Novel insights into the complexity of ischaemic heart disease derived from combined coronary pressure and flow velocity measurements
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Chapter 7

Diagnostic and prognostic implications of coronary flow capacity: a comprehensive cross-modality physiological concept in ischemic heart disease

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ABSTRACT

Background
Although ischemic heart disease (IHD) results from a combination of focal obstructive, diffuse, and microcirculatory involvement of the coronary circulation, its diagnosis remains focused on focal obstructive causes. Coronary flow capacity (CFC) comprehensively documents flow impairment in IHD, regardless of its origin, by interpreting coronary flow reserve (CFR) in relation to maximal flow (hAPV), and overcomes the limitations of using CFR alone. This is governed by the understanding that ischemia occurs in vascular beds with substantially reduced hAPV and CFR, while ischemia is unlikely when hAPV or CFR is high.

Objectives
To evaluate whether CFC improves discrimination of patients at risk for major adverse cardiac events (MACE) compared with CFR alone, and to study the diagnostic and prognostic implications of CFC in relation to contemporary diagnostic tests for IHD, including fractional flow reserve (FFR).

Methods
Intracoronary pressure and flow were measured in 299 vessels (228 patients), where revascularization was deferred in 154. Vessels were stratified as normal, mildly reduced, moderately reduced, or severely reduced CFC. The occurrence of MACE after deferral of revascularization was recorded during 11.9 years of follow-up (Q1,Q3: 10.0, 13.4 years).

Results
Combining CFR and hAPV improved the overall prediction of MACE over CFR alone (p=0.01). After stratification in CFC, MACE rates throughout follow-up were strongly associated with advancing impairment of CFC (p=0.002). After multivariate adjustment, mildly and moderately reduced CFC were associated with 2.1-fold (95%-CI: 1.1–4.0, p=0.017), and 7.1-fold (95%-CI: 2.9–17.1, p<0.001) increase in MACE hazard, respectively, compared with normal CFC. Severely reduced CFC was identified by FFR≤0.80 in 90% of cases, while ≥40% of vessels with normal or mildly reduced CFC still had FFR≤0.80.

Conclusion
CFC provides a robust cross-modality platform for the diagnosis and risk-stratification of IHD, and enriches the interpretation of contemporary diagnostic tests in IHD.
INTRODUCTION

Although ischemic heart disease (IHD) is a complex multilevel process that originates from a combination of focal obstructive, diffuse, and microcirculatory causes of myocardial flow impairment, contemporary clinical practice remains focused on focal epicardial coronary artery obstruction. However, the presence of a strong link between myocardial blood flow impairment and adverse clinical outcome regardless of its origin, urges a comprehensive diagnostic approach towards IHD, not restricted to the epicardial domain.

The coronary flow reserve (CFR) is a well-validated index that allows the assessment of blood flow impairment originating from either obstructive, diffuse, or microcirculatory involvement of the coronary circulation. However, its use has been limited due to a reported sensitivity towards resting hemodynamics. As a result, the coronary pressure-derived fractional flow reserve (FFR) is considered the preferred surrogate for blood flow impairment in the catheterization laboratory. Nonetheless, FFR is an invasive tool that was introduced to identify significant epicardial coronary artery obstruction by means of trans-stenotic pressure drops, which by definition do not occur in the presence of diffuse coronary artery disease or microcirculatory involvement in IHD, and can be concealed when obstructive, diffuse, and microcirculatory causes coincide. Therefore, both CFR and FFR seem insufficient to comprehensively diagnose IHD.

An alternative approach towards the diagnosis of IHD can be found in the concept of coronary flow capacity (CFC), which integrates both CFR and maximal hyperemic flow to depict myocardial blood flow impairment due to a combination of obstructive, diffuse, and microcirculatory involvement of the coronary vasculature. First derived from positron emission tomography (PET), CFC may potentially provide a comprehensive and robust physiological platform, likely applicable to all invasive and non-invasive modalities aiming to detect myocardial blood flow impairment, and which may overcome many of the limitations of using CFR or FFR alone. However, the complementarity of CFR and hyperemic flow in terms of risk-stratification in IHD has not been documented, nor its comparison with other contemporary invasive and non-invasive diagnostic tests in IHD.

