Laidlaw Undergraduate Research and Leadership Programme Research Report

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Introduction

Roughly half of all individuals who undergo coronary angiography are found to have non-obstructive coronary artery disease (NOCAD) [1]. In more than half of these cases, the underlying mechanism is coronary microvascular dysfunction (CMD), which involves both structural and functional abnormalities within the coronary microcirculation [2]. CMD has been linked to poorer long-term outcomes [3].

Although invasive coronary angiography remains the reference standard for diagnosing obstructive coronary artery disease, its relatively low sensitivity and semi-quantitative nature limit its diagnostic role in NOCAD. Accordingly, current clinical guidelines advise performing invasive coronary function testing to evaluate CMD [4]. The index of microcirculatory resistance (IMR) provides a direct, quantitative measurement of CMD that is independent of the status of the epicardial arteries, and has proven prognostic value across several clinical settings [5–8].

Nevertheless, wire-based IMR measurement requires intracoronary instrumentation, pharmacologic hyperaemia, and complex procedural steps. As a result, CMD evaluation is usually restricted to a single artery—most commonly the left anterior descending artery (LAD) [4]—assuming uniform distribution of microvascular dysfunction across the myocardium. However, emerging studies indicate that CMD can vary between vascular territories, suggesting that single-vessel testing may underestimate total disease burden [9–11]. The prognostic implications of assessing CMD across multiple vessels remain unclear.

Angiography-derived IMR (angio-IMR) is a novel, wire-free method for CMD evaluation. Prior work has shown strong agreement between angio-IMR and conventional wire-based IMR in patients with angina or myocardial ischaemia without obstructive coronary artery disease [12–13]. Angio-IMR enables a comprehensive appraisal of microvascular health. The present study evaluates the prognostic utility of multi-vessel angio-IMR in NOCAD.

Methods

Study design

Baseline demographic and clinical data were collected at the time of the index procedure and extracted from electronic health records. Ethical approval was granted by the Institutional Review Board of the University of Hong Kong and the West Cluster of the Hong Kong Hospital Authority. The study followed the principles of the Declaration of Helsinki. Due to its retrospective design, the requirement for informed consent was waived.

Study population

Eligible participants were aged 18 years or older and underwent coronary angiography at Queen Mary Hospital, Hong Kong, for suspected coronary artery disease between 1 January 2014 and 31 December 2017. Indications for angiography included angina, dyspnoea, abnormal electrocardiogram findings, a positive treadmill stress test, or physician referral based on clinical judgement.

Patients were classified as having NOCAD if all three major coronary arteries showed <50% stenosis on angiography and an angiography-derived fractional flow reserve >0.80. Exclusion criteria were:

1. Severe hepatic or renal impairment

2. Active or prior malignancy
3. Significant valvular heart disease
4. Previous coronary artery bypass graft surgery
5. Left ventricular ejection fraction <50%
6. Acute coronary syndrome (STEMI or NSTEMI) within seven days of angiography
7. Unsuitable images for angio-IMR analysis in any of the three major vessels (e.g., due to overlap, artefacts, or poor quality)

Angiographic analysis

Procedures were performed by board-certified cardiologists in accordance with local best practice. Angio-IMR was calculated for the LAD, left circumflex artery (LCX), and right coronary artery (RCA) using the FlashAngio system (Rainmed Ltd., Suzhou, China) [14–16].

Definitions

Hypertension was defined as systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg. Hyperlipidaemia was defined as total cholesterol, triglyceride, or LDL cholesterol above the 90th percentile of the general population. A vessel-level angio-IMR ≥25 was considered indicative of CMD [16–19].

Grouping strategies

To compare prognostic performance, patients were stratified by:

1. LAD angio-IMR ≥25 vs. <25
2. Number of vessels with angio-IMR ≥25 (0–3)

Outcomes and follow-up

The primary endpoint was major adverse cardiovascular events (MACE), comprising cardiovascular death, hospitalisation for heart failure, and revascularisation, as per Academic Research Consortium definitions [20]. Deaths were classified as cardiovascular unless a non-cardiac cause was confirmed. Median follow-up duration was 4.3 years (IQR 3.9–4.6).

