Received: 3 March 2022 | Revised: 7 September 2022 | Accepted: 9 October 2022

DOI: 10.1002/ccd.30445

ORIGINAL ARTICLE - CLINICAL SCIENCE

WILEY

Age-related changes in the coronary microcirculation influencing the diagnostic performance of invasive pressure-based indices and long-term patient prognosis

Daniel Faria MD[1,2] | Hernan Mejia-Renteria MD, PhD[1] | Joo Myung Lee MD, MPH, PhD[3] | Seung Hun Lee MD[3] | Alejandro Travieso MD[1] | Ji-Hyun Jung MD[4] | Joon-Hyung Doh MD, PhD[5] | Chang-Wook Nam MD, PhD[6] | Eun-Seok Shin MD, PhD[7] | Masahiro Hoshino MD[8] | Tomoyo Sugiyama MD[8] | Yoshihisa Kanaji MD[8] | Nieves Gonzalo MD, PhD[1] | Tsunekazu Kakuta MD, PhD[8] | Bon-Kwon Koo MD, PhD[4,9] | Javier Escaned MD, PhD[1]

[1]Interventional Cardiology, Hospital Clinico San Carlos IDISCC, Complutense University of Madrid, Madrid, Spain

[2]Hospital Professor Doutor Fernando Fonseca, Amadora, Portugal

[3]Division of Cardiology, Department of Internal Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

[4]Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, Seoul, Korea

[5]Department of Medicine, Inje University Ilsan Paik Hospital, Goyang, Korea

[6]Department of Medicine and Cardiovascular Center, Keimyung University Dongsan Medical Center, Daegu, Korea

[7]Department of Cardiology, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea

[8]Division of Cardiovascular Medicine, Tsuchiura Kyodo General Hospital, Ibaraki, Japan

Abstract

Objectives: Investigate age-related changes in coronary microvascular function, its effect on hyperemic and non-hyperemic indices of stenosis relevance, and its prognostic implications.

Background: Evidence assessing the effect of age on fractional flow reserve (FFR), resting mean distal intracoronary pressure/mean aortic pressure (Pd/Pa), and microcirculatory function remains scarce.

Methods: This is a post hoc study of a large prospective international registry (NCT03690713) including 1134 patients (1326 vessels) with coronary stenoses interrogated with pressure and flow guidewires. Age-dependent correlations with functional indices were analyzed. Prevalences of FFR, resting Pd/Pa, and coronary flow reserve (CFR) classification agreement were assessed. At 5 years follow-up, the relation between resting Pd/Pa, CFR, and their age-dependent implications on FFR-guided percutaneous coronary intervention (PCI) deferral (deferred if FFR > 0.80) were investigated using vessel-oriented composite outcomes (VOCO) composed of death, myocardial infarction, and repeated revascularization.

Results: Age correlated positively with FFR ($r = 0.08$, 95% confidence interval [CI]: 0.03 to 0.13, $p = 0.005$), but not with resting Pd/Pa ($r = -0.03$, 95% CI: -0.09 to 0.02,

Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; CFR, coronary flow reserve; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; IMR, index of microcirculatory resistance; IMR_{corr}, corrected index of microcirculatory resistance; LAD, left anterior descending; Pa, aortic pressure; PCI, percutaneous coronary intervention; Pd, distal pressure; RRR, resistive reserve ratio; Tmn, mean transit time; VOCO, vessel-oriented composite outcomes.

Commentary: Expert Article Analysis for: Age and the cascade impact on coronary flow reserve (CFR) and discordance of fractional flow reserve and non-hyperemic pressure ratios (NHPR)

[9]Institute on Aging, Seoul National University, Seoul, Korea

Correspondence
Javier Escaned, MD, PhD, Interventional Cardiology, Hospital Clínico San Carlos, Complutense University of Madrid, Calle del Prof Martín Lagos, 28040, Madrid, Spain.
Email: escaned@secardiologia.es

$p = 0.242$). CFR correlated negatively with age ($r = -0.15$, 95% CI: −0.21 to −0.10, $p < 0.001$) due to a significant decrease in maximal hyperemic flow in older patients. Patients over 60 years of age with FFR-guided deferred-PCI abnormal resting Pd/Pa or abnormal CFR had increased risk of VOCO (hazard ratio [HR]: 2.10, 95% CI: 1.15 to 4.36, $p = 0.048$; HR: 2.46, 95% CI:1.23 to 4.96, $p = 0.011$; respectively).

Conlusions: Aging is associated with decrease in microcirculatory vasodilation, as assessed with adenosine-based methods like CFR. In patients older than 60 years in whom PCI is deferred according to FFR > 0.80, CFR and resting Pd/Pa have an incremental value in predicting future vessel-oriented patient outcomes.

1 | INTRODUCTION

The proportion of elderly patients undergoing coronary revascularization is increasing and the potential implications of this demographic trend on clinical decisions and outcomes are yet to be clarified. Aging causes functional and structural changes that affect both epicardial and microcirculatory domains, as shown by significant differences in hyperemic flow and myocardial perfusion reserve following adenosine administration.[1,2] Hence, although fractional flow reserve (FFR) is recommended by clinical practice guidelines to guide percutaneous coronary intervention (PCI), there is little evidence regarding the effect of aging on this physiological index. The same is true for nonhyperemic indices, which recently have gained large attention as an alternative to guide PCI due to a number of advantages over FFR in the assessment of coronary stenoses.

A recent analysis of the A Denosine Vasodilator Independent Stenosis Evaluation II study found that patient age has an impact on pressure-derived indices. For the same coronary stenosis severity, FFR values increase in older patients, while instantaneous wave-free ratio (iFR) values remain constant throughout the age spectrum.[3] However, solid evidence outlining the mechanisms behind age-related differences in intracoronary pressure-based indices, as well as its potential impact on outcomes and clinical decision making, is still missing.

The purpose of our study was to investigate, based on intracoronary pressure and flow measurements, the impact of aging on pressure-derived coronary physiology and microcirculatory indices and the influence of this effect on clinical outcomes in a large cohort of patients.

2 | METHODS

2.1 | Study population

This study is based on a post hoc analysis of a large prospective international registry (International Collaboration of Comprehensive Physiologic Assessment, NCT03690713) that has already served as a basis for several publications.[4–9] Key exclusion criteria included patients with hemodynamic instability, severe left ventricular systolic dysfunction (ejection fraction < 40%), left main stenosis, surgical grafts, contraindications to adenosine, and severe vessel tortuosity or calcification. In all enrolling centers, invasive angiography was performed as clinically indicated and according to local practice. All the enrolled patients underwent invasive intracoronary pressure and flow measurements, including FFR, coronary flow reserve (CFR), and the hyperemic index of coronary microcirculatory resistance (IMR) for at least one coronary artery. From this registry, we selected patients with stable angina or acute coronary syndrome (ACS) who had coronary stenosis (at least 30% diameter lesion by quantitative assessment) in one or more major epicardial vessels or its branches suitable for PCI. In patients with ACS, noninfarct-related arteries with significant angiographical lesions were interrogated in a second procedure. The patients were followed-up during 5 years for the patient and vessel-orientated outcomes. Individual patient data for pooled analysis were collected using standardized spreadsheets. The study protocol was authorized by institutional review boards or ethics committees at corresponding centers. All patients were granted written informed consent.

