Primary versus iatrogenic (post-PCI) coronary microvascular dysfunction: a wire-based multimodal comparison

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ABSTRACT

Background Although there are studies examining each one separately, there are no data in the literature comparing the magnitudes of the iatrogenic, percutaneous coronary intervention (PCI)-induced, microvascular dysfunction (Type-4 CMD) and coronary microvascular dysfunction (CMD) in the setting of ischemia in non-obstructed coronary arteries (INOCA) (Type-1 CMD).

Objectives We aimed to compare the characteristics of Type-1 and Type-4 CMD subtypes using coronary haemodynamic (resistance and flow-related parameters), thermodynamic (wave energy-related parameters) and hyperemic ECG changes.

Methods Coronary flow reserve (CFR) value of <2.5 was defined as CMD in both groups. Wire-based multimodal perfusion markers were comparatively analysed in 35 patients (21 INOCA/CMD and 14 CCS/PCI) enrolled in NCT05471739 study.

Results Both groups had comparably blunted CFR values per definition (2.03±0.22 vs 2.11±0.37; p: 0.518) and similar hyperemic ST shift in intracoronary ECG (0.16±0.09 vs 0.18±0.07 mV; p: 0.537). While the Type-1 CMD was characterised with impaired hyperemic blood flow acceleration (46.52±12.83 vs 68.20±28.63 cm/s; p: 0.017) and attenuated diastolic microvascular decompression wave magnitudes (p=0.042) with higher hyperemic microvascular resistance (p<0.001), Type-4 CMD had blunted CFR mainly due to higher baseline flow velocity due to post-occlusive reactive hyperemia (33.6±13.7 vs 22.24±5.3 cm/s; p=0.003).

Conclusions The perturbations in the microvascular milieu seen in CMD in INOCA setting (Type-1 CMD) seem to be more prominent than that of seen following elective PCI (Type-4 CMD), although resulting reversible ischemia is equally severe in the downstream myocardium.

INTRODUCTION

Background Components of the coronary circulation, from major epicardial arteries to the distal capillary bed, harmonically attempt to sustain myocardial perfusion to meet the need.¹ If a perturbation at any point of this continuous structure cannot be compensated by regulatory mechanisms, a perfusion defect will occur, resulting in ischemia in the related myocardial tissue.² Flow-limiting epicardial atherosclerosis is the leading cause of the myocardial ischemia, but not infrequently, an ischemic insult may be present...
without flow limiting epicardial coronary artery disease. Patients who have myocardial ischaemia presenting with anginal complaints without haemodynamically relevant epicardial stenoses (ischaemia in the setting of non-obstructed coronary arteries (INOCA)) may have myocardial perfusion abnormalities due to functionally and/or structurally diseased microvascular milieu which is termed as coronary microvascular dysfunction (CMD, Type-1). Indeed, up to 60% of patients with INOCA have been documented to have CMD, which has been shown to be associated with myocardial ischaemia. CMD with this ongoing myocardial ischaemic insult has been repeatedly shown to be associated with a poor long-term cardiovascular outcome in these patients. The deeper endotyping into structural and functional CMD has revealed the equally poor long-term outcomes. In order to explain pathophysiological background of this association, magnitude and extent of CMD and its consequences need to be understood more comprehensively.

Although percutaneous coronary intervention (PCI) forms the basis of treatment for flow-limiting epicardial coronary stenosis, it can also induce an iatrogenic form of CMD mainly due to the distal atherothrombotic embolization and autonomic dysfunction constituting Type-4 CMD. Although the underlying mechanisms may vary, both Type-4 and Type-1 CMD have been shown to adversely affect cardiovascular prognosis and increase the frequency of major adverse cardiovascular events. In the literature, however, there is a paucity of data comparing the characteristics of the PCI-induced (iatrogenic) Type-4 and Type-1 CMD.

**Purpose**

In this study, we aimed to compare the CMD characteristics in Type-1 and Type-4 settings using coronary haemodynamic (resistance and flow-related parameters), thermodynamic (wave energy-related parameters) and intracoronary electrocardiographic indices to understand the driving mechanisms of blunted coronary flow reserve (CFR) in both groups as well as the severity of resulted reversible ischaemia.

**METHODS**

**Study population**

Data of patients with INOCA were retrieved from ‘Simultaneous Assessment of Coronary Microvascular Dysfunction and Ischaemia with Non-obstructed Coronary Arteries With Intracoronary ECG and Intracoronary Doppler’ study (Clinical Trials NCT05417739). Original dataset had 21 meticulously selected patients with INOCA/CMD (with documented ischaemia via myocardial perfusion scan and angiographically no visual atherosclerotic disease). In the INOCA/CMD group, all patients had at least one major epicardial coronary artery with CFR <2.5.