Statistical analysis

Normality was assessed by the Kolmogorov–Smirnov test and visual inspection of Q-Q plots and histograms. Continuous variables were expressed as mean ± SD or median (IQR) depending on distribution; categorical variables as frequencies (%). Group comparisons employed chi-square tests for categorical data and t-tests, Mann–Whitney U tests, ANOVA, or Kruskal–Wallis tests for continuous data.

The total 3V angio-IMR cut-off was derived from maximally selected log-rank statistics. Kaplan–Meier analysis assessed cumulative MACE incidence, with log-rank tests for between-group differences. Cox regression estimated hazard ratios (HRs) and 95% confidence intervals (CIs), adjusting for variables identified via a directed acyclic graph (DAG) in DAGitty: diabetes, smoking, hypertension, hyperlipidaemia, and prior myocardial infarction. Incremental prognostic value over a base model (age, sex, smoking) was evaluated using the C-index, integrated discrimination improvement (IDI), and net reclassification index (NRI). Analyses used R v4.4.1 and Prism 10; significance threshold was two-sided $P < 0.05$.

Results

Study population

Out of 2,435 angiography patients, 500 met NOCAD criteria. After applying exclusions, 439 patients (1,317 vessels) formed the analytic cohort. Median age was 65 years, 55% were male. Diabetes affected 34%, hypertension 40%, and hyperlipidaemia 36%.

LAD angio-IMR

Patients with LAD angio-IMR ≥25 more frequently had elevated LCX and RCA angio-IMR values and a higher prevalence of hypertension and hypertriglyceridaemia. Other baseline variables were comparable.

MACE occurred in 24.8% vs. 7.0% for LAD ≥25 vs. <25 (P<0.001), driven by more heart failure hospitalisations (16.5% vs. 3.0%) and revascularisations (8.3% vs. 3.0%), with no difference in cardiovascular death. LAD ≥25 predicted MACE both univariately (HR = 3.895, 95% CI 2.233–6.796) and after adjustment (HR = 4.158, 95% CI 2.372–7.289; P<0.001).

Total 3V angio-IMR

The optimal cut-off was 70.3. Above this threshold, patients more often had CMD in all three arteries and higher angio-IMR values in each vessel. Hypertension was also more prevalent. MACE rates were 28.7% vs. 4.7% (P<0.001), driven by more heart failure admissions (18.0% vs. 1.9%) and revascularisations (9.8% vs. 2.2%), with no cardiovascular mortality difference. Total 3V ≥70.3 strongly predicted MACE (adjusted HR = 7.331, 95% CI 3.977-13.512; P<0.001).

Incremental prognostic value

Adding LAD angio-IMR to the clinical model improved discrimination (C-index 0.729 vs. 0.663, P=0.031) and reclassification (IDI 0.084, NRI 0.303; both P=0.030). Adding total 3V angio-IMR produced greater prognostic value (C-index 0.778, IDI 0.153, NRI 0.469; all P<0.001) when compared with baseline model and outperformed LAD-only measures (all P<0.020).

Clinical Implications

The present study demonstrates that multi-vessel assessment of angio-IMR substantially improves prognostic stratification in patients with NOCAD, compared to conventional single-vessel evaluation. These findings have several important implications for the management of patients with angina or ischaemia in the absence of obstructive epicardial disease.

First, our results challenge the prevailing paradigm of single-vessel invasive coronary function testing—typically limited to the LAD—by showing that CMD is frequently heterogeneous across coronary territories. In our cohort, over one-fifth of patients with CMD would have been missed if only the LAD were interrogated. This underlines the risk of underestimating global microvascular disease burden when assuming uniform distribution, and suggests that broader anatomic coverage could lead to more accurate diagnosis and risk assessment.

Second, total three-vessel angio-IMR emerged as a stronger predictor of MACE than LAD-only angio-IMR, with incremental prognostic value over established clinical risk factors. This suggests that aggregate microvascular resistance across all major coronary territories may better capture the overall haemodynamic compromise of the myocardium, thereby refining prognostic modelling. Such comprehensive assessment could help identify high-risk patients who may otherwise appear low-risk using traditional angiographic or single-vessel physiological data.