2.2 | Coronary angiography

Coronary angiography was performed according to standard practice. Angiographic views were obtained after the administration of intracoronary nitrates (100 or 200 µg). Quantitative coronary angiography (QCA) was performed using validated software (CAAS II, Pie Medical Imaging) and quantitative parameters were obtained including percent diameter stenosis, minimal luminal diameter, reference-vessel size, and lesion length (median [Q1, Q3]).

2.3 | Coronary physiology

Physiology measurements were obtained after coronary angiography. In cases where PCI was performed, preinterventional measurements were used for analysis. The measurement protocols for FFR, CFR, and IMR were standardized among the enrolling centers. Coronary arteries were engaged with a 5-7 F guide catheter without side holes. Intracoronary nitrates were administrated before each measurement. A pressure wire (St. Jude Medical) was introduced and positioned at the distal segment of the target vessel and mean aortic pressure (Pa) and mean distal intracoronary pressure (Pd) were obtained. Mean transit time (T_{mn}) was derived after obtaining three thermodilution curves by injecting 4 ml of saline at room temperature. Hyperemia was induced following intravenous infusion of adenosine (140 µg/kg/min) and hyperemic Pa, Pd, and T_{mn} were measured during sustained hyperemia. FFR was calculated as the lowest Pd/Pa ratio average of three consecutive beats during stable hyperemia. Hemodynamic severity was defined as FFR ≤ 0.80 and PCI was recommended as stated by societal recommendations.[10] CFR was calculated as resting T_{mn}/hyperemic T_{mn}.[5,11] IMR was calculated by hyperemic Pd/hyperemic T_{mn} and all IMR values were then corrected for coronary wedge pressure using the method proposed by Yong et al. (IMR_{corr} = Pa x T_{mn} x ([1.35 x Pd/Pa] −0.32)).[12] Resistive reserve ratio (RRR) was calculated as (resting T_{mn}/hyperemic T_{mn}) x (resting Pd/hyperemic Pd).[13] IMR_{corr}, RRR, and CFR were considered abnormal if values ≥ 25, < 3.5 or ≤ 2.0, respectively. Both angiograms and physiological data were analyzed by a core lab in a blinded fashion.

2.4 | Age and pressure-derived indices relationship

Age correlations with invasive physiological indices were assessed. The patients were then stratified into two groups according to the 60 years-old cut-off, based on research reporting important differences in hyperemic flow and myocardial perfusion reserve after vasodilator administration starting from that age.[1,2] The respective prevalences of FFR and resting Pd/Pa concordance (defined as FFR ≤ 0.80 + Pd/Pa ≤ 0.92 or FFR > 0.80 + Pd/Pa > 0.92) and discordance (defined as FFR ≤ 0.80 + Pd/Pa > 0.92 and FFR > 0.80 + Pd/Pa ≤ 0.92), were calculated and compared between groups.

2.5 | Follow-up and clinical outcomes

Follow-up data were obtained by outpatient visits or by telephone contact. Clinical outcomes included cardiac death, myocardial infarction, target vessel revascularization, and vessel-orientated composite outcomes (VOCO), defined as all-cause mortality, any myocardial infarction and any revascularization. Patients were grouped by FFR + resting Pd/Pa and FFR + CFR concordance/discordance groups and outcomes were compared between groups.

2.6 | Statistical analysis

Continuous variables normally distributed were reported as mean and standard deviation. Continuous variables with non-normally distributed were reported as median and with first and third quartiles (Q1, Q3). Categorical variables were expressed as absolute count and respective percentages. The 95% confidence intervals (CIs) of the means of continuous variables and percentages of categorical variables were calculated with *t* tests and Clopper–Pearson (Exact) approaches, respectively. The Student unpaired *t* test and Mann–Whitney test were used to analyze differences between normally and non-normally distributed variables, respectively. The Pearson's or Spearman's correlation coefficients (*r*) between age and coronary physiology indices were computed. Correlations between coronary physiology indices and age were adjusted for several potential cofounders, including, lesion stenosis diameter by QCA, interrogated target vessel with proximal LAD artery lesion, presence of hypertension, diabetes, renal failure, number of vessels interrogated per patient and patients presenting with ACS. Linear regression was performed to calculate correlations adjusted for the potential confounders. Receiver operator characteristics (ROC) curves using FFR and resting Pd/Pa to predict abnormal CFR values (≤ 2.0) in both age groups were performed. The χ^2 test was used to compare prevalences between the different groups. Kaplan–Meier survival curves were computed to compare outcomes between concordant and discordant groups. Hazard ratios (HR) with 95% CI for VOCO at 5 years in patients with deferred PCI on the basis of FFR > 0.80 and abnormal resting Pd/Pa (≤ 0.92) and/or abnormal CFR (≤ 2.0) were calculated using Cox proportional hazards regression. We used generalized estimation equations (GEEs) to correct for possible unknown effects between more than one vessel interrogated per patient when predicting CFR and FFR-resting Pd/Pa discordance. All statistical analyses were performed using commercially available software (SPSS 23.0, IBM and STATA 13.2, StataCorp). Statistical significance was defined as a bilateral *p*-value <0.05.

3 | RESULTS

3.1 | Study population and hemodynamic parameters

Clinical and angiographic characteristics of the study population are shown in Table 1. As expected, group stratification according to age led to differences regarding the prevalence of baseline risk factors for coronary artery disease (CAD). Older age was associated with higher systolic blood pressure and higher prevalence of hypertension and diabetes mellitus. Younger subjects, on the other hand, had higher prevalence of males, obesity, and active smoking status. Overall, stable angina was the most common clinical presentation (85.4%) and the left anterior descending artery (LAD) was the most frequently interrogated vessel (63.9%). Importantly, there were no significant differences regarding target vessel interrogation, median stenosis severity, clinical presentation, or clinical outcomes during follow-up between age groups.

As shown in Tables 1 and 2, the overall study population was comprised of stenosis of intermediate angiographic (diameter stenosis: 50.9 [42.2, 60.6] %) and physiological severity (FFR 0.81 ± 0.11 and resting Pd/Pa 0.92 ± 0.08), representing the most