In the present study, we aimed to document 1) the applicability of the CFC concept to invasive measurements, 2) whether the physiological complementarity of CFR and hyperemic flow translates into an improved discrimination of patients at risk for adverse outcome, and 3) the diagnostic and prognostic implications of CFC in relation to contemporary diagnostic tests for IHD.
Chapter 7

METHODS

Data source
Between April 1997 and September 2006, we evaluated patients with stable IHD referred for evaluation of ≥1 coronary artery stenosis (40-70% diameter stenosis at visual assessment). Patients were enrolled in a series of study protocols, and data were entered in a dedicated database. These protocols excluded patients with renal function impairment (calculated glomerular filtration rate <30mL/min/1.73m²), significant left main disease, atrial fibrillation, recent myocardial infarction (<6 weeks prior to screening), prior coronary artery bypass graft surgery, as well as vessels with ostial stenosis, serial stenoses, or visible collaterals. The institutional ethics committee approved the study procedures, and all patients gave written informed consent.

Myocardial perfusion scintigraphy (MPS)
MPS was performed prior to coronary angiography using ⁹⁹ᵐ⁻Technetium sestamibi or ⁹⁹ᵐ⁻Technetium tetrofosmin, according to a two-day stress/rest protocol. A blinded expert panel evaluated the scintigraphic images. Perfusion defects were classified as dubious, mild, moderate or severe. Improvement at rest of ≥1 grade was considered a “reversible” perfusion defect, and improvement of ≤1 grade a “persistent” perfusion defect. The result was considered positive when a reversible perfusion defect was allocated to the perfusion territory of interest.

Coronary angiography and physiological measurements
Coronary angiography was performed according to standard practice. Quantitative coronary angiography (QCA) analyses were performed offline using validated software (QCA-CMS version 3.32, MEDIS, Leiden, The Netherlands). Intracoronary pressure was measured with a 0.014” pressure sensor-equipped guide wire (Volcano Corp., San Diego, USA), and coronary blood flow velocity was subsequently measured with a 0.014” Doppler crystal-equipped guide wire (Volcano Corp., San Diego, USA). Hyperemia was induced by an intracoronary bolus of adenosine (20-40 µg). Flow velocity measurements were additionally performed in a reference vessel, defined as a coronary artery with less than 30% epicardial narrowing, if available.

Long-term follow-up
Three-, 6-, 12-month, and long-term follow-up was performed by clinical visits or telephone contact to document major adverse cardiac events (MACE), defined as the composite of cardiac death, myocardial infarction not clearly attributable to non-target vessels, and clinically driven (urgent) revascularization of the target vessel. All patient-
reported adverse events were adjudicated after evaluating hospital records, or contact-
ing treating physicians.

Definition of physiological parameters

FFR was calculated as the ratio of mean distal-to-aortic pressure during hyperemia, where FFR≤0.80 was considered abnormal.\textsuperscript{15} CFR was calculated as the ratio of hyperemic to basal average peak blood flow velocity (hAPV and bAPV, respectively), where CFR<2.0 was considered abnormal.\textsuperscript{16} We additionally determined the hyperemic stenosis resistance index (HSR)\textsuperscript{14} as the ratio of the trans-stenotic pressure drop to hAPV, where HSR>0.80 mm Hg/cm/s was considered abnormal,\textsuperscript{16} and the hyperemic microvascular resistance index (HMR), as the ratio of distal coronary pressure to hAPV.\textsuperscript{9} Parameter definitions are detailed in Table 1.

