

RESEARCH ARTICLE
Emerging Technologies in Cardiovascular Physiology

Relevance of autoregulation in the diagnosis of coronary artery disease with CT-FFR

 **Fredrik E. Fossan**,^{1,2}
 **Anders T. Bråten**,^{3,7}
 **Alessia Lucca**,⁴
 **Lucas O. Müller**,⁵
 **Arve Jørgensen**,^{6,7}
 **Rune Wiseth**,^{3,7} and **Leif R. Hellevik**²

¹Center for Innovation, Medical Devices and Technology, St. Olavs Hospital, Trondheim, Norway; ²Department of Structural Engineering, Norwegian University of Science and Technology, Trondheim, Norway; ³Clinic of Cardiology, St. Olavs Hospital, Trondheim, Norway; ⁴Department of Civil, Environmental and Mechanical Engineering, University of Trento, Trento, Italy; ⁵Department of Mathematics, University of Trento, Trento, Italy; ⁶Department of Radiology and Nuclear Medicine, St. Olavs Hospital, Trondheim, Norway; and ⁷Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway

Abstract

Vasodilation and vasoconstriction of small resistance vessels in the coronary microcirculation are key mechanisms for regulating coronary blood flow. This dynamic regulation acts as a reserve system that ensures adequate perfusion under varying physiological conditions and metabolic demands. In the presence of coronary artery stenosis, part of this vasodilatory reserve may already be used, triggered by pressure-flow autoregulation mechanisms that maintain normal blood flow at rest. Fractional flow reserve (FFR), measured during pharmacologically induced maximum vasodilation/hyperemia (typically with adenosine), remains the gold standard for diagnosing coronary artery disease. Computed tomography-derived FFR (CT-FFR) provides noninvasive FFR estimates and is increasingly recommended as a gatekeeper to invasive evaluation. Most current CT-FFR models assume a fixed microvascular response to adenosine, treating vasodilation capacity as constant and optimal for all patients and lesions. Using intracoronary pressure measurements, we quantified how stenosis severity affects the microcirculatory response to adenosine. Based on these findings, we developed a CT-FFR algorithm that incorporates autoregulation. In comparison across 280 lesions, the autoregulation-based model reduced prediction variability (SD = 0.1006 vs. 0.1167, *P* value = 0.013) and improved the coefficient of determination (R^2 = 0.398 vs. 0.179) relative to a fixed-response model, using invasive FFR as reference. However, the area under the curve (AUC) remained unchanged. Sensitivity analyses showed that autoregulation effects were minor in lesions with CT-FFR > 0.7. Feature analysis showed that vessel location, patient sex, and heart rate are associated with the microvascular response to adenosine, emphasizing the need to consider these factors in the combined assessment of epicardial and microvascular disease.

NEW & NOTEWORTHY We present a novel autoregulation-aware model of microvascular resistance for CT-FFR computations. The model improves prediction accuracy compared with conventional approaches for modeling the hyperemic state. Integration of CCTA-derived anatomy and invasive pressures reveals sex- and territory-dependent microvascular responses to adenosine, highlighting the diagnostic role of combined assessment of epicardial and microvascular disease.

autoregulation; coronary microvascular resistance; CT-FFR; microvascular response; microvascular dysfunction

INTRODUCTION

Regulation of coronary blood flow involves several mechanisms, including coronary perfusion pressure, myogenic responses, local metabolic factors, endothelial function, and neural and hormonal influences (1). Collectively, these mechanisms regulate coronary resistance and ensure sufficient myocardial oxygen delivery via the coronary circulation (1). The regulation of resistance primarily occurs through active vasodilation/vasoconstriction of the small arterioles (<100 μ m) in

the peripheral coronary microcirculation (1). Hence, maximum coronary flow (hyperemia) is achieved in states with maximum peripheral vasodilation (i.e., minimal microvascular resistance). The ability to increase flow to hyperemic levels relative to a basal level is known as the coronary flow reserve (CFR). CFR describes the functional capacity of the coronary circulation to increase blood supply upon an increase in demand. In a clinical setting, maximal hyperemia is achieved by administration of pharmacological vasodilators (e.g., adenosine) that specifically target the peripheral coronary microcirculation.



Correspondence: F. E. Fossan (fredrik.eikeland.fossan@stolav.no).
Submitted 16 June 2025 / Revised 4 July 2025 / Accepted 11 November 2025



In patients with ischemic heart disease, the ability to meet sufficient blood supply is compromised. Focal coronary artery disease (CAD) is caused by atherosclerosis in large epicardial arteries, resulting in an obstruction of the lumen (a stenosis), an impediment to flow, and a reduced perfusion pressure (2). In a basal state, blood supply is normally maintained even for severe stenoses due to partial vasodilation of the peripheral microcirculation triggered by pressure-flow autoregulation mechanisms (1, 3–5). The ability to achieve maximal hyperemia, on the other hand, might be compromised, leading to a reduced hyperemic blood flow and, consequently, a reduced CFR (3–5). However, several other factors can affect the ability to increase blood supply to the myocardium, such as diffuse disease in the coronary microcirculation (i.e., vasodilatory dysfunction) (2). Hence, CFR assesses the overall coronary circulation, including both epicardial and microvascular function, which confounds its ability to identify treatable focal disease. Instead, fractional flow reserve (FFR) has, through the last decades, been established as the gold standard for quantifying lesion-specific ischemia (6–8). FFR is measured during invasive coronary angiography by insertion of a guidewire with a pressure sensor and is calculated as the ratio between the cardiac cycle-averaged pressure distal and proximal to the stenosis. If FFR is below 0.8, the stenosis is considered hemodynamically significant, and it is generally recommended to intervene by percutaneous coronary intervention (PCI). If FFR is above 0.8, optimal medical therapy alone is recommended. FFR measurements are performed during pharmacologically induced hyperemia; however, the corresponding pressure ratio can also be measured in a resting/basal state without adenosine and is commonly denoted Pd/Pa.

Although FFR quantifies the relative reduction of flow caused by the stenosis, the clinical value depends on the vasodilatory capacity of the microcirculation, similar to CFR. In particular, discordance between CFR and FFR represents divergent extremes of microvascular and focal disease (2). Hence, insights into the relation between epicardial stenoses, the vasodilatory capacity of the microcirculation, the effective increase in flow, and its effect on FFR are warranted. This is particularly important with new guidelines supporting the use of tomography-derived FFR (CT-FFR) as a gatekeeper to further invasive testing in patients with suspected symptomatic, stable CAD (9). CT-FFR combines the noninvasive imaging technique coronary computed tomography angiography (CCTA) and computational fluid dynamics to predict FFR noninvasively. In CT-FFR models, the epicardial coronary anatomy is extracted from the CCTA data, whereas the contribution of the peripheral microcirculation is represented in a lumped manner in terms of resistance (and potentially also capacitance) elements attached to outlets (10). Hence, although epicardial coronary arteries are represented patient-specifically in CT-FFR models, the peripheral microcirculation is, in principle, represented by a single parameter, namely the hyperemic microvascular resistance. Several groups have demonstrated high diagnostic accuracy of CT-FFR against dichotomous FFR ($\text{FFR} \leq 0.8$). However, absolute quantitative error remains high, where uncertainty and variability related to the hyperemic microvascular resistance have been established as one of the major contributors to errors in CT-FFR prediction (11–14). Still, current methods to model hyperemia in CT-FFR prediction assume that the

microcirculation reacts predictably to adenosine, where the hyperemic microvascular resistance can be estimated directly from basal levels by assuming a fourfold reduction in resistance (10, 15–18). However, the assumption of the predictability of the microvascular response is largely based on a study on healthy individuals (19), and hence has limited justification based on knowledge of coronary pathophysiology and regulation.

The presence of relevant autoregulation mechanisms occurring in stenosed coronary arteries has been documented *in vivo* (3–5), but the relevance of autoregulation in CT-FFR prediction has not been studied. In this study, we used intracoronary pressure measurements and CT-derived epicardial coronary geometry to derive patient/lesion-specific information about the microvascular response to adenosine (see illustration in Fig. 1). Specifically, the microvascular response to adenosine was quantified in terms of the adenosine-induced reduction in microvascular resistance from rest to hyperemia. We used these data to document potential connections between the microvascular response to adenosine and the relative drop in resting perfusion pressure caused by the epicardial stenosis. In particular, a lowered basal perfusion pressure accompanied by a reduced microvascular response to adenosine was regarded as indicative of exhausted vasodilatory capacity resulting from autoregulatory mechanisms. Furthermore, based on this analysis, we developed and evaluated a model for the hyperemic microvascular resistance that considers autoregulation mechanisms. We hypothesized that a CT-FFR model that incorporates patient-specific microvascular autoregulation better reflects the true hemodynamic impact of a stenosis than models using fixed resistance assumptions. A secondary purpose of the study was to establish potential relationships between the microvascular response to adenosine and patient and vessel characteristics.

