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Age-related structural remodelling of the coronary circulation

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Abstract

Background: While it is broadly accepted that ageing is associated with impairment of coronary microvascular function, little is known about the underlying mechanisms.

Aims: We investigated age-related changes in coronary microvascular structure in patients with stable angina without epicardial coronary stenoses.

Methods: In an analysis of the IDEAL registry, a total of 165 vessels without coronary stenosis were interrogated with combined pressure/Doppler guidewires. We calculated diastolic microvascular conductance (DMVC) and backward expansion wave (BEW), and compared them between age tertiles. We calculated the prevalence of CMD, defined by reduced coronary flow reserve (CFR), and the prevalence of low BEW and low DMVC in each group.

Results: The three study groups were defined as having 37–53, 54–66, and 67–77 years of age, respectively. Oldest (3rd tertile) patients showed lower hyperemic flow velocity (46.7 ± 14.4 vs. 45.1 ± 12.4 vs. 38.4 ± 11.5 cm s^{-1}, $p = 0.019$), lower DMVC (1.90 ± 0.71 vs. 1.44 ± 0.56 vs. 1.37 ± 0.67 cm s^{-1} $mmHg^{-1}$, $p < 0.001$) and lower BEW intensity (5.9 [2.9–8.4] vs. 4.8 [2.9–6.8] vs. 4.4 [3.4–6.3] × 10^6 W m^{-2} s^{-1}, $p = 0.094$). Older age was independently associated with lower BEW intensity (*B*: −0.10, 95% confidence interval [CI]: −0.17 to −0.09, $p = 0.021$) and DMVC (*B*: −0.25 95% CI: −0.45 to −0.09, $p = 0.027$). In patients with

Abbreviations: APV, average peak flow velocity; BCW, backward compression wave; BEW, backward expansion wave; BEW-EF, backward expansion wave energy fraction; CFR, coronary flow reserve; CMD, coronary microcirculatory dysfunction; C-BEW, cumulative backward expansion wave; DMVC, diastolic microvascular conductance; FCW, forward compression wave; FEW, forward expression wave; FFR, fractional flow reserve; HMR, hyperemic microvascular conductance; IDEAL, Iberian-Dutch-English; Pa, mean aortic pressure; Pd, mean distal coronary pressure; QCA, quantitative coronary angiography; WIA, wave intensity analysis.

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CFR < 2.5, the prevalence of BEW intensity and DMVC below the 25th percentile increased with age (25.0% vs. 52.0% vs. 72.7%, $p = 0.010$).

Conclusions: Ageing is independently associated with structural microcirculatory remodeling that is reflected in BEW intensity and DMVC measurements, and with an increased prevalence of structural CMD. These results are important to understand non-obstructive mechanisms of myocardial ischemia in the elderly.

KEYWORDS
coronary artery disease, coronary microcirculatory dysfunction

1 | INTRODUCTION

Emerging evidence suggests the presence of age-related microcirculatory dysfunction. This phenomenon is characterized by dampened myocardial blood flow increase in response to adenosine and increased microvascular resistance on invasive coronary physiology studies[1,2]

Coronary microcirculatory dysfunction (CMD) is a complex pathophysiological phenomena that can obey to functional or structural derangements.[3,4] Functional coronary CMD refers to an endotype characterized by low CFR in the presence of normal microvascular resistance. This can result from increased myocardial demand or dysfunctional coronary autoregulation, increasing resting myocardial blood flow despite unchanged myocardial workload and normal microcirculation during maximal hyperemia. Structural CMD can be characterized by reduced capillary density (rarefaction), inward hypertrophic arteriolar remodeling and periarteriolar fibrosis, which can lead to decreased microcirculatory conductance and myocardial ischemia. Despite the distinctive pathophysiology, both endotypes can cause myocardial ischemia and confer worse long-term prognosis.[3–7]

Several intracoronary physiology indices have been validated against pathological evidence of structural microvascular remodeling. Diastolic microvascular conductance (DMVC), reflected by the instantaneous hyperemic diastolic velocity pressure slope, was first proposed by Mancini et al. as an index to determine epicardial stenosis severity that was independent from hemodynamics, unlike CFR.[8] This concept was later applied to the coronary microcirculation by our group.[9] DMVC is calculated as part of an intracoronary pressure-flow analysis using distal pressures and flow velocity during mid and end-diastole. It was first validated in post-heart transplant patients, where it showed good correlation with arteriolar obliteration and capillary rarefaction in the context of allograft vasculopathy.[10]

Previous studies have shown that this index reflects better the hemodynamic consequences of arteriolar obliteration and capillary rarefaction than coronary flow reserve (CFR) or whole-cycle microcirculatory resistance.[9] The backward expansion wave (BEW), an index derived from wave intensity analysis (WIA), constitutes a surrogate for increase in microvascular capacitance over early diastole, which is also largely determined and negatively correlated with capillary density.[10–13]

As the fundamental pathological mechanisms of age-induced CMD remain largely unknown, in this study, we sought to comprehensively assess the pathophysiology underlying age-related microcirculatory dysfunction using WIA, DMVC and invasive indices of coronary physiology.

2 | METHODS

2.1 | Study population

This study is an analysis of the Iberian-Dutch-English (IDEAL) registry, which is an international, multicenter registry that contains prospective collected data from combined pressure and Doppler flow velocity measurements from patients with stable angina who were treated at three participating centers: Amsterdam Medical Center in the Netherlands, Imperial College in the United Kingdom and Hospital Clínico San Carlos in Spain.[14] Patients were included if they had symptoms of CAD and were eligible to undergo invasive coronary angiography with physiological interrogation. The methodology for acquiring physiological data was standardized across all participating centers. Patients were excluded if they had: (1) recent acute coronary syndrome (<6 weeks): (2) left ventricle systolic dysfunction; (3) significant left main CAD; (4) patent coronary artery bypass grafts; (5) significant diffuse CAD; (6) contra-indication for contrast or adenosine administration. Our study focused on patients without epicardial coronary stenosis on angiography and without conditions that are associated with both structural and functional derangements of the microcirculation that might impede a clear outlining of the relationship between age and structural microvascular remodeling such as left ventricular hypertrophy, aortic stenosis, heart failure and diabetes mellitus.[15,16] Additional details regarding the inclusion and exclusion criteria can be found in the supplementary appendix of the original study and Figure S1.[14]

2.2 | Coronary angiography intracoronary physiology

Coronary angiography and pressure-flow assessments were conducted according to standard protocols. Following the administration of intracoronary nitrates (100 mcg or 200 mcg), angiographic views were

obtained and quantitative coronary angiography was performed using validated software (CAAS II, Pie Medical Imaging). Physiology measurements were taken after coronary angiography. A ComboWire XT guidewire (Philips Volcano) that combines pressure and Doppler flow velocity measurements was advanced into the distal target coronary artery after pressure equalization at the coronary ostium. Patients underwent wire-based recordings of mean aortic pressure (Pa), mean distal intracoronary pressure (Pd) and Doppler-flow velocities (resting and hyperemic flow by average peak velocity in mL/min). Stable hyperemia was achieved using intravenous adenosine perfusion at 140 mcg/Kg/min for a minimum of 2 min, or by intracoronary bolus injection. A pressure drift check was performed and considered acceptable if final Pd/Pa at the catheter tip was ≤0.02. All electrocardiogram, pressure and flow velocity data were extracted from the device console (ComboMap, Volcano Corporation).