TABLE 1 Baseline characteristics

	Total population (*n* = 1134), vessels (*n* = 1326)[a]	Age < 60 years (*n* = 318), vessels (*n* = 392)[a]	Age ≥ 60 years (*n* = 816), vessels (*n* = 934)[a]	*p* value
Demographics				
Age ± SD, years	65 ± 10	53 ± 6	70 ± 6	<0.001
Male, n (%)	889 (78)	283 (89)	606 (74)	<0.001
Systolic blood pressure ± SD, mmHg	133 ± 18	129 ± 19	135 ± 17	<0.001
Diastolic blood pressure ± SD, mmHg	79 ± 10	79 ± 11	79 ± 10	0.453
Resting heart rate ± SD, bpm	68 ± 12	70 ± 12	68 ± 12	0.099
Hyperemic heart rate ± SD, bpm	77 ± 13	78 ± 12	76 ± 13	0.012
Body mass index ± SD, Kg/m^2	25.0 ± 3.6	25.4 ± 3.5	24.8 ± 3.7	0.017
Hypertension, n (%)	760 (67)	179 (56)	581 (71)	<0.001
Diabetes mellitus, n (%)	406 (36)	99 (31)	307 (38)	0.041
Obesity, n (%)	509 (45)	167 (55)	342 (43)	0.001
Smoking, *n* (%)	251 (22)	115 (36)	136 (17)	<0.001
Presentation				
Stable angina, n (%)	969 (85)	282 (89)	687 (84)	0.054
UA/NSTEMI, n (%)	135 (12)	30 (9)	105 (13)	0.109
STEMI, n (%)	32 (3)	7 (2)	25 (3)	0.431
Angiography				
Patients with 1 interrogated vessel, n (%)	848 (64)	253 (65)	595 (64)	0.228
Patients with 2 interrogated vessels, n (%)	200 (15)	66 (17)	134 (14)	0.228
Patients with 3 interrogated vessels, n (%)	278 (21)	73 (18)	205 (22)	0.288
Quantitative parameters[a]				
Diameter stenosis [Q1, Q3], %	50.9 (42.2, 60.6)	48.5 (38.9, 61.1)	51.9 (42.9, 60.5)	0.084
Minimal luminal diameter [Q1, Q3], mm	1.40 (1.10, 1.72)	1.45 (1.12, 1.77]	1.37 (1.10, 1.71)	0.057
Reference vessel size [Q1, Q3], mm	2.89 (2.46, 3.31)	2.98 (2.50, 3.37)	2.88 (2.43, 3.29)	0.310
Lesion length [Q1, Q3], mm	11.7 (8.09, 17.5)	11.9 (7.64, 18.7)	11.7 (8.10, 17.2)	0.628

Abbreviations: NSTEMI, non ST-segment elevation myocardial infarction; Q1, first quartile; Q3, third quartile; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

[a]Per vessel analysis.

TABLE 2 Baseline intracoronary physiology indices (per vessel analysis)

Coronary physiology indices	Total population (*n* = 1134), vessels (*n* = 1326)	Age < 60 years (*n* = 318), vessels (*n* = 392)	Age ≥ 60 years (*n* = 816), vessels (*n* = 934)	*p* value
Resting Pd/Pa ± SD	0.92 ± 0.08	0.93 ± 0.07	0.92 ± 0.08	0.042
FFR ± SD	0.81 ± 0.11	0.81 ± 0.12	0.81 ± 0.11	0.781
CFR ± SD	2.83 ± 1.27	3.02 ± 1.30	2.74 ± 1.26	<0.001
IMR_{corr} (Q1, Q3)	17.2 (12.4, 24.7)	16.2 (11.9, 22.5)	17.9 (12.6, 25.8)	0.006
RRR (Q1, Q3)	3.95 (2.73, 5.31)	3.93 (2.78, 5.25)	3.42 (2.40, 4.69)	<0.001

Note: Baseline intracoronary physiology indices values and their respective comparison between age groups.

Abbreviations: CFR, coronary flow reserve; FFR, fractional flow reserve; IMRcorr, corrected index of microcirculatory resistance; Pa, mean aortic pressure; Pd, mean distal intracoronary pressure; Q1, first quartile; Q3, third quartile; RRR, resistive reserve ratio; SD, standard deviation.

frequent scenario for coronary physiology in clinical practice, namely for establishing functional relevance of intermediate coronary lesions. Interestingly there was an overall tendency for abnormal microvascular function in older patients, as shown by lower CFR, higher IMR_{corr} and lower RRR values.

3.2 | Effect of age on pressure-based and microcirculation functional indices

All correlations were performed after adjustment for stenosis severity, target vessel, number of vessels interrogated per patient, hypertension, diabetes, and body mass index (BMI). Overall, there was a positive correlation between age and FFR values ($r = 0.08$, 95% CI: 0.03 to 0.13, $p = 0.005$; Figure 1A). Conversely, there was no significant correlation between resting Pd/Pa and age ($r = -0.03$, 95% CI: −0.09 to 0.02, $p = 0.242$; Figure 1B).

Age correlations with microvascular resistance indices were in line with findings described above. CFR and RRR both correlated negatively with age ($r = -0.15$, 95% CI: −0.21 to −0.10, $p < 0.001$; Figure 1C and $r = -0.19$, 95% CI: −0.24 to −0.14, $p < 0.001$; Figure 1D, respectively). The same correlations with age and the above-mentioned indices were maintained even in the absence of angiographically significant stenosis (<50%)—Supporting Information: Table 1. Importantly, as shown in Figure 2 and Supporting Information: Table 2, the decrease in CFR with age appeared to be