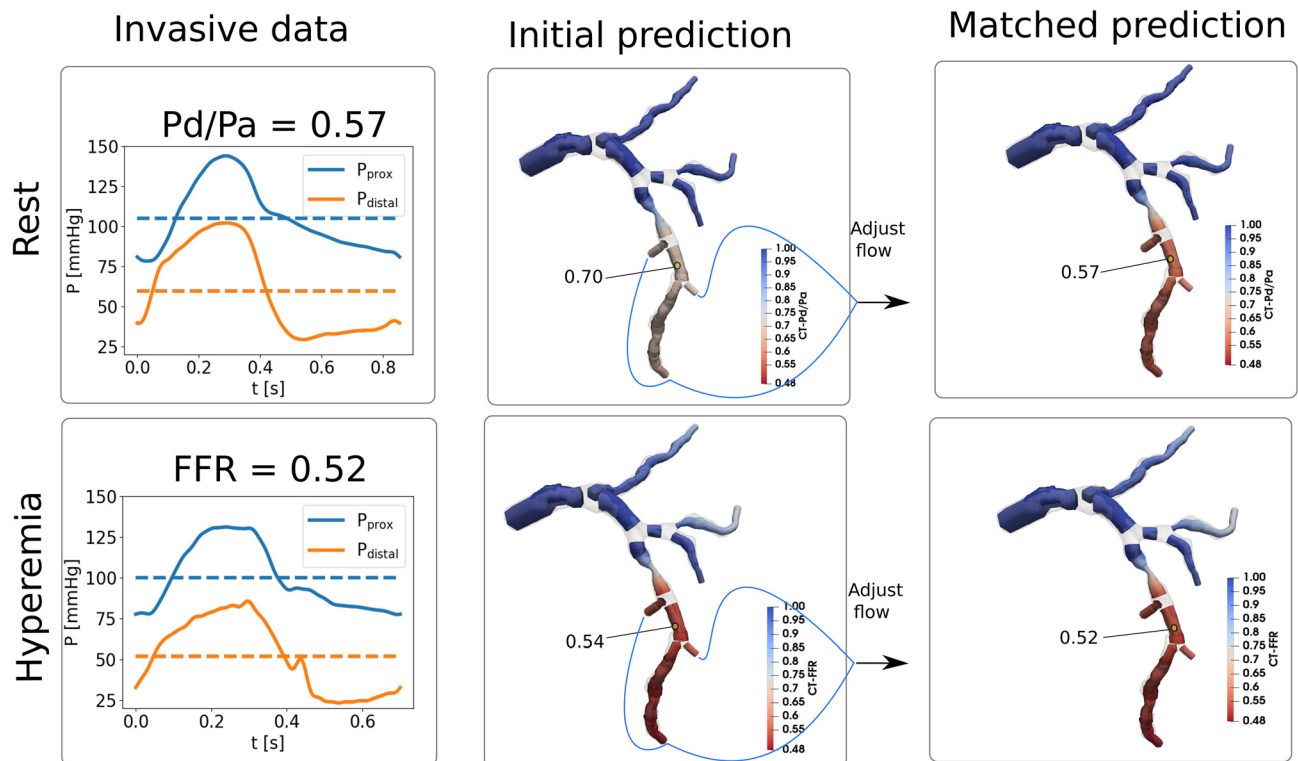
MATERIALS AND METHODS

Data Collection and Processing

Population.

Patients with symptoms of stable CAD and a positive CCTA referred for subsequent invasive coronary angiography were prospectively recruited as part of a clinical trial at St. Olavs University Hospital, Trondheim, Norway (20). Symptom and risk assessment of stable CAD was based on contemporary guidelines, which included sex-specific risk evaluation related to age and symptom interpretation (21). Of the included patients, 37% were females and 63% were males. Women were more frequently included based on anginal symptoms (80% of female and 61% of male patients had chest pain classified as anginal). Furthermore, female patients were older than males (average age of females/males: 63 yr/59 yr). Importantly, these data represent sex/age-specific information of included patients, i.e., patients with a clinical indication of CAD and a positive CCTA. Unfortunately, information about patients with a clinical indication of stable CAD but a negative CCTA was not collected/available. Exclusion criteria included previous coronary revascularization, chronic total occlusions, nondiagnostic quality of CCTA imaging, contraindications to adenosine administration, age >75, and body mass index >40. In addition, participants with clinically significant arrhythmia, valvular heart disease, congenital coronary anomaly, or cardiomyopathy

Procedure for matching invasive pressure data



Quantification of the microvascular response to adenosine

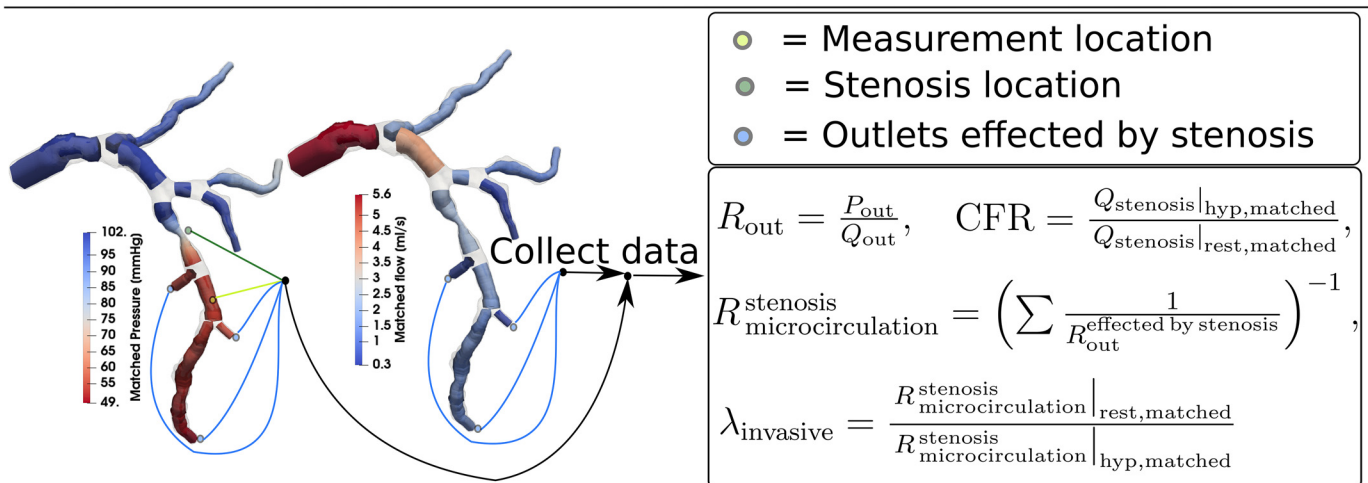


Figure 1. The coronary blood flow model was used in combination with invasive pressure data to derive hemodynamics at rest and hyperemia corresponding to the invasive pressure data. The *top* part of the figure illustrates the pressure-matching approach, whereas the *bottom* part of the figure illustrates the approach for quantifying the microvascular response to adenosine. The microvascular response was quantified as the reduction in peripheral/microvascular resistance from rest to adenosine-induced hyperemia. The resulting increase in flow from rest to adenosine-induced hyperemia, CFR, was also quantified. CFR, coronary flow reserve.

were considered ineligible. All enrolled participants completed the study; no attrition occurred. The study protocol received approval from the Regional Ethics Committee of Central Norway (2016/1609) and was registered at ClinicalTrials.gov (NCT03045601). The research was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants.

CCTA and segmentation.

All CCTA scans were performed at St. Olavs Hospital and five collaborating local hospitals. Six different CT scanners from three different vendors were employed. Postprocessing with segmentation of the left ventricle and coronary geometry was performed semiautomatically using a commercially available software (Materialise Mimics 24.0). Manual correction of the

segmented geometries was performed when appropriate. In detail, the coronary arteries were segmented down to the level at which they could no longer be reliably distinguished from the surrounding tissue, corresponding to a vessel radius of ~ 1 mm. Postprocessing of the segmentations, including surface and centerline generation, was performed using the open-source software VMTK (22).

Invasive pressure measurements.

Proximal and distal pressure were measured using Verrata Plus (Philips Volcano, San Diego) pressure wires according to standard practice. Intracoronary nitroglycerine (0.2 mg) was given to all patients before advancing the pressure wire into the coronary arteries. For a subset of the patients, the dual (proximal, distal) measurements were performed without further medication (i.e., at rest), whereas for all patients/lesions, pressure recordings were acquired during hyperemia. Hyperemia was induced by continuous intravenous infusion of adenosine at a rate of at least 140 $\mu\text{g/kg/min}$. At the end of the procedures, the interventional cardiologist retracted the pressure wire back to the equalization point at the tip of the guiding catheter to ensure there was no pressure drift. Invasive pressure tracings were recorded and made available for further processing. The left part of Fig. 1 shows an example case/lesion with measurements at rest and hyperemia.

Model for Blood Flow in Coronary Arteries

The pressure and flow distributions in the coronary networks were solved by a previously validated machine learning-augmented reduced-order model (23). The coronary network was divided into healthy segments, stenoses, and junctions. Pressure drops across each segment were first estimated using a simplified [one-dimensional(1-D)/zero-dimensional (0-D)] physics-based model. These estimates were then refined using a neural network trained to capture complex three-dimensional (3-D) fluid dynamics. The blood flow model was implemented using an in-house developed Python code. Full details of the implementation can be found in Ref. 23.

In the current article, we used the model for blood flow in coronary arteries in two ways. First, in *Quantification of the microvascular response to adenosine*, we describe how we used the blood flow model together with invasive pressure data to obtain information about translesional flow and peripheral microvascular resistance at rest and during adenosine-induced hyperemia. Second, in *CT-FFR prediction*, we describe the pipeline for the prediction of CT-FFR from non-invasive data, including the specification of hyperemic microvascular resistance at outlets.

Quantification of the microvascular response to adenosine.

