p values are of adj.means.

**Figure 3.** Schematic representation of the coronary hemodynamic patterns documented in this study. Panel A: vessel located in the C of the FFR/CFR relationship, with concordantly abnormal FFR and CFR and normal (low) IMR. Panel B: vessel in B with a non-severe focal stenosis without associated DAN or MCD. Panel C: vessel in D with a focal stenosis and DAN. Despite a normal FFR, an abnormal CFR with low IMR suggests that diffuse epicardial atherosclerosis is the predominantly affected compartment. Panel D depicts a stenosis located also in D. At a difference with the case shown in panel C, the presence of MCD, and not DAN, may account for the discrepancy between FFR and CFR. The abnormal hemodynamics illustrated in panel C and D can be only identified by combining information of FFR, CFR and IMR. Panel E: vessel with a stenosis located in A that,
despite showing an abnormal FFR, has preserved CFR as a result of well-preserved microcirculation and absence of significant DAN.

**Figure 4.** Representative cases of vessels with adequate and concordant and reduced and concordant values of FFR and CFR. **Panel A:** vessel located in B with a non-severe stenosis with normal FFR and CFR values (note the well separated baseline and hyperemic thermodilution curves); IMR is close to the 75% percentile value. **Panel B:** vessel located in C, with a severe stenosis, showing abnormal FFR and an exhausted CFR (CFR=1.0, baseline and hyperemic thermodilution curves are overimposed) and low microvascular resistance.

**Figure 5.** Representative cases of vessels with normal FFR and abnormal CFR. These two tracings illustrate the separate contribution of DAN and MCD to abnormal coronary hemodynamics in some vessels with normal FFR. **Panel A:** vessel located in D, in which the dominant feature is an abnormal CFR with normal IMR. The theoretical explanation is that DAN is the dominant cause of abnormal hemodynamics. **Panel B:** vessel also in D, with virtually identical FFR and CFR values than the one in **Panel A** that, however, shows very high IMR values suggestive of MCD.
Coronary flow reserve (CFR)

Predominantly focal

Predominantly diffuse

Reduced and concordant

Adequate and concordant

Lone microcirculatory dysfunction

Fractional flow reserve (FFR)

Figure 1
Figure 2

Prevalence of arteries with high-IMR (%)

Index of microcirculatory resistance, U

- Overall p=0.016
- Predominantly local dysfunction
- Reduced and concordant diffuse dysfunction
- Adequate and concordant diffuse dysfunction
- Predominantly diffuse dysfunction

Figure 2
Figure 3
Figure 4
Disturbed Coronary Hemodynamics in Vessels with Intermediate Stenoses Evaluated with Fractional Flow Reserve: A Combined Analysis of Epicardial and Microcirculatory Involvement in Ischemic Heart Disease


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### Supplemental table

Summary values of FFR, CFR and IMR among patients with and without cardiovascular risk factors.

