ESC European Society of Cardiology

European Heart Journal Open (2025) **5**, oeaf050
https://doi.org/10.1093/ehjopen/oeaf050

**ORIGINAL ARTICLE**
*Coronary artery disease*

# The impact of high microvascular resistance on coronary wave energetics depends on coronary microvascular functionality

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*Received 14 February 2025; revised 20 April 2025; accepted 30 April 2025; online publish-ahead-of-print 5 May 2025*

Handling editor: Maciej Banach

**Aims**

The pathophysiological relevance of high hyperemic microvascular resistance (hMR) in stable coronary artery disease is controversial. Using wave intensity analysis (WIA, defined as the product of the time derivatives of the coronary pressure and velocity), we aim to compare the impact of high hMR on coronary wave energetics with respect to coronary microvascular dysfunction (CMD), defined as reduced coronary flow reserve (CFR < 2.5), in unobstructed arteries.

**Methods and results**

The study population ($n = 258$, mean age = 68 ± 10 years, 73% male) had a high cardiovascular risk profile including dyslipidemia (88%), hypertension (70%), smoking (55%) and diabetes (28%). The mean fractional flow reserve was 0.89 ± 0.05. Vessels ($n = 312$) were divided into four endotypes: no CMD-low hMR (CFR ≥ 2.5, hMR < 2.5 mmHg.s.cm$^{-1}$), Functional CMD (CFR < 2.5, hMR < 2.5 mmHg.s.cm$^{-1}$), Structural CMD (CFR < 2.5, hMR ≥ 2.5 mmHg.s.cm$^{-1}$), and no CMD-high hMR (CFR ≥ 2.5, hMR ≥ 2.5 mmHg.s.cm$^{-1}$). The no CMD-high hMR endotype had the lowest mean resting velocity (bAPV = 10 ± 3 cm.s$^{-1}$ $P < 0.001$), highest mean basal microvascular resistance (bMR = 9 ± 2 mmHg/cm.s$^{-1}$ $P < 0.001$) amongst all endotypes, yet, it had reference-level CFR, microvascular resistance reserve and resistive reserve ratio ($P > 0.05$ for all compared to no CMD-low hMR), unlike CMD endotypes ($P < 0.05$ compared to CMD endotypes). The no CMD–high hMR endotype exhibited the highest hyperemic increase in the accelerating wave energy proportion (AEP) (13% ± 13%, $P = 0.042$), indicating an intact autoregulatory response. Only in the CMD endotypes, high hMR was associated with reduced AEP ($r = -0.229$, $P < 0.001$), unlike no CMD endotypes ($P = 0.383$).

**Conclusion**

High hMR alone is not a definitive CMD marker. In line with the adaptive high hMR hypothesis, increased hMR does not necessarily limit augmentation of AEP, and is associated with robust autoregulatory capacity in vessels with preserved CFR. Cardiologists should be alert to a potential adaptive no CMD–high hMR endotype to avoid misdiagnosis.

**Registration**

NCT02328820.

**Keywords**

Microvascular Resistance • Coronary Microvascular Dysfunction • Wave Intensity Analysis

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# Introduction

Up to half of the patients with chest pain suggestive of myocardial ischemia undergoing invasive coronary angiography have no hemodynamically relevant epicardial disease, consistent with angina/ischemia in unobstructed coronary arteries (ANOCA/INOCA) diagnosis.[1,2] The leading pathology observed in these patients is myocardial perfusion perturbances of microvascular origin, referring to coronary microvascular dysfunction (CMD), i.e. impaired vasodilation and/or abnormal vasoconstriction. The guideline-based diagnosis of CMD (impaired vasodilation) is made via intracoronary flow and/or resistance indices. Abnormalities of the indices that measure hyperemic coronary flow (velocity) augmentation capacity, such as coronary flow reserve (CFR) or microvascular resistance reserve (MRR), unequivocally relate to a worse prognosis. Increased hyperemic minimal microvascular resistance (hMR), however, has no independent or additive prognostic value in the stable coronary artery disease (CAD) or ANOCA patients according to large multi-nation multi-centre studies such as DEFINE-FLOW study or ILIAS registry.[3,4] Despite this, the use of hMR has been endorsed by major diagnostic guidelines for CMD (impaired CFR and/or increased hMR)[5,6] including the latest chronic coronary syndrome (CCS) guidelines of the American Heart Association/American College of Cardiology (2023)[7] and the updated CCS guideline of the European Society of Cardiology (2024).[8]

Recently, we have hypothesized and demonstrated the possible presence of a distinctive adaptive vasomotor response in vessels with high hMR but preserved CFR characterized by physiologically increased resting microvascular resistance enhancing the arterial pressure reservoir capacity to overcome the systemic relative hyperperfusion state seen in CMD.[9] In this context, the impact of high hMR on the phasic characteristics of the coupling between ventricle and coronary arteries with respect to proposed adaptive response vs. CMD should be better understood.

Wave-intensity analysis (WIA), based on simultaneously measured pressure and flow (velocity) tracings, quantitatively evaluates the coupled hemodynamic effects originating from both the distal intramyocardial pump[10] and the proximal aorta on distal coronary flow with high temporal resolution.[11] WIA serves as a valuable tool to study characteristics of cardiac-coronary coupling from a mechanical perspective.

The present study aims to define the cardiac-coronary coupling characteristics of this potentially adaptive endotype (no CMD-high hMR) compared with other CMD and no CMD endotypes using the wave energy transfer characteristics, with the help of WIA.[12] In parallel, we aim to elucidate the effect of high hMR on the cardiac-coronary coupling in vessels with or without CMD (defined for this analysis as reduced CFR) to explore the differences between potential 'adaptive' vs. pathological high hMR endotypes.

# Methods

## Study population

This study was conducted on the open-access multi-centre DEFINE-FLOW data,[13] containing deidentified raw pressure and flow velocity signals, core laboratory and on-site measurements for physiological measures (FFR, iFR, Pd/Pa, CFR etc.), angiographic as well as clinical and laboratory data from 455 patients with stable CAD. The detailed original study protocol including catheter laboratory protocol has been published in detail elsewhere.[14] The present study was conducted on the same cases used in the adaptive high MR hypothesis study,[9] in order to link the findings to the preceding work. The measurements were core laboratory approved measurements excluding repeat measurements for the same vessels (according to the numerical order of measurement in the recurrent cases before the signal analysis) and the vessels with flow limiting CAD identified as fractional flow reserve (FFR) $\leq$ 0.80. The final number was 312 unique vessels from 258 patients. *Figure 1* demonstrates the flow chart and the averaged hemodynamic signals with WIA.

## Signal analysis

Simultaneously obtained raw pressure and Doppler derived flow velocity signals (ComboWire XT, Phillips Volcano, San Diego, California, USA) were imported into MATLAB (v R2024a, The MathWorks, USA). Sampling frequencies in the original data were 100 and 200 Hz for Doppler and pressure signals, respectively. The Doppler signals were filtered with a second-order Savitzky-Golay filter (window length of 11 samples). The hyperemic and resting time windows were automatically selected in MATLAB following maximum mean changes and approved via visual inspection for the quality of envelopes and correctness of the beginning of the hyperemic stimulus. The analysis excluded the period with abrupt perturbation of signal during adenosine administration and initial flow augmentation until achievement of a stable state, and the hyperemic window was truncated to the plateau state of maximum hyperaemia, minimising beat-to-beat variability. For the resting time windows, there was no routine, frequent source of perturbations, but in case of irregularities causing potential deviations from the true baseline (e.g. extrasystoles), visual approval of automatized selection was completed with truncating the period into a shorter window. Then, pressure and flow velocity waveforms in the selected time-windows were ensemble-averaged to a single representative cardiac cycle for both resting and hyperemic windows (*Figure 1*). This ensemble average beat enabled the analysis of temporal variations in the WI parameters during the beat; information that would otherwise be lost in the variance in signal-averaged measurements.

