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Prognostic Significance of Angiography-Derived Index of Microcirculatory Resistance in Dilated Cardiomyopathy: Integrative Assessment of Coronary Microvascular Dysfunction, Ventricular Remodeling, and Long-Term Clinical Outcomes

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Abstract

Background: Coronary microvascular dysfunction (CMD) is prevalent in dilated cardiomyopathy (DCM) and may independently contribute to adverse ventricular remodeling and clinical deterioration. The angiography-derived index of microcirculatory resistance (angio-IMR) offers a wire-free, contrast-based surrogate of microvascular resistance, yet its prognostic role in DCM remains incompletely characterized. Objectives: To evaluate the prognostic value of angio-IMR in patients with DCM, examining its associations with left ventricular (LV) remodeling parameters and long-term major adverse cardiovascular events (MACE). Methods: In this prospective observational cohort study, 187 DCM patients without obstructive coronary artery disease underwent invasive coronary angiography with simultaneous angio-IMR computation using validated computational fluid dynamics algorithms. Echocardiographic and cardiac magnetic resonance (CMR) parameters were obtained at baseline and at 12-month follow-up. The primary endpoint was MACE at 36 months, defined as a composite of cardiovascular death, heart failure hospitalization, and ventricular arrhythmia requiring intervention. Secondary endpoints included changes in LV ejection fraction (LVEF), LV end-diastolic volume (LVEDV), and global longitudinal strain (GLS). Results: Elevated angio-IMR (>25 U) was detected in 61.5% of patients and was independently associated with MACE (HR 2.84; 95% CI 1.67–4.83; p<0.001) after adjustment for LVEF, NT-proBNP, and late gadolinium enhancement extent. Patients with elevated angio-IMR exhibited significantly greater LV dilation (LVEDV +38 mL vs +11 mL; p=0.003), worse GLS deterioration (–2.1% vs –0.6%; p=0.01), and higher rates of heart failure hospitalization (42.0% vs 17.0%; p<0.001). Angio-IMR demonstrated incremental prognostic value beyond conventional risk markers (integrated discrimination improvement 0.112; p=0.002). Conclusions: Angio-IMR is a powerful, independently prognostic biomarker in DCM, identifying patients at heightened risk of adverse remodeling and MACE. Routine microvascular assessment via angio-IMR may refine risk stratification and guide intensified therapeutic strategies in this population.

Kew Words: angio-IMR; · dilated cardiomyopathy; · coronary microvascular dysfunction; · ventricular remodeling; · heart failure · MACE; cardiac magnetic resonance; global longitudinal strain

Introduction

1. Dilated cardiomyopathy (DCM) is defined by the presence of left ventricular (LV) dilation and systolic dysfunction in the absence of sufficient coronary artery disease (CAD), hypertension, valvular disease, or congenital heart disease to account for the observed myocardial impairment.[1] Despite advances in pharmacological and device-based therapies, DCM remains a leading cause of heart failure (HF) with reduced ejection fraction (HFrEF), accounting for approximately 30–40% of HF cases in Western populations and carrying a five-year mortality exceeding 20% in contemporary series.[2,3]
2. Coronary microvascular dysfunction (CMD), characterized by impaired vasodilatory capacity, increased microvascular resistance, and reduced coronary flow reserve (CFR), has

emerged as a pathophysiologically relevant mechanism in DCM that extends beyond epicardial coronary disease.4 Histopathological studies have demonstrated microvascular rarefaction, perivascular fibrosis, and endothelial dysfunction in DCM myocardium, all contributing to subendocardial ischemia and progressive cardiomyocyte loss even in the absence of epicardial stenoses.[5,6] These microstructural changes are clinically meaningful: CMD assessed by invasive coronary physiology or cardiac positron emission tomography (PET) independently predicts adverse outcomes in non-ischemic cardiomyopathy.[7]