\( n = 78 \)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Yes</th>
<th>No</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men, n (%)</strong></td>
<td>74 (81.3%)</td>
<td>0.82 (0.78 to 0.87)</td>
<td>0.597</td>
</tr>
<tr>
<td>FFR</td>
<td>0.81 (0.78 to 0.83)</td>
<td>1.96 (1.75 to 2.17)</td>
<td>0.728</td>
</tr>
<tr>
<td>CFR</td>
<td>1.96 (1.75 to 2.17)</td>
<td>1.90 (1.6 to 2.19)</td>
<td>0.876</td>
</tr>
<tr>
<td>IMR</td>
<td>23.3 (19.7 to 26.8)</td>
<td>23.9 (16.3 to 31.5)</td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>69 (75.8%)</td>
<td>0.81 (0.78 to 0.84)</td>
<td>0.758</td>
</tr>
<tr>
<td>FFR</td>
<td>0.80 (0.75 to 0.86)</td>
<td>2.01 (1.80 to 2.23)</td>
<td>0.097</td>
</tr>
<tr>
<td>CFR</td>
<td>2.01 (1.80 to 2.23)</td>
<td>1.73 (1.48 to 1.99)</td>
<td></td>
</tr>
<tr>
<td>IMR</td>
<td>22.74 (19.1 to 26.3)</td>
<td>25.5 (18.6 to 32.3)</td>
<td>0.495</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>23 (25.3%)</td>
<td>0.82 (0.79 to 0.85)</td>
<td>0.326</td>
</tr>
<tr>
<td>FFR</td>
<td>0.82 (0.79 to 0.85)</td>
<td>1.90 (1.56 to 2.25)</td>
<td>0.780</td>
</tr>
<tr>
<td>CFR</td>
<td>1.90 (1.56 to 2.25)</td>
<td>1.96 (1.76 to 2.17)</td>
<td></td>
</tr>
<tr>
<td>IMR</td>
<td>22.72 (14.50 to 23.93)</td>
<td>24.81 (20.91 to 28.71)</td>
<td>0.073</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>63 (69.2%)</td>
<td>0.81 (0.78 to 0.84)</td>
<td>0.977</td>
</tr>
<tr>
<td>FFR</td>
<td>0.81 (0.78 to 0.84)</td>
<td>2.03 (1.82 to 2.26)</td>
<td>0.104</td>
</tr>
<tr>
<td>CFR</td>
<td>2.03 (1.82 to 2.26)</td>
<td>1.75 (1.49 to 2.02)</td>
<td></td>
</tr>
<tr>
<td>IMR</td>
<td>23.3 (19.3 to 27.2)</td>
<td>23.7 (18.2 to 29.1)</td>
<td>0.903</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>22 (24.2%)</td>
<td>0.80 (0.74 to 0.87)</td>
<td>0.688</td>
</tr>
<tr>
<td>FFR</td>
<td>0.80 (0.74 to 0.87)</td>
<td>1.89 (1.61 to 2.17)</td>
<td>0.673</td>
</tr>
<tr>
<td>CFR</td>
<td>1.89 (1.61 to 2.17)</td>
<td>1.97 (1.75 to 2.18)</td>
<td></td>
</tr>
<tr>
<td>IMR</td>
<td>22.8 (16.5 to 29.1)</td>
<td>23.6 (19.9 to 27.3)</td>
<td>0.839</td>
</tr>
<tr>
<td>Obesity, n (%)</td>
<td>50 (40.7%)</td>
<td>0.80 (0.76 to 0.85)</td>
<td>0.698</td>
</tr>
<tr>
<td>FFR</td>
<td>0.80 (0.76 to 0.85)</td>
<td>2.01 (1.72 to 2.30)</td>
<td>0.549</td>
</tr>
<tr>
<td>CFR</td>
<td>2.01 (1.72 to 2.30)</td>
<td>1.90 (1.67 to 2.12)</td>
<td></td>
</tr>
<tr>
<td>IMR</td>
<td>22.8 (18.3 to 27.7)</td>
<td>23.7 (19.3 to 28.0)</td>
<td>0.839</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>49 (53.8%)</td>
<td>0.80 (0.76 to 0.83)</td>
<td>0.169</td>
</tr>
<tr>
<td>FFR</td>
<td>0.80 (0.76 to 0.83)</td>
<td>1.88 (1.67 to 2.10)</td>
<td>0.422</td>
</tr>
<tr>
<td>CFR</td>
<td>1.88 (1.67 to 2.10)</td>
<td>2.03 (1.74 to 2.31)</td>
<td></td>
</tr>
<tr>
<td>IMR</td>
<td>21.0 (16.6 to 25.4)</td>
<td>26.2 (21.6 to 30.8)</td>
<td>0.110</td>
</tr>
<tr>
<td>Multivessel disease, n (%)</td>
<td>48 (52.7%)</td>
<td>0.83 (0.80 to 0.86)</td>
<td>0.110</td>
</tr>
<tr>
<td></td>
<td>FFR</td>
<td>CFR</td>
<td>IMR</td>
</tr>
<tr>
<td>--------</td>
<td>--------------</td>
<td>--------------</td>
<td>--------------</td>
</tr>
<tr>
<td></td>
<td>0.82 (0.79 to 0.86)</td>
<td>0.80 (0.76 to 0.84)</td>
<td>0.385</td>
</tr>
<tr>
<td></td>
<td>1.92 (1.64 to 2.21)</td>
<td>1.97 (1.78 to 2.17)</td>
<td>0.779</td>
</tr>
<tr>
<td></td>
<td>21.12 (17.2 to 25.2)</td>
<td>25.9 (20.8 to 30.9)</td>
<td>0.154</td>
</tr>
</tbody>
</table>

Values are n (%) or adj means (95% CI).

*Mixed effect regression models