<table>
<thead>
<tr>
<th>Table 1. Physiological parameter definitions</th>
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<tbody>
<tr>
<td>FFR = mean Pdistal /mean Paorta (during hyperemia)</td>
</tr>
<tr>
<td>CFR = hyperemic flow velocity (hAPV) / basal flow velocity (bAPV)</td>
</tr>
<tr>
<td>HSR= (mean Paorta – mean Pdistal)/ APV (during hyperemia)</td>
</tr>
<tr>
<td>HMR = mean Pdistal / APV (during hyperemia)</td>
</tr>
</tbody>
</table>

Pdistal (Pd): distal coronary pressure, Paorta (Pa): aortic pressure, APV: average peak flow velocity dis-
tal to the coronary lesion, HSR: hyperemic stenosis resistance index, HMR: hyperemic microvascular resistance index

Derivation of the invasive coronary flow capacity map

Figure 1 shows the invasive coronary flow capacity (CFC) map. Analogous to the PET-
derived CFC concept, coronary flow was categorized into clinically meaningful ranges using well-documented thresholds of CFR derived from invasive measurements. The highest coronary flows are encountered in patients without significant epicardial coronary narrowing (normal flow capacity).\textsuperscript{17} The subsequent category depicts slightly reduced coronary flows; lower than in patients without epicardial narrowing, but of adequate magnitude to prevent myocardial ischemia (mildly reduced flow capacity). Moderately reduced flows lie within the range of flows reported to be related to inducible myocardial ischemia, and can produce some manifestations of myocardial ischemia (moderately re-
duced flow capacity).\textsuperscript{18} Finally, severely reduced flows lie below the lower flow threshold reported for myocardial ischemia (severely reduced flow capacity).

The above-mentioned flow ranges have been well documented for invasively derived CFR, but not for hAPV. Therefore, categorization was based on literature-derived CFR ranges, and hAPV values matched according to the corresponding percentiles, as follows. Normal CFC was defined as a CFR≥2.8, as encountered in patients with risk factors for IHD without epicardial narrowing,\textsuperscript{17} with its corresponding hAPV of ≥49.0 cm/s. Mildly
reduced CFC was defined as a CFVR < 2.8, but > 2.1, which reflects the upper limit of reported CFR cut-off values for inducible ischemia,\textsuperscript{18} and the corresponding hAPV of < 49.0 cm/s, 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,\textsuperscript{18} and the corresponding hAPV of ≤ 33.0 cm/s and > 26.0 cm/s, respectively. Finally, severely reduced CFC was defined as a CFR ≤ 1.7, which is the lower limit of CFR cut-off values reported for inducible myocardial ischemia\textsuperscript{18} and analogous to the ischemic CFR threshold on non-invasive imaging,\textsuperscript{19} and the corresponding hAPV of ≤ 26.0 cm/s.

Figure 1 | Invasive coronary flow capacity map. Since coronary flow reserve (CFR) equals hyperemic to baseline average peak flow velocity (hAPV), a two-dimensional map of CFR versus hAPV comprehensively describes the invasive flow characteristics of the coronary vasculature under investigation. Within this concept, four clinically meaningful categories are defined (coded with different colours in the graph) based on well-validated invasive CFR cut-off values and the according hAPV percentiles. See text for further details.
Statistical analysis
Data were analyzed on per-patient basis for clinical characteristics, and on per-vessel basis for all other calculations. Normality and homogeneity of the variances were tested using Shapiro-Wilk and Levene tests. Continuous variables are presented as mean±standard deviation or median [1st, 3rd quartile (Q1, Q3)], and were compared with Student’s t test or Mann-Whitney U test. Categorical variables are presented as counts and percentages, and were compared with Chi square or Fisher´s exact test. Analyses of linear trends across CFC categories were performed with polynomial contrasts.