3. The index of microcirculatory resistance (IMR), originally described by Fearon et al. using thermodilution-based pressure-temperature wire methodology, represents the first quantitative, vessel-specific measure of microvascular resistance validated against microsphere-derived resistance in animal models and correlated with microvascular obstruction on cardiac magnetic resonance (CMR) in clinical studies.8,9 However, the requirement for adenosine infusion and a dedicated pressure-temperature guidewire has limited its widespread adoption in clinical practice.
4. The angiography-derived IMR (angio-IMR) was developed as a wire-free alternative that computes microvascular resistance from conventional coronary angiography frames using computational fluid dynamics (CFD) and thrombolysis in myocardial infarction (TIMI) frame count methodology, without requiring hyperemic agents or physiological wires[.10,11] Validation studies have demonstrated good agreement between angio-IMR and wire-based IMR (Pearson r = 0.72–0.81), with diagnostic accuracy for CMD exceeding 80% in stable coronary disease.[12] Nevertheless, its application and independent prognostic significance specifically in DCM—a population with diffuse microvascular involvement, altered myocardial mechanics, and complex neurohumoral activation—have not been prospectively examined.
5. The present study was therefore designed to: (1) characterize the prevalence and distribution of elevated angio-IMR in a well-phenotyped DCM cohort; (2) assess its associations with CMR-derived ventricular remodeling parameters including LV end-diastolic volume (LVEDV), LV ejection fraction (LVEF), and late gadolinium enhancement (LGE) extent; (3) determine its independent prognostic value for major adverse cardiovascular events (MACE) at 36 months; and (4) evaluate whether angio-IMR provides incremental risk discrimination beyond established biomarkers.

2. Methods

2.1 Study Design and Population

This prospective, single-center observational cohort study enrolled consecutive adults (≥18 years) with a new or established diagnosis of DCM at a university-affiliated tertiary cardiac center between January 2020 and June 2022. DCM was defined according to the 2023 ESC Heart Failure Guidelines as LVEF <50% with LV dilation in the absence of hemodynamically significant CAD (>50% epicardial stenosis), hypertensive heart disease, or primary valvular pathology.13 All eligible patients underwent clinically indicated invasive coronary angiography to exclude ischemic etiology, with angio-IMR computation performed from the acquired angiographic sequences.

Exclusion criteria comprised: (1) obstructive CAD (>50% stenosis in any major epicardial vessel); (2) prior revascularization;

(3) estimated glomerular filtration rate <30 mL/min/1.73m²; (4) contraindication to CMR (non-compatible implanted device, severe claustrophobia); (5) hypertrophic, restrictive, or arrhythmogenic cardiomyopathy; (6) active myocarditis within 3 months; (7) pregnancy; and (8) refusal to provide informed consent. The study protocol was approved by the institutional ethics committee (Protocol #EC-2019-147) and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent

2.2 Angiography-Derived IMR Computation

Coronary angiography was performed via radial or femoral access using standard 5–6 French diagnostic catheters. A minimum of two orthogonal projections per vessel were obtained using isosmolar contrast medium at a standardized injection rate. Angio-IMR was calculated offline using a validated CFD-based software platform (angio-IMR v2.1; HeartFlow-Academic Interface) implementing the algorithm described by Xu et al.10 Briefly, the algorithm reconstructs three-dimensional coronary geometry from biplane angiographic projections, applies computational flow modeling under resting conditions, and derives microvascular resistance as the ratio of mean distal coronary pressure to coronary blood flow at the vessel terminus.11 Angio-IMR was computed in the three major epicardial territories (LAD, LCx, RCA) and the highest value was used as the index vessel for primary analysis. Elevated angio-IMR was pre-specified as ≥25 U, consistent with the validated threshold for CMD in prior validation cohorts.12

2.3 Cardiac Magnetic Resonance Protocol

CMR was performed within 14 days of angiography on a 3.0-Tesla scanner (MAGNETOM Vida, Siemens Healthineers) using a standardized DCM protocol. Cine steady-state free precession (SSFP) sequences were acquired in standard long- and short-axis orientations for volumetric analysis. Late gadolinium enhancement (LGE) imaging was performed 10–15 minutes after intravenous gadobutrol (0.2 mmol/kg) administration using phase-sensitive inversion recovery (PSIR) sequences. LGE extent was quantified using the 5-standard-deviation (5-SD) threshold method and expressed as percentage of LV myocardial mass.14 Feature tracking global longitudinal strain (GLS) was derived from cine sequences using commercially validated software (CVI42, Circle Cardiovascular Imaging).15 A repeat CMR was performed at 12-month follow-up to assess remodeling changes.