## Wave intensity analysis

The WIA used to quantitatively evaluate the coronary arterial energy transfer characteristics was performed with an updated version of Kim H. Parker's dedicated software (Imperial College, UK)[12] used in our previous studies.[15,16] Net wave intensity (WI) was computed with arterial blood pressure and flow velocity signals as previously described (WI = (dP/dt)×(dU/dt), $W.m^{-2}.s^{-2}$) (*Figure 1*).[12,15–17] Variables of interest were peak amplitudes of forward compression (FCW), backward compression (BCW), forward expansion (FEW) and backward expansion (BEW) waves.[17] (*Figure 1*) The accelerating wave energy proportion (AEP), previously called the perfusion efficiency by some authors,[18] was defined as the proportion of accelerating waves (FCW + BEW)/(FCW + BEW + FEW + BCW) expressed as a percentage. ΔAEP was defined as the difference between hyperemic AEP—resting AEP.

## Measures of CMD

The CFR and hMR were automatically calculated from the resting and hyperemic time windows. Basal (bMR) and hyperemic (hMR) microvascular resistances were calculated per their definitions (bMR = Pd basal/bAPV (basal average peak velocity = mean resting velocity) and hMR = Pd hyperemic/hAPV (hyperemic average peak velocity = mean hyperemic velocity)) over a cardiac cycle. CFR was calculated as the ratio of hAPV/bAPV. Vessels with FFR $\leq$ 0.80 were labelled to have obstructive CAD as per protocol and thus excluded. Vasodilator capacity of coronary microvasculature was evaluated with Doppler derived CFR with adenosine administration as previously described.[14,19] For CFR the cut off value of 2.5 was used to identify CMD. In the categorical analysis for minimal hyperemic microvascular resistance (hMR), 2.5 $mmHg.s.cm^{-1}$ was used.[20,21] Vessels with CFR $\geq$ 2.5 + hMR < 2.5 $mmHg.s.cm^{-1}$ were labelled as *No CMD* (reference group). Those with CFR < 2.5 + hMR < 2.5 $mmHg.s.cm^{-1}$ were classified to have *Functional CMD* whereas reduced flow reserve with high resistance (CFR < 2.5 + hMR $\geq$ 2.5 $mmHg.s.cm^{-1}$) is defined as *Structural CMD*. Vessels with *preserved CFR despite high hMR* (CFR $\geq$ 2.5 + hMR $\geq$ 2.5 $mmHg.s.cm^{-1}$) were labelled as '*No CMD–high hMR*'.[9] For the analysis of hyperemic microvascular vasodilatory capacity, a measure of CMD, we have additionally included MRR [MRR = (CFR/FFR) × (Pa rest/Pa hyperemic)], an epicardial disease-independent microcirculation specific index, compared with unadjusted CFR[22–24] and resistive reserve ratio (RRR) (=bMR/hMR), a marker of autoregulatory capacity, with proven robust prognostic value[25] in addition to CFR.[19]

## Statistical analysis

To prevent bias and ensure standardisation, whenever multiple recordings for the same vessel were included in the database, the first recording with adequate data was used.

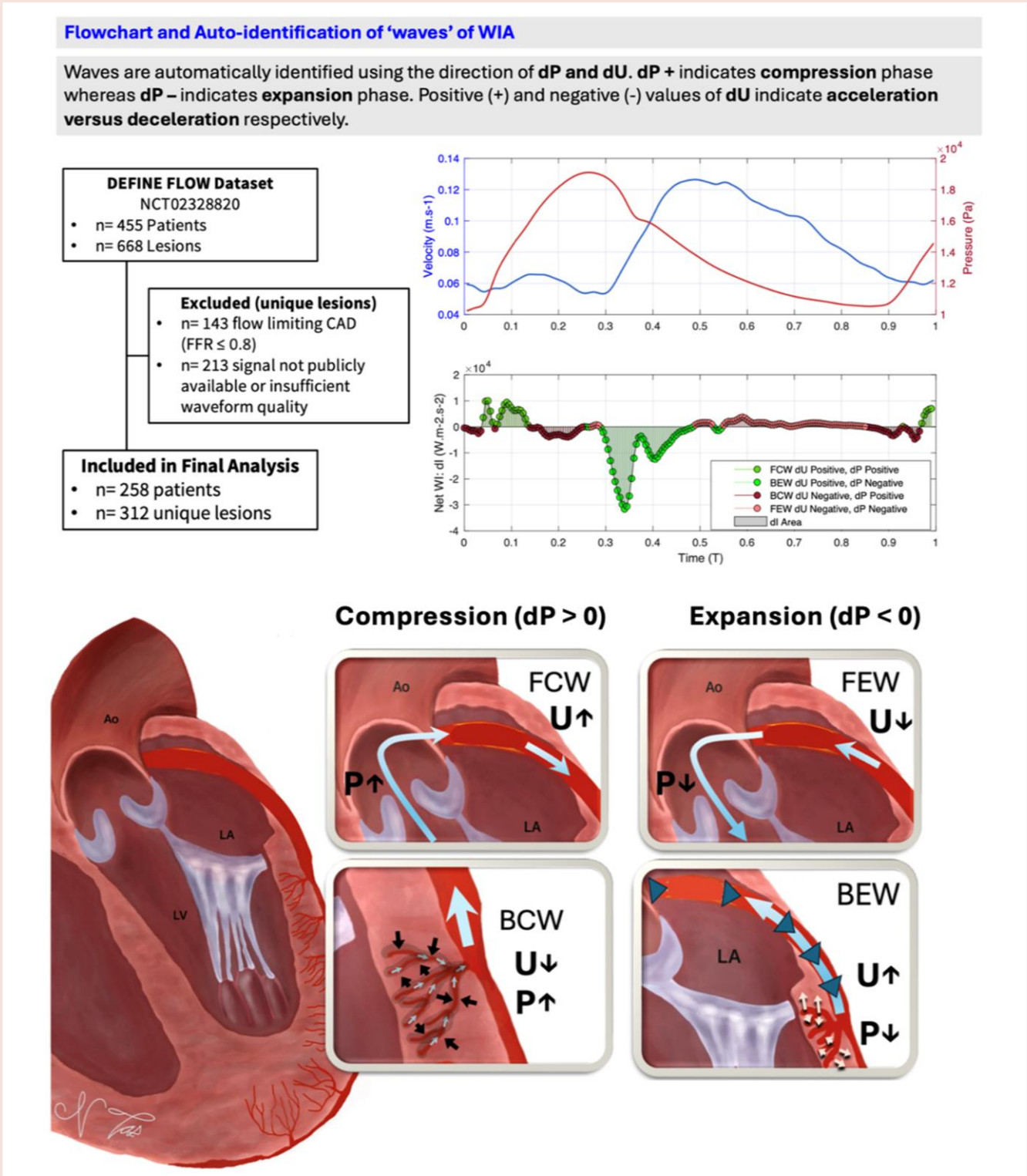


**Figure 1** Flow chart and WIA. For P. dP > 0 indicates compression and dP < 0 indicates expansion, whereas for U, dU> indicates acceleration and dU < 0 indicates deceleration.

Continuous variables were expressed as mean ± standard deviation or mean [95% Confidence Intervals]. Normality of variables was assessed using the Shapiro-Wilk's test. Means were compared using ANOVA and Kruskal Wallis tests in independent samples. Pairwise comparisons between disease severity groups were made via Post-hoc Tukey's or The Dwass-Steel-Critchlow-Fligner tests (following ANOVA) according to normality. Correlations were evaluated using Pearson's or Spearman's correlation coefficients when applicable. The *P* value of <0.05 was considered

statistically significant. All data were blindly analyzed offline using R-based JAMOVI statistical software (The Jamovi Project, Sydney, Australia). Figures were made using MATLAB (v R2024a, The MathWorks, USA) and JAMOVI (The Jamovi Project, Sydney, Australia).