In the presence of multiple coronary stenoses, one was randomly marked as index and used for clinical outcome analyses, which were restricted to patients in whom revascularization was deferred. First, the prognostic value of CFR and hyperemic flow for long-term MACE were assessed using separate Cox regression analyses, adjusted for the effect of relevant clinical and angiographic characteristics. Optimal models were identified using Akaike’s information criterion, where candidate co-variates were: clinical characteristics (Table 1), percent diameter stenosis, and the interrogated vessel (left anterior descending (LAD), left circumflex (LCx), or right (RCA) coronary artery). Results are presented as standardized hazard ratios (sHR), and their 95% confidence intervals (95%CI), which were estimated from these models by exponentiating the β-coefficient multiplied by the SD [exp(β × SD)]. Second, the incremental prognostic value of hyperemic flow to CFR was assessed in a multivariable Cox regression model, including both CFR and hyperemic flow as well as adjustments for relevant characteristics as defined previously. As a sensitivity analysis, the additive value of hyperemic flow to CFR was evaluated with the continuous net reclassification index (NRI), integral discrimination improvement (IDI) and relative IDI (rIDI) (Supplemental Methods). Third, after stratification into CFC categories, event rates over time were estimated using the Kaplan-Meier (KM) method, and linear trends were tested with log rank tests. Finally, adjusted Cox proportional hazard analyses were used to assess the impact of CFC on long-term MACE. A p-value <0.05 (two-sided) was considered statistically significant. The STATA 13.1 (StataCorp, College Station, Texas) software package was used for calculations.

RESULTS
Patient population
A total of 228 patients with 299 coronary stenoses were included. Baseline characteristics are depicted in Table 2. Revascularization was deferred in 159 patients, and follow-up was obtained in 154 patients (97%) with 183 stenoses. In patients with multiple stenoses, one was chosen at random for MACE analyses, which consequently included 154 patients with 154 stenoses (Supplemental Table 1). Median follow-up in these
patients was 11.9 years (Q1, Q3: 10.0, 13.4 years). The distribution of FFR values in this deferred study population resembled that of reported clinical populations undergoing FFR-measurements (Supplementary Figure 1).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Baseline characteristics</th>
</tr>
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<tr>
<td>Number of patients</td>
<td>228</td>
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<table>
<thead>
<tr>
<th>Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coronary risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Positive family history</td>
</tr>
<tr>
<td>Cigarette smoking</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
</tr>
<tr>
<td>Prior coronary intervention</td>
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</table>

<table>
<thead>
<tr>
<th>Medication at hospital admission</th>
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<tbody>
<tr>
<td>Beta-blocker</td>
</tr>
<tr>
<td>Nitrates</td>
</tr>
<tr>
<td>Calcium antagonists</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
</tr>
<tr>
<td>Lipid-lowering drugs</td>
</tr>
<tr>
<td>Aspirin</td>
</tr>
</tbody>
</table>

ACE: Angiotensin-converting enzyme

**Improvement in risk stratification by integrating CFR and hyperemic flow**

In separate adjusted Cox proportional hazards models (adjusted for angiotensin-inhibitor use, diabetes, diameter stenosis, and interrogated vessel), both CFR and hAPV were significantly associated with long-term MACE (CFR sHR: 0.5, 95%CI: 0.4–0.8, p<0.001; hAPV sHR: 0.7, 95%CI: 0.5 – 0.9, p=0.02). Adding hAPV to the CFR adjusted Cox model yielded a significant model improvement (Likelihood-ratio test p=0.01), and both CFR and hAPV remained independent predictors for long-term MACE (CFR sHR: 0.5, 95%CI: 0.4–0.7, p<0.001; hAPV sHR: 0.7, 95% CI: 0.5 – 0.9, p=0.01).

The sensitivity analyses using NRI, IDI and rIDI supported these findings, showing a significant improvement in the prediction of MACE by adding hAPV to CFR (Supplementary Table 2). In contrast, FFR, HSR or MPS did not improve prediction of MACE over CFR alone (Supplementary Table 2).
Clinical outcome after deferral of revascularization

Figure 2 shows the KM curves of MACE across CFC categories. The severely reduced CFC category was omitted because only two patients within this category were deferred, and both suffered a MACE within the first year of follow-up. MACE increased significantly with advancing impairment of CFC at all time-points (logrank for trend p=0.002; Figure 2).