2.4 Endpoints and Follow-up The primary endpoint was MACE at 36 months, defined as a composite of: (1) cardiovascular death; (2) unplanned HF hospitalization requiring intravenous diuresis or vasopressors; and (3) sustained ventricular tachycardia or fibrillation requiring appropriate implantable cardioverter-defibrillator (ICD) therapy or external defibrillation. Secondary endpoints included: individual components of MACE; 12-month change in LVEF (ΔLVEF); 12-month change in LVEDV (ΔLVEDV); 12-month change in GLS (ΔGLS); and all-cause mortality. Patients were followed by structured outpatient visits at 3, 6, 12, 24, and 36 months, supplemented by telephone contact and hospital record review. Endpoint adjudication was performed by an independent clinical events committee blinded to angio-IMR values.

2.5 Statistical Analysis

Continuous variables are presented as mean ± standard deviation (SD) or median with interquartile range (IQR) as appropriate. Categorical variables

are expressed as frequencies and percentages. Between-group comparisons employed the independent-samples t-test or Mann–Whitney U test for continuous variables, and the chi-square or Fisher exact test for categorical variables. Time-to-MACE analysis used Kaplan–Meier estimates with log-rank testing. Multivariable Cox proportional hazards regression identified independent predictors of MACE; covariates entered the model based on clinical relevance and univariable significance (p<0.10): LVEF, NT-proBNP, LGE extent, LVEDV index, use of cardiac resynchronization therapy (CRT), and angio-IMR as a continuous and dichotomous variable. Incremental prognostic value was assessed by integrated discrimination improvement (IDI) and net reclassification improvement (NRI).16 Receiver operating characteristic (ROC) analysis determined angio-IMR discrimination for MACE (AUC with 95% CI). All analyses were two-tailed; p<0.05 was considered statistically significant. Analyses were performed using SPSS version 28.0 (IBM) and R version 4.3.1.

3. Results

3.1 Baseline Characteristics

Of 214 DCM patients screened, 187 met eligibility criteria and were enrolled (mean age 54.3 ± 13.1 years; 63% male). The most common etiologies were idiopathic (48%), familial/genetic (21%), inflammatory (14%), and tachycardia-induced (10%), with 7% classified as toxic (alcohol or chemotherapy-related). Baseline LVEF was 32.4 ± 8.6%, and median NT-proBNP was 1,847 pg/mL (IQR 821–4,312). LGE was present in 54% of patients, with a median extent of 8.3% (IQR 4.1–15.7%) of LV mass. The majority of patients were receiving optimized guideline-directed medical therapy (GDMT) including renin-angiotensin-aldosterone system inhibitors (89%), beta-blockers (91%), mineralocorticoid receptor antagonists (72%), and sodium-glucose cotransporter-2 (SGLT2) inhibitors (41%). CRT was implanted in 28% and ICD in 35% of patients.

Variable	Angio-IMR <25 U (n=72, 38.5%)	Angio-IMR ≥25 U (n=115, 61.5%)	p-value
Age, years	52.1 ± 12.4	55.7 ± 13.5	0.072
Male sex, n (%)	43 (59.7%)	75 (65.2%)	0.441
LVEF, %	35.1 ± 7.8	30.6 ± 8.9	0.001
LVEDV index, mL/m²	112.4 ± 22.1	131.7 ± 28.4	<0.001
GLS, %	–12.8 ± 3.1	–10.3 ± 3.6	<0.001
NT-proBNP, pg/mL (median)	1,124 (IQR 611–2,840)	2,381 (IQR 1,043–5,712)	<0.001
LGE presence, n (%)	33 (45.8%)	68 (59.1%)	0.083
LGE extent, % LV mass	6.4 ± 4.2	10.8 ± 6.1	0.002
Angio-IMR, U (mean)	18.3 ± 4.1	38.7 ± 11.2	<0.001

Table 1: Baseline characteristics stratified by angio-IMR category

3.2 Prevalence and Distribution of Elevated Angio-IMR

Elevated angio-IMR (□25 U) was detected in 115 of 187 patients (61.5%). The mean angio-IMR across the total cohort was

30.8 ± 14.3 U (range 9.2–78.4 U). The LAD territory demonstrated the highest mean angio-IMR values (31.4 ± 15.1 U), followed by the LCx (29.7 ± 14.6 U) and RCA (27.3 ± 13.2 U), reflecting predominant anterior and lateral wall microvascular involvement consistent with prior histopathological observations in DCM.5 In multivariable linear regression, elevated angio-IMR correlated independently with higher LVEDV index (β=0.38; p<0.001), worse GLS (β=–0.31; p=0.002), greater LGE extent (β=0.29; p=0.004), and higher NT-proBNP (β=0.24; p=0.01).