We hypothesized that the vasodilatory capacity of coronary arteries is affected by the severity of the disease due to a partial exhaustion of the microvascular response related to autoregulation mechanisms for meeting basal supply demands. We sought to test this hypothesis by matching the actual coronary pressure and flow distributions in the segmented geometries both in rest and hyperemia, and from this derive an estimate of the resistance of the microcirculation in both states. We had available

invasive pressure measurements at rest and hyperemia for a subset of the interrogated lesions analyzed in this study and designed a procedure to match the measurements as illustrated in Fig. 1. Departing from our flow pipeline described in *CT-FFR prediction*, we modified the flow through the stenosis by updating the flow through outlets affected by the stenosis in both states to match the measurements at rest (Pd/Pa) and hyperemia (FFR). Next, we calculated the resting and hyperemic resistance of the microcirculation peripheral to the lesion and used this to quantify the microvascular response to adenosine:

$$\lambda_{\text{invasive}} = \frac{R_{\text{microcirculation}}^{\text{stenosis}}|_{\text{rest,matched}}}{R_{\text{microcirculation}}^{\text{stenosis}}|_{\text{hyp,matched}}}, \quad (1)$$

where $\lambda_{\text{invasive}}$ is the reduction in resistance from rest to adenosine-induced hyperemia derived from the invasive pressure data. Hence, $\lambda_{\text{invasive}}$ reflects the vessel-specific response in the myocardial microcirculation peripheral to the stenosis. A $\lambda_{\text{invasive}}$ value of ≈ 4 reflects a textbook value for a normal reduction of the microvascular resistance from rest to hyperemia (i.e., healthy), whereas a value of 1 reflects no change in resistance (i.e., no microvascular response/vasodilation). A reduced $\lambda_{\text{invasive}}$ can be attributed to microvascular dysfunction or to an expanded vasodilatory capacity related to autoregulation mechanisms for meeting basal supply demands. The increase in flow from rest to adenosine-induced hyperemia, CFR, was also quantified. Lesions with a Pd/Pa greater than 0.99 were excluded from this analysis, as estimated resistance from low ΔP and/or low flow can be ill-defined (24).

CT-FFR prediction.

We adopted the strategy presented earlier in Ref. 25, which provides a natural approach to model the coronary circulation during rest and hyperemia:

- 1) estimate the resting coronary flow and distribute it among the network's N_{out} outlets: $Q_{\text{out},l}$, with $l = 1, \dots, N_{\text{out}}$;
- 2) perform a resting-state simulation with prescribed inlet pressure P_{inlet} and prescribed outlet flows defined in the previous step to find $P_{\text{out},l}^{\text{rest}}$, with $l = 1, \dots, N_{\text{out}}$;
- 3) compute resistances at outlets as

$$R_{\text{out},l}^{\text{rest}} = \frac{P_{\text{out},l}^{\text{rest}} - P_v}{Q_{\text{out},l}^{\text{rest}}}, \quad \text{with } l = 1, \dots, N_{\text{out}}, \quad (2)$$

where $P_{\text{out},l}^{\text{rest}}$ is the pressure at the l th outlet resulting from the simulation performed in the previous step, and P_v is a reference venous pressure, which is set to $P_v = 5$ mmHg throughout this work;

- 4) perform a hyperemic-state simulation with prescribed inlet pressure P_{inlet} and prescribed resistances at outlets. Such resistances were computed as

$$R_{\text{out},l}^{\text{hyp}} = \frac{R_{\text{out},l}^{\text{rest}}}{\lambda}, \quad \text{with } l = 1, \dots, N_{\text{out}}, \quad (3)$$

where λ is the factor by which peripheral coronary resistance drops from its value at resting conditions to its value in hyperemia. Two different approaches were used to specify λ , as detailed in *Incorporation of autoregulation mechanisms in CT-FFR prediction*.

The resting flow to each outlet was derived in a stepwise manner by first estimating the total coronary flow to the myocardium:

$$Q_{\text{cor}} = \zeta \cdot \text{TMM},$$

where $\zeta = 0.8 \text{ mL/min/g}$ is a perfusion factor representing normal myocardial perfusion (26) and where the total myocardial mass, TMM, was estimated from the segmented left ventricle mass (LVM) according to (25)

$$\text{TMM} = 2.4 \cdot \text{LVM}.$$

Finally, the blood supply to the coronary microcirculation peripheral to each outlet was estimated as a fraction of the total coronary flow:

$$Q_{\text{out},l} = m_l \cdot Q_{\text{cor}},$$

where m_l is the portion of the myocardial mass supplied by each outlet, which was estimated by the Voronoi algorithm (27, 28). The inlet pressure was derived from noninvasive brachial cuff measurements according to

$$P_{\text{inlet}} = \frac{1}{3} \text{SBP} + \frac{2}{3} \text{DBP}, \quad (4)$$

where SBP and DBP are the systolic and diastolic pressures acquired from cuff measurements.

Incorporation of autoregulation mechanisms in CT-FFR prediction.

The prevalent assumption in available CT-FFR approaches is that the microcirculation reacts predictably to achieve maximal hyperemia (10, 15–18). In this study, we compared such a fixed-response model where the microvascular response is modeled as a constant value for all vessels/patients, versus a novel approach where the microvascular response is exponentially reduced depending on the severity of the disease (29). The two models differ in how the reduction of resistance from rest to hyperemia was calculated:

$$R_{\text{out},l}^{\text{hyp}} = \frac{R_{\text{out},l}^{\text{rest}}}{\lambda}, \quad \text{with } l = 1, \dots, N_{\text{out}}. \quad (5)$$

For the fixed-response model, λ was modeled as a constant (c):

$$\lambda_{\text{fixed}} = c. \quad (6)$$

For the new approach, the reduction of the resistance from rest to hyperemia was designed to exponentially decay for increasing pressure loss in the resting condition:

$$\lambda_{\text{autoregulation}} = 1 + (\lambda_{\text{healthy}} - 1) \cdot e^{-\beta \cdot x}, \quad x = 1 - \text{Pd}/\text{Pa}_{\text{rest,out},l}, \quad (7)$$

where $\text{Pd}/\text{Pa}_{\text{rest,out},l}$ is the resting Pd/Pa at outlet l , and λ_{healthy} represents the microvascular response before any exhaustion due to autoregulation (i.e., for vessels without any pressure

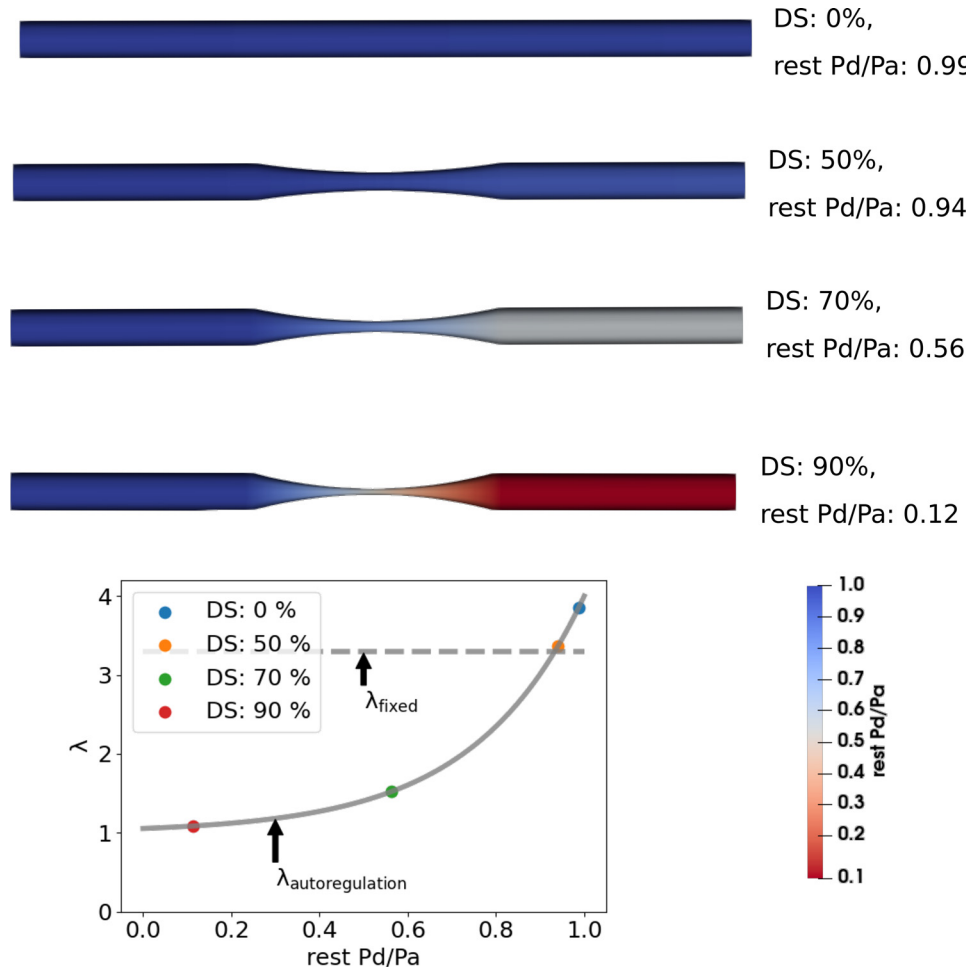


Figure 2. Illustration of the microvascular response for the fixed-response model, λ_{fixed} , and for the model that accounts for autoregulation, $\lambda_{\text{autoregulation}}$. As illustrated, $\lambda_{\text{autoregulation}}$ is reduced with increasing stenosis severity (DS, diameter stenosis), whereas the drop in resistance from rest to hyperemia is maintained at a constant level for λ_{fixed} .

Table 1. Baseline characteristics

Variables/Clinical Characteristics	
Number of patients	156
Male/female	98/58 (63%/37%)
Age, yr	60.8 ± 7.9
Risk factors	
Hypertension	79 (51 %)
Diabetes	21 (13 %)
Dyslipidemia	59 (38%)
Atrial fibrillation	10 (6%)
Smoking history	72 (46%)
Family history of CAD	71 (46%)
BMI, kg/m ²	27.9 ± 3.6
Angina status	
Non anginal chest pain	50 (32%)
Anginal chest pain	106 (68%)
Typical angina	81 (52%)
Atypical angina	25 (16%)

BMI, body mass index; CAD, coronary artery disease.

loss $Pd/Pa = 1$ and $x = 0$ and, such that $\lambda_{\text{autoregulation}} = \lambda_{\text{healthy}}$. Finally, β is a decay factor that controls how the microvascular response drops for increasing severity of the disease. Figure 2 illustrates the response of an idealized vessel for different stenosis severities.

Cross validation and comparison with invasive FFR.