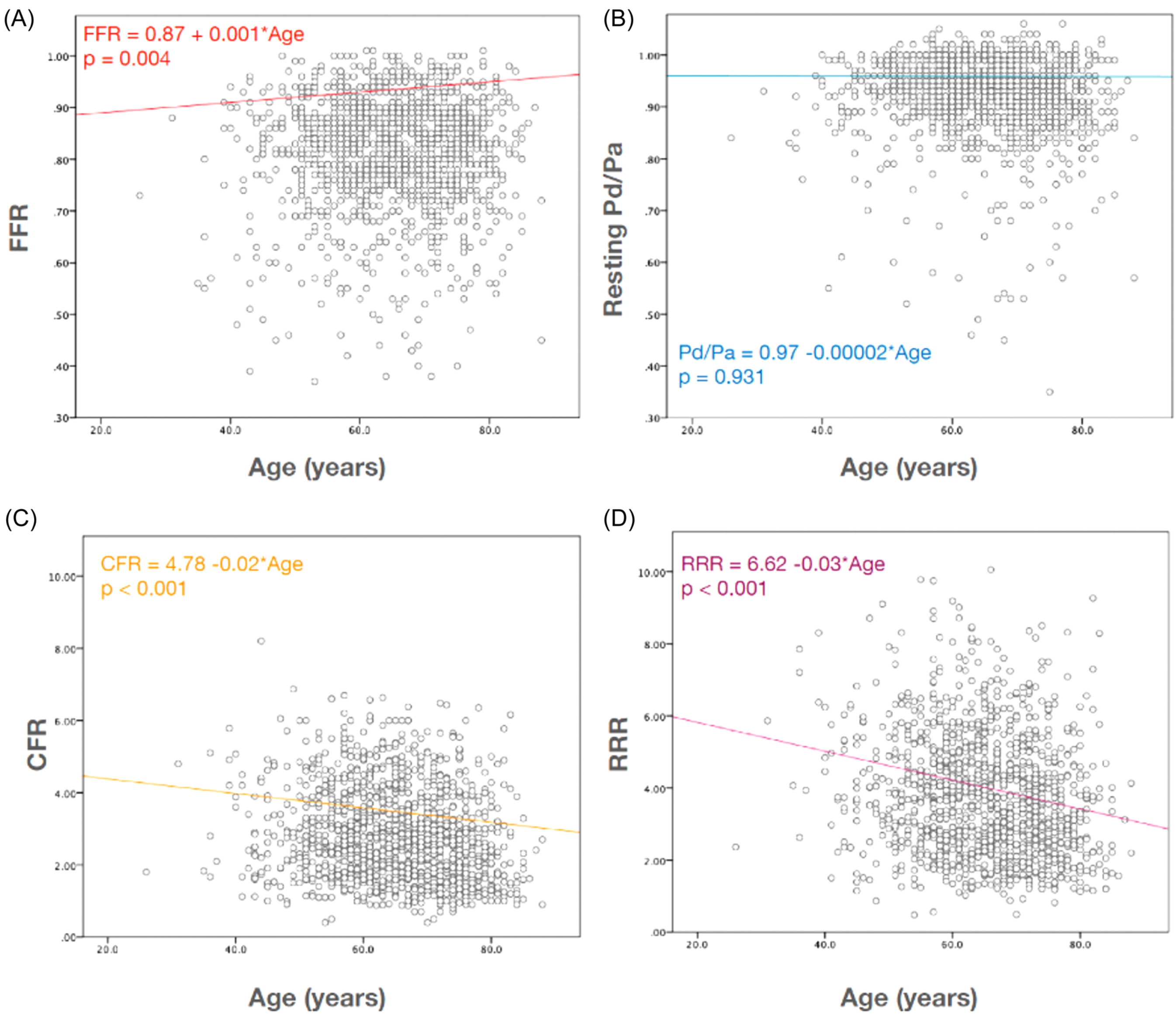

FIGURE 1 Scatter plots between age and intracoronary physiology indices with linear regression lines after adjusting for confounders, (A) age correlation with FFR; (B) age correlation with resting Pd/Pa; age correlation with CFR; (D) Age correlation with RRR. CFR, coronary flow reserve; D, resistive reserve ratio; FFR, fractional flow reserve; Pa, mean aortic pressure; Pd, mean distal intracoronary pressure. [Color figure can be viewed at wileyonlinelibrary.com]

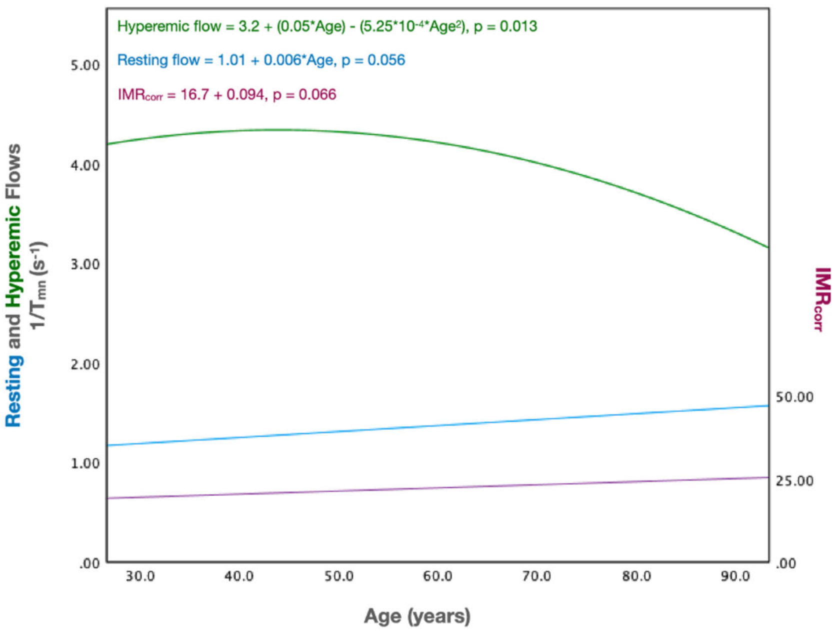

FIGURE 2 Age correlation with Resting and Hyperemic coronary flows and IMR_{corr}. Regression lines for hyperemic flow (green); resting flow (blue) and IMR_{corr} (purple). Coronary hyperemic flow stats to significantly decrease after 60 years of age, marking the point in time on which microcirculatory remodeling begins to be functionally evident. On the other hand, both resting flow and IMR_{Corr} progressively increase with age. T_{mn}, mean transit time; IMR_{corr}, corrected index of microcirculatory resistance. [Color figure can be viewed at wileyonlinelibrary.com]

mainly secondary to a decrease in maximal myocardial flow (1/hyperemic T_{mn}), with nonsignificant increases in baseline flow (1/basal T_{mn}) and microvascular resistance (IMR_{corr}).

3.3 | Effect of age on the relationship between pressure-derived indices and coronary flow reserve

Overall, CFR showed a stronger correlation with resting Pd/Pa than FFR ($r = 0.29$, 95% CI: 0.23 to 0.34, $p < 0.001$ and $r = 0.21$, 95% CI: 0.16 to 0.26, $p < 0.001$, respectively). The higher predictive value of resting Pd/Pa than FFR for CFR < 2.0 was marked in patients older than 60 years (area under the curve [AUC]: 0.63, 95% CI: 0.56 to 0.67 and AUC: 0.72, 95% CI: 0.69 to 0.75, for FFR and resting Pd/Pa, respectively, $p = 0.024$), but not in patients younger than 60 years (AUC: 0.62, 95% CI: 0.55 to 0.69 and AUC: 0.65, 95% CI: 0.58 to 0.73, for FFR and resting Pd/Pa, respectively, $p = 0.156$) (Figure 3, Supporting Information: Table 3).

3.4 | Effect of aging on the agreement between hyperemic and nonhyperemic indices of stenoses relevance

Figure 4 shows the agreement/discordance relationship between FFR and resting Pd/Pa and FFR and CFR, in terms of functional stenosis relevance, per age group (below or above 60 years old). The older group had higher prevalence of discordance due to high FFR (8.9% vs. 13.4%; $p = 0.047$). Interestingly, no significant differences in the prevalence of discordance due to abnormal resting Pd/Pa were found, although a nonsignificant trend toward decrement with age was noted (9.9% vs. 7.9%, $p = 0.244$). Similarly, older patients had higher prevalence of discordance due to abnormal CFR (15.7% vs. 12.5%, $p = 0.047$). Supporting Information: Table 4 shows the tendency for increased discordance between FFR > 0.80 and resting Pd/Pa ≤ 0.92 associated with aging and abnormal CFR. Supporting Information: Table 5 illustrates a model to predict this discordance using generalized estimating equations, showing independent contributions from both older age and CFR.

3.5 | Implications of aging for clinical-decision making based on pressure-derived coronary indices

Overall, at a mean follow-up of 5 years, there were no significant differences in VOCO nor in the individual components of the primary endpoint when comparing patients with below and over 60 years (Table 3 and Supporting Information: Table 6).

However, as shown in Table 4 and Figure 5 deferring PCI according to FFR in the presence of abnormal resting Pd/Pa was associated with a significant lower survival rate compared with normal resting Pd/Pa (Figure 5). Furthermore, in patients ≥60 years old in whom PCI was deferred based on FFR, the presence of abnormal CFR was associated with a significant lower survival compared with patients with preserved CFR. Of note, this finding was not observed in the younger group.

As shown in Table 4 and Figure 5, discriminating patients with FFR-guided deferred PCI on the basis of resting Pd/Pa concordance showed a significantly lower survival for VOCO events in the overall population (Log-rank (2) = 14.414, $p < 0.001$; HR: 2.74, 95% CI: 1.43 to 5.24, $p = 0.002$). However, when discriminating patients on the basis of CFR concordance, older patients with FFR-deferred PCI and abnormal CFR had a significantly lower survival for VOCO events (Log-rank (2) = 9.129, $p = 0.0010$; HR: 2.46, 95% CI: 1.23 to 4.96, $p = 0.011$); Table 4 and Figure 6. As shown in Supporting Information: Table 7, age on was not an independent predictor of VOCO.