For this analysis, we included the ischaemia-related vessels (IRVs) of 21 patients from CMD/INOCA (Type-1 CMD) group via detected by myocardial perfusion scan. Fourteen consecutive patients with chronic coronary syndrome (CCS) undergoing PCI for a flow limiting stenosis were included in the study as the comparator arm. Of which, those with post-PCI CFR <2.5 were labelled as Type-4 CMD (n=11). Doppler wire (FloWire) was used to cross the lesion. After completion of the successful stent implantation with TIMI 3 flow, intracoronary flow and intracoronary ECG (ICECG) data were recorded over FloWire during rest and under hyperemia. Figure 1 demonstrates the study tree, the number of patients available for each paired analysis.

**Physiological study**

Intracoronary flow velocity was acquired using a Doppler guidewire (FloWire, Philips/Volcano) and pressure was obtained from the guiding catheter. Average Doppler peak flow velocity and mean aortic pressure (P_a) were simultaneously and continuously recorded with a 200 Hz sampling frequency of with the ComboMap console (ComboMap console, Philips, Volcano) and stored offline. All haemodynamic signals were recorded at rest and under maximum hyperemia induced by intracoronary bolus Adenosine administration (100 µg for the right and 200 µg for the left coronary artery and circumflex artery). The retrieved data were then processed via Study Manager (Amsterdam) for Matlab (The MathWorks, USA) environment. ICECG was recorded via FloWire attached to an ECG machine alongside the standard extremity leads. The Wilson’s central terminal was constructed by attaching the limb electrodes to the ECG machine. V₃ lead of the ECG device was then connected to the FloWire via an insulated cable having alligator clips at both ends. The wave-intensity analysis was performed in MATLAB environment with a commonly used non-commercial dedicated software (Imperial College, UK).

**Derivation of variables**

Consecutive, adequate quality signal segments were used for each cases. Resting (basal microvascular resistance (BMR) and hyperemic microvascular resistance (HMR) and CFR were calculated per their definitions (BMR: P_a/average peak velocity basal (APVB); HMR: P_a/average peak velocity hyperemia (APVH); CFR: APVH/APVB). The variable of interest in ICECG was absolute hyperemic ST segment shift compared with resting state (ΔST). Net wave intensity (WI) was computed with the resting arterial blood pressure (P_a) and flow velocity (distal coronary) signals as previously described (WI=(dP/Δt)*(dU/Δt), W/m²/s²) to evaluate the unstimulated resting thermodynamics of coronary flow (figure 2). Wave separation was performed using the sum of squares method. Signal analysis was performed using MATLAB (R2021b, Mathworks, USA). The ICECG was recorded and stored physically on paper format by an investigator during rest and hyperemia (EC) simultaneously with intracoronary haemodynamic signal recordings (by MS and SU). Two investigators (AT and YA), who were blinded to ICECG records at that time, performed the wave intensity analysis.
Coronary artery disease

The only operator dependent part of the analysis was the selection of adequate quality resting time frame, since the resting analysis runs automatically.

**Utilization of aortic pressure in the absence of distal coronary pressure**

In order to evaluate the relationship between Pd and Pa, we have calculated the cross-correlations between resting Pa and Pd waveforms in 455 unique vessels with fractional flow reserve (FFR) values ranging from 0.40 to 1.00 from open access Define-Flow dataset (unpublished observations).16 The cross-correlation coefficients ranged between 0.8965 and 0.9988 with a mean value of 0.9866±0.0146. In vessels with FFR <0.80, the mean cross-correlation between Pa and Pd was as high as

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**Figure 1**  Study diagram. CAD, coronary artery disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; IC, intracoronary; ICECG, intracoronary ECG; INOCA, ischaemia in the setting of non-obstructed coronary arteries; PCI, percutaneous coronary intervention; MPS, myocardial perfusion scan; WIA, wave intensity analysis.

**Figure 2** Wave intensity analysis.
0.9770±0.0205 (n=312) whereas in the FFR ≥0.80 it was 0.9910±0.074 (n=143). This findings support to potential use of Pa in the absence of Pd both in coronary arteries.