In summary, multi-vessel angio-IMR assessment can improve the detection, prognostication, and potential management of CMD in NOCAD. Its integration into clinical workflows could represent a paradigm shift towards a more comprehensive and physiologically grounded evaluation of coronary artery disease, enabling earlier intervention and better long-term outcomes for a substantial subset of patients who currently remain underdiagnosed and undertreated.

References

1. Rahman H, Corcoran D, Aetesam-Ur-Rahman M, Hoole SP, Berry C, Perera D. Diagnosis of patients with angina and non-obstructive coronary disease in the catheter laboratory. Heart. 2019 Oct;105(20):1536-1542.
2. Sara JD, Widmer RJ, Matsuzawa Y, Lennon RJ, Lerman LO, Lerman A. Prevalence of Coronary Microvascular Dysfunction Among Patients With Chest Pain and Nonobstructive Coronary Artery Disease. JACC Cardiovasc Interv. 2015 Sep;8(11):1445-1453.
3. Del Buono MG, Montone RA, Camilli M, Carbone S, Narula J, Lavie CJ, Niccoli G, Crea F. Coronary Microvascular Dysfunction Across the Spectrum of Cardiovascular Diseases: JACC State-of-the-Art Review. J Am Coll Cardiol. 2021 Sep 28;78(13):1352-1371.
4. Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, Banning AP, Budaj A, Buechel RR, Chiariello GA, Chieffo A, Christodorescu RM, Deaton C, Doenst T, Jones HW, Kunadian V, Mehilli J, Milojevic M, Piek JJ, Pugliese F, Rubboli A, Semb AG, Senior R, Ten Berg JM, Van Belle E, Van Craenenbroeck EM, Vidal-Perez R, Winther S; ESC Scientific Document Group. 2024 ESC Guidelines for the management of chronic coronary syndromes. Eur Heart J. 2024 Sep 29;45(36):3415-3537.
5. Fearon WF, Shah M, Ng M, Brinton T, Wilson A, Tremmel JA, Schnittger I, Lee DP, Vagelos RH, Fitzgerald PJ, Yock PG, Yeung AC. Predictive value of the index of microcirculatory resistance in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol. 2008 Feb 5;51(5):560-5.
6. Murai T, Yonetsu T, Kanaji Y, Usui E, Hoshino M, Hada M, Hamaya R, Kanno Y, Lee T, Kakuta T. Prognostic value of the index of microcirculatory resistance after percutaneous coronary

intervention in patients with non-ST-segment elevation acute coronary syndrome. Catheter Cardiovasc Interv. 2018 Nov 15;92(6):1063-1074.

7. Nishi T, Murai T, Ciccarelli G, Shah SV, Kobayashi Y, Derimay F, Waseda K, Moonen A, Hoshino M, Hirohata A, Yong ASC, Ng MKC, Amano T, Barbato E, Kakuta T, Fearon WF. Prognostic Value of Coronary Microvascular Function Measured Immediately After Percutaneous Coronary Intervention in Stable Coronary Artery Disease: An International Multicenter Study. Circ Cardiovasc Interv. 2019 Sep;12(9):e007889.
8. Ahn JM, Zimmermann FM, Arora S, Solberg OG, Angerås O, Rolid K, Rafique M, Aaberge L, Karason K, Okada K, Luikart H, Khush KK, Honda Y, Pijls NHJ, Lee SE, Kim JJ, Park SJ, Gullestad L, Fearon WF. Prognostic value of comprehensive intracoronary physiology assessment early after heart transplantation. Eur Heart J. 2021 Dec 21;42(48):4918-4929.
9. Hoshino M, Hoek R, Jukema RA, Dahdal J, van Diemen P, Raijmakers P, Driessen R, Twisk J, Danad I, Kakuta T, Knuuti J, Knaapen P. Homogeneity of the coronary microcirculation in angina with non-obstructive coronary artery disease. Eur Heart J Cardiovasc Imaging. 2025 Jun 30;26(7):1120-1127.
10. Rehan R, Wong CCY, Weaver J, Chan W, Tremmel JA, Fearon WF, Ng MKC, Yong ASC. Multivessel Coronary Function Testing Increases Diagnostic Yield in Patients With Angina and Nonobstructive Coronary Arteries. JACC Cardiovasc Interv. 2024 May 13;17(9):1091-1102.
11. Elharram M, Hillier E, Hawkins S, Mikami Y, Heydari B, Merchant N, White JA, Anderson T, Friedrich MG, Pilote L. Regional Heterogeneity in the Coronary Vascular Response in

Women With Chest Pain and Nonobstructive Coronary Artery Disease. Circulation. 2021 Feb 16;143(7):764-766.