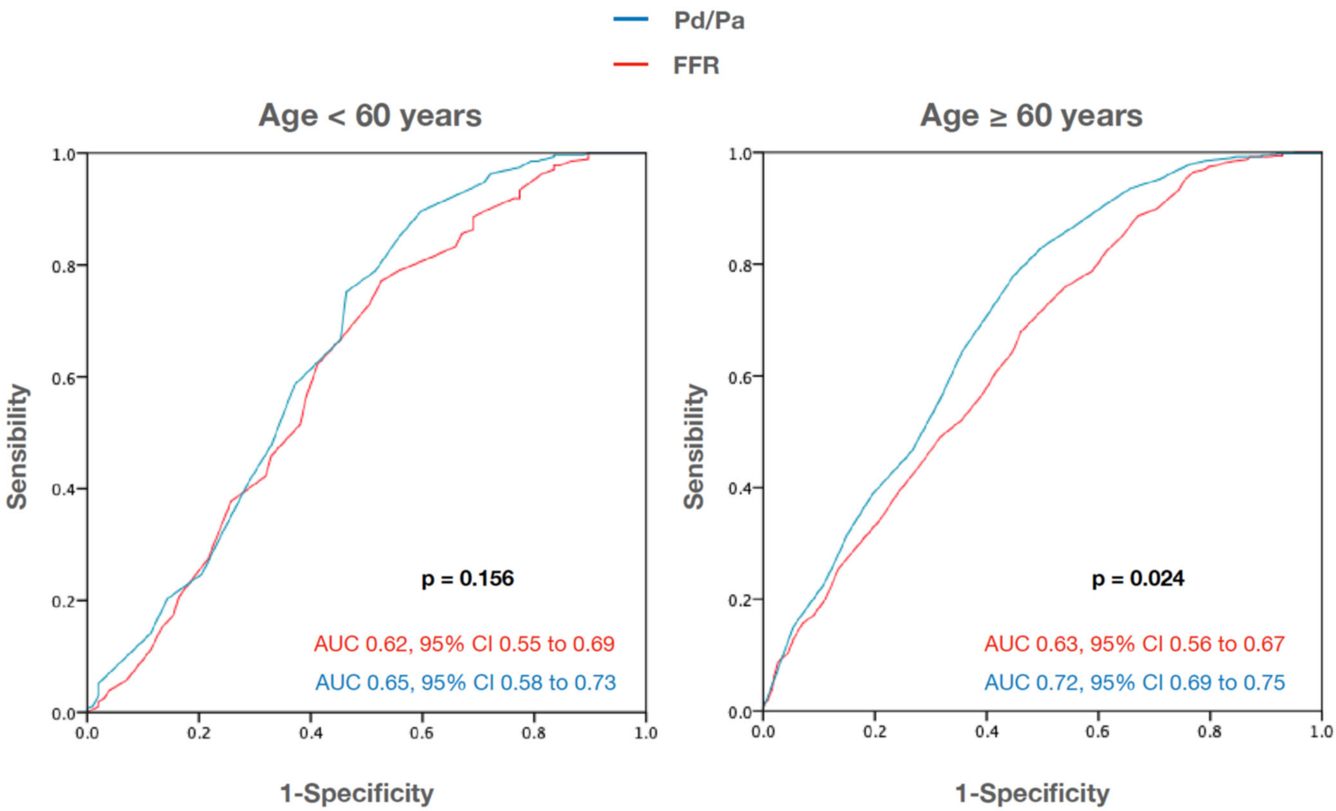

FIGURE 3 Receiver operator characteristics (ROC) curve analysis for coronary flow reserve (CFR) ≤ 2.0 prediction in patients younger and older than 60 years. Receiver operator characteristics curves using FFR and resting Pd/Pa to predict abnormal CFR values (≤2.0) in both age groups. Blue: resting, Pd/Pa; Pa, mean aortic pressure; Pd, mean distal intracoronary pressure; Red: FFR, fractional flow reserve; AUC, area under the curve. [Color figure can be viewed at wileyonlinelibrary.com]

However, there was a positive significant interaction between age and resting Pd/Pa in predicting events (HR: 1.05, 95% CI: 1.01 to 1.12, $p = 0.008$). Supporting Information: Figures 1 and 2 show the Kaplan–Meier curves for each component of VOCO, showing that repeated revascularizations were the main driver for the differences in VOCO between groups.

4 | DISCUSSION

The main findings of this study are the following: (1) aging is associated with a marked decrease in vasodilation of the coronary microcirculation, as assessed with CFR and other indices based on adenosine-induced hyperemia; (2) as a result, the discrepancy between hyperemic (FFR) and nonhyperemic (resting Pd/Pa) indices of stenosis severity varies with age; (3) in older patients (≥60 years) in whom PCI is deferred on the grounds of FFR values, both CFR and resting Pd/Pa have an incremental value in predicting future vessel-oriented patient outcomes. These findings and their implications are discussed in the following paragraphs.

In our study, we documented a significant decrease in CFR associated with aging, both in the overall study population and in patients in whom PCI was deferred on the grounds of FFR values. RRR, an index of arteriolar dynamicity, also decreases with age. The dominant mechanism leading to CFR impairment is a progressive decrease in hyperemic flow beyond 60 years of age (Figure 2). These observations are concordant with previous studies based on position emission tomography, that also identified age 60 years-old as the age over which significant changes in the microcirculation are observed.[1,2] Of note, we failed to reproduce the significant increase in baseline flow that previous studies have shown with aging, as a cause of low CFR, neither a significant increase in the coronary microcirculatory resistance. We also found that CFR correlates strongly with resting Pd/Pa than with FFR. An explanation for this phenomenon can be found in previous studies showing that nonhyperemic indices, such as iFR, correlate better with flow indices than FFR, either by intracoronary Doppler assessment,[14] or by positron emission tomography.[15]

Our study also shows how the above-mentioned effect of aging translates into patient outcomes when FFR is used as a tool to defer coronary revascularization. As Figure 6 shows, in patients over 60 years in whom revascularisation was deferred on the grounds of FFR values, the presence of impaired CFR was associated with an important increase of VOCO. Of note, these events distributed evenly over a long follow-up period and exceeded the event rate observed in patients who had undergone PCI. Previous research had