We designed a 10-fold randomized cross-validation experiment where we optimized the value of c in λ_{fixed} and λ_{healthy} in $\lambda_{\text{autoregulation}}$ in CT-FFR_{fixed} and in CT-FFR_{autoregulation}, respectively. The optimization was performed by maximizing the coefficient of determination (R^2 score) between the predicted and invasive FFR. The decay-factor β (in Eq. 7) was fixed to a value of 4 during the optimization of CT-FFR_{autoregulation}. Fixation of β resulted in more reliable predictions, and the value ($\beta = 4$) was specified through an initial optimization procedure. Finally, we collected the predictions from the pooled test set to obtain representative predictions for all lesions.

$$\begin{cases} \lambda_{\text{model}} < 0.5 & \text{use fixed model } (\lambda \rightarrow \lambda_{\text{fixed}}, \lambda_{\text{variation}} \rightarrow c \text{ in Eq. 6}) \\ \lambda_{\text{model}} \geq 0.5 & \text{use autoreg. model } (\lambda \rightarrow \lambda_{\text{autoregulation}}, \lambda_{\text{variation}} \rightarrow \lambda_{\text{healthy}} \text{ in Eq. 7}). \end{cases} \quad (8)$$

The relative importance of accounting for autoregulation versus the influence of the intrinsic uncertainty in the microvascular response on predicted CT-FFR was quantified in terms of first-order Sobol indices, using the Monte Carlo method as described by Saltelli (31).

Diagnostic accuracy, specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) were calculated with a 95% confidence interval (CI) using CT-FFR with a cutoff limit of ≤ 0.80 indicating hemodynamic significance. Similarly, invasive FFR ≤ 0.80 was considered hemodynamically significant. Accuracy, specificity, and sensitivity were compared using McNemar's test, with a P value of < 0.05 considered statistically significant. Correlations between CT-FFR predictions and invasively measured FFR were assessed using the Pearson correlation coefficient and the coefficient of determination. The agreement between calculated and measured FFR-values was assessed by Bland-Altman analyses, estimating 95% limits of agreement. Receiver operating characteristics (ROC) curves with areas under the curve (AUCs) were estimated with a 95% CI and compared using the method of DeLong (30).

Quantification of the Importance of Autoregulation by Sensitivity Analysis

Previous studies have found a very strong influence on CT-FFR predictions arising from uncertainty in adenosine response (11–14). To evaluate the importance of including a model which accounts for autoregulation, we performed a Sobol sensitivity analysis that included two parameters: $\lambda_{\text{variation}}$ and λ_{model} . Here, $\lambda_{\text{variation}}$ represents the population variation of the microvascular response, and λ_{model} was included as a discrete variable with options [λ_{fixed} , $\lambda_{\text{autoregulation}}$]. The population variation in the microvascular response, $\lambda_{\text{variation}}$, was modeled as a gamma distribution with shape parameter 3, scale factor 0.75 and shifted to 1. Such a distribution approximates the population variation in the microvascular response to adenosine in reference or nonischemic vessels (14). Effectively, λ_{model} was modeled as a uniform distribution between 0 and 1, and depending on the value, either the constant or the autoregulation model was used to specify λ in Eq. 3:

Association between the Microvascular Response to Adenosine and Patient/Lesion Characteristics: Feature Analysis

We sought to establish potential relationships between the microvascular response to adenosine and patient and

Table 2. Model agreement between CT-FFR and invasive FFR for the two different models for the microvascular response

Model	Mean Difference	Std. Deviation	Limits of Agreement	Pearson r	Coefficient of Determination (R^2)
CT-FFR _{fixed}	−0.0175	0.1167	−0.246 to 0.211	0.694	0.179
CT-FFR _{autoregulation}	−0.0098	0.1006	−0.207 to 0.187	0.698	0.398
P value		0.013		0.9218	

CT-FFR, computed tomography-derived fractional flow reserve; FFR, fractional flow reserve.

Table 3. Diagnostic performance of CT-FFR for the two different models for the microvascular response

Model	Accuracy	Sensitivity	Specificity	PPV	NPV	AUC
CT-FFR _{fixed}	78.2 (72.9–82.9)	58.1 (48.1–67.7)	90.3 (84.9–94.2)	78.2 (68.9–85.3)	78.2 (74.0–81.9)	0.845 (0.797–0.885)
CT-FFR _{autoregulation}	80.4 (75.2–84.8)	68.6 (58.8–77.3)	87.4 (81.6–92.0)	76.6 (68.4–83.1)	82.3 (77.7–86.1)	0.845 (0.797–0.886)
<i>P</i> value	0.238	0.0033	0.063			0.915

The numbers in parentheses indicate the 95% confidence interval. For accuracy, sensitivity, and specificity, the *P* value was compared using McNemar's test, whereas the *P* value for AUC was calculated using the method of DeLong et al. (30). PPV and NPV are prevalence-dependent and were not directly compared in terms of statistical significance. CT-FFR, computed tomography-derived fractional flow reserve; PPV, positive predictive value; NPV, negative predictive value.

vessel characteristics. For each patient, we had available information about the sex, age, weight, height, body surface area (BSA), body mass index (BMI), ambulant heart rate, and clinical history (diabetes, dyslipidemia, hypertension, family history of CAD, atrial fibrillation, angina status, smoking status). The *F*-score between all features and the target value $\lambda_{invasive}$ (derived from invasive pressure data) was calculated. The *F*-score analysis is a quick linear model for testing the effect of a single feature, sequentially for many features. Given the relatively limited number of cases evaluated, specific correction for multiple testing was not performed. We used the *F*-score to rank the features according to the association with the derived microvascular response.

RESULTS

Baseline Characteristics

Between March 2017 and March 2021, a total of 182 participants (mean age 61 yr, 63% males) were prospectively enrolled. Intracoronary pressure measurements were performed successfully during hyperemia in 280 vessels in 156 patients included in the final analysis. One hundred seventy-one of the vessels had additional resting state pressure measurements (i.e., pressure recordings before injection of adenosine). Patient characteristics are listed in Table 1.

Importance of Including Autoregulation in CT-FFR Modeling

Table 2 provides the mean difference, standard deviation, limits of agreement, and correlation metrics of CT-FFR

versus invasive FFR. Here, the CT-FFR predictions for the fixed-response model and the model including autoregulation were obtained as described in the cross-validation experiment in *Cross validation and comparison with invasive FFR*. Similarly, Table 3 provides diagnostic performance for the two models, and Fig. 3 provides a comparison of the models' agreement with invasive FFR (*left* and *middle*) and a direct comparison between the two models (*right*). Finally, Fig. 4 shows the first-order Sobol sensitivity index from the sensitivity analysis described in *Quantification of the Importance of Autoregulation by Sensitivity Analysis*.

Estimation of the Microvascular Response to Adenosine from Pressure Data

Table 4 provides summarized results from the estimation of the lesion/patient-specific microvascular response to adenosine derived from invasive pressure data (see described in *Quantification of the microvascular response to adenosine*). The median value of Pd/Pa, FFR, and diameter stenosis from quantitative coronary angiography (QCA) is also provided. Furthermore, the data are presented for all lesions and stratified according to lesion location and sex. Figure 5 provides a graphical illustration of the derived microvascular response to adenosine versus Pd/Pa (*left*) and derived CFR versus FFR (*right*). The prevalence of ischemia ($FFR \leq 0.8$) was 0.46, which was much higher for males (0.52) than for females (0.32). The prevalence of flow limitation according to $CFR \leq 2$ was 0.54 and was similar for males (0.54) and females (0.55). Furthermore, Table 5 provides the summarized results from the feature analysis on the microvascular response to adenosine for variables with a *P* value < 0.1. See Table 6 for the full overview of the feature analysis.

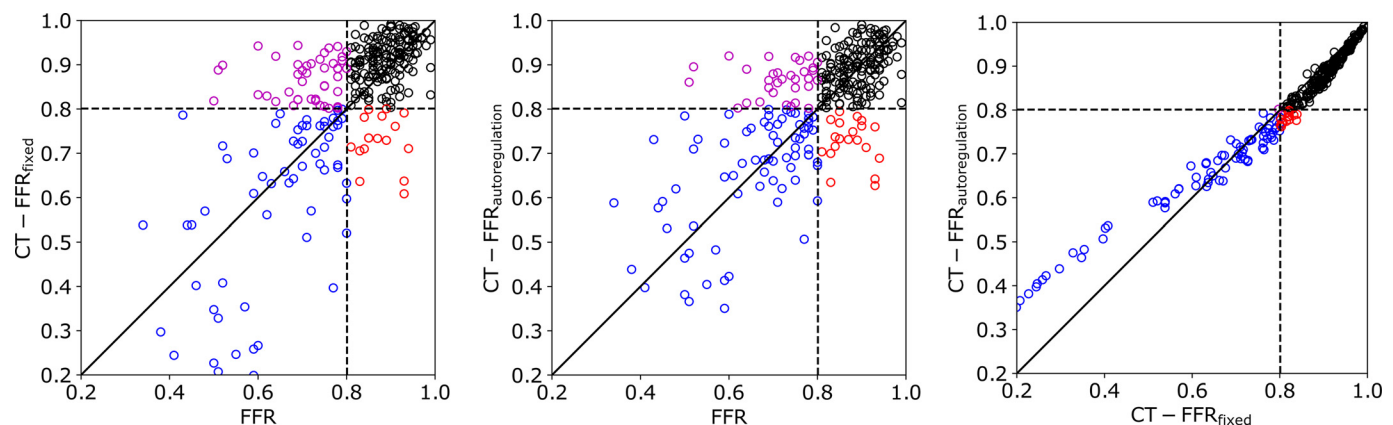


Figure 3. Scatter plot of CT-FFR vs. FFR for the fixed-response model (*left*) and autoregulation model (*middle*), and a direct comparison of CT-FFR_{autoregulation} vs. CT-FFR_{fixed} (*right*). *n* = 280. CT-FFR, computed tomography-derived fractional flow reserve; FFR, fractional flow reserve.