### Ethical review

Each local site and the data management centre received approval from its applicable Institutional Review Board, and all subjects provided written informed consent prior to enrolment. The study was registered at ClinicalTrials.gov (NCT02328820). The present study was performed retrospectively on the open-access unidentifiable dataset; hence, additional review was not sought.

## Results

The study population mostly included elderly males with a high cardiovascular risk profile (*Table 1*). For this secondary analysis of cases with non-obstructed arteries, only vessels with FFR > 0.80 were included as per the study protocol and guidelines. The mean FFR was 0.89 ± 0.05 in the studied vessels, and there was no appreciable difference between the endotypes (*P*:0.098). A total of 77.6% ($n = 242$) of the vessels had CFR < 2.5. Of these vessels with CMD, 160 vessels (51.3% of all included vessels) classified as structural CMD, and 82 vessels (26.3% of all included vessels) classified as functional CMD were included. Of those with no CMD, a total of 44 vessels had normal hMR, whereas 26 vessels had high hMR despite normal CFR (no CMD–high hMR) (*Table 2*).

### Coronary wave energetics: characteristics of WIA

The peak amplitudes of WI were only trivially and inconsistently correlated to CFR, RRR, or MRR at rest or during hyperemia, and the magnitudes were mainly determined by velocity and microvascular resistance (*Table 3*). Likewise, there were CMD and no-CMD endotypes with high or low MR, and high or low average peak velocity (APV) (*Table 2*). Namely, functional CMD, which is characterized by augmented bAPV and attenuated bMR, had the numerically highest mean WI magnitudes (although statistically similar to no CMD- low hMR endotype) including the BEW whereas the no CMD–high hMR vessels had the smallest BEW amplitudes at rest (19.9 ± 16.5 vs. 4.8 ± 2.9 × $10^4$.W.$m^{-2}$.$s^{-2}$, $P < 0.001$) (*Table 2*). On the other hand, structural CMD endotype had relatively smaller WI amplitudes (*Table 2*). Despite the higher mean, the increased SD resulted in no statistical difference between the two endotypes. The functional CMD endotype also had the highest proportion of accelerating wave energy flux at rest (68% ± 12%) (structural CMD: 64% ± 15%, reference: 65% ± 13%, no CMD high hMR: 61% ± 13%, *P* for ANOVA = 0.048).

During hyperemia, augmentation of APV was accompanied by increased WI amplitudes. The AEP significantly increased from 65% ± 14% to 73% ± 10% ($P < 0.001$). This augmentation (ΔAEP) was higher in the no CMD vessels (11% ± 14% vs. 5% ± 14% *P*:0.020). Importantly, hMR did not correlate to ΔAEP (*r*:0.080, *P*:0.200). The no CMD–high hMR endotype, which had the lowest AEP at rest (61% ± 13%), displayed the most pronounced hyperemic AEP augmentation (13% ± 13%, $P = 0.042$, comparable with reference: 11% ± 14%). All endotypes had comparable AEP during hyperemia ($P = 0.065$) despite different augmentations compared with resting state (*Figure 2*). In addition, hyperemic WI amplitudes of functional CMD and reference group were comparably high whereas structural CMD and no CMD high hMR endotype had similarly suppressed amplitudes. The excellent response of no CMD–high hMR endotype to hyperemic stimulus despite high hMR was consistent with the very high RRR and CFR (*Table 2*).

**Table 1 Patient characteristics**

| Total number ($N = 258$) | Missing data (*n*) | Mean ± SD, or number (%) |
|---|---|---|
| Age, years | 0 | 68 ± 10 |
| Female | 0 | 70 (27%) |
| BMI kg/$m^2$ | 0 | 26 ± 4 |
| Smoking | 17 | 133 (55%) |
| Hypertension | 4 | 179 (70%) |
| Dyslipidemia | 2 | 225 (88%) |
| Diabetes Mellitus | 1 | 71 (28%) |
| CAD in the family | 18 | 91 (38%) |
| CRD | 1 | 21 (8%) |
| Hemodialysis | 1 | 2 (<1%) |
| Medications | | |
| Nitrate | 4 | 108 (43%) |
| Ranolazine | 3 | 1 (<1%) |
| Ivabradine | 3 | 2 (<1%) |
| Nicorandil | 3 | 7 (3%) |
| Trimetazidine | 3 | 2 (<1%) |
| Beta-blockers | 3 | 151 (59%) |
| Calcium Antagonists | 4 | 104 (41%) |
| Diuretic(s) | 4 | 45 (18%) |
| RAAS inhibitor | 3 | 139 (55%) |
| Alpha-blockers | 4 | 6 (2%) |
| ASA | 4 | 224 (88%) |
| Antiplatelet | 4 | 175 (69%) |
| Anticoagulant | 3 | 27 (11%) |
| Statin | 3 | 204 (80%) |
| Other Antihyperlipidemic(s) | 3 | 15 (6%) |
| Antiarrhythmic(s) | 3 | 7 (3%) |
| Oral Antidiabetic(s) | 3 | 41 (16%) |
| Insulin | 3 | 13 (5%) |

ASA, acetylsalicylic acid; CAD, coronary artery disease; CRD, chronic renal disease; RAAS, renin-angiotensin-aldosterone system.

### Impact of high microvascular resistance on accelerating wave energy Flux

In vessels with preserved microvascular vasodilatory capacity (no CMD, CFR ≥ 2.5), increasing values of MR (bMR and/or hMR) did not alter the AEP (*Figure 3*). In contrast, MR augmentation (bMR and/or hMR) was associated with mildly suppressed AEP in CMD group at rest but not during hyperemia (*Figure 3*). (CMD group: $r = -0.216$ $P < 0.001$ for bMR-AEP; $r = -0.229$ $P < 0.001$ for hMR-AEP). Importantly, while the CMD group had higher hMR compared with no CMD (3.1 ± 1.2 vs. 2.6 ± 0.9 mmHg/cm.$s^{-1}$ $P < 0.001$), no CMD group had higher bMR values (6.4 ± 2.3 vs. 5.1 ± 1.9 mmHg/cm.$s^{-1}$ $P < 0.001$), indicating that the observations are not due to heterogeneous MR distribution. These findings cumulatively demonstrate that the increased MR alters the perfusion energetics only in the vessels with diseased microvascular function, CMD, supporting the adaptively elevated MR in no CMD vessels.