Several physiological indices were derived from the collected data. CFR was calculated as the ratio of the hyperemic averaged peak flow velocity (APV) to that during rest in mL/min.[17] HMR was calculated as the ratio between hyperemic Pd to hyperemic APV and expressed as mmHg cm^{-1} s^{-1}.[18] DMVC was defined as the slope (beta coefficient) of the relationship between hyperemic Pd and AVP flow in mid to end diastole and was represented by a regression line ($y = a + bx$), expressed in cm s^{-1} $mmHg^{-1}$.[9]

Wave Intensity is a measure of energy per area carried by arterial waves that travel through the cardiovascular system and is obtained by analyzing the phasic changes in local pressure and flow velocity.[10] A dedicated software described elsewhere was used for calculations.[12] The recordings of pressure and Doppler flow velocity were filtered using the Savitzky-Golay method[12,19] and analyzed for 30 cardiac cycles. The changes in pressure were separated into wave components that originated from the proximal vessel or the coronary microcirculation. The speed of the wave was estimated using the sum of squares method, assuming a blood density of 1050 Kg m^{-3}.[20]

We assessed a total of six intracoronary waves, including three proximal (aortic or forward) waves and three distal (myocardial or backward) originating waves (Figure 1). The first forward wave occurring during ventricular systole, after the opening of the aortic valve, was defined as the forward compression wave (FCW). The slowing of ventricular contraction during end-systole created the forward expansion wave, which had a suction effect applied from the proximal coronary tree. The FCW has an identifiable second peak that originates when the aortic valve closes and creates a small, but measurable compressing wave with an accelerating effect on coronary blood flow. The early backward compression wave (BCW) is created by ventricular isovolumetric contraction, while a late BCW is created during early systole as the sum of sustained compression of the microcirculation and as a reflection of the FCW from distal reflecting sites in the coronary three. Finally, the BEW, the most clinically relevant wave, originates at the end of the systole

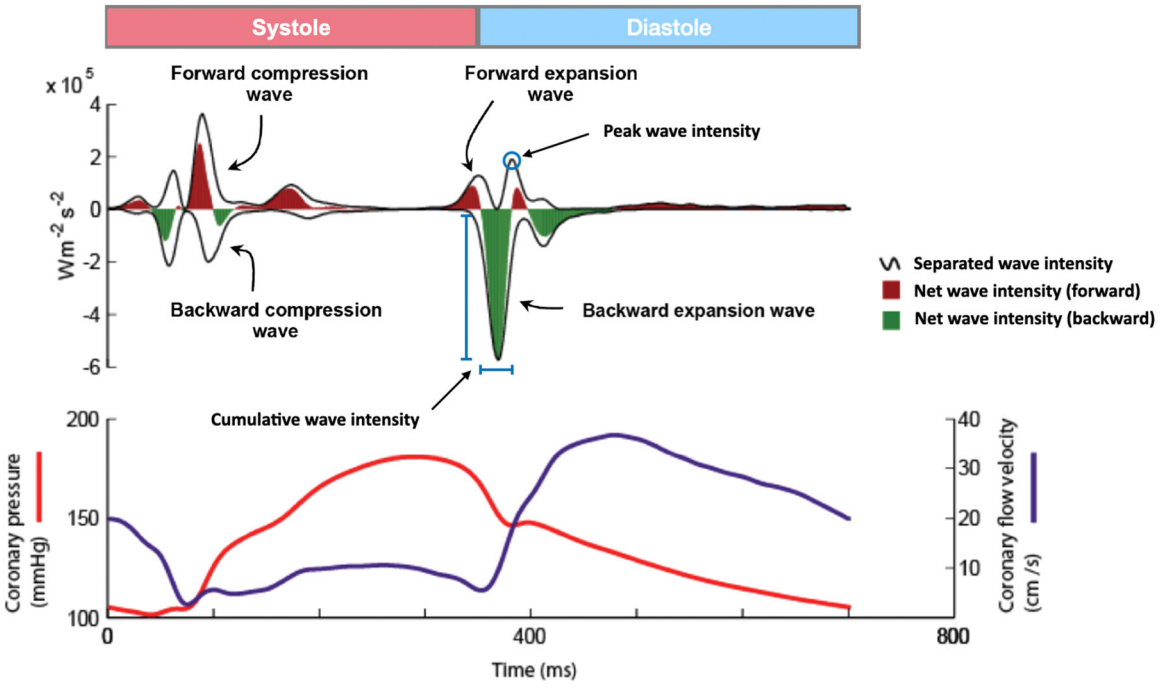


FIGURE 1 Wave intensity profile in a coronary artery. Upper panel: waves originating from both the proximal (positive values—red) and distal circulation (negative values—green). Six waves are present but the BEW is the main determinant of coronary flow. Lower panel: wave intensity can explain the complex pressure-flow relationship in the coronary artery throughout the cardiac cycle, showing reductions in pressure in increments in coronary flow during diastole due to the decompression of the microcirculation (From Sen S, Petraco R, Mayet J and Davies J. Wave intensity analysis in the human coronary circulation in health and disease. Current Cardiol Rev. 2014; 10:17-23; with permission). [Color figure can be viewed at wileyonlinelibrary.com]

and during isovolumetric relaxation and is created by the re-expansion of the compressed intra-myocardial arteries with a sudden drop in resistance in the coronary microcirculation. We calculated the energy ($W \times m^{-2}/s^2 \times 10^5$) from cumulative (area under the curve) BEW (C-BEW) and compared them between groups. To simplify interpretation, BEW values were presented as positive numbers. We also calculated the BEW energy fraction (BEW-EF), defined as the cumulative wave intensity divided by its integral over the cardiac period, which represents the fraction of the BEW energy relative to the net wave energy generated throughout the cardiac cycle.

2.3 | Age and physiology indices relationship

To assess the impact of age on intracoronary physiology indices, we stratified our patient cohort into three groups based on age tertiles. We then evaluated correlations between these indices and age. Additionally, we calculated the C-BEW and compared it between the different age groups. Finally, we calculated the prevalence of CMD, defined by reduced CFR (CFR < 2.5) in the absence of epicardial lesions, and calculated the prevalence of low BEW and low DMVC (as determined by values below the 25th percentile) in each group. As a supplementary analysis, we also studied the relationship between BEW and structural CMD endotype as defined according to Rahman et al.,[3] by using CFR and HMR groups, with functional CMD defined as CFR < 2.5 and HMR < 2.5 mmHg cm^{-1} s^{-1} and structural CMD defined as CFR < 2.5 and HMR ≥ 2.5 mmHg cm^{-1} s^{-1}.