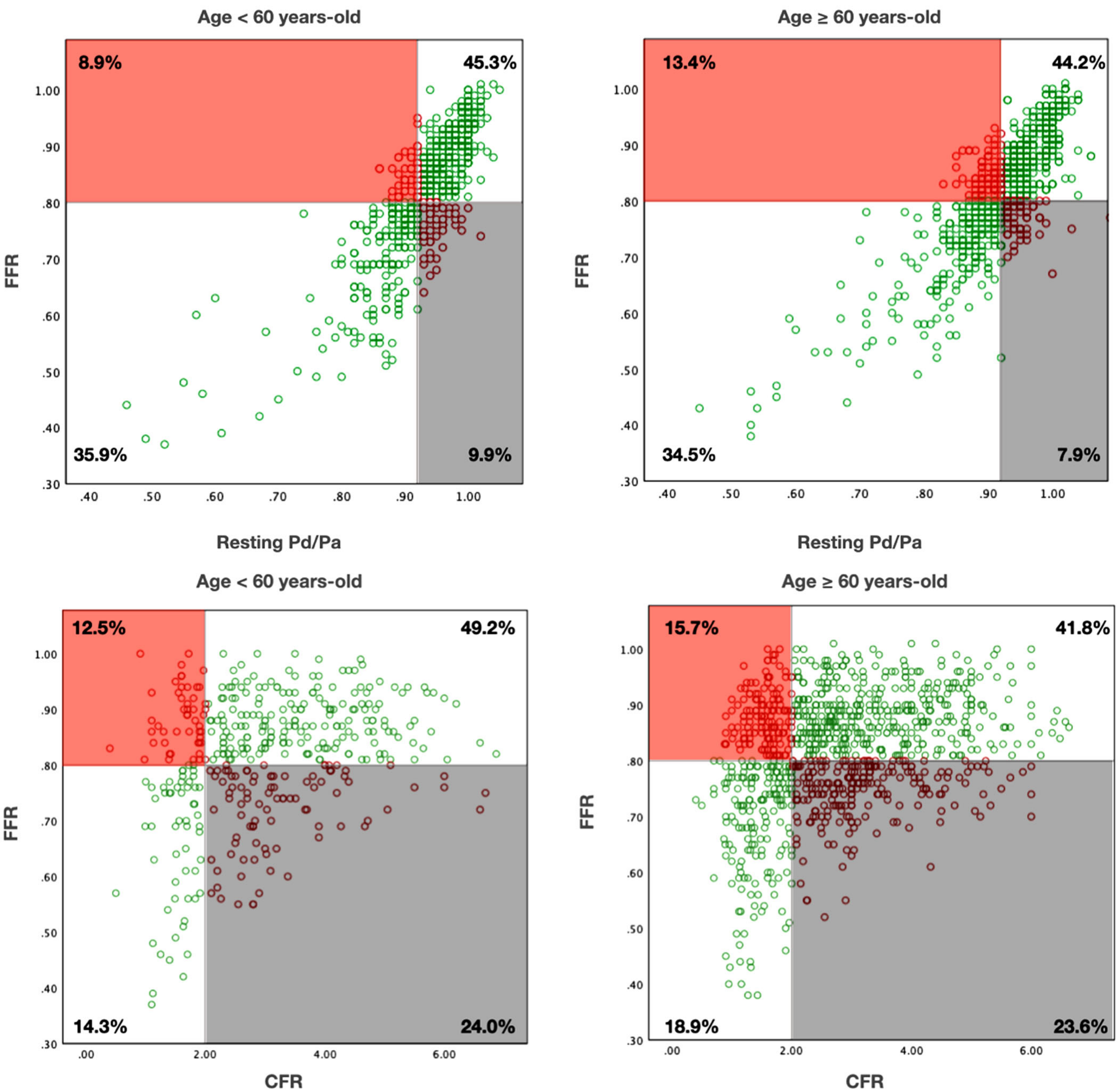

FIGURE 4 Concordant and discordant FFR and Resting Pd/Pa groups in terms of functional stenosis classification and according to age groups. Concordance-Discordance scatter-plots for each age group Upper Panel: FFR and resting Pd/Pa. Lower panel: FFR and CFR. Percent of cases in concordant (white) and discordant (gray and red) groups are shown in as figures within each quadrant. Discordant values are shown as red circles. CFR, coronary flow reserve; FFR, fractional flow reserve; Pa, mean aortic pressure; Pd, mean distal intracoronary pressure. [Color figure can be viewed at wileyonlinelibrary.com]

demonstrated that impaired CFR in patients with FFR > 0.80 has an incremental prognostic value.[5,16,17] As increased VOCO rate was not observed in younger patients with high FFR and low CFR, our study suggests an interaction between aging and CFR in terms of patient outcomes.

While the performance of additional CFR measurements on top of FFR measurements seems to contribute to a better risk profile in elderly patients undergoing FFR, it has to be kept in mind that only a minority of catheterization laboratories perform routinely assessment of the coronary microcirculation with either Doppler- or thermodilution-dedicated guidewires. In this regard, our findings provide a unique opportunity to perform such stratification of risk using a conventional pressure guidewire to measure resting Pd/Pa, which has a better sensitivity than FFR to predict abnormal CFR (Figure 3). In this regard, we found that the incremental prognostic value of resting Pd/Pa over FFR in elderly patients is similar to that of CFR (Figures 5 and 6, Table 4).

TABLE 3 Clinical outcomes at 5 years follow-up

Outcomes	Total population (*n* = 1134)	Age < 60 years (*n* = 318)	Age ≥ 60 years (*n* = 816)	*p* value
Any event, *n* (%)	151 (13)	34 (11)	117 (14)	0.104
Cardiac death, *n* (%)	17 (2)	3 (1)	14 (2)	0.336
Myocardial infarction, *n* (%)	23 (2)	10 (3)	13 (2)	0.096
Target vessel revascularization, *n* (%)	64 (6)	15 (5)	49 (6)	0.399
VOCO, *n* (%)	83 (7)	20 (6)	63 (8’)	0.406

Note: Cardiovascular outcomes in the overall population and their respective comparison between age groups. Data are expressed as number, (%).
Abbreviation: VOCO, vessel-oriented composite outcomes.

TABLE 4 Cox proportional hazard regression for VOCO at 5 years in patients with deferred PCI on the basis of FFR > 0.80 and abnormal Pd/Pa and/or CFR

Physiology index	All population HR (95% CI)	All population *p* value	Age < 60 years HR (95% CI)	Age < 60 years *p* value	Age ≥ 60 years HR (95% CI)	Age ≥ 60 years *p* value
Resting Pd/Pa ≤ 0.92	2.74 (1.43 to 5.24)	0.002	7.34 (1.64 to 32.8)	0.009	2.10 (1.15 to 4.36)	0.048
CFR ≤ 2.0	2.41 (1.28 to 4.53)	0.006	1.67 (0.32 to 8.62)	0.540	2.46 (1.23 to 4.96)	0.011

Abbreviations: CFR, coronary flow reserve; HR, hazard ratio; Pa, mean aortic pressure; Pd, mean distal intracoronary pressure.