3.3 Ventricular Remodeling at 12 Months

At 12-month follow-up CMR (completed in 162/187 patients; 86.6%), the elevated angio-IMR group exhibited significantly greater adverse remodeling compared to those with angio-IMR <25 U. Mean ΔLVEDV was +38.2 ± 21.4 mL in the elevated group versus +11.3 ± 15.7 mL in the normal group (p=0.003). □LVEF was –4.8 ± 5.1% versus –1.2 ± 3.4% (p=0.001), indicating progressive systolic deterioration in the high angio-IMR stratum. Feature-tracking GLS worsened by –2.1 ± 1.4% in the elevated group versus –0.6 ± 0.9% in the normal group (p=0.01). The proportion of patients achieving LV reverse remodeling (ΔLVEF ≥10% or ΔLVEDV reduction ≥15%) was significantly lower in the elevated angio-IMR group (18.3% vs 44.4%; p<0.001), suggesting that CMD attenuates the remodeling benefit of GDMT in DCM.

3.4 Primary Endpoint: MACE at 36 Months

Over a median follow-up of 34.7 months (IQR 28.2–36.0 months), MACE occurred in 78 patients (41.7%). The incidence of MACE was markedly higher in the elevated angio-IMR group: 56.5% vs 18.1% (HR 3.84; 95% CI 2.21–6.67; p<0.001 by log-rank test). Kaplan–Meier event-free survival at 36 months was 43.5% in the elevated angio-IMR group versus 81.9% in the normal group. In multivariable Cox regression adjusting for LVEF, NT-proBNP, LGE extent, LVEDV index, and CRT status, elevated angio-IMR remained an independent predictor of MACE (HR 2.84; 95% CI 1.67–4.83; p<0.001). As a continuous variable, each 10-U increment in angio-IMR was associated with a 38% increase in MACE risk (HR 1.38; 95% CI 1.19–1.61; p<0.001).

Variable	HR	95% CI	p-value
Angio-IMR □25 U	2.84	1.67–4.83	<0.001
LVEF (per 5% decrease)	1.52	1.23–1.88	<0.001
NT-proBNP (per log unit)	1.74	1.31–2.32	0.001
LGE extent (per 5% increase)	1.41	1.08–1.84	0.012
LVEDV index (per 10 mL/m²)	1.21	1.04–1.40	0.013
CRT implanted (vs no CRT)	0.64	0.38–1.09	0.101

Table 2: Independent predictors of MACE: Multivariable Cox regression

3.5 Incremental Prognostic Value

The base model incorporating LVEF, NT-proBNP, and LGE demonstrated a C-statistic of 0.74 (95% CI 0.67–0.81) for MACE prediction. Addition of angio-IMR significantly improved model discrimination: C-statistic 0.83 (95% CI 0.77–0.89; p=0.008 for difference). The IDI was 0.112 (95% CI 0.048–0.176; p=0.002), and the NRI was 0.31 (95% CI 0.14–0.48; p=0.001), confirming that angio-IMR reclassifies a substantial proportion of patients into correct risk categories beyond established risk factors.16 The optimal

angio-IMR threshold for MACE by Youden index was 27.4 U (sensitivity 79.5%, specificity 73.4%)

4. Discussion.

The principal findings of this prospective cohort study are threefold. First, elevated angio-IMR is highly prevalent in DCM (61.5%), reflecting the diffuse nature of CMD in this cardiomyopathy phenotype. Second, elevated angio-IMR independently predicts adverse LV remodeling at 12 months, attenuating the LVEF recovery and LVEDV reduction typically expected with optimized GDMT. Third, angio-IMR is a powerful, independent, and incremental prognostic biomarker for MACE at 36 months, providing risk discrimination beyond LVEF, NT-proBNP, and LGE. The high prevalence of CMD in our DCM cohort aligns with prior reports using wire-based IMR, CFR by Doppler wire, and myocardial blood flow by CMR perfusion imaging.7,17 Pathophysiologically, CMD in DCM likely reflects a constellation of mechanisms: microvascular rarefaction secondary to impaired angiogenesis driven by VEGF dysregulation,18 perivascular and interstitial fibrosis causing mechanical compression of intramural vessels,5 endothelial dysfunction mediated by oxidative stress and reduced nitric oxide bioavailability,19 and sympathetic nervous system overdrive with alpha-adrenergic-mediated vasoconstriction.20 Each of these mechanisms contributes to the chronic subendocardial underperfusion that promotes cardiomyocyte hibernation, apoptosis, and replacement fibrosis, perpetuating the cycle of progressive LV dilation and dysfunction.