### Impact of female sex

High hMR preserved CFR vessels predominantly included the male cases. Despite the small group sizes, the observations were mainly

**Table 2 Hemodynamic characteristics of study groups**

| Variable | | CMD-Functional $n = 82$ | CMD-Structural $n = 160$ | No CMD Reference $n = 44$ | No CMD High hMR $n = 26$ | Total $n = 312$ | *P* from ANOVA |
|---|---|---|---|---|---|---|---|
| Rest | **bAPV** cm.s$^{-1}$ | 25 (9) $^{a,b,d}$ | 15 (4)$^{a,c,d}$ | 17 (4)$^{b,c,d}$ | 10 (3)$^{a,b,c}$ | 17 (8) | **<0.001** |
| | **bMR** mmHg/cm.s$^{-1}$ | 3.3 (1.0)$^{a,b,d}$ | 6.0 (1.7)$^{a,c,d}$ | 5.0 (1.0)$^{b,c,d}$ | 8.8 (2.0)$^{a,b,c}$ | 5.4 (2.1) | **<0.001** |
| | **MAP** mmHg | 90 (14) | 94 (13) | 91 (14) | 94 (12) | 93 (14) | 0.112 |
| Hyperemia | **hAPV** cm.s$^{-1}$ | 48 (17)$^{b,d}$ | 26 (7)$^{a,c}$ | 46 (10)$^{b,d}$ | 28 (7)$^{a,c}$ | 35 (15) | **<0.001** |
| | **hMR** mmHg/cm.s$^{-1}$ | 2.0 (0.4)$^{b,d}$ | 3.7 (1.0)$^{a,c}$ | 2.0 (0.3)$^{b,d}$ | 3.5 (0.8)$^{a,c}$ | 3.0 (1.2) | **<0.001** |
| | **MAP** mmHg | 78 (15) | 83 (14) | 80 (13) | 82 (11) | 81 (14) | 0.077 |
| Overall Characteristics | **bAPV** < 25th% **(–)** | 80 (100%) | 105 (66%) | 39 (89%) | 3 (11%) | 227 (73%) | **<0.001** |
| | percentile **(+)** | 0 (0%)$^{a,b,d}$ | 54 (34%)$^{a,c,d}$ | 5 (11%)$^{b,c,d}$ | 23 (89%)$^{a,b,c}$ | 82 (27%) | |
| | **CFR** | 1.9 (0.3)$^{a,d}$ | 1.8 (0.4)$^{a,d}$ | 2.8 (0.3)$^{b,c}$ | 2.9 (0.3)$^{b,c}$ | 2.1 (0.5) | **<0.001** |
| | **MRR** | 2.4 (0.4)$^{a,b,d}$ | 2.2 (0.5)$^{a,c,d}$ | 3.3 (0.4)$^{b,c}$ | 3.5 (0.4)$^{b,c}$ | 2.5 (0.6) | **<0.001** |
| | **RRR** | 2.3 (0.4)$^{a,d}$ | 2.1 (0.4)$^{a,d}$ | 3.2 (0.3)$^{b,c}$ | 3.3 (0.4)$^{b,c}$ | 2.4 (0.6) | **<0.001** |
| | **FFR** | 0.88 (0.05) | 0.90 (0.05) | 0.88 (0.04) | 0.88 (0.05) | 0.89 (0.05) | 0.093 |
| | **Pd/Pa** | 0.0.95 (0.03) | 0.96 (0.03) | 0.95 (0.03) | 0.95 (0.03) | 0.95 (0.03) | 0.354 |
| WIA characteristics of study groups | | | | | | | |
| Rest | **FCW** $10^4$.W.m$^{-2}$.s$^{-2}$ | 5.4 (5.3)$^{b,d}$ | 3.1 (2.1)$^{c,d}$ | 3.5 (2.4)$^{d}$ | 2.0 (1.5)$^{a,b,c}$ | 3.7 (3.4) | **<0.001** |
| | **BCW** $10^4$.W.m$^{-2}$.s$^{-2}$ | 5.5 (3.9)$^{b,d}$ | 4.4 (3.5)$^{c}$ | 5.1 (3.1)$^{d}$ | 3.6 (4.1)$^{a,c}$ | 4.8 (3.7) | **0.045** |
| | **FEW** $10^4$.W.m$^{-2}$.s$^{-2}$ | 2.9 (2.5)$^{b,d}$ | 1.9 (2.2)$^{a,c}$ | 2.5 (2.1)$^{b,d}$ | 1.1 (0.7)$^{a,c}$ | 2.2 (2.2) | **<0.001** |
| | **BEW** $10^4$.W.m$^{-2}$.s$^{-2}$ | 16.9 (16.5)$^{b,d}$ | 8.6 (6.6)$^{c,d}$ | 11.4 (7.8)$^{d}$ | 4.8 (2.9)$^{a,b,c}$ | 11.0 (10.8) | **<0.001** |
| | **AEP** | 68 (12) %$^{d}$ | 64 (15) % | 65 (13) % | 61 (13) %$^{c}$ | 65 (14) % | **0.048** |
| Hyperemia | **FCW** $10^4$.W.m$^{-2}$.s$^{-2}$ | 8.3 (7.5)$^{b,d}$ | 5.1 (3.9)$^{a,c}$ | 7.5 (2.4)$^{b,d}$ | 2.0 (1.5)$^{a,c}$ | 6.2 (5.2) | **<0.001** |
| | **BCW** $10^4$.W.m$^{-2}$.s$^{-2}$ | 4.8 (3.8)$^{b,d}$ | 3.3 (2.3)$^{a,c}$ | 4.1 (1.3)$^{b,d}$ | 3.3 (3.1)$^{a,c}$ | 3.8 (2.8) | **<0.001** |
| | **FEW** $10^4$.W.m$^{-2}$.s$^{-2}$ | 2.6 (2.4) | 2.3 (2.5) | 3.0 (3.1) | 1.7 (1.7) | 2.4 (2.5) | 0.176 |
| | **BEW** $10^4$.W.m$^{-2}$.s$^{-2}$ | 15.0 (12.2)$^{b}$ | 9.6 (6.1)$^{a,c}$ | 16.7(10.5)$^{b,d}$ | 9.4 (5.5)$^{a}$ | 12.0 (9.2) | **<0.001** |
| | **AEP** | 74 (10) % | 72 (10) % | 76 (10) % | 74 (11) % | 73 (10) % | 0.065 |

Data is expressed as mean (SD). AEP, accelerating wave energy flux proportion (FCW + BEW)/(FCW + BEW + FEW + BCW). For post-hoc pairwise comparisons after significant *P* value in ANOVA. The *P*-values < 0.05 are presented in bold text.
[a]Indicates significant mean difference compared with reference.
[b]Indicates significant mean difference compared with structural CMD.
[c]Indicates significant mean difference compared with functional CMD.
[d]Indicates significant mean difference compared with no CMD high hMR.

concordant with the entire group. In women, the WI profile did not vary between CMD vs. no-CMD endotypes. The below vs. above mean bAPV and bMR groups had similar microvascular vasodilatory capacity (CFR, MRR, and RRR) and AEP despite different individual WI amplitudes (*Table 4*).

# Discussion

Recent large clinical studies including DEFINE-FLOW and ILIAS Registry have shown that high hMR has no prognostic significance in the setting of stable CAD and NOCAD.[3,4] We have previously proposed a CFR-preserving adaptive mechanism responsible for augmentation of hMR to explain this observation. In this study, we expand on this hypothesis by investigating the cardiac-coronary coupling characteristics of this potential adaptive high MR endotype and its impact on coronary wave energy flux using WIA. Our key findings are (*Figure 4*/Visual Abstract):

(1) Coronary WIA patterns are not directly related to CMD status; high and low WI amplitudes can be observed in both CMD and no-CMD groups, just as how high and low flow can be seen in both healthy or CMD groups. Also, no WI amplitude parameter, including AEP or BEW, is unequivocally related to CFR, MRR, or RRR in stable NOCAD.
(2) WIA, however, revealed some distinctive features of the hypothesized adaptive high MR endotype. This group showed the highest increase in AEP in response to adenosine during hyperemia, comparable to that of reference group, indicating excellent autoregulatory capacity along with high RRR. This robust response suggests adequate flow augmentation capacity, and importantly, implies that if increased flows were needed at rest, this adaptive group has the capacity to increase flow, supporting the concept that resting flow is adaptively suppressed via augmentation of microvascular resistance in this group, unlike in the structural CMD endotype.
(3) Neither hMR nor bMR had a significant effect on AEP in the no-CMD group. In the CMD group, however, both hMR and bMR were associated with a modest decrease in AEP. Consistent with the adaptive high MR hypothesis, high MR (neither bMR nor hMR) is not associated with a *major* perturbation in cardiac-coronary coupling or coronary wave energy flux, but proportionally readjusts the coronary circulation to operate at lower flow rates and an attenuated energy profile to maintain perfusion within a physiologically appropriate range while preserving an adequate flow reserve.