2.4 | Statistical analysis

Continuous variables that followed a normal distribution were reported as mean and standard deviation, while categorical variables were presented as absolute counts an percentages. We calculated 95% confidence intervals (CIs) for means of continuous variables and percentages of categorical variables were calculated using *t*-tests and Clopper-Pearson (Exact) approaches, respectively. To adjust for potential confounders, including interrogated target vessel with LAD artery lesion, presence of coronary artery disease risk factors and number of interrogated vessels per patient, we calculated adjusted correlations between coronary physiology indices and age. For variables that followed a normal distribution, we used *t*-tests, one-way analysis of variance test and Tukey's post hoc analysis were used to compare means. Variable with non-normal distribution were compared using Mann–Whitney *U*-tests. The Chi-square test was used to compare prevalences between different groups. We applied linear regression analysis to predict BEW intensity based on a broad range of admission parameters. To correct for possible unknown effects between more than one vessel interrogated per patient, we used generalized estimation equations (GEEs). All statistical analyzes were performed using commercially available software (SPSS 28.0, IBM). Statistical significance was defined as a bilateral $p < 0.05$.

3 | RESULTS

3.1 | Study population

Table 1 shows the clinical and angiographic characteristics of the study population. We stratified the total population (99 patients and 165 vessels) into tertiles based on age resulting in the following groups: 1st tertile: 37–53 years; 2nd tertile: 54–66 years; and 3rd tertile: 67–77 years. We observed a higher proportion of male gender and active smoking status in the younger age groups ($p = 0.029$ and $p = 0.008$, respectively), while the prevalence of hypertension was higher in the older age groups ($p = 0.010$).

3.2 | Hemodynamic parameters

Table 2 shows that in the interrogated vessel population ($n = 165$) there were no significant differences between the groups in terms of the interrogated coronary artery or the number of interrogated arteries per patient. We found a positive linear correlation between C-BEW and BEW-EF ($r^2 = 0.35$, 95% CI: 0.11–0.48, $p = 0.012$). C-BEW also correlated positively with DMVC ($r^2 = 0.21$, 95% CI: 0.07–0.37, $p = 0.040$) and negatively with HMR ($r^2 = -0.23$, 95% CI: −0.40 to −0.10, $p = 0.023$). These findings reinforce the intrinsic direct relationship between capillary density, microcirculatory conductance and resistance.

3.3 | Effect of age on pressure and flow based functional indices

A significant reduction of hyperaemic flow velocity was noted in older patients alongside with a trend to increased basal flow velocity in the same tertiles ($p = 0.019$ and $p = 0.118$, respectively—Table 2). Age correlated negatively with C-BEW intensity ($r^2 = -0.13$, 95% CI: −0.27 to −0.05, $p = 0.037$—Figure 2A), DMVC ($r^2 = -0.35$, 95% CI: −0.48 to −0.17, $p < 0.001$—Figure 2B) and CFR ($r^2 = -0.16$, 95% CI: −0.35 to −0.07, $p = 0.033$—Figure 2C) and positively with HMR ($r^2 = 0.31$, 95% CI: 0.19–0.41, $p < 0.001$—Figure 2D). Furthermore, older patients had a significant higher prevalence of increased microvascular dysfunction as defined by HMR ≥ 2.5 (11.8% vs. 24.4% vs. 39.3% for 1st, 2nd, and 3rd age tertiles, respectively, $p = 0.019$).

3.4 | Effect of age on BEW intensity

C-BEW intensity was compared between the age tertiles, and lower intensity values were observed in the older age groups ($p = 0.044$). The same trend was observed regarding BEW-EF, although statistical significance in this case was not reached ($p = 0.085$)—Table 3. After adjusting for demographic (gender, hypertension, smoking status, body mass index, dyslipidemia) and angiography (target vessel and number of interrogated vessels per patient) related factors, we found

TABLE 1 General characteristics of the study population (per patient analysis).

	Overall (*n* = 99)	[37–53] years (*n* = 33)	[54–66] years (*n* = 29)	[67–77] years (*n* = 37)	*p*-value
Baseline demographics					
Age (years)	57.7 ± 8.9	48.2 ± 3.8	56.7 ± 2.3	66.9 ± 5.0	–
Male (%)	60.6	78.8	48.3	54.1	0.029
BMI (Kg/m^2)	26.9 ± 3.6	26.3 ± 3.8	28.7 ± 3.9	26.3 ± 3.0	0.064
Medical history					
Prior MI (%)	4.0	9.1	3.4	0.0	0.153
Hypertension (%)	43.4	27.3	37.9	62.2	0.010
Dyslipidemia (%)	51.5	51.5	62.1	43.2	0.316
Smoker (%)	36.4	57.6	27.6	24.3	0.008
Current medication					
Beta-blocker (%)	50.5	51.5	51.7	48.6	0.960
Statin (%)	59.6	63.6	65.5	51.4	0.429
ACE inhibitor (%)	12.1	6.1	6.9	12.1	0.081
Calcium chanel blocker (%)	16.2	12.1	24.1	13.5	0.377
Acetyl salicylic acid (%)	69.7	69.7	65.5	73.0	0.807

Abbreviations: ACE, angiotensin converting enzyme; BMI, body mass index; MI, myocardial infarction.

TABLE 2 Invasive physiological assessment (per vessel analysis).

	Population (*n* = 99, vessels = 165)	[37–53] years (*n* = 33, vessels = 51)	[54–66] years (*n* = 29, vessels = 66)	[67–77] years (*n* = 37, vessels = 48)	*p*-value
Interrogated artery					
Right coronary (%)	24.8	19.6	24.2	25.0	0.282
Left anterior descending (%)	40.0	47.1	39.4	39.6	0.574
Left circumflex (%)	35.2	33.3	36.4	35.4	0.947
Vessels per patient	1 [1,2]	1 [1,2]	2 [1,2]	1 [1,2]	0.352
Physiological and angiographic indices					
Basal Pd/Pa	0.98 ± 0.03	0.98 ± 0.02	0.98 ± 0.02	0.99 ± 0.03	0.069
Baseline flow velocity (cm s^{-1})	17.2 ± 6.15	16.6 ± 4.4	17.0 ± 6.3	18.5 ± 6.6	0.118
Hyperemic flow velocity (cm s^{-1})	44.6 ± 15.7	46.7 ± 14.4	45.1 ± 12.4	38.4 ± 11.5	0.019
CFR	2.71 ± 0.79	2.77 ± 0.80	2.70 ± 0.81	2.51 ± 0.73	0.048
HMR	2.21 ± 0.80	1.92 ± 0.49	2.60 ± 0.74	2.73 ± 0.81	0.002
BMR	6.24 ± 2.33	5.62 ± 1.83	6.41 ± 2.65	6.89 ± 1.88	0.040
DMVC					
IHSVPS	1.57 ± 0.66	1.90 ± 0.71	1.44 ± 0.56	1.37 + 0.67	<0.001

Abbreviations: BEW, backward expansion wave; BMR, basal microvascular resistance; CFR, coronary flow reserve; FFR, fractional flow reserve; HMR, hyperemic microvascular resistance; iFR, instantaneous wave-free ratio; IHDVPS, instantaneous hyperemic diastolic velocity pressure slope; Pa, aortic pressure; Pd, distal pressure.