12. Wang J, Li C, Zhang M, Zhou J, Zhang Q, Guo W, Pan C, Yu H, Chang S, Lu H, Chen Z, Shi H, Zhang F, Qian J, Ge J. The performance of angiography-derived index of microcirculatory resistance for ischemia in angina with non-obstructive coronary artery disease: Validated by wire-based IMR and SPECT-MPI. Int J Cardiol. 2025 Jul 15;431:133236.
13. Mejía-Rentería H, Wang L, Chipayo-Gonzales D, van de Hoef TP, Travieso A, Espejo C, Núñez-Gil IJ, Macaya F, Gonzalo N, Escaned J. Angiography-derived assessment of coronary microcirculatory resistance in patients with suspected myocardial ischaemia and non-obstructive coronary arteries. EuroIntervention. 2023 Apr 3;18(16):e1348-e1356.
14. Choi KH, Dai N, Li Y, Kim J, Shin D, Lee SH, Joh HS, Kim HK, Jeon KH, Ha SJ, Kim SM, Jang MJ, Park TK, Yang JH, Song YB, Hahn JY, Doh JH, Shin ES, Choi SH, Gwon HC, Lee JM. Functional Coronary Angiography-Derived Index of Microcirculatory Resistance in Patients With ST-Segment Elevation Myocardial Infarction. JACC Cardiovasc Interv. 2021 Aug 9;14(15):1670-1684.
15. Zhang W, Singh S, Liu L, Mohammed AQ, Yin G, Xu S, Lv X, Shi T, Feng C, Jiang R, Mohammed AA, Mareai RM, Xu Y, Yu X, Abdu FA, Che W. Prognostic value of coronary microvascular dysfunction assessed by coronary angiography-derived index of microcirculatory resistance in diabetic patients with chronic coronary syndrome. Cardiovasc Diabetol. 2022 Oct 29;21(1):222.

16. Ai H, Feng Y, Gong Y, Zheng B, Jin Q, Zhang HP, Sun F, Li J, Chen Y, Huo Y, Huo Y. Coronary Angiography-Derived Index of Microvascular Resistance. Front Physiol. 2020 Dec 16;11:605356.
17. Fearon WF, Kobayashi Y. Invasive Assessment of the Coronary Microvasculature: The Index of Microcirculatory Resistance. Circ Cardiovasc Interv. 2017 Dec;10(12):e005361.
18. Melikian N, Vercauteren S, Fearon WF, Cuisset T, MacCarthy PA, Davidavicius G, Aarnoudse W, Bartunek J, Vanderheyden M, Wyffels E, Wijns W, Heyndrickx GR, Pijls NH, de Bruyne B. Quantitative assessment of coronary microvascular function in patients with and without epicardial atherosclerosis. EuroIntervention. 2010 Apr;5(8):939-45.
19. Solberg OG, Ragnarsson A, Kvarsnes A, Endresen K, Kongsgård E, Aakhus S, Gullestad L, Stavem K, Aaberge L. Reference interval for the index of coronary microvascular resistance. EuroIntervention. 2014 Jan 22;9(9):1069-75.
20. Garcia-Garcia HM, McFadden EP, Farb A, Mehran R, Stone GW, Spertus J, Onuma Y, Morel MA, van Es GA, Zuckerman B, Fearon WF, Taggart D, Kappetein AP, Krucoff MW, Vranckx P, Windecker S, Cutlip D, Serruys PW; Academic Research Consortium. Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document. Circulation. 2018 Jun 12;137(24):2635-2650.