Adjusted Cox regression analysis identified CFC as an independent predictor for long-term MACE. Compared with normal CFC, a mildly and moderately reduced CFC were associated with a 2.1-fold (95% CI: 1.1 – 4.0, p=0.017), and a 7.1-fold (95% CI: 2.9 – 17.1, p<0.001) increase in MACE, respectively. Using the same cut-off values, CFR alone showed a more modest discrimination: mildly reduced vs. normal CFR (HR 1.6 (95% CI: 0.8 – 3.5), p=0.20), and moderately reduced CFR vs. normal CFR (HR 3.8 (1.7 – 8.3), p=0.001)).

Comparison with contemporary diagnostic tests in IHD

The distribution of all 299 vessels across CFC categories is shown in Figure 3. A total of 121 vessels (40.5%) had normal CFC, 99 vessels (33.1%) mildly reduced CFC, 30 vessels (10.0%) moderately reduced CFC, and 49 (16.4%) severely reduced CFC (Table 3).

The frequency of abnormal values of FFR, CFR, HSR, and MPS across the CFC categories is shown in Table 3, and is visualized in Figure 4. Identification of severely reduced CFC was good for all tests, particularly for FFR≤0.80 (90%) and HSR>0.80 mm Hg/cm/s (92%). With increasing CFC, however, discordance with CFC increased substantially (Table 3; Figure 4), particularly for FFR.
<table>
<thead>
<tr>
<th>Coronary Flow Capacity</th>
<th>Normal</th>
<th>Minimally to mildly reduced</th>
<th>Moderately reduced</th>
<th>Severely reduced</th>
<th>P-value for linear trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of stenoses</td>
<td>121</td>
<td>99</td>
<td>30</td>
<td>49</td>
<td></td>
</tr>
</tbody>
</table>

**Angiographic parameters**

- **Interrogated vessel**
  - LAD: 71 (59) 43 (43) 13 (43) 19 (39) 0.03
  - LCX: 15 (12) 33 (33) 12 (40) 11 (22) 0.08
  - RCA: 35 (29) 23 (23) 5 (17) 19 (39) 0.45

- **Measurement location**
  - Proximal vessel: 30 (25) 19 (19) 9 (30) 12 (24) 0.67
  - Middle Vessel: 66 (55) 53 (54) 15 (50) 23 (47) 0.34
  - Distal vessel or side branch: 25 (21) 27 (27) 6 (20) 14 (29) 0.49

- **Diameter Stenosis, %**

- **Reference diameter, mm**
  - 3.0 [2.5, 3.4] 2.9 [2.6, 3.3] 2.8 [2.3, 3.0] 2.8 [2.3, 3.3] 0.12

- **Minimal lumen diameter, mm**
  - 1.4 [1.2, 1.7] 1.2 [1.0, 1.6] 1.3 [1.0, 1.4] 0.9 [0.7, 1.1] <0.001

**Hemodynamic parameters**

- **APV (Basal), cm/s**

- **APV (Hyperemia), cm/s**

- **Aortic pressure (Basal), mm Hg**
  - 99±13 99±12 96±8 98±16 0.66

- **Aortic pressure (Hyperemia), mm Hg**
  - 95±13 96±12 89±8 95±17 0.51

- **Distal pressure (Basal), mm Hg**
  - 95 [84, 100] 93 [85, 102] 86 [78, 92] 65 [55, 79] <0.001

- **Distal pressure (Hyperemia), mm Hg**
  - 78 [70, 88] 79 [68, 91] 72 [61, 78] 47 [39, 62] <0.001

- **Pressure drop (Basal), mm Hg**

- **Pressure drop (Hyperemia), mm Hg**
Table 3 | Angiographic and hemodynamic characteristics according to coronary flow capacity groups (continued)