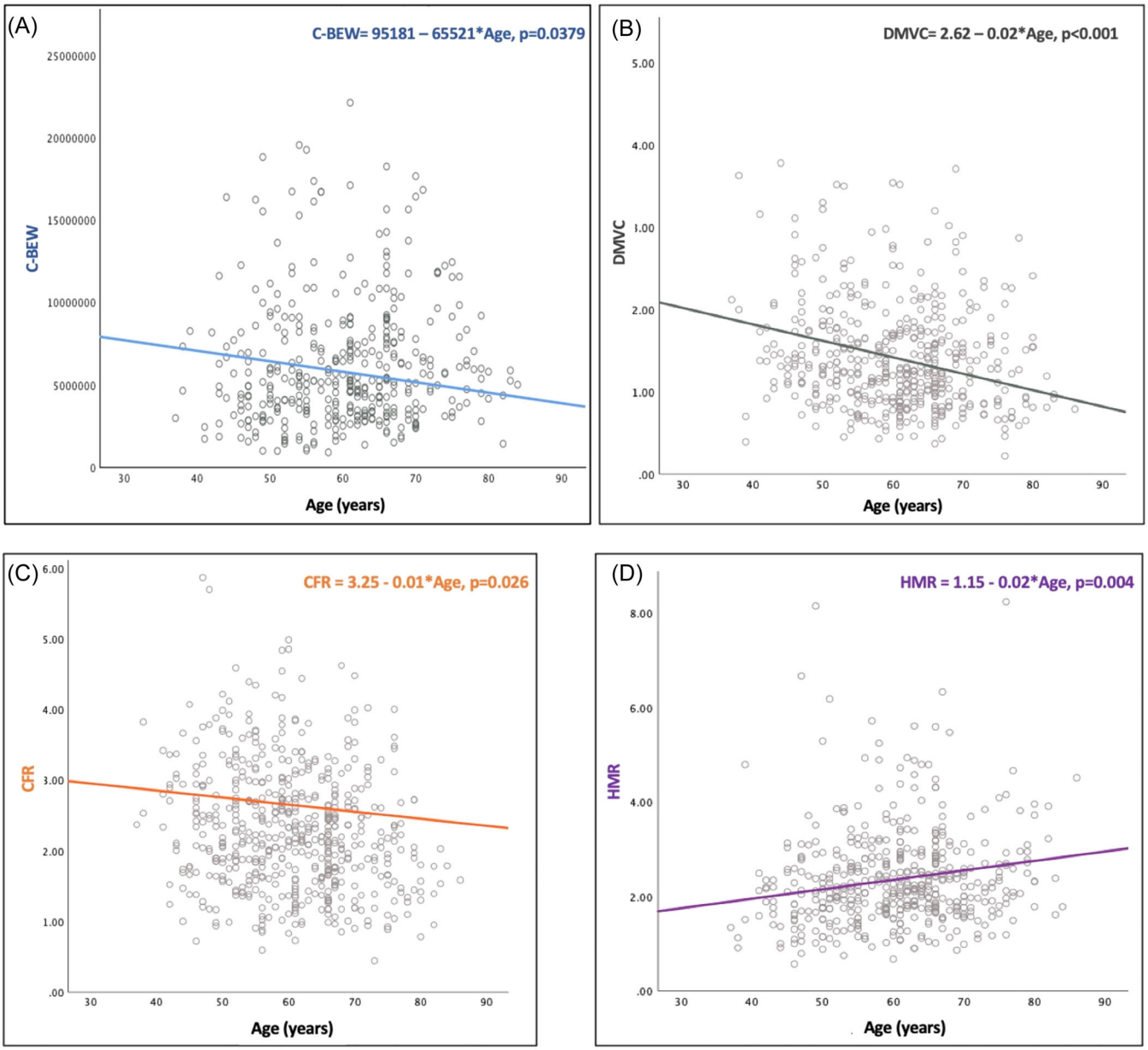


FIGURE 2 Age correlation with microcirculatory physiology indices (per vessel analysis). (A) Age correlation with C-BEW: (B) age correlation with DMVC; (C) age correlation with CFR; (D) age correlation with HMR. C-BEW, cumulative backward expansion wave; CFR, coronary flow reserve; DMVC, diastolic microvascular conductance; HMR, hyperemic microvascular resistance. [Color figure can be viewed at wileyonlinelibrary.com]

that age was a significant and independent predictor of lower cumulative BEW intensity ($p = 0.030$)—Table 4.

3.5 | Age and CMD mechanisms

Figure 3A illustrates the underlying mechanisms of age-related CMD. In this population, the prevalence of CMD, as determined by CFR < 2.5, was found in 52.5% of patients ($n = 52$). We also found a higher proportion of patients with reduced CFR in older patients (48.5% vs. 51.0% vs. 64.7%, for the 1st, 2nd, and 3rd age tertiles, respectively, $p = 0.039$) and the proportion of patients with CMD whose C-BEW or DMVC values are below the 25th percentile also increased significantly with age (25.0% vs. 52.0% vs. 72.7%, for the 1st, 2nd, and 3rd age tertiles, respectively, $p = 0.010$). This suggests that CMD in the elderly is determined predominantly by structural derangement of the coronary microcirculation in opposition to younger patients. In contrast, in the absence of CMD (47.5%, $n = 47$), no differences were found in the proportion of patient with low C-BEW or DMVC values between age groups (23.5% vs. 29.4% vs. 33.3%, for the 1st, 2nd, and 3rd age tertiles, respectively, $p = 0.961$—Figure 3B).

TABLE 3 Wave intensity analysis for each wave component (per vessel analysis).

	Population (n = 99, vessels = 165)	[37–53] years (n = 33, vessels = 51)	[54–66] years (n = 29, vessels = 66)	[67–77] years (n = 37, vessels = 48)	p-value
Wave intensity analysis					
Cumulative FCW ($\times 10^6$ W m^{-2} s^{-1})	4.5 [3.1–10.1]	6.7 [3.6–10.5]	4.7 [3.0–7.6]	3.9 [2.3–8.3]	0.995
Cumulative FCW 2nd peak ($\times 10^6$ W m^{-2} s^{-1})	2.3 [1.0–4.9]	1.3 [0.7–4.5]	1.3 [0.8–3.1]	0.7 [0.3–1.8]	0.648
Cumulative FEW ($\times 10^6$ W m^{-2} s^{-1})	2.4 [0.8–5.7]	1.5 [0.5–6.5]	2.1 [0.7–5.9]	2.8 [1.9–5.8]	0.778
Cumulative early BCW ($\times 10^6$ W m^{-2} s^{-1})	0.5 [0.2–2.1]	1.1 [0.2–2.4]	1.6 [0.5–2.7]	0.9 [0.5–3.4]	0.622
Cumulative late BCW ($\times 10^6$ W m^{-2} s^{-1})	2.4 [1.4–5.6]	1.7 [0.9–2.9]	2.3 [1.4–4.6]	2.0 [0.7–4.4]	0.534
Cumulative BEW ($\times 10^6$ W m^{-2} s^{-1})	5.1 [3.4–7.6]	6.3 [2.9–8.4]	4.9 [2.9–6.8]	4.4 [3.4–6.3]	0.044
BEW energy fraction (%)	32.7 ± 6.8	35.9 ± 9.7	31.3 ± 11.2	29.2 ± 9.9	0.085

Abbreviations: BCW, backward compression wave; BEW, backward expansion wave; FCW, forward compression wave; FEW, forward compression wave.

TABLE 4 Generalized estimating equations linear model for BEW intensity and energy fraction prediction.