Statistical analysis
Continuous variables were expressed as mean±SD or mean (95% CI). Normality of variables was assessed by Shapiro-Wilks test. Means were compared using Mann-Whitney U and Student’s t-tests in independent samples. One sample t-test was used to compare the means of the present study groups to the values reported in previous studies. Pearson’s or Spearman’s correlation coefficients were calculated to interrogate continuous relationships between variables as appropriate. The analysis of variance (ANOVA) and Kruskal-Wallis Tests were used to compare means between right coronary (RCA), left anterior descending (LAD) and left circumflex (LCX) arteries. The p value of <0.05 was considered to be statistically significant. All data were blindly analysed offline using SPSS (V.28.0.1.1 IBM) and JAMOVI statistical analysis software was used for visualisation of the relationships (The jamovi project (2023). Jamovi (Version 2.3)).

Ethical statement
The study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by Istanbul University’s Istanbul Faculty of Medicine ethics committee (File Identifier: 2019/1285). The clinical trial registration number is Clinical Trials NCT05471739 (https://www.clinicaltrials.gov).

RESULTS
Population characteristics
The CMD/INOCA (Type-1) group predominantly consisted of female patients (n: 17, 81%) whereas the majority of the CCS/PCI (Type-4) group were men (n: 8, 73%). Mean ages were 59.5±6.6 and 59.6±8.0 years in Type-4 and Type-1 CMD groups, respectively (p: 0.979). Left anterior descending artery was the IRV in the majority of Type-4 (82%, n: 9) and Type-1 CMD 62% (n: 13) groups. Mean stent length was 26.4±8.4 mm. Table 1 comparatively demonstrates the baseline and angiographic characteristics of the study groups.

Haemodynamic data
There were no significant differences in baseline haemodynamic characteristics between male and female patients (mean arterial pressure (MAP): 94±16 vs 90±9 mm Hg, p=0.38; APVB: 24±5 vs 27±13 cm/s; BMR: 4.1±1.1 vs 3.8±1.6 mm Hg/s/cm, p=0.21; CFR: 2.14±0.36 vs 2.18±0.47, p=0.85). The mean values of APVB (p=0.82), APVH (p=0.66), CFR (p=0.96), BMR (p=0.88) and HMR (p=0.61) were also indifferent between the studied vessel groups in the entire group analysis (mean values are not reported) (APVB (p=0.76), APVH (p=0.72), CFR (p=0.76), BMR (p=0.93) and HMR (p=0.92)).

Coronary blood flow
The Type-4 group had significantly higher resting mean flow velocities (APVB) following PCI compared with that of the Type-1 group (33.6±13.7 vs 22.2±5.3 cm/s; p: 0.003). The Type-1 group had significantly blunted hyperemic flow velocity (APVH) compared with PCI group (46.52±12.83 vs 68.20±28.63 cm/s; p: 0.017). Both groups had similar CFR values (2.11±0.37 vs 2.03±0.22; p: 0.518) (table 2, figure 3). Impaired CFR was driven by relative basal hyperemia in Type-4 group and by blunted hyperemic microvascular resistance attenuation causing low APVH in Type-1 group.

Microvascular resistance
The Type-1 group had higher BMR and HMR values (p<0.001 for both) (Means±SDs are provided in table 2, figure 3).

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BP, blood pressure; CMD, coronary microvascular dysfunction; LDL, low density lipoprotein; PCI, percutaneous coronary intervention.
Coronary artery disease

Wave intensity analysis

As shown in table 2 and figure 4, Type-1 and Type-4 CMD groups had remarkable differences in WIA pattern. Backward expansion wave (BEW) and forward expansion wave (FEW) intensities were smaller in Type-1 group before and after wave separation. However, mean forward compression wave (FCW) intensities were indifferent (paired Means±SD
provided for each in table 2, figure 4). No significant relationship between HMR/CFR and WIA parameters could be observed. Interobserver agreement assessed by BEW peak magnitude correlations (R²: 0.859; p: 0.002) was good.