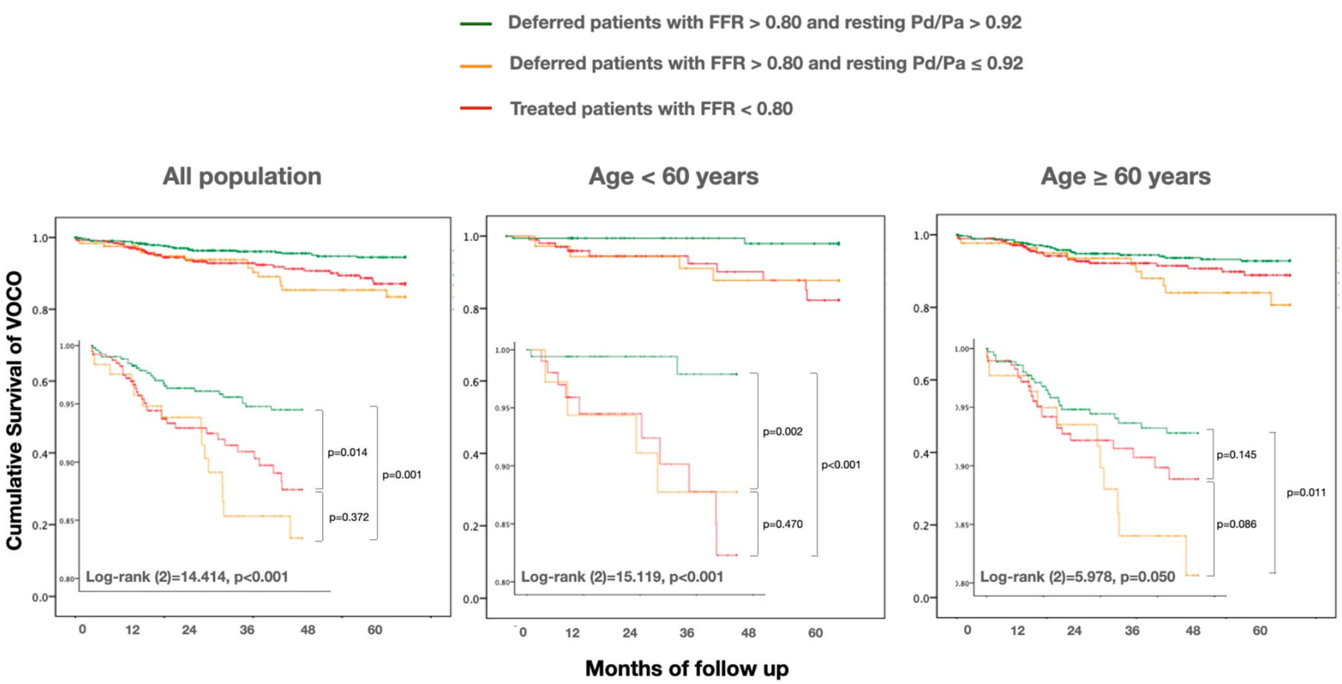

FIGURE 5 Kaplan–Meier curves for VOCO outcomes at 5 years follow-up on the basis of FFR and resting Pd/Pa concordance. Analysis performed in the overall population and in both age groups. Red line: treated patients with FFR ≤ 0.80; Yellow line: deferred patients with FFR > 0.80 and discordant resting Pd/Pa ≤ 0.92; Green line: deferred patients with FFR > 0.80 with concordant resting Pd/Pa > 0.92. FFR, fractional flow reserve; Pa, mean aortic pressure; Pd, mean distal intracoronary pressure; VOCO, vessel-oriented composite outcomes. [Color figure can be viewed at wileyonlinelibrary.com]

In fact, low CFR being identified as a strong prognostic indicator in patients with FFR > 0.80 and deferred revascularization was repeatedly demonstrated in various registries.[4,5] Our study adds, however, that this discordance is particularly significant in older patients, resonating with the reported differences in hyperemic flow and myocardial perfusion reserve in this subgroup.[1,2]

What our study cannot answer is whether PCI should be performed in patients with FFR > 0.80 and resting Pd/Pa ≤ 0.92. There

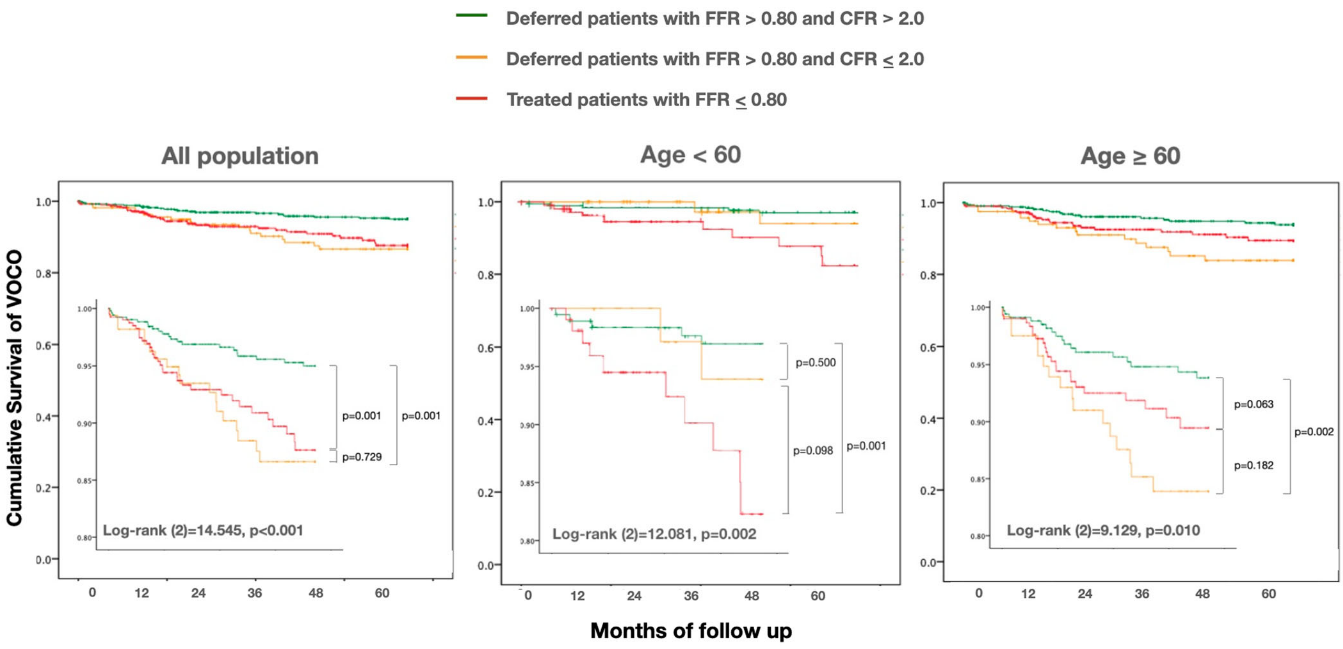

FIGURE 6 Kaplan–Meier curves for VOCO outcomes at 5 years follow-up on the basis of FFR and CFR concordance. Analysis performed in the overall population and in both age groups. Red line—treated patients with FFR ≤ 0.80; Yellow line—deferred patients with FFR > 0.80 and discordant CFR ≤ 2.0; Green line—deferred patients with FFR > 0.80 with concordant CFR > 2.0. CFR, coronary flow reserve; FFR, fractional flow reserve; VOCO, vessel-oriented composite outcomes. [Color figure can be viewed at wileyonlinelibrary.com]

are two possible hypothetical answers for this implication. On the one hand, we can hypothesize that, should the diagnostic yield of FFR be diminished in identifying ischemia-generating stenoses in the elderly, resting Pd/Pa guided PCI for those vessels with FFR > 0.80 might achieve better clinical outcomes in elderly patients than taking decision solely based on FFR. Ultimately, this might lead to the recommendation of nonhyperemic indices for the assessment of stenosis severity in the elderly. Alternatively, we could also hypothesize that, should abnormal resting Pd/Pa values reflect the existence nonreversible microcirculatory dysfunction causing myocardial ischemia, PCI would not confer a better prognosis. An important caveat of this hypothesis is that resting Pd/Pa values remain constant over age and, therefore, do not seem to reflect age-related changes in the microcirculation, but the hemodynamic effect of epicardial stenoses. Further studies are needed to clarify which therapeutic attitude should be followed in case of this type of discrepancy between FFR and resting Pd/Pa.

5 | LIMITATIONS

Our study is limited in that it is a retrospective subgroup analysis of an observational registry. Henceforth, our conclusions are mainly hypothesis generating rather than hypothesis testing. Nevertheless, there is a clear biological and clinical rationale for performing this analysis, as the microcirculatory and epicardial modifications associated with age had been previously described.