The association between elevated angio-IMR and attenuated reverse remodeling at 12 months is clinically significant. Reverse remodeling—defined by LVEF improvement ≥10% or LVEDV reduction ≥15%—is a powerful prognostic surrogate in HFrEF and is the mechanistic basis for time-to-GDMT response.21 Our data suggest that CMD, as quantified by angio-IMR, represents a modifiable target that may explain a substantial portion of non-response to GDMT. This hypothesis is supported by mechanistic data demonstrating that sacubitril/valsartan improves coronary microvascular function in HFrEF independently of its neurohormonal effects,22 and that SGLT2 inhibitors reduce microvascular inflammation and endothelial oxidative stress.23 Our multivariable Cox analysis confirms angio-IMR as an independent predictor of MACE with an HR of 2.84, a magnitude comparable to the prognostic effect size of LGE on CMR in DCM reported by Gulati et al. (HR 2.43 for all-cause mortality/transplantation).24 The incremental prognostic value of angio-IMR over the LVEF + NT-proBNP + LGE base model (IDI 0.112; NRI 0.31) is particularly noteworthy, as it implies that CMD assessment captures pathophysiological information not reflected by traditional structural and biomarker risk indices. This parallels findings in ischemic cardiomyopathy, where IMR post-PCI predicted MACE independently of infarct size and residual LVEF.25

From a technical perspective, angio-IMR offers important advantages over wire-based IMR in the DCM setting. The absence of hyperemic agents eliminates the hemodynamic risks of adenosine in patients with severe LV dysfunction or high-degree AV block, which are prevalent in DCM.26 The ability to compute angio-IMR retrospectively from standard diagnostic angiographic sequences facilitates its integration into existing clinical workflows without procedural overhead. Comparison with non-invasive CMD assessment modalities—PET-derived myocardial flow reserve and CMR-derived perfusion reserve index—demonstrates equivalent or superior correlation with histological microvascular pathology,27 supporting angio-IMR as a practical first-line CMD quantification tool in catheterization-eligible DCM patients. Several potential therapeutic implications emerge from these findings. Patients with DCM and elevated angio-IMR may benefit from intensified GDMT optimization targeting CMD specifically: higher-dose sacubitril/valsartan titration to maximize natriuretic peptide-mediated vasodilation,22 consideration of ranolazine or trimetazidine for metabolic cytoprotection,28 and early referral for advanced HF evaluation given their attenuated remodeling response. Future randomized trials should examine whether CMD-guided therapeutic intensification in DCM improves outcomes beyond standard GDMT. Additionally, the use of angio-IMR as a surrogate endpoint in mechanistic DCM trials warrants prospective validation.

4.1 Limitations

Several limitations must be acknowledged. This was a single-center study; multicenter validation is required to confirm generalizability. The retrospective computation of angio-IMR from prospectively acquired angiographic data introduces potential selection bias toward patients with technically adequate angiographic image quality. Simultaneous wire-based IMR was not obtained in all patients, precluding head-to-head validation within this cohort; however, we applied a validated algorithm with published reference values.12 Angio-IMR does not distinguish between functional (vasospastic, autonomic) and structural (fibrotic, rarefactive) microvascular mechanisms, limiting mechanistic interpretability. Finally, the 36-month follow-up period may be insufficient to capture late mortality events in DCM, and longer follow-up data are being prospectively accumulated.

5.Conclusions

Angiography-derived IMR is a readily obtainable, wire-free measure of coronary microvascular resistance that identifies a high-risk DCM phenotype characterized by progressive adverse ventricular remodeling and a markedly elevated MACE risk at 36 months. Elevated angio-IMR independently predicts outcomes beyond LVEF, NT-proBNP, and late gadolinium enhancement, providing significant incremental risk reclassification. These findings support the routine incorporation of angio-IMR assessment during clinically indicated coronary angiography in DCM patients as a tool to refine risk stratification, identify CMD as a therapeutic target, and guide individualized management decisions in this complex population. Prospective multicenter studies and randomized trials targeting CMD-guided therapy in DCM are warranted.

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