	Cumulative BEW ($\times 10^5$ W m^{-2} s^{-1})			BEW energy fraction (%)		
	B ($\times 10^6$)	95% CI ($\times 10^6$)	p-value	B	95% CI	p-value
Intercept	107.1	–	–	19.2	–	–
Age (years)	−0.41	−0.71 to −0.20	0.030	−1.1	−2.8 to 0.1	0.117
Male gender	0.95	−19.5 to 21.4	0.927	2.1	−3.7 to 5.4	0.915
Hypertension	12.9	9.8 to 16.2	<0.001	4.5	−0.7 to 7.4	0.216
Dyslipidaemia	8.2	−5.5 to 7.1	0.800	1.7	−2.2 to 3.9	0.405
Smoker	8.9	−13.5 to 31.4	0.433	3.6	−1.2 to 6.9	0.377
BMI	−0.12	−0.81 to 0.6	0.727	0.2	−0.5 to 1.6	0.518
Betablocker	8.8	3.4 to 14.3	0.002	7.4	4.2 to 16.0	0.003
ACE inhibitor	20.6	−10.8 to 51.3	0.187	5.3	−5.5 to 12.9	0.399
Calcium chanel blocker	−6.7	−23.7 to 10.4	0.443	9.7	−10.1 to 21.7	0.894
Statin	6.9	−10.1 to 24.6	0.445	1.2	−7.1 to 5.6	0.603
Left coronary artery	11.9	5.1 to 18.7	<0.001	6.7	1.9 to 11.3	<0.001

Abbreviations: ACE, angiotensin conversion enzyme; BMI, body mass index.

3.6 | Age and CMD endotypes

Recently, a dichotomous classification of CMD as having a structural or functional cause has been proposed by Rahman et al.[3] based on combined measurements of Doppler-based CFR and whole-cycle microcirculatory resistance (HMR). These authors propose, based on CFR and HMR values, the existence of either functional CMD (CFR < 2.5 and HMR < 2.5 mmHg cm^{-1} s^{-1}) and structural (CFR < 2.5 and HMR ≥ 2.5 mmHg cm^{-1} s^{-1}) CMD endotypes. We applied the same dichotomous classification to our population and found that patients with structural CMD were older (64.6 ± 7.1 vs. 56.7 ± 8.4 years, p < 0.001) and that its increased progressively across age tertiles (3.0% vs. 16.3% vs. 41.2% for the 1st, 2nd and 3rd age tertiles, respectively, p = 0.002). At a difference, patients with functional CMD were younger (53.4 ± 8.7 years vs. 59.4 ± 8.2 years, p = 0.049) and its prevalence decreased across age tertiles (45.5% vs. 34.7% vs. 23.5% for the 1st, 2nd and 3rd age tertiles, respectively, p = 0.029)—Figure 4. In addition, we also constructed a GEE binary logistic model to identify predictors of structural CMD and found an independent association with older age (p < 0.001), lower C-BEW intensity (p < 0.001), lower BEW-EF (p = 0.009) and lower DMVC (p = 0.041)—Table 5.

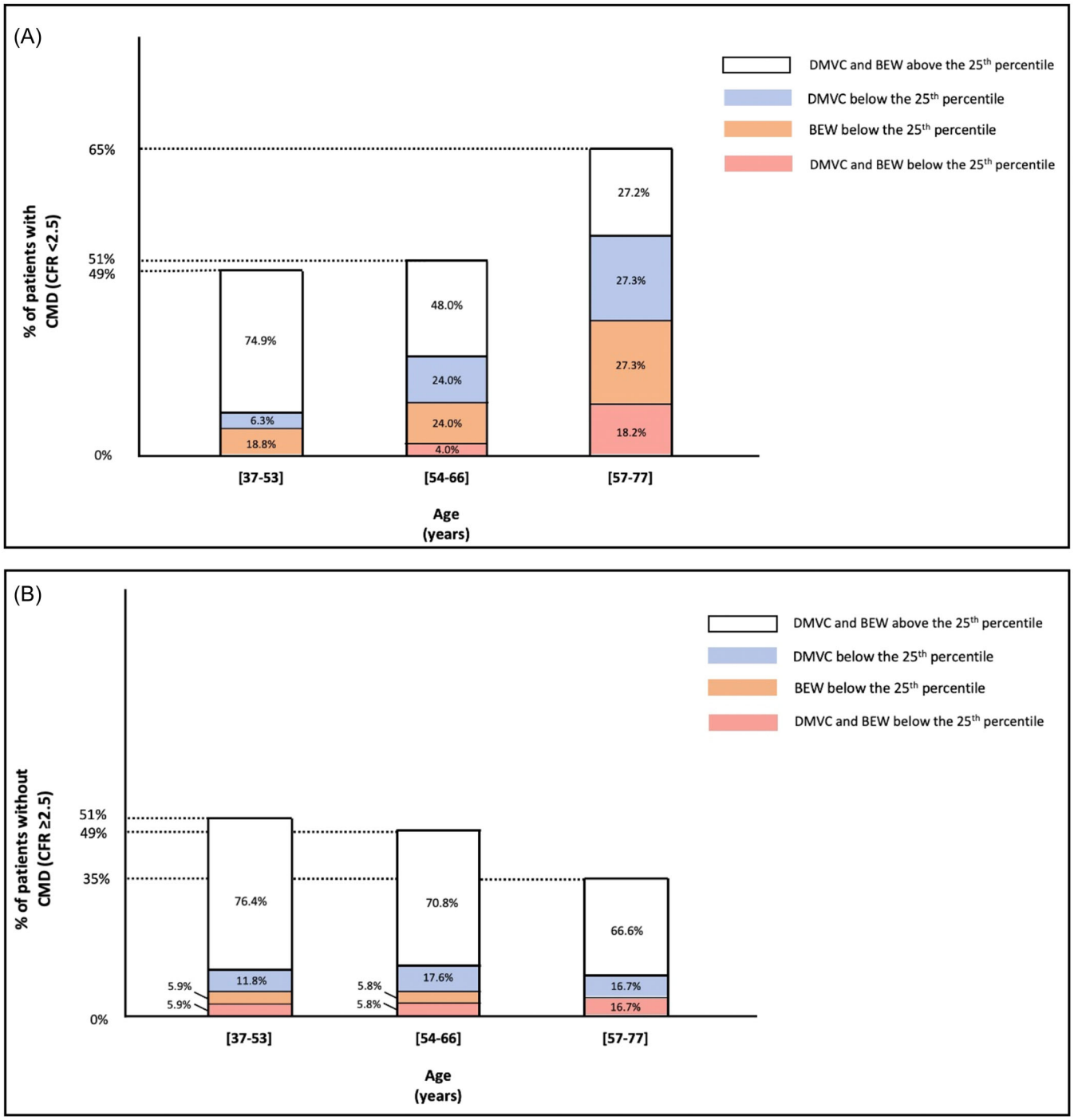


FIGURE 3 Relationship between low BEW and low DMVC in age-related CMD (per vessel analysis). (A) The prevalence of CMD as determined by CFR < 2.5 increases with age. However, unlike younger patients, CMD in the elderly is associated with higher prevalence of structural remodeling, as showed by higher proportion of patients with BEW and DMVC values below the 25th percentile. (B) In patients with normal CFR, the proportion of patients with BEW and DMVC values below the 25th percentile does not vary significantly. C-BEW, cumulative backward expansion wave; CMD, coronary microcirculatory dysfunction; DMVC, diastolic microvascular conductance. [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

In our study we hypothesized that structural remodeling is the main pathophysiological mechanism for the development of age-related CMD. To test our hypothesis, we used WIA and DMVC as diagnostic tools in a cohort of non-diabetic patients with chronic coronary syndromes without angiographic epicardial lesions. We examined age-related changes in C-BEW intensity and DMVC, their influence on invasive indices of coronary physiology and in the prevalence of structural CMD.