## Clinical significance of high hMR

Recent large multi-centre studies have demonstrated that increased MR does not hold prognostic relevance in either stable coronary disease or

**Table 3 Correlations between WI peak amplitudes and coronary perfusion and CMD parameters**

| WIA parameters | | | bAPV | hAPV | bMR | hMR | RRR | CFR | MRR |
|---|---|---|---|---|---|---|---|---|---|
| **Rest** | **FCW** | ***r*** | 0.638 | 0.565 | −0.357 | −0.300 | −0.111 | −0.099 | −0.113 |
| | | ***P*** | **< 0.001** | **< 0.001** | **< 0.001** | **< 0.001** | 0.050 | 0.082 | **0.046** |
| | **BCW** | ***r*** | 0.265 | 0.244 | −0.234 | −0.179 | −0.056 | −0.064 | −0.123 |
| | | ***P*** | **< 0.001** | **< 0.001** | **< 0.001** | **0.001** | 0.323 | 0.261 | **0.030** |
| | **FEW** | ***r*** | 0.308 | 0.260 | −0.268 | −0.124 | −0.151 | −0.139 | −0.132 |
| | | ***P*** | **< 0.001** | **< 0.001** | **< 0.001** | **0.029** | **0.008** | **0.014** | **0.020** |
| | **BEW** | ***r*** | 0.646 | 0.587 | −0.415 | −0.357 | −0.122 | −0.099 | −0.099 |
| | | ***P*** | **< 0.001** | **< 0.001** | **< 0.001** | **< 0.001** | **0.031** | 0.081 | 0.081 |
| | **AEP** | ***r*** | 0.297 | 0.276 | −0.172 | −0.177 | −0.045 | −0.015 | 0.015 |
| | | ***P*** | **< 0.001** | **< 0.001** | **0.002** | **0.002** | 0.429 | 0.787 | 0.790 |
| **Hyperemia** | **FCW** | ***r*** | 0.545 | 0.541 | −0.297 | −0.353 | 0.023 | 0.041 | −0.005 |
| | | ***P*** | **< 0.001** | **< 0.001** | **<0.001** | **< 0.001** | 0.690 | 0.481 | 0.925 |
| | **BCW** | ***r*** | 0.358 | 0.360 | −0.276 | −0.277 | −0.034 | −0.022 | −0.028 |
| | | ***P*** | **< 0.001** | **< 0.001** | **< 0.001** | **< 0.001** | 0.563 | 0.702 | 0.624 |
| | **FEW** | ***r*** | 0.239 | 0.273 | −0.128 | −0.175 | 0.047 | 0.051 | 0.015 |
| | | ***P*** | **< 0.001** | **< 0.001** | **0.027** | **0.002** | 0.417 | 0.377 | 0.795 |
| | **BEW** | ***r*** | 0.465 | 0.533 | −0.279 | −0.376 | 0.103 | 0.123 | 0.085 |
| | | ***P*** | **< 0.001** | **< 0.001** | **< 0.001** | **< 0.001** | 0.075 | **0.033** | 0.140 |
| | **AEP** | ***r*** | 0.133 | 0.208 | −0.030 | −0.129 | 0.138 | 0.153 | 0.103 |
| | | ***P*** | **0.021** | **< 0.001** | 0.605 | **0.026** | **0.016** | **0.008** | 0.074 |

The *P*-values < 0.05 are presented in bold text.

unobstructed coronary arteries[3,4,19,26] in contrast to CFR, i.e. a normal CFR is associated with a good clinical outcome while a low CFR has a worse prognosis. Moreover, traditional cardiovascular risk factors do not intrinsically associate with high hMR and a significant proportion of those with increased hMR have no endothelial dysfunction.[21,27] Very recently we have demonstrated that the increased resistance in the No CMD vessels may occur within the scope of an adaptive vasomotor response, enhancing the arterial reservoir capacity,[9] to normalize the systemic relative hyperemic state seen in the functional CMD. This adaptive endotype is reflected in the no CMD–high hMR vessels of the present study. These vessels had the lowest mean bAPV among DEFINE-FLOW patients and, concordantly, also exhibited the smallest BEW amplitudes. This hypothesis of adaptively increased hMR has been utilized to explain the observations from other CMD studies as well.[28,29] Functional CMD with high bAPV seemingly has high BEW amplitude and high AEP at rest, comparable to that of healthy reference vessels. During hyperemia, the AEP of all groups were comparable, but in CMD endotypes, this was mostly driven by the AEP already achieved at rest with lower response to hyperemic stimulus. Although the AEP itself does not correlate to CMD indices, this distinctive difference in hyperemic relative AEP changes provide physiological insights into the preserved autoregulatory capacity of adaptive hMR endotype. While the WIA-derived indices could not directly differentiate between healthy and diseased microcirculation, we have demonstrated, for the first time, that the increased microvascular resistance in No CMD vessels (bMR and/or hMR) does not hinder the hyperemic augmentation of AEP, while readjusting the coronary perfusion to operate at lower resting flow rates, whereas in the CMD endotypes (structural and/or functional CMD), increased microvascular resistance suppresses the proportion and limits hyperemic response. Importantly, the first endotype has repeatedly been shown to have a good prognosis despite the high hMR and lower bAPV.[20] This observation mechanistically reinforces the arguments against the use of high hMR alone for CMD diagnosis. Still, in a diseased population subgroup with prolonged exposure to metabolic syndrome components and chronic inflammatory stimulus, a higher frequency of structural CMD is likely to be observed. In this population, hMR may reflect the diagnosis of CMD (CFR < 2.5) via detection of reduced hAPV. Yet, in real-world patient groups, those with adaptively increased hMR despite no CMD will be misdiagnosed by this approach.

## Use of WI characteristics for CMD studies

Since its first appearance in the literature, BEW, as a parameter of WIA, has been almost unequivocally attributed to microvascular health. For the last 25 years, it was considered that the positive relationship between higher microvascular decompression wave energy flux (higher BEW) driving the diastolic filling, and better microvascular vasodilatory reserve reflects a healthier coronary microcirculation.[30,31] Indeed, the idea itself is directly parallel to the notion of slower flow being an indicator of worse perfusion and higher bAPV is an indicator of a healthier microcirculation. Given that vessels with CMD and no CMD may have attenuated or augmented flow at rest, it follows that amplified or attenuated WI profiles will be seen in healthy or diseased microcirculation endotypes. It is therefore clear that raw comparison between WI amplitudes to detect microvascular pathologies is an unreliable method. The absence of significant correlations between CFR and BEW in the current NOCAD analysis aligns with our previous observations from the context of intermediate stenoses, suggesting the broader applicability of this finding.[16] In parallel, the unique relationship between pressure and flow (velocity) in the coronary circulation is a major obstacle for employing pressure-only estimations, unlike successful utilisation of pressure-only WIA in the systemic arteries.[32,33] Everywhere else in the arterial bed, the blood flow is driven by increasing pressure through systole and it decays during diastole, parallel to pressure in terms of magnitude and waveform morphology. In coronary arteries, however, contraction of myocardium generates an incremental compressive