<table>
<thead>
<tr>
<th>Coronary Flow Capacity</th>
<th>Number of stenoses</th>
<th>Normal</th>
<th>Minimally to mildly reduced</th>
<th>Moderately reduced</th>
<th>Severely reduced</th>
<th>P-value for linear trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (Basal), BPM</td>
<td>68±11</td>
<td>69±11</td>
<td>70±11</td>
<td>68±10</td>
<td></td>
<td>0.81</td>
</tr>
<tr>
<td>Heart rate (Hyperemia), BPM</td>
<td>69±11</td>
<td>69±11</td>
<td>73±10</td>
<td>69±10</td>
<td></td>
<td>0.44</td>
</tr>
<tr>
<td>Derived indices</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFR</td>
<td>2.9 [2.4, 3.3]</td>
<td>2.3 [2.0, 2.5]</td>
<td>1.9 [1.8, 2.0]</td>
<td>1.3 [1.1, 1.4]</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>CFR≤2.0</td>
<td>13 (11)</td>
<td>28 (28)</td>
<td>22 (73)</td>
<td>49 (100)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>FFR</td>
<td>0.84 [0.77, 0.90]</td>
<td>0.84 [0.74, 0.91]</td>
<td>0.77 [0.71, 0.81]</td>
<td>0.49 [0.40, 0.64]</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>FFR≤0.80</td>
<td>48 (40)</td>
<td>43 (43)</td>
<td>20 (67)</td>
<td>44 (90)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>HSR, mm Hg/cm/s</td>
<td>0.30 [0.19, 0.53]</td>
<td>0.46 [0.26, 0.77]</td>
<td>0.78 [0.60, 0.94]</td>
<td>3.00 [1.80, 4.38]</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>HSR&gt;0.80 mm Hg/cm/s</td>
<td>7 (6)</td>
<td>21 (21)</td>
<td>13 (43)</td>
<td>45 (92)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Inducible ischemia on MPS</td>
<td>18 (15)</td>
<td>22 (22)</td>
<td>11 (37)</td>
<td>38 (78)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; RCA: right coronary artery; APV: average peak velocity; BPM: beats per minute; CFR: coronary flow reserve; FFR: fractional flow reserve; HSR: hyperemic stenosis resistance index; MPS: myocardial perfusion scintigraphy. Pressure drop equals aortic pressure minus distal coronary pressure.
Figure 5 shows the distribution of FFR across the CFC categories (overall p<0.001). FFR was not statistically different between the normal and mildly reduced CFC groups (median FFR: 0.84 [Q1, Q3: 0.77-0.90] vs 0.84 [Q1, Q3: 0.74-0.91]; P=0.99), but 40% and 43% of vessels within these categories had an FFR≤0.80, despite only mildly reduced or normal flow characteristics. With a further reduction in CFC, FFR decreased significantly to a median of 0.77 [Q1, Q3: 0.71-0.81] in the moderately reduced, and to 0.49 [Q1, Q3: 0.40-0.64] in the severely reduced CFC category, where 75% of stenoses had an FFR<0.65 (Table 3). HSR increased significantly with decreasing CFC (Table 3; P<0.001), and showed a lower discordance with CFC than FFR (6% and 11% for normal or mildly reduced CFC, respectively). Finally, MPS reversible perfusion deficits were present in 78% of severely reduced CFC vessels, whilst discordance in higher CFC categories was limited to 15% and 22% for normal or mildly reduced CFC, respectively.

Notably, 13 out of 15 vessels associated with moderately (9 out of 10 vessels) or severely reduced CFC (4 out of 5 vessels) that were not identified by FFR≤0.80, were characterized by high HMR (3.24 mm Hg/cm/s [2.69 – 3.37 mm Hg/cm/s]), and low HSR (0.53 mm Hg/cm/s [0.46 – 0.60 mm Hg/cm/s]), suggestive of a dominant non-obstructive origin of flow impairment. The other two stenoses were characterized by a positive HSR (>0.80 mm Hg/cm/s) and a very high HMR (>3.5 mm Hg/cm/s), suggestive of concomitant obstructive and non-obstructive origins of flow impairment.
Chapter 7