Another potential limitation is the absence of consensus in defining "older-age" in the literature. "Elderly" is a definition mainly dependent on ethnical and cultural background, ranging from 55 to 75 years or higher. Nevertheless, our study does not aim to provide a new cut-off for older age. We used the mentioned 60 years old as a separating point based on studies demonstrating that this is when significant changes in resting and hyperemic coronary flows start to appear.

6 | CONCLUSIONS

Aging is associated with a marked decrease in the vasodilatory response of the microcirculation to adenosine administration, as assessed with CFR. This fact influences the degree of concordance between hyperemic and nonhyperemic indices in terms of functional stenosis classification. In patients older than 60 years in whom PCI is deferred on the grounds of FFR values, both CFR and resting Pd/Pa have an incremental value in predicting future vessel-oriented patient outcomes.

ACKNOWLEDGMENTS

The authors of this study are solely responsible for the design and conduct, all analysis, manuscript drafting and editing, and are responsible for its final contents.

CONFLICTS OF INTEREST

Dr. Mejía-Renteria served as speaker at educational events organized by Abbott, Boston Scientific and Philips Healthcare. Dr. Joo Myung Lee received a Research Grant from Abbott Vascular and Philips

Volcano. Dr. Gonzalo has served as consultant and speaker at educational events organized by Abbott and Boston. Dr. Bon-Kwon Koo received Institutional Research Grants from Abbott Vascular and Philips. Dr. Escaned has served as consultant and speaker at educational events for Abbott, Boston Scientific and Philips. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Daniel Faria http://orcid.org/0000-0003-3837-6786
Hernan Mejia-Renteria http://orcid.org/0000-0003-1030-1926
Joo Myung Lee http://orcid.org/0000-0002-2178-4014
Seung Hun Lee http://orcid.org/0000-0002-2337-7826
Alejandro Travieso http://orcid.org/0000-0003-3013-2592
Eun-Seok Shin http://orcid.org/0000-0002-9169-6968
Masahiro Hoshino http://orcid.org/0000-0003-3661-1914
Tomoyo Sugiyama http://orcid.org/0000-0002-3754-6117
Nieves Gonzalo http://orcid.org/0000-0003-3827-945X
Tsunekazu Kakuta http://orcid.org/0000-0002-4004-5292
Bon-Kwon Koo http://orcid.org/0000-0002-8188-3348

REFERENCES

1. Uren NG, Camici PG, Melin JA, et al. Effect of aging on myocardial perfusion reserve. *J Nucl Med*. 1995;36(11):2032-2036.
2. Chareonthaitawee P, Kaufmann PA, Rimoldi O, Camici PG. Heterogeneity of resting and hyperemic myocardial blood flow in healthy humans. *Cardiovasc Res*. 2001;50(1):151-161. doi:10.1016/s0008-6363(01)00202-4
3. Faria DC, Lee JM, Van Der Hoef T, et al. Age and functional relevance of coronary stenosis: a post hoc analysis of the ADVISE II trial. *EuroIntervention*. 2021;17(9):757-764. doi:10.4244/EIJ-D-20-01163
4. Lee JM, Jung JH, Hwang D, et al. Coronary flow reserve and microcirculatory resistance in patients with intermediate coronary stenosis. *J Am Coll Cardiol*. 2016;67(10):1158-1169. doi:10.1016/j.jacc.2015.12.053
5. Lee JM, Choi KH, Hwang D, et al. Prognostic implication of thermodilution coronary flow reserve in patients undergoing fractional flow reserve measurement. *JACC Cardiovasc Interv*. 2018;11(15):1423-1433. doi:10.1016/j.jcin.2018.05.005
6. Echavarria-Pinto M, Escaned J, Macías E, et al. Disturbed coronary hemodynamics in vessels with intermediate stenoses evaluated with fractional flow reserve a combined analysis of epicardial and microcirculatory involvement in ischemic heart disease. *Circulation*. 2013;128(24):2557-2566. doi:10.1161/CIRCULATIONAHA.112.001345
7. Mejía-Rentería H, Lee JM, Lauri F, et al. Influence of microcirculatory dysfunction on angiography-based functional assessment of coronary stenoses. *JACC Cardiovasc Interv*. 2018;11(8):741-753. doi:10.1016/j.jcin.2018.02.014
8. Hamaya R, Yonetsu T, Kanaji Y, et al. Diagnostic and prognostic efficacy of coronary flow capacity obtained using pressure-temperature sensor–tipped wire–derived physiological indices. *JACC Cardiovasc Interv*. 2018;11(8):728-737. doi:10.1016/j.jcin.2018.01.249
9. Hoshino M, Hamaya R, Kanaji Y, et al. Sex differences in Long-Term outcomes in patients with deferred revascularization following fractional flow reserve assessment: international collaboration registry of comprehensive physiologic evaluation. *J Am Heart Assoc*. 2020;9(4):e014458. doi:10.1161/JAHA.119.014458
10. Neumann F-J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40(2):87-165. doi:10.1093/EURHEARTJ/EHY394
11. De Bruyne B, Pijls NHJ, Smith L, Wievegg M, Heyndrickx GR. Coronary thermodilution to assess flow reserve experimental validation. *Circulation*. 2001;104(17):2003-2006. doi:10.1161/hc4201.099223
12. Yong AS, Layland J, Fearon WF, et al. Calculation of the index of microcirculatory resistance without coronary wedge pressure measurement in the presence of epicardial stenosis. *JACC Cardiovasc Interv*. 2013;6(1):53-58. doi:10.1016/J.JCIN.2012.08.019
13. Lee SH, Lee JM, Park J, et al. Prognostic implications of resistive reserve ratio in patients with coronary artery disease. *J Am Heart Assoc*. 2020;9(8):015846. doi:10.1161/JAHA.119.015846
14. Cook CM, Jeremias A, Petraco R, et al. Fractional flow reserve/instantaneous wave-free ratio discordance in angiographically intermediate coronary stenoses: an analysis using Doppler-derived coronary flow measurements. *JACC Cardiovasc Interv*. 2017;10(24):2514-2524. doi:10.1016/j.jcin.2017.09.021
15. Lee JM, Hwang D, Park J, Tong Y, Koo BK. Physiologic mechanism of discordance between instantaneous wave-free ratio and fractional flow reserve: insight from 13N-ammonium positron emission tomography. *Int J Cardiol*. 2017;243:91-94. doi:10.1016/j.ijcard.2017.05.114
16. Van De Hoef TP, Van Lavieren MA, Damman P, et al. Physiological basis and long-term clinical outcome of discordance between fractional flow reserve and coronary flow velocity reserve in coronary stenoses of intermediate severity. *Circ Cardiovasc Interv*. 2014;7(3):301-311. doi:10.1161/CIRCINTERVENTIONS.113.001049
17. TP van de H, M B PD, et al. Impaired coronary autoregulation is associated with long-term fatal events in patients with stable coronary artery disease. *Circ Cardiovasc Interv*. 2013;6(4):329-335. doi:10.1161/CIRCINTERVENTIONS.113.000378

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Faria D, Mejia-Renteria H, Lee JM, et al. Age-related changes in the coronary microcirculation influencing the diagnostic performance of invasive pressure-based indices and long-term patient prognosis. *Catheter Cardiovasc Interv*. 2022;100:1195-1205. doi:10.1002/ccd.30445