Comparison of WIA characteristics with previously reported CMD groups

Regarding the coronary arterial energy transfer characteristics, our Type-4 group had mean BEW peak magnitude of 149 883 W/m²/s² (net) and 165 344 W/m²/s² (separated), which are similar to that of previously reported in patients with anginal complaints and positive functional test results without relevant epicardial stenoses (indicating that the symptoms are of a microvascular origin, angina with non-obstructive coronary arteries (ANOCA) reported by Broyd et al 17 (−149 000±78 000, one sample t-test p: 0.627 and 0.977 for separated and net BEW of our BEW mean, respectively) Type-1 CMD group had an attenuated mean BEW magnitude than previously reported ANOCA series (Type-4 CMD vs reference ANOCA group of Broyd et al; one sample t-test, 88 533±57 330 vs −149 000±78 000 W/m²/s², p<0.001). 17 In parallel, the mean BEW amplitude (Our Type-1 CMD group mean: 88 533±57 330 W/m²/s²) was almost one SD lower than the mean BEW value (5.5±4.6−0.9×10⁵ W/m²/s²) than that of previously reported in angiographically normal coronary arteries by Davies et al (mean BEW: 5.5±4.6×10⁵ W/m²/s², p<0.001 in one sample t-test). 17, 18

Intracoronary ECG

Hyperemic absolute ST shifts (ΔST) were indifferent in magnitude between the two groups (0.16±0.09 vs 0.18±0.07 mV; p: 0.537) (table 2, figure 3). Magnitude of the BCW was correlated with ΔST (r: −0.415; p: 0.039) (figure 5).

DISCUSSION

In this comparative study, we have provided a multimodal demonstration of the microvascular perfusion parameters in patients with Type-1 (Anginal episodes+no obstructive epicardial lesion+CFR<2.5+proven myocardial ischaemia) and Type-4 CMD (Post-PCI TIMI 3 flow+CFR<2.5) (figure 6). The study included coronary haemodynamic (flow and resistance), electrocardiographic (hyperemic

Figure 5 The relationship between BCW and ∆ST. BCW, backward compression wave.

Figure 6 Visual abstract: differences between Type-1 and Type-4 CMD. APVB, average peak velocity basal; APVH, average peak velocity hyperemia; BMR, basal microvascular resistance; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; HMR, hyperemic microvascular resistance; ICECG, intracoronary ECG; INOCA, ischaemia in the setting of non-obstructed coronary arteries; PCI, percutaneous coronary intervention.
evaluate ischaemic electrical voltage changes in the coronary lesions and only very recently to assess presence of the presence of reversible myocardial ischaemia of microvascular origin at similar magnitude in both groups. The ICECG is an established method to monitor the ischaemic changes beginning from the very early stages following PCI. It provides an opportunity to detect ischaemia much more conspicuously and conceivably sooner and better than the surface ECG. ICECG was used to predict myocardial viability, to assess severity of bifurcation lesions, and ischaemic potential of epicardial coronary lesions and only very recently to assess presence and severity of microvascular dysfunction and ischaemia in INOCA patients (ClinicalTrials.gov ID NCT05417399). Notably, an independent relationship between hyperemic ST shift with a worse prognosis has been previously reported. Considering the fact that we have objectively proven the perfusion defects via myocardial perfusion scan (MPS) in the INOCA group as part of study protocol prior to haemodynamic measurements, the demonstrated relationships between AST, CMD and perfusion defects suggest that the subsequent electrical heterogeneity between neighbouring myocardial territories occurs due to regional perfusion defects with microvascular origin in nonobstructed vessels with CMD. Mechanistically, several theories may be suggested to explain how hyperemic ST shift and this perfusion defects/ischaemia is associated. Adenosine may be exacerbating the perfusion heterogeneity leading to an increased electrical voltage potential gradient, which may be more overt between adjacent healthier (normal flow reserve) and diseased myocardial territories in terms of microcirculation. This may be a microvascular analogue of the transmural steal phenomenon. In line with this explanation, patchy hyperemic perfusion defects at microvascular bed has been previously reported in the setting of the hypertrophic cardiomyopathy without obstructive coronary artery disease (CAD). In the current study, mean hyperemic ST – shift (mV) in both groups were similar which implies the presence of same magnitude of reversible ischaemia in Type-1 and Type-4 CMD groups. Consistent with the literature, while the impaired flow reserve (CFR) is mainly driven by post-occlusive relative hyperemia, which significantly amplifies resting coronary flow following PCI, in the Type-4 group. It was mainly driven by blunted hyperemic flow augmentation and inadequate resistance attenuation due to worse microvascular expansibility, reflected by higher HMR and lower BEW values indicating structural microvascular abnormality in the Type-1 CMD. Notably, Type-1 and Type-4 CMD groups showed different coronary wave intensity profiles. The mean BEW, BCW and FEW magnitudes were significantly smaller in Type-1 CMD, however, the mean FCW amplitudes were indifferent. Lower peak BEW values found in Type-1 group indicating a worse microvascular expansibility during diastole, together with the higher HMR may display the distinctive features of pathomechanisms in both groups, whereas, the similar mean ∆ST values highlighting the severity of resulting ischaemia is eventually indifferent. Nonetheless, Type-4 CMD occurs acutely as a functional consequence of reperfusion and tend to attenuate and normalise in follow-up whereas Type-1 CMD develops over years and constitutes a permanent and progressive entity.