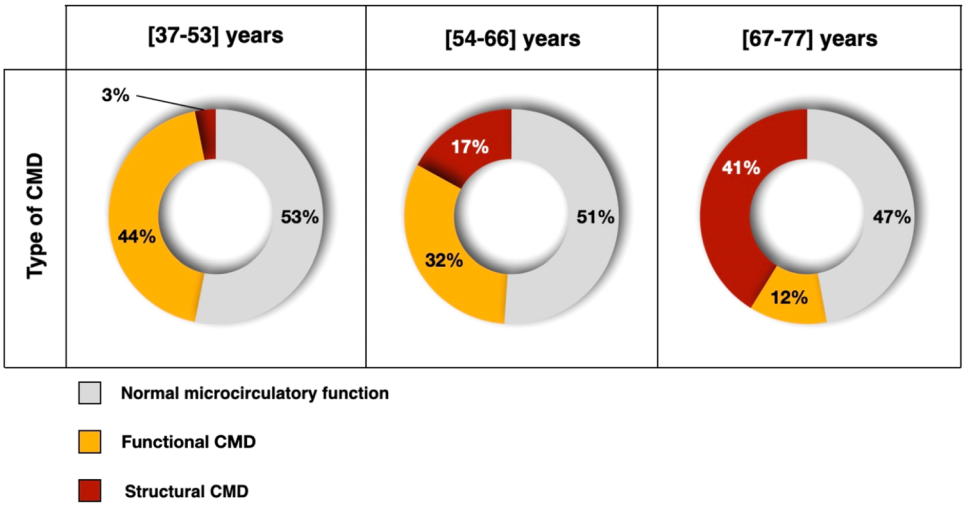


FIGURE 4 Prevalence and type of CMD across the age tertiles as classified by Rahman et al.[3] (per patient analysis). Functional CMD is more prevalent in younger patients and decreases along the age spectrum, while structural CMD has the opposite distribution. CMD, coronary microcirculatory dysfunction. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 5 Generalized estimating equations binary logistic regression model for CMD endotype prediction according to Rahman et al.[3]

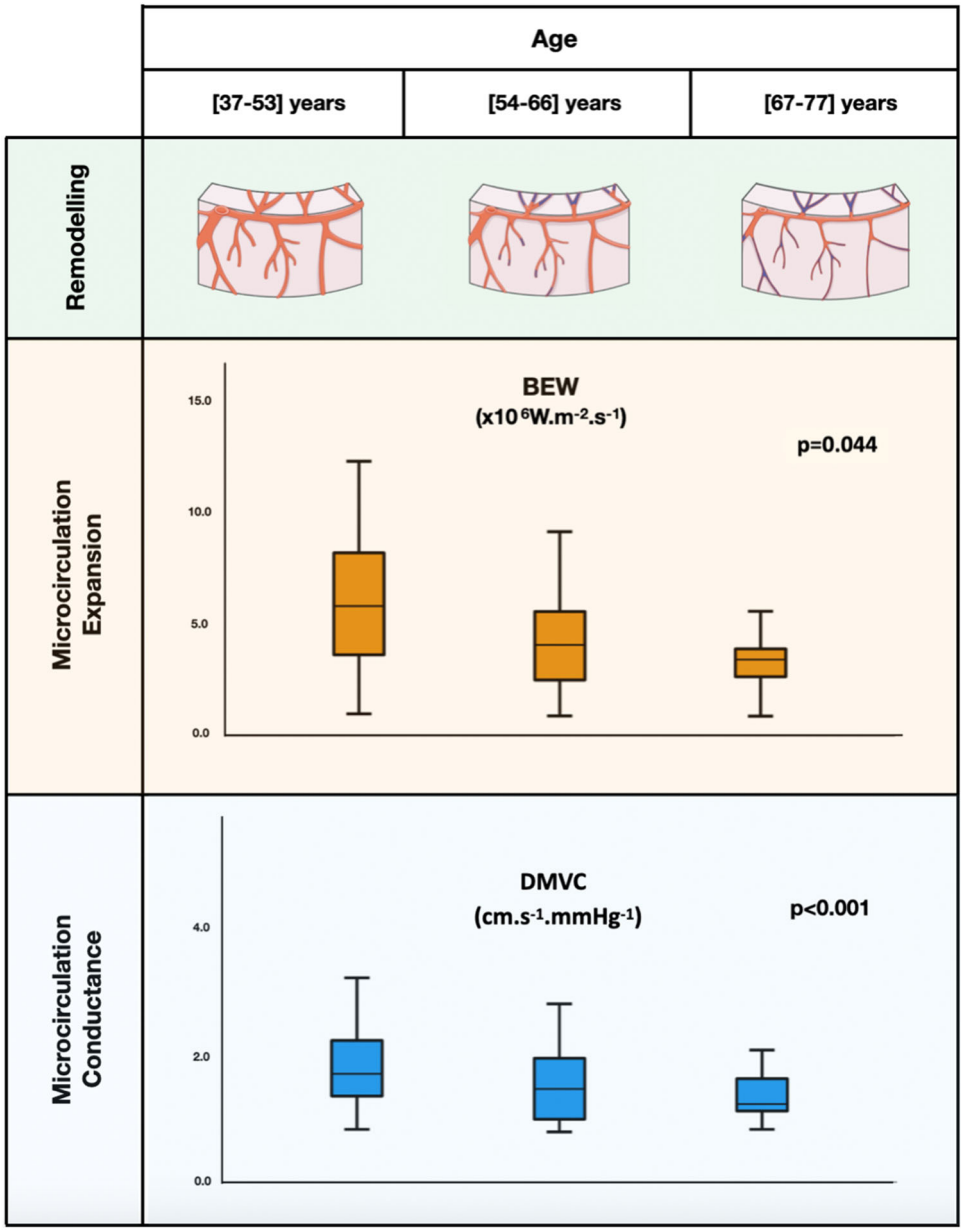
	Functional (CFR < 2.5 + HMR < 2.5)			Structural (CFR < 2.5 + HMR ≥ 2.5)		
CMD endotype	**OR**	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
Older Age (3rd strata)	0.98	0.84–1.03	0.875	1.77	1.33–2.20	<0.001
Male sex	0.44	0.12–1.73	0.245	2.13	0.52–2.86	0.070
Hypertension	0.54	0.12–2.41	0.425	1.07	1.02–1.24	0.002
Dyslipidaemia	1.12	0.32–3.87	0.863	0.91	0.74–1.24	0.158
BMI ($Kg\,m^{-2}$)	0.96	0.81–1.15	0.664	0.89	0.55–1.45	0.128
Smoking	3.98	1.24–15.9	0.046	1.15	0.05–26.5	0.721
MVC ($cm\,s^{-1}\,mmHg^{-1}$)	3.04	0.87–10.9	0.080	0.77	0.23–2.52	0.041
Cumulative BEW ($W\,m^{-2}\,s^{-1}$)	1.01	0.97–1.04	0.783	0.95	0.91–0.98	<0.001
BEW energy fraction (%)	0.99	0.95–1.03	0.901	0.81	0.77–0.92	0.009

Abbreviations: BEW, backward expansion wave; BMI, body mass index; CI, confidence interval; MVC, microcirculatory conductance; OR, odds ratio.