Discussion

The physiological complementarity of CFR and hyperemic flow, integrated within the CFC concept, translates into meaningful incremental risk discrimination for adverse clinical outcomes compared with CFR alone, which is not attainable by other contemporary diagnostic tests in IHD. CFC provides a robust cross-modality physiological platform for the comprehensive diagnosis and risk-stratification of IHD, incorporating the consequences of both focal obstructive, diffuse, and microcirculatory causes of myocardial blood flow impairment.
Coronary flow capacity rationale: complementarity of CFR and hyperemic flow

Myocardial ischemia originates from impairment of myocardial perfusion resulting from both focal obstructive, diffuse, and microcirculatory causes, and occurs when the maximal achievable perfusion is insufficient to meet myocardial demand. The principle of CFR has been extensively applied to both invasive and non-invasive diagnostic techniques, including intracoronary Doppler- and thermodilution-derived flow, transthoracic echocardiography, PET and magnetic resonance imaging. Nonetheless, its sensitivity towards resting hemodynamics has been considered an important limitation in its use to diagnose myocardial flow limitation, despite repeated documentation of a substantial ability to stratify the risk for MACE.2-4

The rationale behind CFC relies on the fact that the combination of CFR with hyperemic flow comprehensively captures all relevant flow characteristics of the vasculature under investigation.11 For example, as suggested by Johnson and Gould, in the setting of anxiety or increased myocardial workload, baseline flow may be high, whilst maximal flow is adequate. In this situation, CFR may be low while no signs or symptoms of ischemia occur. Conversely, in patients on beta blockade therapy, maximal flow may be reduced to ischemic levels, while basal flow can be low due to the beta blockade effects, resulting in a normal CFR preventing signs or symptoms of inducible ischemia. Hence, combining hyperemic flow with CFR conceivably provides a more comprehensive assessment and overcomes many limitations of using CFR alone to diagnose clinically pertinent impairment of myocardial flow.

We documented that the physiological complementarity of hyperemic flow and CFR, as the basis of the CFC concept, translates into an improved discrimination of patients at risk for MACE compared with CFR alone. In contrast, none of the contemporary tests for ischemia, including FFR, provided improvement in discrimination above CFR (Supplementary Table 2). It is likely that this advantage derives from the fact that CFC 1) assesses both focal obstructive, diffuse, and microcirculatory causes of IHD,20 and 2) is less susceptible to the limitations of CFR linked to the baseline state.

Although CFC was initially derived from PET-studies, the present results expand this concept to invasive coronary flow assessment. The demonstrated improvement in MACE discrimination together with its previous validation in PET studies suggests that CFC is a potentially disruptive physiological concept, likely applicable to both invasive and non-invasive IHD diagnostic modalities that measure flow, including intracoronary Doppler- and thermodilution-derived flow, transthoracic echocardiography, PET and magnetic resonance imaging.
Relationship between contemporary diagnostic tests for IHD and coronary flow capacity

The CFC concept is governed by the understanding that vascular beds perfused by vessels with severely reduced maximal flow and exhausted CFR will exhibit signs of ischemia and that the latter will be unlikely in myocardial territories perfused by vessels showing high maximal flow or high CFR. On this basis, we sought to relate established indices for ischemia with CFC (Figure 4). We observed that FFR, HSR and MPS were very likely to be abnormal in vessels with severely reduced CFC, which corroborates the documented high sensitivity of FFR for the detection of inducible myocardial ischemia, and the high accuracy of HSR to identify stenoses associated with perfusion abnormalities on non-invasive imaging. On the other hand, many vessels perfusing vascular territories with normal or only mildly reduced CFC (with high values of either maximal flow or CFR) presented abnormal functional tests, particularly positive FFR values. However, since myocardial function dominantly depends on coronary flow and not on perfusion pressure—as myocardial contraction remains preserved with stable flow, even at very low perfusion pressures (FFR<0.50)—the benefit of revascularization of such stenosis is less clear. It is important to note that FFR values within the severely reduced CFC category were dramatically lower than in the other categories, as 75% of FFR values in this category were <0.65. This finding is in accordance with initial FFR validation and clinical outcome studies, since one of the first proposed FFR cut-offs was 0.66 (derived from electrical manifestations of ischemia), and the clinical benefit of revascularizing FFR-positive stenoses in the FAME II trial was dominant in vessels with FFR<0.65. Moreover, a recent patient-level meta-analysis on the prognostic value of FFR identified an optimal FFR treatment threshold of 0.67. Our findings add to this evidence by suggesting that coronary flow characteristics associated with signs of severe ischemia and impaired clinical outcomes are dominantly associated with FFR values far below contemporary interventional thresholds. Since ischemia is a continuum, further studies should address if the currently adopted FFR threshold is the most optimal to trigger revascularization.