**Coronary microvascular haemodynamics in Type-4 CMD**

CMD following elective coronary interventions is associated with a worse clinical outcome. Type-4 CMD involves a multifactorial process mainly driven by distal microembolisation and thrombus formation in capillary bed accompanied by a perivascular inflammatory process as well as the release of miscellanea of vasoactive substances and/or myocardial oedema developing in varying extents in the early hyperemic period. In acute phase, resting blood flow may temporarily increase contributing to lower CFR values, which may not recover immediately and last up to couple of months (persistent functional CMD). In severe cases, even periprocedural infarctions with remarkable periprocedural troponin increase may be seen. At long-term follow-up, periprocedural troponin elevation has been shown to be related with a 50% increased risk of subsequent major cardiac events and increased risk of re-PCI and death.

Patients with Type-4 CMD showed evidence of ischaemia in downstream myocardium assessed by ICECG with comparable dynamic hyperemic ST shift to the Type-1 CMD group patients. Type-4 group was mainly characterised by increased baseline flow velocity (post-occlusive hyperemia) as expected. Post-PCI mean HMR value was also remarkably lower than that of CMD/INOCA group. This finding is also in line with the basic principle of coronary physiology and functional nature of the pathology. The microvascular resistance vessels are known to be pressure distensible and controlled by autoregulatory mechanisms. In maximally dilated coronary bed, coronary blood flow, hence the microvascular perfusion, is fully and linearly pressure-dependent.

Flow-limiting significant epicardial stenosis is compensated by an autoregulatory maximum vasodilation and resistance attenuation to sustain the blood flow. In this setting, treatment of a highly stenotic epicardial segment leads to an acute further basal flow augmentation by restoring distal perfusion pressure while the resistance is still low in Type-4 CMD group.

Regarding the coronary arterial energy transfer characteristics, our Type-4 group had similar mean BEW peak magnitude to that of previously reported in patients with anginal complaints and positive functional test results without relevant epicardial stenoses (indicating that the symptoms are of a microvascular origin, ANOCA)
reported by Broyd et al.\textsuperscript{17} This findings indicate the comparable impairment in microvascular expansibility in acute phase of Type-1 CMD following elective stenting and in patients with primary CMD (Type-1). Furthermore, in the setting of chronic obstructive CAD, attenuated BEW amplitudes in the acute phase were seen 30 min after a 1 min-long ballooning, which was performed to assess the impact of myocardial stunning, may be attributed to microvascular stunning.\textsuperscript{35} No continuous relationship between HMR and BEW could be observed in this study. However, lower HMR and higher BEW values observed in Type-4 in comparison with Type-1 CMD are consistent with the current physiological knowledge as Type-1 is mainly driven by the impaired vasodilatory capacity with higher minimal microvascular resistance and worse arteriolar expansibility, whereas the main reason of reduced flow reserve is relative hyperemia in Type-4 CMD in which microvascular resistance attenuation capacity at hyperemia is preserved.\textsuperscript{35}

The BCW has been recently proposed to be a measure of myocardial viability in patients with heart failure secondary to ischaemic cardiomyopathy, where the greater amplitudes are related to a larger viable myocardial mass in the related territory.\textsuperscript{36} Although Type-1 group had smaller BCW amplitudes, lack of any gold standard methods for viability limits the interpretability of this wave in the present study. Likewise although significant, difference in the FEW magnitudes is of limited interpretability in our cohort as (1) the SD are relatively big, (2) the study was not designed hence equipped to investigate the meanings of WIA waveforms and (3) literature lacks of data and knowledge about this wave. Nonetheless, patients with Type-4 CMD with satisfactory TIMI 3 flow following PCI has similarly severe reversible ischaemia in related vessel-specific territory in comparison with patients with Type-1 CMD although the drivers largely differ in terms of coronary wave energy transfer features as well as haemodynamic characteristics.