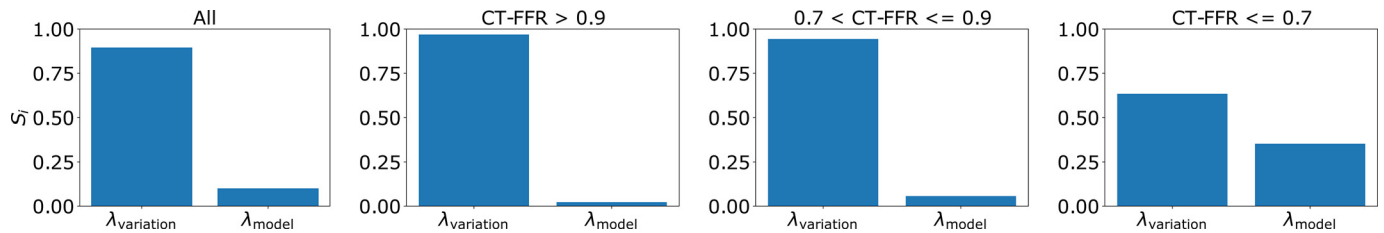


Figure 4. Results from the sensitivity analysis presenting the first-order Sobol sensitivity index (S_i) for quantification of the importance of accounting for autoregulation (λ_{model}) relative to the natural variation in the microvascular response to adenosine ($\lambda_{\text{variation}}$). The sensitivity analysis indicated that autoregulation modeling had the highest relative influence on CT-FFR predictions in vessels with CT-FFR ≤ 0.7 , whereas for vessels with higher CT-FFR values, the influence of autoregulation modeling was minor. For high CT-FFR values, population variation/uncertainty in microvascular response (irrespective of autoregulation mechanisms) was completely dominant. CT-FFR, computed tomography-derived fractional flow reserve.

DISCUSSION

From intracoronary pressure measurements, we estimated the factor by which the resistance in the coronary microcirculation is reduced from rest to hyperemia and found a significant correlation (P value 0.008) of this parameter with the severity of the epicardial stenosis. These findings inspired the development of a CT-FFR algorithm with a lesion-specific model for the hyperemic microvascular resistance that accounts for coronary autoregulation (CT-FFR_{autoregulation}). The autoregulation model assumed increasing exhaustion of the microvascular response for lower (normalized) perfusion pressure, Pd/Pa. We compared this novel approach with a fixed-response model that assumes a uniform microvascular response in all patients and vessels (CT-FFR_{fixed}). CT-FFR_{autoregulation} provided predictions with significantly reduced standard deviation (0.1006 vs. 0.1167, P value = 0.013), narrower limits of agreement, and improved coefficient of determination compared with CT-FFR_{fixed}. Moreover, there was a significant improvement in the sensitivity to detect ischemia-causing lesions (FFR ≤ 0.8) for CT-FFR_{autoregulation} compared with CT-FFR_{fixed} (68.6 vs. 58.1, P value = 0.003). However, with respect to overall diagnostic performance, no difference in AUC was observed. The improvements in standard deviation and limits of agreement were mainly driven by better agreement in predictions in moderate to severe lesions, whereas predictions in low-grade stenoses were less sensitive to the way hyperemia was

modeled. This is natural because the behavior of the two models is similar in low-grade stenosis cases. The latter was also made evident from our Sobol sensitivity analysis, which showed that the applied model for autoregulation only played a secondary role in lesions with CT-FFR values greater than 0.7. However, because CT-FFR models omit autoregulatory mechanisms, optimization can yield an unfavorable sensitivity-specificity trade-off, as the fit is pushed to maximize agreement metrics (e.g., the variance explained, standard deviation, etc.) in addition to diagnostic performance. Hence, despite providing similar AUC, the reduced variance, the improved R^2 score, and a better trade-off between sensitivity and specificity in CT-FFR_{autoregulation} ultimately improve the overall credibility of the model compared with CT-FFR_{fixed}.

Although our coronary autoregulation model improved agreement with FFR, variability in microvascular response to adenosine (see Fig. 5) and sensitivity analysis (see Fig. 4) suggest that additional factors are required to explain differences in adenosine response in symptomatic patients with stable CAD. The feature analysis confirmed an association between resting Pd/Pa and the microvascular response and thus affirming the relevance of autoregulation mechanisms in stable CAD. However, the analysis revealed that lesion location had an even stronger association, with left anterior descending artery (LAD) lesions exhibiting a lower response than non-LAD lesions. The latter observation indicates a regional dependence on vasomotor response in our cohort of patients with stable CAD. However, these results are in contrast with the study by Wilson et al. (19), where a similar increase in coronary blood flow velocity was observed in the left coronary artery (CFR = 4.6) and the right coronary artery (CFR = 4.4) in response to adenosine. Likewise, Bauman et al. (32) reported similar vasodilator reserve in myocardial tissue surrounding the right and left ventricles of dogs. Importantly, the studies by Wilson et al. and Bauman et al. only included healthy individuals, and it is known that even moderate atherosclerosis is associated with a reduced CFR (2). In agreement with our findings, a lower CFR was observed in LAD versus non-LAD vessels/territories across different degrees of disease in a recent study (33). This forms a hypothesis that the regional variations in vasomotor response might be caused by regional differences in regulation in the presence of CAD. In the left ventricle, the high resting level of oxygen extraction (70–80%) necessitates an increase in coronary blood flow even at low levels of exercise (34). For the right ventricle, oxygen extraction during resting

Table 4. Resting and hyperemic data for lesions with Pd/Pa and hyperemic FFR measurements, including the derived reduction of resistance ($\lambda_{\text{invasive}}$) from rest to hyperemia and CFR

Artery or Sex	n	Invasive Data			Derived Data	
		Pd/Pa [–]	FFR [–]	QCA [%]	$\lambda_{\text{invasive}}$ [–]	CFR [–]
All	171	0.943	0.820	43.5	2.40	1.92
LAD	104	0.937	0.820	38.0	2.25	1.78
Non-LAD	67	0.959	0.810	47.0	3.04	2.22
CX	29	0.955	0.760	51.0	3.15	2.50
RCA	36	0.959	0.815	46.5	2.80	2.14
Male	115	0.939	0.800	44.5	2.54	1.95
Female	56	0.948	0.850	41.5	2.17	1.82

Quantitative coronary angiography (QCA) is reported as percent diameter stenosis, whereas the other metrics are unitless. CFR, coronary flow reserve; CX, circumflex; FFR, fractional flow reserve; LAD, left anterior descending artery; RCA, right coronary artery.

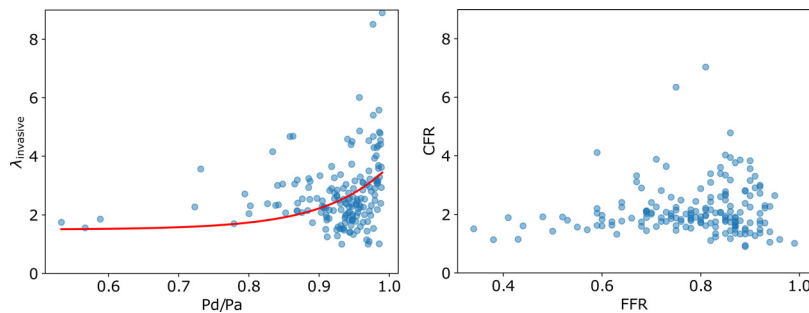


Figure 5. Left: scatter plot of Pd/Pa vs. the microvascular response to adenosine derived from invasive pressure data, $\lambda_{\text{invasive}}$. The red line shows Eq. 7 fitted to the data, which indicates a general decline in the derived microvascular response to adenosine for increasing stenosis severity. This trend supports the hypothesis of increasing expenditure of microvascular capacity due to autoregulation mechanisms. However, a large amount of scatter is present, indicating a large variability in the response, which cannot be explained by autoregulation mechanisms. Right: scatter plot of FFR vs. the derived CFR. $n = 171$. CFR, coronary flow reserve; FFR, fractional flow reserve.

conditions is much lower ($\approx 50\%$), such that increased oxygen demand can be achieved by both increased oxygen extraction and by increasing blood flow via vasodilation (34). Hence, there are regional differences in terms of the relative importance of regulating 1) oxygen extraction and 2) microvascular resistance to meet supply demands in the myocardium. In particular, our results indicate that the presence of moderate CAD requires a greater exhaustion of the vasodilatory capacity in the LAD than in non-LAD arteries. Furthermore, other studies have found regional variations in resting perfusion with particularly high levels in the anterior wall, but no systematic regional variation during hyperemia (35). This suggests that certain regions may function at a level closer to maximum capacity in the baseline state, making them more vulnerable to disease and injury (35–37).

In addition to lesion location and Pd/Pa, ambulant heart rate, height, body surface area, and sex showed the highest F -scores and were most strongly linked to the reduction in microvascular resistance from rest to hyperemia. Higher heart rate, lower height, smaller body surface area, and female sex were associated with a reduced microvascular response. However, the variations in height and body surface area were mainly driven by sex-related differences, with males and females having significantly different distributions of height and body surface area according to the Kolmogorov–Smirnov test (P value $\ll 0.05$). This is in agreement with previous studies that have documented a higher frequency of impaired microvascular function in females (38–41) and thereby a lower microvascular response and a reduced CFR compared with males (38, 40, 42). Heart rate

was also different for males and females, with females having a higher heart rate than males (68 vs. 65), which means that the association with the microvascular response could in part be explained by physiological variations related to sex. However, the sex-related difference in heart rate was not significant (P value = 0.41). It is more likely that the association between heart rate and the microvascular response could be explained by increased levels of basal flow in patients with high heart rate, as the oxygen demand required for contraction correlates closely with heart rate (43–45).