Implications for clinical practice

Accumulated evidence strongly supports a multi-level involvement of the coronary circulation in IHD, which urges reconsideration of contemporary stenosis-centered diagnostic strategies in this complex disease. Although the documented clinical benefit of FFR-guided revascularization illustrates important progress in the treatment and risk-stratification of IHD, inadvertently, this clinical merit has led several reports to suggest FFR as a gold standard test for diagnosis of IHD, and to dismiss the prognostic pertinence of non-obstructive involvement in IHD. Although FFR is a simple and effective surrogate for focal obstructive flow impairment, IHD goes beyond the domain that can be interrogated by FFR. In this regard, the CFC concept provides a robust cross-modality physi-
ological platform for IHD diagnosis and risk stratification purposes, which overcomes many of the limitations of using CFR and FFR alone. In addition, CFC seems to enrich the interpretation of contemporary diagnostic standards in IHD, like FFR.

Limitations
Although conceptually applicable to the spectrum of IHD, our conclusions refer to patients with a clinical indication for intracoronary interrogation of epicardial stenosis, which constituted the study population. Assessment of flow velocity is sensitive for technical failures. However, all measurements in this study were performed by operators with ample experience. In the absence of an established cut-off value or normal ranges for hAPV, the proposed cut-off values were derived from the percentiles of hAPV corresponding to literature-defined CFR cut-offs. Particularly the hAPV cut-off value for severely reduced CFC should be subject to confirmation, which may allow further optimization of the invasive CFC concept. Importantly, because nature normalizes coronary artery wall stress, coronary flow velocity is intrinsically normalized for myocardial mass in the arterial distribution.27,28 This constitutes a theoretical concern, since some normal but anatomically reduced myocardial territories could therefore exhibit lower values of hAPV.29 However, only 6 (3%) reference vessels in our study showed an hAPV within the severely reduced CFC region (Supplemental Figure 2), and none of these vessel had a reduced CFR (range 2.2 – 4.6). This strongly suggests that clinically relevant coronary branches, suitable for invasive physiological interrogation, can be adequately stratified by means of the proposed invasive CFC concept. The diagnostic accuracy of MPS for definite ischemia should be interpreted carefully, since a positive MPS requires the presence of perfusion deficit reversibility. It cannot be excluded that some of the MPS-CFC discordance occurred in the presence of persistent perfusion defects. Finally, this study is limited by the assessment of adverse events at long-term follow-up partly performed by means of a telephone survey. Such an approach is sensitive towards a possible patient recall bias, which may have resulted in underreporting of adverse events. Nonetheless, the long-term MACE rates reported in the present study are generally comparable with those reported in contemporary observational studies using FFR guidance.30

CONCLUSIONS
The CFC concept provides a comprehensive cross-modality platform for the diagnosis and risk-stratification of IHD, and allows to enrich the interpretation of contemporary diagnostic tests in IHD. CFC may thereby provide a robust and disruptive physiological framework in IHD, likely applicable to all invasive and non-invasive diagnostic modalities that measure flow.
REFERENCES


**Supplemental Figure 1** | Distribution of FFR values across the deferred study population.

**Supplemental Figure 2** | Distribution of hyperemic average peak flow velocity (hAPV) values within the studied reference coronary arteries. Dashed red line indicates the threshold for severely reduced hAPV (<26.1).