Coronary microvascular haemodynamics in Type-1 CMD model (INOCA)

Presence of the ischaemia in the setting of non-obstructed coronary arteries (INOCA) is encountered in up to half of the patients undergoing angiography for anginal complaints.\textsuperscript{7,37} CMD comprises the major pathology in this group.\textsuperscript{38} These patients are typically characterised by blunted hyperemic flow velocity augmentation (lower CFR values). A specific subgroup of CMD with higher minimal microvascular resistance (HMR), named structural CMD, had distinctive macrostructural and microstructural alterations in addition to impaired microvascular functionality.\textsuperscript{39,40}

Our study has included the IRVs identified through myocardial perfusion scan from patients with Type-1 CMD, which had similar hyperemic ST segment shift compared with post-elective PCI CMD (Type-4 CMD). Patients with CMD/INOCA with angiographically normal coronary arteries have comparable electrophysiological reversible ischaemia measures (ΔST) with post-PCI status, and these vessels had significantly higher HMR values compared with the Type-1 group. The significantly worse microvascular expansibility in our Type-1 CMD group with CFR <2.5 and perfusion scan proven ischaemia in comparison to previously reported values\textsuperscript{17,18} may suggest that patients with documented CFR <2.5 with objective ischaemia proof have worse microvascular expansibility in comparison with the ANOCA patients with positive functional test results alone.

On the other hand, significantly smaller in BCW intensities found in Type-1 CMD group should be approached cautiously since larger BCW values are associated with viability in the downstream myocardium\textsuperscript{36} but also they have been reported in patients with poorer microcirculation and CMD.\textsuperscript{5} This difference can probably be attributed to the dissimilarity in the context of studies. In a study measuring the intracoronary pressure and flow velocity data in the ischaemia-related artery (IRA) with the presence of a large infarct (=smaller, less contractile viable myocardium downstream) in comparison to healthy reference arteries, smaller BCW values in IRA are expected to be observed considering the difference in contractility between territories. On the other hand, a study involving CMD in the setting of INOCA may arguably display relatively augmented microvascular compression waves in comparison to a healthy reference group.

These findings of the present study, which had comparatively analysed Type-1 and Type-4 CMD groups utilising ICECG, IC Doppler and WIA parameters, collectively indicate that, CMD induced reversible ischaemia is as severe as that of acute seen following elective PCI in the setting of chronic CAD, although the drivers may be different and the microvascular milieu is more severely affected in Type-1, as reflected by poorer microvascular expansibility.

Limitations and strengths

The current analysis has several technical limitations alongside the small sample size. The PCI group had no information regarding preprocedural CMD and postprocedural troponin values. For the calculation of microvascular resistance and wave intensity, we have relied on the aortic pressure (Pa) in the absence of Pd, given that there were no epicardial stenoses angiographically and our recent unpublished observations on Pd–Pa relationships demonstrating very high cross-correlation coefficients even in the presence of very low FFR values. However, there were no post-stent Pd/Pa or FFR measurements to uncover small diffusely developing pressure gradients throughout the artery. Although, the potential low residual pressure gradients in the Post-PCI/CMD group with no visual residual disease could expectedly have no relevant impact on the previous observations, calculation with distal pressure measurements would be more reliable. Inclusion of postprocedural physiological/ imaging-based assessment methods would provide valuable information about residual epicardial ischaemia.
The present analysis, as a mechanistic single centre study, could demonstrate no difference in haemodynamic characteristics with respect to sex and epicardial vessel in the entire group. Due to the small sample size, further analysis in CMD versus No-CMD cases in this regard could not be performed. Considering the previously reported differences in the literature, however, further studies should take the impact of these confounders into account. On the other hand, our study included only CMD/INOCA patients with MPS-documented evident-ischaemia and studied the IRVs, which forms a well-defined and evidence based CMD-vessel group rather than considering only impaired surrogate haemodynamic indices.

CONCLUSION
The perturbations in the microvascular milieu seen in CMD in INOCA setting (Type-1 CMD) seem to be more prominent than that of temporarily seen following elective PCI (Type-4 CMD), although resulting reversible ischaemia is equally severe in the downstream myocardium. Utilisation of contemporary multimodal microcirculatory assessment methods may provide new insight into pathomechanisms considering the observed differences in WIA patterns. This finding may partially aid explaining the poor long-term prognosis observed in patients with INOCA.

CLINICAL IMPLICATIONS
Invasive physiological assessment of coronary microcirculation and CMD via pressure and Doppler sensors can be improved via addition of WIA and ICECG analysis without significant additional procedural time and costs, allowing a deeper understanding on ventricle–arterial thermodynamic coupling and detection of real time inducible electrical heterogeneities indicative of patchy microvascular perfusion defects, which would otherwise necessitate high-cost additional modalities like MPS.

REFERENCES