The prevalence of microvascular dysfunction (most frequently classified by a reduced CFR ≤ 2) in patients with angina or demonstrable ischemia but without obstructive epicardial disease is 41% according to a recent meta-analysis, and is higher in females than in males (46). A reduced CFR in reference vessels (i.e., vessels with less than 30% diameter stenoses) in stable CAD patients was also found to be associated with an increased rate of fatal events, which was attributed to an impaired coronary autoregulation according to a study by Hoef et al. (42). The indication of an impaired autoregulation was represented by elevated levels of basal flow and was more frequent in females than in males. In other words, microvascular dysfunction is a highly prevalent and heterogeneous disease that is difficult to diagnose (47), which might also explain the lack of improvement in overall diagnostic performance from our simplified model for coronary autoregulation. Nevertheless, our results are in agreement with previous findings that demonstrate higher rates of ischemia induced by focal disease in males (FFR ≤ 0.8) (48, 49), whereas females tend to have stronger indications of impaired microvascular response (38, 40, 42). And although the demonstration of ischemia with FFR ≤ 0.8 or the presence of a significant lesion on invasive coronary angiography is normally considered an indication for revascularization, microvascular disease is often left undiagnosed. Consequently, the absence of a flow-limiting stenosis may be falsely interpreted as evidence that the symptoms of the patient are noncardiac in nature and irrelevant for patient prognosis (47). However, anginal chest pain arising from microvascular dysfunction with and without focal disease receives increasing attention in contemporary guidelines (50). Still, major knowledge gaps exist with several unresolved issues that need to be investigated within this topic (51). In this study, we combined invasively derived pressure at rest and during hyperemia with CCTA-derived geometry and computational fluid dynamics to derive both flow and resistance data. This made it possible to separate the actual increase in blood flow (CFR) from changes in

Table 5. Summary of the feature analysis for features with a P value less than 0.1

Feature	Median Feature-Value	Median Value of $\lambda_{\text{invasive}}$ Stratified by Feature	P Value
LAD vs. non-LAD		Lad: 2.25 non-LAD: 3.05	1.2×10^{-7}
Pd/Pa	0.93	Above median: 2.68 Below median: 2.30	0.008
Heart rate	66 beats/min	Above median: 2.34 Below median: 2.56	0.023
Height	175 cm	Above median: 2.73 Below median: 2.15	0.038
BSA	2.0 kg/m ²	Above median: 2.54 Below median: 2.33	0.065
Sex		Male: 2.54 Female: 2.17	0.086

See Table 6 for the full overview of the feature analysis. Heart rate is given in beats/min, height in cm, and body surface area (BSA) in kg/m².

Table 6. *F*-statistic and *P* value for the full list of features

Feature	<i>F</i> -Statistic	<i>P</i> Value
LAD vs. non-LAD	30.392	0.000
Pd/Pa	7.231	0.008
HR	5.231	0.023
Height	4.378	0.038
BSA	3.444	0.065
Sex	2.975	0.086
Weight	2.278	0.133
Hypertension	1.536	0.217
Angina	1.290	0.258
Dyslipidemia	1.012	0.316
Age	0.656	0.419
Atrial fibrillation	0.398	0.529
Family history of CAD	0.290	0.591
BMI	0.099	0.753
Smoke	0.093	0.761
Diabetes	0.078	0.781

BMI, body mass index; CAD, coronary artery disease; LAD, left anterior descending artery.

microvascular resistance, giving new insight into how the microvascular response to adenosine varies and how autoregulation relates to patient and vessel characteristics in stable CAD. In Fig. 6, we illustrate the added value of extended physiological evaluation in the interpretation of disease- and symptom-presentation for two cases with typical angina but with divergent pathophysiology.

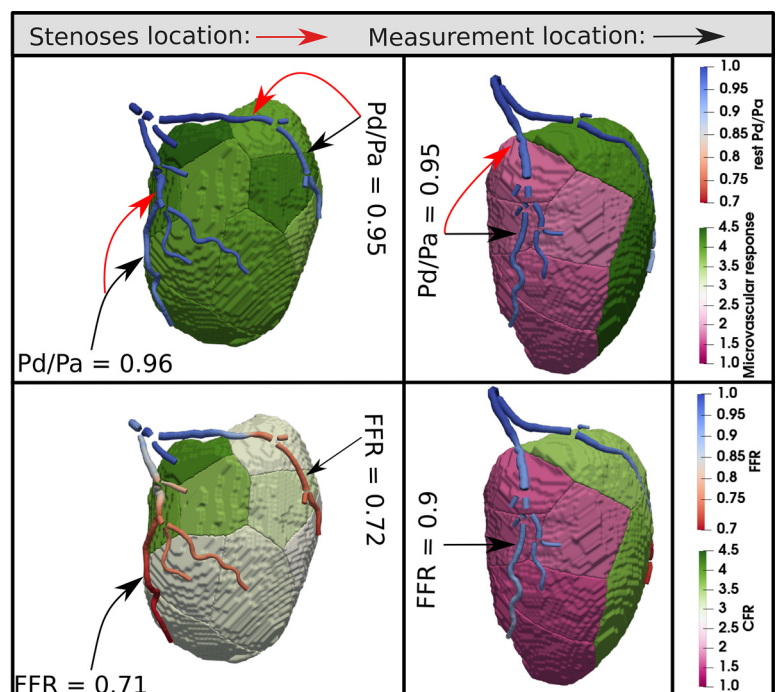
Limitations

The number of patients and lesions included in this study was limited, preventing a proper multivariate analysis, which could potentially have revealed other relationships between patient characteristics and the microvascular response to adenosine. In particular, previous studies have found reduced

response in patients with diabetes mellitus and hypertension (52, 53), whereas we did not find such an association in our cohort. Furthermore, there are studies that indicate an association between plaque characteristics and the downstream microvascular response, which is independent of the degree of stenosis (54, 55). Unfortunately, data on plaque morphology were not available in the present study. Stable CAD represents a heterogeneous group of patients with a high variety of obstructive disease and microvascular response. Moreover, the skewed number of females versus men, and in particular, the low number of female patients was a hindrance to performing individual feature analysis stratified by sex. Studies in much larger populations are needed to fully analyze the association between focal disease, microvascular response, and patient and lesion characteristics.

Previous studies have shown that a combination of angiography-derived anatomy and pressure data with computational fluid dynamics can reliably estimate flow and resistance (56). However, errors in segmented geometry, combined with the optimization process used to align with invasive pressure data, can affect the estimation of derived flow and resistance metrics. The right part of Fig. 5 shows the derived CFR versus invasive FFR, which is qualitatively similar to previous comparisons of invasive CFR versus FFR (2). However, although a modest but significant linear relationship between CFR and FFR was found in Ref. 2, we did not find a significant linear relationship in our data. This could be related to the exclusion of lesions with low resting ΔP ($Pd/Pa > 0.99$) in our analysis, which can be reflected in the underrepresentation of healthy cases (i.e., high FFR) in the right part of Fig. 5 compared with the data reported in Ref. 2. Nevertheless, future validation studies should focus on the comparison of CCTA-derived (changes in) flow and resistance with other noninvasive (positron emission tomography)

Figure 6. Two example patients with typical angina. The *top* row shows data from rest (Pd/Pa and a graphical representation of the derived microvascular response to adenosine in the different regions of the left ventricle). The *bottom* row shows data during hyperemia (FFR and the derived flow increase from rest, CFR, to the different regions of the left ventricle). *Left* case: male patient with a moderate stenosis in the left anterior descending artery (LAD) and in the left circumflex (CX). Both FFR measurements indicated hemodynamic significance ($FFR < 0.8$) and thus likely to induce ischemia. Both lesions were stented according to guidelines. Our analysis indicates a normal/healthy microvascular response throughout the left ventricle (LV) and relatively well-maintained CFR. *Right* case: female patient with a moderate stenosis in the LAD without hemodynamic significance and no indication for revascularization. The invasive assessment suggests that the patient's symptoms are non-cardiac. However, our analysis indicates a significantly reduced response in the coronary microvasculature in the anterior wall of the left ventricle and a significantly reduced CFR. CFR, coronary flow reserve; FFR, fractional flow reserve; LAD, left anterior descending artery.



and invasive approaches (invasive Doppler ultrasound and thermodilution) for quantifying flow and resistance.

Conclusions

We developed a novel method for the estimation of hyperemic microvascular resistance in CT-FFR models that accounts for autoregulation. We compared this autoregulation-aware model with a fixed-response model in which the hyperemic microvascular resistance is derived from basal levels, assuming a uniform response across all patients and lesions. CT-FFR_{autoregulation} provided predictions with significantly lower standard deviation, narrower limits of agreement, and a higher coefficient of determination compared with CT-FFR_{fixed}. However, no difference in diagnostic performance (AUC) was observed. Sensitivity analysis revealed that factors in addition to autoregulation are required to account for the observed variability in the microvascular response to adenosine in patients with stable CAD. We found a significant difference in microvascular response to adenosine depending on lesion location, with markedly lower response in LAD lesions. We hypothesize that the regional difference may be related to distinct regulatory pathways, where LAD vessels require greater exhaustion of vasodilatory capacity in moderate CAD. Furthermore, we observed associations between the microvascular response to adenosine and patient sex, as well as sex-related features such as height and body surface area. These findings may relate to known sex-specific differences in CAD presentation, including a higher prevalence of impaired coronary autoregulation and microvascular dysfunction in females. By combining image-based vessel geometry with invasive pressure data at rest and during hyperemia, we gained new insights and identified opportunities for improved research and diagnosis in patients with both focal and microvascular coronary disease.

DATA AVAILABILITY

The raw data used in this study contain sensitive information and sharing is not allowed by the regional ethics committee. However, the derived data supporting the findings of this study are available from the corresponding author upon reasonable request.