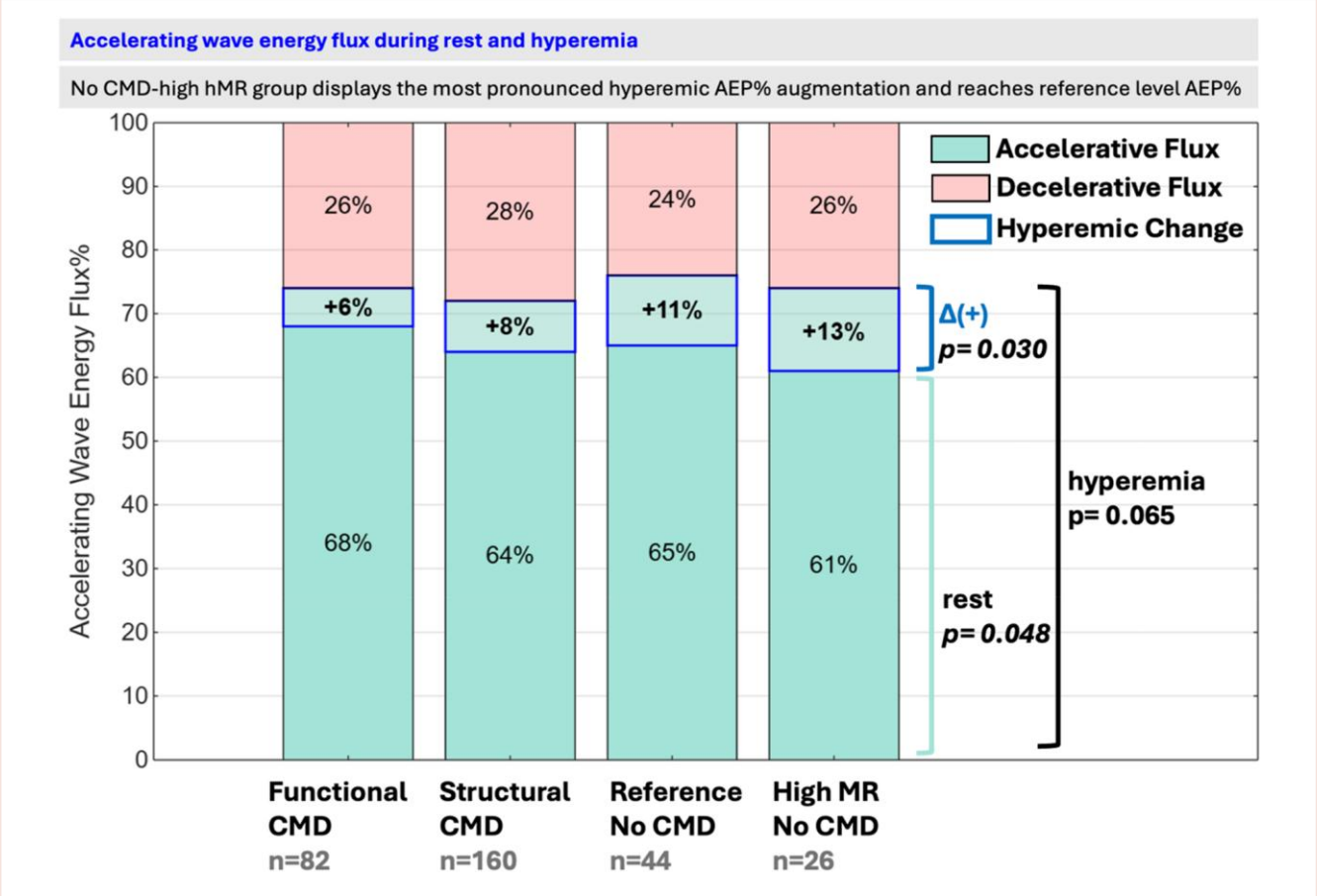


**Figure 2** CMD - no CMD endotypes and proportion of accelerating wave energy flux during rest and hyperemia. Standard deviation of presented data is provided in the *Table 2*. The functional CMD endotype had the highest proportion of accelerating wave energy flux at rest (68% ± 12%) (structural CMD: 64% ± 15%, reference: 65% ± 13%, no CMD high hMR: 61% ± 13%, *P* for ANOVA = 0.048). During hyperemia, augmentation of APV was accompanied by increased WI amplitudes. The AEP significantly increased from 65% ± 14% to 73% ± 10% ($P < 0.001$). This augmentation (ΔAEP) was higher in the no CMD vessels (11% ± 14% vs. 5% ± 14% *P*:0.020). Importantly, hMR did not correlate to ΔAEP (*r*:0.080 *P*:0.200). The no CMD–high hMR-AEP at rest (61% ± 13%), displayed the most pronounced hyperemic AEP augmentation (13% ± 13%, $P = 0.042$, comparable with reference: 11% ± 14%).

force on the intramyocardial vascular network at the beginning of systole limiting the systolic flow until the reduced ejection phase, marked by the peak systolic pressure. With the beginning of attenuation of the arterial pressure, the 'expansion or decompression' phase starts with a dominant accelerative microvascular suction effect, mainly responsible for diastolic filling. This causes a distinct difference in the pressure-flow patterns in coronary arteries compared with other systemic arteries. Even in the different coronary arteries of a single person, the microvascular functionality may be spatially heterogenous, resembling a patchy involvement,[34,35] further complicating a non-invasive assessment based on systemic pressure tracings and highlighting the need for flow (velocity) measurements. Moreover, the concept of 'perfusion efficiency in WIA' (analogous to AEP in the present study), although advocated by prominent coronary physiology groups,[18] may also have theoretical pitfalls for similar reasons while the proportion of accelerating WI is not robustly associated with CFR, MRR, or RRR. Previous studies that utilized this index did not include the no CMD-high hMR vessels as an independent group, which may have led to the potentially misleading conclusions drawn.[2,18]

On the other hand, in the present study, the numerically highest WI amplitudes were observed in the functional CMD endotype (although statistically comparable with reference endotype) and lowest in the no CMD–high hMR endotype, directly as a function of the large contrast of high vs. low bMR of these groups, without any nuances amongst WIA subcomponents. Moreover, the previously suggested 'perfusion efficiency index' (AEP) and BEW do not positively correlate to CFR, RRR, or MRR and, hence, should not be considered as unequivocal markers of microvascular health. Adaptively increased MR and abnormally high MR have different impacts on coronary dynamics; the former seems to proportionally modify the wave energy transfer pattern, and the latter disproportionally suppresses the AEP and hyperemic flow augmentation capacity.

The complex and multifactorial nature of coronary microcirculation necessitates a pathophysiology based, comprehensive interpretation of WIA parameters, rather than dichotomization of individual wave magnitudes or ratios into 'good' or 'bad'. The augmentation capacity of accelerating wave energy flux, alongside the preserved CFR and RRR correlates with the good prognosis seen in the no CMD–high hMR cases, supporting the adaptive high MR concept. This indicates reconsideration of the use of high hMR for diagnosis of CMD in the setting of CCS. Interventional cardiologists and coronary physiologists should be alert to a potential adaptive no CMD–high hMR endotype to avoid misdiagnosis, as both DEFINE-FLOW and ILIAS Registry demonstrated a very good prognosis for this group of patients.[9,28]