While there is growing awareness that myocardial ischemia in chronic coronary syndromes may result from obstructive and non-obstructive causes,[21,22] there is limited evidence on the effect of age on microcirculatory function, a knowledge gap that requires urgent attention due to the growing number of elderly people worldwide. Our findings support that older age is independently associated with significant reductions in C-BEW intensity and DMVC, supporting the existence of age-induced structural remodeling of the coronary microcirculation (Central Illustration 1).

The pathophysiology of CMD is complex and multifactorial, involving both functional and structural mechanisms.[4] The BEW (also known as backward decompression or "suction" wave), caused by the rapid re-expansion of the capillary bed during early-diastole after being compressed during systole, is the largest contributor to coronary blood flow.[9] Structural changes of the microcirculation, such as perivascular fibrosis, arteriolar thickening and capillary rarefaction can decrease BEW intensity, as previously shown in patients with hypertrophic cardiomyopathy, aortic stenosis, myocardial infarction, heart failure and cardiac allograft patients.[11,23–25] Our study demonstrates that ageing is also independently associated with this structural remodeling phenomena.

Previous research by our group has demonstrated that ageing is associated with a decrease in the microcirculatory vasodilatory response to adenosine administration. This leads to an increase in functional stenosis classification discrepancies between hyperaemic and non-hyperaemic indices, as reflected by an age-dependent increase in Fractional Flow Reserve (FFR) values.[1,26] Other researchers have also described the impact of other age-related modifications in the coronary microcirculation, which can further explain



CENTRAL ILLUSTRATION 1 Age-related microvascular remodeling and its impact on microvascular expansion and conductance. Upper panel: From left to right—Schematic representation of progressive microvascular structural remodeling and rarefaction associated with age. Middle panel: Boxplot graphic for cumulative BEW for each age strata (*p*-value obtained from linear regression GEE). Lower panel: Boxplot graphic for MVC for each age strata. C-BEW, cumulative backward expansion wave, DMVC, diastolic microvascular conductance, GEE, generalized estimation equation. [Color figure can be viewed at wileyonlinelibrary.com]

our findings[27–29] Nevertheless, our current study provides invasive physiology data that adds knowledge to the understanding of the pathophysiology of age-induced reduction hyperaemic blood flow, particularly in patients older than 60 years.[30]

Our study also revealed that the prevalence of structural CMD, as defined by CFR/HMR groups, increases with age, while the prevalence of functional CMD is higher in younger patients. This finding adds evidence to support the concept that functional CMD could represent an early stage of the disease, as characterized by endothelial dysfunction, microvascular spasm, and transient microcirculatory impairment. With sustained chronic inflammation, microvascular injury and maladaptation, it can evolve to a structural CMD endotype, hallmarked by perivascular fibrosis, capillary rarefaction and irreversible tissue damage, and raising awareness for the importance of early detection and management to prevent disease progression.[31] This hypothesis is further supported by a recent published study by Jansen et al. showing the existence of an age-dependent physiological increase in minimal microvascular resistance and microvascular function represented by decreased maximal coronary blood flow microvascular resistance reserve that was present in patients both with and without CMD.[32]

Finally, our study also suggests that age-related reductions in BEW intensity and DMVC could be used as surrogates to predict the development of structural CMD in ageing populations.

5 | STRENGTHS AND LIMITATIONS OF THE STUDY

We believe that our study has several methodological strengths, including (1) the use of combined intracoronary Doppler and pressure, a powerful combo that allows analysis of specific segments of the cardiac cycle such as DMVC and WIA; (2) using as a standard of reference physiology indices that have been validated against histological changes in microcirculatory structure in endomyocardial biopsies; (3) restricting the analyzes to patients without epicardial stenosis which might modulate the status of the subtended microcirculation[33]; and (4) excluding patients with diabetes mellitus due to its effect on microvascular structure.[34] As limitations we must highlight that this is a subgroup analysis of the IDEAL registry,[13] and that therefore, we cannot rule out the effect of selection bias and confounding variables. Of note, patients in the IDEAL registry did not undergo coronary acetylcholine testing, and therefore, the status of endothelium-dependent pathway remains unknown. Furthermore, there are limitations of using BEW and DMVC. Quality of flow velocity tracings is crucial for calculating conductance and WIA. However, perfect Doppler signals are difficult to obtain as previous studies have shown that approximately 25% of measurements are not possible due to suboptimal flow tracings.[35] On the other hand, BEW can be reduced in other conditions that compromise diastolic myocardial perfusion such as left ventricle hypertrophy, aortic stenosis, heart failure and diabetes mellitus.[12] To account for this, we purposefully excluded these patients from our analysis.

6 | CONCLUSIONS

Ageing is associated with structural remodeling of the coronary microcirculation manifested by reductions in BEW intensity and DMVC that are associated with higher prevalence of structural CMD. These findings contribute to explain the lower hyperemic flow found in older populations and the observed age-related differences between hyperaemic and non-hyperaemic indices of functional stenosis classification.

7 | IMPACT ON DAILY PRACTICE

Ageing is independently associated with structural remodeling of the coronary microcirculation. This phenomena is reflected by decreased hyperemic flow response to pharmacological hyperemia and can explain the observed age-related differences between hyperemic and non-hyperemic indices of functional stenosis classification.

CONFLICT OF INTEREST STATEMENT

Dr. Lombardi has served as speaker for Phillips. Dr. Travieso has received unconditional educational grants from Philips. Dr. Nijjer has served as speaker and/or advisory board member for Philips. Dr. Piek has served as speaker and/or advisory board member for Philips. Dr. van de Hoef is a consultant for Philips. Dr. Echarravía-Pinto has received speaker fees from Boston Scientific. Dr. Mejía-Renteria served as speaker at educational events organized by Abbott, Boston Scientific and Philips Healthcare. Dr. Davies holds IP pertaining to iFR technology and is also a consultant and recipient of research funding from Philips Volcano. Dr. Escaned is supported by the Intensification of Research Activity Project INT22/00088 from the Spanish Instituto de Salud Carlos III and has served as speaker and/or advisory board member for Abbott, Boston Scientific and Philips. Dr. Faria, Dr. van der Hoeven, Dr. Heemelaar, Dr. de Waard, Dr. Sen, Dr, van de Hoef, Dr. Petraco and Dr. Niels van Royen have nothing to declare.