GRANTS

This study was financed by Samarbeidsorganet (Project No. 30466, Project Name: Model-Augmented CT).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

F.E.F., L.O.M., R.W., A.T.B., and L.R.H. conceived and designed research; F.E.F., A.T.B., and A.L. performed experiments; F.E.F., A.T.B., L.O.M., and A.J., analyzed data; F.E.F., A.T.B., A.L., L.O.M., and A.J. interpreted results of experiments; F.E.F. and A.T.B. prepared figures; F.E.F. and A.T.B. drafted manuscript; F.E.F., A.T.B., A.L., L.O.M., A.J., R.W., and L.R.H. edited and revised manuscript;

F.E.F., A.T.B., A.L., L.O.M., A.J., R.W., and L.R.H. approved final version of manuscript.

REFERENCES

- Goodwill AG, Dick GM, Kiel AM, Tune JD. Regulation of coronary blood flow. *Compr Physiol* 7: 321–382, 2017. doi:10.1002/j.2040-4603.2017.tb00750.x.
- Johnson NP, Kirkeeide RL, Gould KL. Is discordance of coronary flow reserve and fractional flow reserve due to methodology or clinically relevant coronary pathophysiology? *JACC Cardiovasc Imaging* 5: 193–202, 2012. doi:10.1016/j.jcmg.2011.09.020.
- Uren NG, Melin JA, De Bruyne B, Wijns W, Baudhuin T, Camici PG. Relation between myocardial blood flow and the severity of coronary-artery stenosis. *N Engl J Med* 330: 1782–1788, 1994. doi:10.1056/NEJM199406233302503.
- Nijjer SS, de Waard GA, Sen S, van de Hoef TP, Petraco R, Echavarría-Pinto M, van Lavieren MA, Meuwissen M, Danad I, Knaapen P, Escaned J, Piek JJ, Davies JE, van Royen N. Coronary pressure and flow relationships in humans: phasic analysis of normal and pathological vessels and the implications for stenosis assessment: a report from the Iberian–Dutch–English (IDEAL) collaborators. *Eur Heart J* 37: 2069–2080, 2016. doi:10.1093/eurheartj/ehv626.
- Lee JM, Hwang D, Park J, Zhang J, Tong Y, Kim CH, Bang JI, Suh M, Paeng JC, Cheon GJ, Koo BK. Exploring coronary circulatory response to stenosis and its association with invasive physiologic indexes using absolute myocardial blood flow and coronary pressure. *Circulation* 136: 1798–1808, 2017. doi:10.1161/CIRCULATIONAHA.117.029911.
- Pijls NH, Van Gelder B, Van der Voort P, Peels K, Bracke FA, Bonnier HJ, el Gamal MI. Fractional flow reserve. A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. *Circulation* 92: 3183–3193, 1995. doi:10.1161/01.CIR.92.11.3183.
- Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van't Veer M, Klauss V, Manoharan G, Engström T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 360: 213–224, 2009. doi:10.1056/NEJMoa0807611.
- De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Möbius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Robert O, Curzen N, Johnson JB, Jüni P, Fearon WF; FAME 2 Trial Investigators. Fractional flow reserve–guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 367: 991–1001, 2012. doi:10.1056/NEJMoa1205361.
- Gulati M, Levy PD, Mukherjee D, Amsterdam E, Bhatt DL, Birtcher KK, Blankstein R, Boyd J, Bullock-Palmer RP, Conejo T, Diercks DB, Gentile F, Greenwood JP, Hess EP, Hollenberg SM, Jaber WA, Jneid H, Joglar JA, Morrow DA, O'Connor RE, Ross MA, Shaw LJ. 2021 AHA/ACC/AHA/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the evaluation and diagnosis of chest pain: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 144: e368–e454, 2021. doi:10.1161/CIR.0000000000001030.
- Taylor CA, Fonte TA, Min JK. Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve: scientific basis. *J Am Coll Cardiol* 61: 2233–2241, 2013. doi:10.1016/j.jacc.2012.11.083.
- Sankaran S, Kim HJ, Choi G, Taylor CA. Uncertainty quantification in coronary blood flow simulations: impact of geometry, boundary conditions and blood viscosity. *J Biomech* 49: 2540–2547, 2016. doi:10.1016/j.jbiomech.2016.01.002.
- Morris PD, Silva Soto DA, Feher JFA, Rafiroiu D, Lungu A, Varma S, Lawford PV, Hose DR, Gunn JP. Fast virtual fractional flow reserve based upon steady-state computational fluid dynamics analysis: results from the VIRTU-Fast Study. *JACC Basic Transl Sci* 2: 434–446, 2017. doi:10.1016/j.jacbs.2017.04.003.
- Sturdy J, Kjernerlie JK, Nydal HM, Eck VG, Hellevik LR. Uncertainty quantification of computational coronary stenosis assessment and model based mitigation of image resolution limitations. *J Comput Sci* 31: 137–150, 2019. doi:10.1016/j.jocs.2019.01.004.

14. Fossan FE, Sturdy J, Müller LO, Strand A, Bråten AT, Jørgensen A, Wiseth R, Hellevik LR. Uncertainty quantification and sensitivity analysis for computational FFR estimation in stable coronary artery disease. *Cardiovasc Eng Technol* 9: 597–622, 2018. doi:10.1007/s13239-018-00388-w.
15. Chung JH, Lee KE, Nam CW, Doh JH, Kim HI, Kwon SS, Shim EB, Shin ES. Diagnostic performance of a novel method for fractional flow reserve computed from noninvasive computed tomography angiography (NOVEL-FLOW Study). *Am J Cardiol* 120: 362–368, 2017. doi:10.1016/j.amjcard.2017.04.057.
16. Coenen A, Rossi A, Lubbers MM, Kurata A, Kono AK, Chelu RG, Segreto S, Dijkshoorn ML, Wragg A, van Geuns RM, Pugliese F, Nieman K. Integrating CT myocardial perfusion and CT-FFR in the work-up of coronary artery disease. *JACC Cardiovasc Imag* 10: 760–770, 2017. doi:10.1016/j.jcmg.2016.09.028.
17. Koo BK, Erglis A, Doh JH, Daniels DV, Jegere S, Kim HS, Dunning A, DeFrance T, Lansky A, Leipsic J, Min JK. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms: results from the Prospective Multicenter DISCOVER-FLOW (diagnosis of ischemia-causing stenoses obtained via noninvasive fractional flow reserve) Study. *J Am Coll Cardiol* 58: 1989–1997, 2011. doi:10.1016/j.jacc.2011.06.066.
18. Tang CX, Liu CY, Lu MJ, Schoepf UJ, Tesche C, Bayer RR, Hudson HT, Zhang XL, Li JH, Wang YN, Zhou CS, Zhang JY, Yu MM, Hou Y, Zheng MW, Zhang B, Zhang DM, Yi Y, Ren Y, Li CW, Zhao X, Lu GM, Hu XH, Xu L, Zhang LJ. CT FFR for ischemia-specific CAD with a new computational fluid dynamics algorithm: a Chinese Multicenter Study. *JACC Cardiovasc Imag* 13: 980–990, 2020. doi:10.1016/j.jcmg.2019.06.018.
19. Wilson RF, Wyche K, Christensen BV, Zimmer S, Laxson DD. Effects of adenosine on human coronary arterial circulation. *Circulation* 82: 1595–1606, 1990. doi:10.1161/01.CIR.82.5.1595.
20. Bråten AT, Wiseth R. Diagnostic Accuracy of CT-FFR Compared to Invasive Coronary Angiography With Fractional Flow Reserve (Online). ClinicalTrials.gov, 2017. <https://clinicaltrials.gov/study/NCT03045601> [2025 Dec 1].
21. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsson T, Escaned J, Gersh BJ, Svitol P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ; ESC Scientific Document Group. ESC Guidelines for the diagnosis and management of chronic coronary syndromes: the task force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *Eur Heart J* 41: 407–477, 2019. doi:10.1093/eurheartj/ehz425.
22. Antiga L, Piccinelli M, Botti L, Ene-Iordache B, Remuzzi A, Steinman DA. An image-based modeling framework for patient-specific computational hemodynamics. *Med Biol Eng Comput* 46: 1097–1112, 2008. doi:10.1007/s11517-008-0420-1.
23. Fossan FE, Müller LO, Sturdy J, Bråten AT, Jørgensen A, Wiseth R, Hellevik LR. Machine learning augmented reduced-order models for FFR-prediction. *Comput Methods Appl Mech Eng* 384: 113892, 2021. doi:10.1016/j.cma.2021.113892.
24. Lautt WW. Resistance or conductance for expression of arterial vascular tone. *Microvasc Res* 37: 230–236, 1989. doi:10.1016/0026-2862(89)90040-X.
25. Müller LO, Fossan FE, Bråten AT, Jørgensen A, Wiseth R, Hellevik LR. Impact of baseline coronary flow and its distribution on fractional flow reserve prediction. *Int J Numer Method Biomed Eng* 37: e3246, 2021. doi:10.1002/cnm.3246.
26. Zipes DP, Libby P, Bonow RO, Mann DL, Tomaselli GF, Braunwald E. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. OCLC, 2019, p. 1021152059.
27. Yang DH, Kang SJ, Koo HJ, Kwon J, Kang JW, Lim TH, Jung J, Kim N, Lee JG, Han S, Ahn JM, Park DW, Lee SW, Lee CW, Park SW, Park SJ, Mintz GS, Kim YH. Incremental value of subtended myocardial mass for identifying FFR-verified ischemia using quantitative CT angiography: comparison with quantitative coronary angiography and CT-FFR. *JACC Cardiovasc Imaging* 12: 707–717, 2019. doi:10.1016/j.jcmg.2017.10.027.
28. Bråten AT, Fossan FE, Müller LO, Jørgensen A, Stensæth KH, Hellevik LR, Wiseth R. Automated computed tomography-derived fractional flow reserve model for diagnosing haemodynamically significant coronary artery disease: a prospective validation study. *Eur Heart J Imaging Methods Pract* 2: qyae102, 2024. doi:10.1093/ehjimp/qyae102.
29. Lance Gould K, Lipscomb K. Effects of coronary stenoses on coronary flow reserve and resistance. *Am J Cardiol* 34: 48–55, 1974. doi:10.1016/0002-9149(74)90092-7.
30. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 44: 837–845, 1988. doi:10.2307/2531595.
31. Saltelli A. Making best use of model evaluations to compute sensitivity indices. *Comput Phys Commun* 145: 280–297, 2002. doi:10.1016/S0010-4655(02)00280-1.
32. Bauman RP, Rembert JC, Greenfield JC Jr. Regional vascular reserve in canine atria and ventricles during rest and exercise. *Am J Physiol Heart Circ Physiol* 269: H1578–H1582, 1995. doi:10.1152/ajpheart.1995.269.5.H1578.
33. Chng CC, Keng BM, Teng XF, Aik KW, Azman MK, Natividad LR, Chong CS, Neela PN, Tan RS, Baskaran L, Chua TS, Keng FY, Koh AS. Going beyond summed stress scores: correlating global and territorial coronary flow reserve by single photon emission tomography with routine myocardial perfusion imaging. *Heliyon* 10: e29629, 2024. doi:10.1016/j.heliyon.2024.e29629.
34. Duncker DJ, Bache RJ. Regulation of coronary blood flow during exercise. *Physiol Rev* 88: 1009–1086, 2008. doi:10.1152/physrev.00045.2006.
35. Chareonthaitawee P, Kaufmann PA, Rimoldi O, Camici PG. Heterogeneity of resting and hyperemic myocardial blood flow in healthy humans. *Cardiovasc Res* 50: 151–161, 2001. doi:10.1016/S0008-6363(01)00202-4.
36. Austin RE Jr, Aldea GS, Coggins DL, Flynn AE, Hoffman JL. Profound spatial heterogeneity of coronary reserve. Discordance between patterns of resting and maximal myocardial blood flow. *Circ Res* 67: 319–331, 1990. doi:10.1161/01.RES.67.2.319.
37. Ghaleh B, Shen YT, Vatner SF. Spatial heterogeneity of myocardial blood flow presages salvage versus necrosis with coronary artery reperfusion in conscious baboons. *Circulation* 94: 2210–2215, 1996. doi:10.1161/01.CIR.94.9.2210.
38. Murthy VL, Naya M, Taqueti VR, Foster CR, Gaber M, Hainer J, Dorbala S, Blankstein R, Rimoldi O, Camici PG, Di Carli MF. Effects of sex on coronary microvascular dysfunction and cardiac outcomes. *Circulation* 129: 2518–2527, 2014. doi:10.1161/CIRCULATIONAHA.113.008507.
39. Aziz A, Hansen HS, Sechtem U, Prescott E, Ong P. Sex-related differences in vasomotor function in patients with angina and unobstructed coronary arteries. *J Am Coll Cardiol* 70: 2349–2358, 2017. doi:10.1016/j.jacc.2017.09.016.
40. Reis SE, Holubkov R, Lee JS, Sharaf B, Reichel N, Rogers WJ, Walsh EG, Fuisz AR, Kerensky R, Detre KM, Sopko G, Pepine CJ. Coronary flow velocity response to adenosine characterizes coronary microvascular function in women with chest pain and no obstructive coronary disease. *J Am Coll Cardiol* 33: 1469–1475, 1999. doi:10.1016/S0735-1097(99)00072-8.
41. Yonetsu T, Murai T, Kanaji Y, Lee T, Matsuda J, Usui E, Hoshino M, Araki M, Niida T, Hada M, Ichijo S, Hamaya R, Kanno Y, Kakuta T. Significance of microvascular function in visual-functional mismatch between invasive coronary angiography and fractional flow reserve. *J Am Heart Assoc* 6: e005916, 2017. doi:10.1161/JAHA.117.005916.
42. van de Hoef TP, Bax M, Damman P, Delewi R, Hassell ME, Piek MA, Chamuleau SA, Voskuil M, van Eck-Smit BL, Verberne HJ, Henriques JP, Koch KT, de Winter Jan RJ, Tijssen GP, Piek JJ, Meuwissen M. Impaired coronary autoregulation is associated with long-term fatal events in patients with stable coronary artery disease. *Circ Cardiovasc Interv* 6: 329–335, 2013. doi:10.1161/CIRCINTERVENTIONS.113.000378.
43. Boerth RC, Covell JW, Seagren SC, Pool PE. High-energy phosphate concentrations in dog myocardium during stress. *Am J Physiol* 216: 1103–1106, 1969. doi:10.1152/ajplegacy.1969.216.5.1103.
44. Jorgensen CR, Gobel FL, Taylor HL, Wang Y. Myocardial blood flow and oxygen consumption during exercise. *Ann NY Acad Sci* 301: 213–223, 1977. doi:10.1111/j.1749-6632.1977.tb38200.x.
45. Vatner SF, Higgins CB, Franklin D, Braunwald E. Role of tachycardia in mediating the coronary hemodynamic response to severe