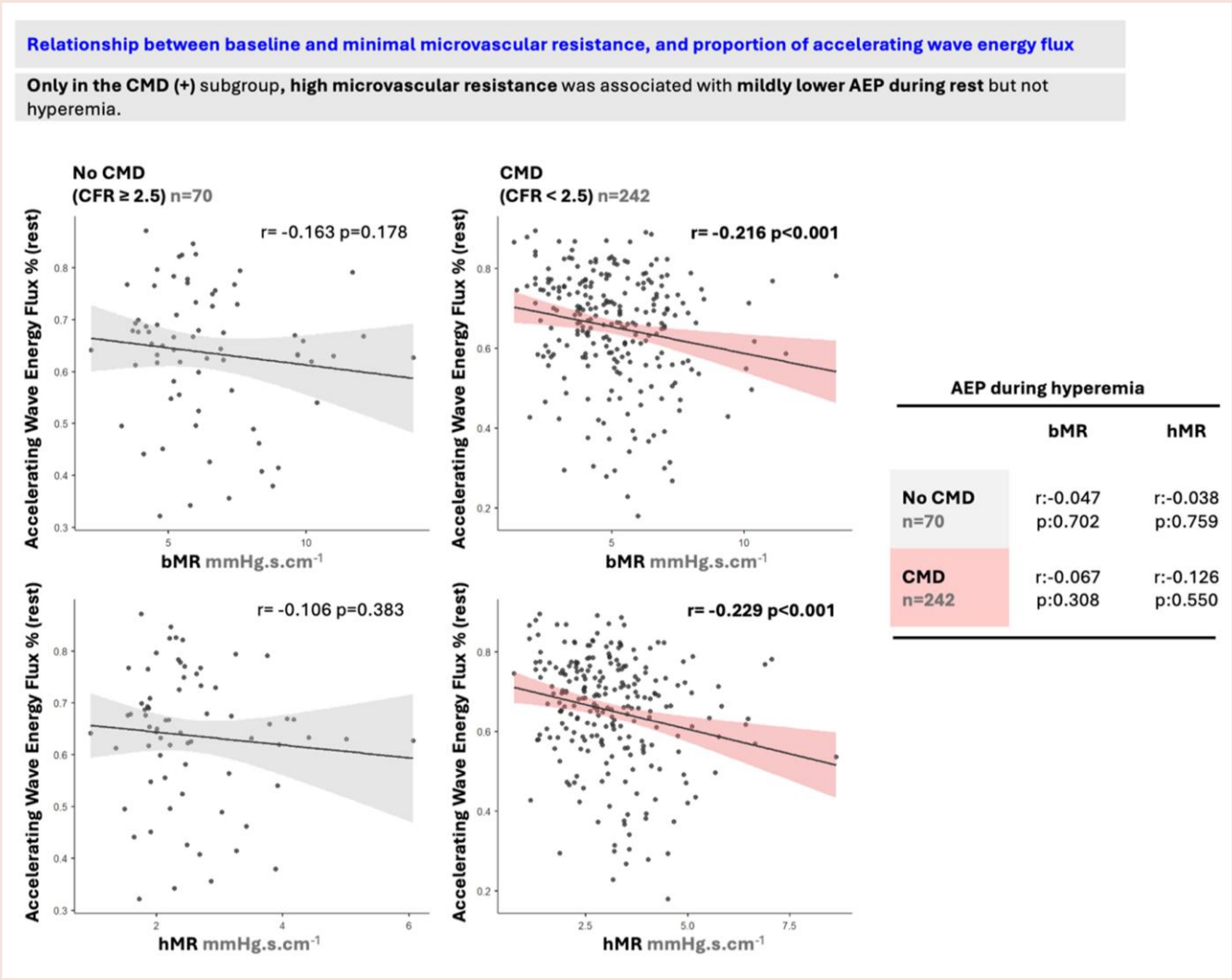


**Figure 3** Impact of high microvascular resistance on accelerating wave energy flux proportion%.

**Table 4 WIA parameters in CMD and low bAPV in women**

| Variables | CMD (+) CFR < 2.5 (*N* = 53) | CMD (−) CFR ≥ 2.5 (*N* = 8) | *P* | bAPV below mean (*N* = 39) | bAPV above mean (*N* = 22) | *P* | bMR below mean (*N* = 34) | bMR above mean (*N* = 27) | *P* |
|---|---|---|---|---|---|---|---|---|---|
| bAPV | 17.8 (5.5) | 16.4 (3.3) | 0.495 | 14.7 (1.7) | 22.8 (5.3) | **<0.001** | 20.1 (5.7) | 14.4 (1.9) | **<0.001** |
| hAPV | 33.0 (11.9) | 45.4 (5.3) | **0.006** | 29.3 (6.5) | 43.9 (13.6) | **<0.001** | 37.8 (13.6) | 30.6 (8.0) | **0.020** |
| bMR | 4.9 (1.2) | 5.4 (1.0) | 0.295 | 5.6 (0.9) | 3.9 (0.9) | **<0.001** | 4.1 (0.8) | 6.1 (0.6) | **<0.001** |
| hMR | 3.1 (0.9) | 2.2 (0.3) | **0.008** | 3.3 (0.9) | 2.4 (0.8) | **<0.001** | 2.6 (0.7) | 3.4 (1.0) | **0.001** |
| CFR | 1.9 (0.4) | 2.8 (0.4) | **<0.001** | 2.0 (0.5) | 1.9 (0.5) | 0.634 | 1.9 (0.4) | 2.1 (0.5) | 0.056 |
| MRR | 2.3 (0.4) | 3.3 (0.5) | **<0.001** | 2.4 (0.5) | 2.3 (0.6) | 0.407 | 2.3 (0.5) | 2.5 (0.6) | 0.284 |
| RRR | 2.1 (0.4) | 3.1 (0.5) | **<0.001** | 2.3 (0.5) | 2.2 (0.6) | 0.355 | 2.2 (0.5) | 2.4 (0.6) | 0.198 |
| FCW | 3.9 (3.3) | 2.9 (1.0) | 0.420 | 2.6 (1.8) | 5.7 (3.9) | **<0.001** | 4.5 (3.7) | 2.8 (1.8) | **0.038** |
| BCW | 4.1 (2.4) | 3.5 (2.6) | 0.561 | 3.4 (2.3) | 5.0 (2.3) | **0.008** | 4.5 (2.5) | 3.2 (2.2) | **0.037** |
| FEW | 2.2 (2.4) | 1.4 (0.7) | 0.370 | 1.3 (0.7) | 3.5 (3.2) | **<0.001** | 2.4 (2.6) | 1.6 (1.5) | 0.169 |
| BEW | 10.9 (11.0) | 8.7 (3.8) | 0.591 | 6.8 (3.2) | 17.1 (15) | **<0.001** | 13.1 (13) | 7.2 (4.1) | **0.026** |
| AEP | 68 (12) | 71 (7) | 0.457 | 67 (11) | 70 (11) | 0.208 | 69 (11) | 67 (12) | 0.438 |

Data is expressed as mean (SD). The *P*-values < 0.05 are presented in bold text.