DATA AVAILABILITY STATEMENT

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

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REFERENCES

1. 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;17:757-764.
2. Mejia-Renteria H, Faria D, Lee JM, et al Association between patient age, microcirculation, and coronary stenosis assessment with fractional flow reserve and instantaneous wave-free ratio. *Catheter Cardiovasc Interv*. 2022;99(4):1104-1114. doi:10.1002/ccd.30092
3. Rahman H, Ryan M, Lumley M, et al. Coronary microvascular dysfunction is associated with myocardial ischemia and abnormal coronary perfusion during exercise. *Circulation*. 2019;140:1805-1816.
4. Mejía-Rentería H, van der Hoeven N, van de Hoef TP, et al. Targeting the dominant mechanism of coronary microvascular dysfunction with intracoronary physiology tests. *Int J Cardiovasc Imaging*. 2017;33:1041-1059.
5. Mohammed SF, Hussain S, Mirzoyev SA, Edwards WD, Maleszewski JJ, Redfield MM. Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. *Circulation*. 2015;131:550-559.
6. Bajaj NS, Singh A, Zhou W, et al. Coronary microvascular dysfunction, left ventricular remodeling, and clinical outcomes in patients with chronic kidney impairment. *Circulation*. 2020;141:21-33.
7. Broyd CJ, Echavarria-Pinto M, Cerrato E, Escaned J. Evaluation of microvascular disease and clinical outcomes. *Interventional Cardiology Clinics*. 2015;4:443-457.
8. Mancini GB, McGillem MJ, DeBoe SF, Gallagher KP. The diastolic hyperemic flow versus pressure relation. A new index of coronary stenosis severity and flow reserve. *Circulation*. 1989;80(4):941-950. doi:10.1161/01.cir.80.4.941

9. van der Hoeven NW, de Waard GA, Quirós A, et al. Comprehensive physiological evaluation of epicardial and microvascular coronary domains using vascular conductance and zero flow pressure. *EuroIntervention*. 2019;14:e1593-e1600.
10. Broyd CJ, Hernández-Pérez F, Segovia J, et al. Identification of capillary rarefaction using intracoronary wave intensity analysis with resultant prognostic implications for cardiac allograft patients. *Eur Heart J*. 2018;39:1807-1814.
11. Escaned J, Flores A, García-Pavía P, et al. Assessment of microcirculatory remodeling with intracoronary flow velocity and pressure measurements: validation with endomyocardial sampling in cardiac allografts. *Circulation*. 2009;120:1561-1568.
12. Broyd CJ, Davies JE, Escaned JE, Hughes A, Parker K. Wave intensity analysis and its application to the coronary circulation. *Global Cardiology Science and Practice*. 2017;2017(1):e201705. doi:10.21542/gcsp.2017.5
13. Davies JE, Whinnett ZI, Francis DP, et al. Evidence of a dominant backward-propagating 'suction' wave responsible for diastolic coronary filling in humans, attenuated in left ventricular hypertrophy. *Circulation*. 2006;113:1768-1778.
14. Nijjer SS, de Waard GA, Sen S, et al. 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*. 2015;37:2069-2080.
15. Sezer M, Kocaaga M, Aslanger E, et al. Bimodal pattern of coronary microvascular involvement in diabetes mellitus. *J Am Heart Assoc*. 2016;5(11):e003995. doi:10.1161/JAHA.116.003995; Erratum in: J Am Heart Assoc. 2017 Jan 11;6(1):e002163. doi:10.1161/JAHA.116.002163
16. Leung M, Leung DY. Coronary microvascular function in patients with type 2 diabetes mellitus. *EuroIntervention*. 2016;11:1111-1117.
17. Fearon WF, Farouque HMO, Balsam LB, et al. Comparison of coronary thermodilution and Doppler velocity for assessing coronary flow reserve. *Circulation*. 2003;108:2198-2200.
18. de Waard GA, Nijjer SS, van Lavieren MA, et al. Invasive minimal microvascular resistance is a new index to assess microcirculatory function independent of obstructive coronary artery disease. *J Am Heart Assoc*. 2016;5:(12):e004482. doi:10.1161/JAHA.116.004482
19. Ladwiniec A, White PA, Nijjer SS, et al. Diastolic backward-traveling decompression (suction) wave correlates with simultaneously acquired indices of diastolic function and is reduced in left ventricular stunning. *Circ Cardiovasc Interv*. 2016;9(9):e003779. doi:10.1161/CIRCINTERVENTIONS.116.003779
20. Parker KH. An introduction to wave intensity analysis. *Med Biol Eng Comput*. 2009;47:175-188.
21. Koller A, Laughlin MH, Cenko E, et al. Functional and structural adaptations of the coronary macro- and microvasculature to regular aerobic exercise by activation of physiological, cellular, and molecular mechanisms: ESC working group on coronary pathophysiology and microcirculation position paper. *Cardiovasc Res*. 2022;118:357-371.
22. Kunadian V, Chieffo A, Camici PG, et al. An 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. *Eur Heart J*. 2020;41:3504-3520.
23. Rolandi MC, Wiegerinck EM, Casadonte L, et al. Transcatheter replacement of stenotic aortic valve normalizes cardiac-coronary interaction by restoration of systolic coronary flow dynamics as assessed by wave intensity analysis. *Circ Cardiovasc Interv*. 2016;9(4):e002356. doi:10.1161/CIRCINTERVENTIONS.114.002356
24. Camici P, Chiriatti G, Lorenzoni R, et al. Coronary vasodilation is impaired in both hypertrophied and nonhypertrophied myocardium of patients with hypertrophic cardiomyopathy: a study with nitrogen-13 ammonia and positron emission tomography. *J Am Coll Cardiol*. 1991;17:879-886.
25. Rolandi MC, Nolte F, van de Hoef TP, et al. Coronary wave intensity during the valsalva manoeuvre in humans reflects altered intramural vessel compression responsible for extravascular resistance. *J Physiol*. 2012;590:4623-4635.
26. 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(7):1195-1205. doi:10.1002/ccd.30445
27. Jenner TL, Mellick AS, Harrison GJ, Griffiths LR, Rose'Meyer RB. Age-related changes in cardiac adenosine receptor expression. *Mech Ageing Dev*. 2004;125:211-217.
28. Echavarría-Pinto M, Gonzalo N, Ibañez B, et al. Low coronary microcirculatory resistance associated with profound hypotension during intravenous adenosine infusion implications for the functional assessment of coronary stenoses. *Circ Cardiovasc Interv*. 2014;7:35-42.
29. Heusch G. Adenosine and maximum coronary vasodilation in humans: myth and misconceptions in the assessment of coronary reserve. *Basic Res Cardiol*. 2010;105:1-5.
30. 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.
31. Crea F, Camici PG, Bairey Merz CN. Coronary microvascular dysfunction: an update. *Eur Heart J*. 2014;35:1101-1111.
32. Jansen TPJ, Crooijmans C, Pijls N, et al. Effects of age on microvascular function in patients with normal coronary arteries. *EuroIntervention*. 2024;20(11):e690-e698.
33. Gould KL. Pressure-flow characteristics of coronary stenoses in unsedated dogs at rest and during coronary vasodilation. *Circ Res*. 1978;43:242-253.
34. Gallinoro E, Paolisso P, Candreva A, et al. Microvascular dysfunction in patients with type II diabetes mellitus: invasive assessment of absolute coronary blood flow and microvascular resistance reserve. *Front Cardiovasc Med*. 2021;8:765071. doi:10.3389/fcvm.2021.765071
35. Escaned J, Colmenarez H, Ferrer MC, et al. Diastolic dysfunction in diabetic patients assessed with Doppler echocardiography: relationship with coronary atherosclerotic burden and microcirculatory impairment. *Rev Esp Cardiol*. 2009;62:1395-1403.

SUPPORTING INFORMATION

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

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