- exercise. *J Appl Physiol* 32: 380–385, 1972. doi:10.1152/jappl.1972.32.3.380.
46. Mileva N, Nagumo S, Mizukami T, Sonck J, Berry C, Gallinoro E, Monizzi G, Candreva A, Munhoz D, Vassilev D, Penicka M, Barbato E, De Bruyne B, Collet C. Prevalence of coronary microvascular disease and coronary vasospasm in patients with nonobstructive coronary artery disease. *J Am Heart Assoc* 11: e023207, 2022. doi:10.1161/JAHA.121.023207.
47. Ong P, Safdar B, Seitz A, Hubert A, Beltrame JF, Prescott E. Diagnosis of coronary microvascular dysfunction in the clinic. *Cardiovasc Res* 116: 841–855, 2020. doi:10.1093/cvr/cvz339.
48. Shah SV, Zimmermann FM, Johnson NP, Nishi T, Kobayashi Y, Witt N, Berry C, Jeremias A, Koo BK, Esposito G, Rioufol G, Park S-J, Oldroyd KG, Barbato E, Pijls NHJ, De Bruyne B, Fearon WF; CONTRAST Study Investigators. Sex differences in adenosine-free coronary pressure indexes: a CONTRAST substudy. *JACC Cardiovasc Interv* 11: 1454–1463, 2018. doi:10.1016/j.jcin.2018.03.030.
49. Kang SJ, Ahn JM, Han S, Lee JY, Kim WJ, Park DW, Lee SW, Kim YH, Lee CW, Park SW, Mintz GS, Park SJ. Sex differences in the visual-functional mismatch between coronary angiography or intravascular ultrasound versus fractional flow reserve. *JACC Cardiovasc Interv* 6: 562–568, 2013. doi:10.1016/j.jcin.2013.02.016.
50. Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, Banning AP, Budaj A, Buechel RR, Chiariello GA, Chieffo A, Christodorescu RM, Deaton C, Doenst T, Jones HW, Kunadian V, Mehilli J, Milojevic M, Piek JJ, Pugliese F, Rubboli A, Semb AG, Senior R, Ten Berg JM, Van Belle E, Van Craenenbroeck EM, Vidal-Perez R, Winther S; ESC Scientific Document Group. ESC Guidelines for the management of chronic coronary syndromes: developed by the task force for the management of chronic coronary syndromes of the European Society of Cardiology (ESC) Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 45: 3415–3537, 2024. doi:10.1093/eurheartj/ehae177.
51. Kunadian V, Chieffo A, Camici PG, Berry C, Escaned J, Maas AHEM, Prescott E, Karam N, Appelman Y, Fraccaro C, Buchanan GL, Manzo-Silberman S, Al-Lamee R, Regar E, Lansky A, Abbott JD, Badimon L, Duncker DJ, Mehran R, Capodanno D, Baumbach A. EAPCI expert consensus document on ischaemia with non-obstructive coronary arteries in collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. *EuroIntervention* 16: 1049–1069, 2021. doi:10.4244/EIJY20M07_01.
52. Nahser PJ Jr, Brown RE, Oskarsson H, Winniford MD, Rossen JD. Maximal coronary flow reserve and metabolic coronary vasodilation in patients with diabetes mellitus. *Circulation* 91: 635–640, 1995. doi:10.1161/01.cir.91.3.635.
53. Galderisi M, Cicala S, Caso P, De Simone L, D’Errico A, Petrocilli A, de Divitiis O. Coronary flow reserve and myocardial diastolic dysfunction in arterial hypertension. *Am J Cardiol* 90: 860–864, 2002. doi:10.1016/s0002-9149(02)02708-x.
54. Shmilovich H, Cheng VY, Tamarappoo BK, Dey D, Nakazato R, Gransar H, Thomson LE, Hayes SW, Friedman JD, Germano G, Slomka PJ, Berman DS. Vulnerable plaque features on coronary CT angiography as markers of inducible regional myocardial hypoperfusion from severe coronary artery stenoses. *Atherosclerosis* 219: 588–595, 2011. doi:10.1016/j.atherosclerosis.2011.07.128.
55. Ahmadi A, Stone GW, Leipsic J, Serruys PW, Shaw L, Hecht H, Wong G, Nørgaard BL, O’Gara PT, Chandrashekar Y, Narula J. Association of coronary stenosis and plaque morphology with fractional flow reserve and outcomes. *JAMA Cardiol* 1: 350–357, 2016. doi:10.1001/jamacardio.2016.0263.
56. Morris PD, Gosling R, Zwierzak I, Evans H, Aubiniere-Robb L, Czechowicz K, Evans PC, Hose DR, Lawford PV, Narracott AJ, Gunn JP. A novel method for measuring absolute coronary blood flow and microvascular resistance in patients with ischaemic heart disease. *Cardiovasc Res* 117: 1567–1577, 2021. doi:10.1093/cvr/cvaa220.