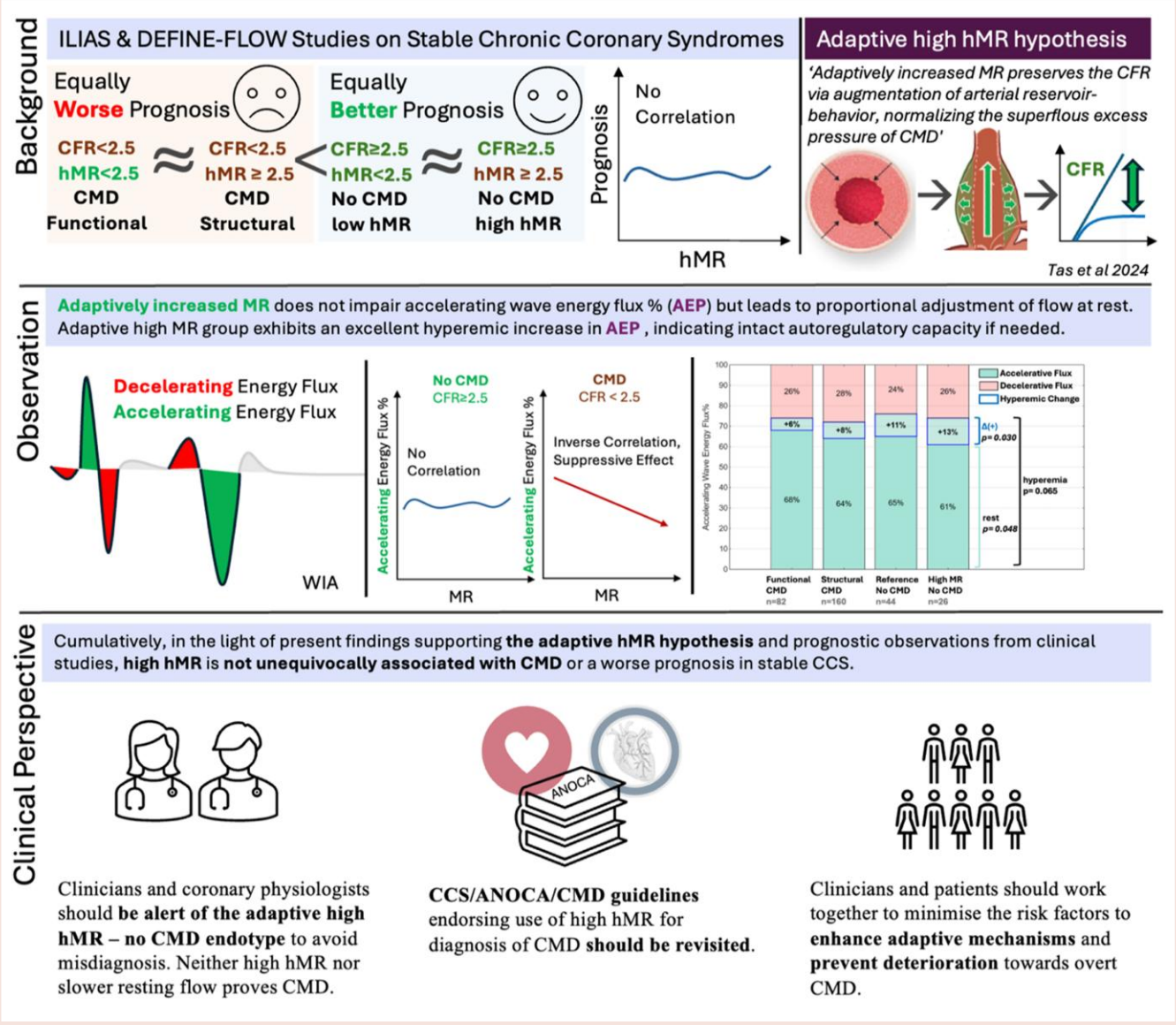


**Figure 4** Visual abstract the excellent augmentation capacity of accelerating wave energy flux, alongside the preserved CFR and RRR correlates the very good prognosis seen in the no CMD–high hMR high hMR—preserved CFR cases, supporting the adaptive high MR concept. This indicates the need for reconsideration of CCS guidelines endorsing use of high hMR for diagnosis of CMD. Interventional cardiologists and coronary physiologists should be alert to a potential adaptive no CMD–high hMR high hMR—no CMD endotype to avoid misdiagnosis, as both DEFINE-FLOW and ILIAS Registry demonstrated a very good prognosis for this group of patients.

## Conclusion

In vessels with preserved CFR, potentially adaptive increases in microvascular resistance do not impair accelerating wave energy flux but lead to proportional adjustment of coronary hemodynamics, allowing for adequate perfusion at lower flow (velocity) rates. Notably, this potentially adaptive high MR endotype exhibits an excellent increase in AEP during hyperemia, indicative of intact autoregulatory capacity. Conversely, in vessels with CMD, increased microvascular resistance is associated with reduced accelerating wave energy, indicating interference with perfusion energetics. These findings challenge the use of high hMR as an independent marker of CMD and highlight the need for a nuanced, physiology-based approach to interpreting coronary microvascular function. The lack of correlation between WIA-derived parameters (BEW and AEP) and established measures of microvascular health (CFR, RRR, and MRR) further underscores the complexity of assessing microvascular function. The present study does not endorse the independent use of high hMR for the diagnosis of CMD in the setting of CCS, as it does not unequivocally indicate CMD. This should be extrapolated to use of angiography-based high hMR for diagnosis of CMD, which relies on the slower flow rates calculated via contrast-movement rate.

## Future directions

The present findings are based upon retrospective analysis of the DEFINE FLOW study cohort and should be verified in prospective studies. This could include evaluation of the impact of intensive risk factor management and adherence to medical therapy on the progression of CMD and the stability of the adaptive high hMR phenotype. Future research should incorporate advanced imaging techniques, such as

cardiac magnetic resonance imaging (MRI) with stress perfusion, to further characterize the microvasculature in different CMD phenotypes, including the potentially adaptive high MR endotype. Prospective studies should include acetylcholine testing to assess endothelial function in the context of the adaptive high MR response. This will help to clarify the role of endothelial dysfunction in modulating wave energetics and the transition from adaptive to pathological states. Given the underrepresentation of women in the current study, future research should specifically focus on the impact of high MR and wave energetics in women with suspected CMD, to determine if the findings are generalizable across sexes and identify any sex-specific differences in pathophysiology and prognosis. Further research is needed to elucidate the mechanisms by which a potentially adaptive high MR state can deteriorate and contribute to adverse outcomes.

## Limitations

The present study mainly enrolled elderly male patients with stable CAD and multiple cardiovascular risk factors may not represent the spectrum of ANOCA/INOCA/CMD patients. The female sex had a low frequency and a further fewer CMD cases; hence, remained underrepresented despite the concordant results with the entire study group. Inclusion of acetylcholine for coronary function testing would provide further insights. Nonetheless, we have originally demonstrated the relationship between MR and coronary wave energetics in a multicentre, multi-national invasive hemodynamic data.

## Special consideration regarding the terminology

In this manuscript, individual forward and backward wave-intensity peaks are referred to as 'waves'. This notion historically originates from observations from the large conduit arteries, where the individual waves can be tracked from site to site in different arteries. Due to the shorter sizes of coronary arteries, it is not clear whether these peaks should be named as waves. For practicality, the present manuscript still utilizes the term 'wave'.

## Disclosure statement

In the present study, no AI model was used in design, analysis or interpretation of the results. Solely, the pre-submission language corrections were made with the help of an open-source AI language model. Each local site and the data management centre received approval from its applicable Institutional Review Board, and all subjects provided written informed consent prior to enrolment. The study was registered at ClinicalTrials.gov (NCT02328820). The present study was performed retrospectively on the open-access unidentifiable dataset; hence, additional review was not sought.

# Lead author biography

Dr. Ahmet Tas, MD (Gomec State Hospital, Turkey) is a member of the coronary physiology working group led by Professor Murat Sezer at Istanbul University, where he received his medical degree. Currently, he is pursuing a PhD in coronary haemodynamics at Amsterdam UMC, co-supervised by Professor Jan J. Piek. Dr. Tas focuses on applying contemporary fluid dynamics concepts such as WI and reservoir analysis in cardiovascular medicine to improve the pathophysiology and diagnosis of macro- and microvascular coronary artery diseases, for which he works under the guidance of Professor Kim H. Parker, a leading bioengineer in this field.

## Data availability

The data of DEFINE-FLOW study is publicly available including raw hemodynamic signals from https://datadryad.org/stash/dataset/doi:10.5061/dryad.h18931zm6. The data supporting the present study can be obtained from the lead author (AT, ahmettas.cor@gmail.com) upon request.

## Funding

None declared.

## Acknowledgements

The authors would like to thank Nehir Tas (Istanbul Medipol University, School of Medicine) for the scientific artwork.

**Conflict of interest:** T.v.d.H. has received speaker fees and institutional research grants from Abbott and Philips. J.J.P. has received support as consultant for Philips/Volcano and has received institutional research grants from Philips. The other authors report no relationship with industry related to this work. The paper is not under consideration elsewhere and none of the paper's contents have been previously published. All authors have read and approved the manuscript.

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