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DOI:

[10.1161/CIRCINTERVENTIONS.124.014477](https://doi.org/10.1161/CIRCINTERVENTIONS.124.014477)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Sinha, A., Rahman, H., Demir, O., De Silva, K., Morgan, H., Li Kam Wa, M., Ryan, M., Ezad, S., Al-Khayatt, B., Ellis, H., Chiribiri, A., Webb, A., & Perera, D. (2024). Microvascular Resistance Reserve Predicts Myocardial Ischemia and Response to Therapy in Patients With Angina and Nonobstructive Coronary Arteries. *Circulation: Cardiovascular Interventions*, 17(9), 866-868. Article e014477. Advance online publication. <https://doi.org/10.1161/CIRCINTERVENTIONS.124.014477>

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1 **Microvascular resistance reserve predicts myocardial ischemia and response to therapy**
2 **in patients with angina and nonobstructive coronary arteries**

3 Running title: diagnostic and therapeutic thresholds of MRR in ANOCA

4

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20 **Keywords**

21 Microvascular resistance reserve, coronary flow reserve, coronary physiology, thresholds

22

23 **Subject terms**

24 Coronary vessels, angina, coronary artery disease

25 **Non-standard Abbreviations and Acronyms**

26 ANOCA: angina with nonobstructive coronary arteries

27 CFR: coronary flow reserve

28 CMD: coronary microvascular disease

29 MRR: microvascular resistance reserve

30

31

32 Coronary microvascular disease (CMD) is associated with an impaired quality of life and
33 heightened risk of adverse cardiovascular outcomes. The hallmark of CMD is a diminished
34 coronary flow reserve¹ (CFR) and CFR<2.5 predicts maladaptive exercise physiology,
35 ischemia on noninvasive assessment and response to anti-ischemic therapy with excellent
36 accuracy^{1,2}. However, CFR is affected by the conductance of both the epicardial and
37 microvascular compartments. Microvascular resistance reserve (MRR) is a novel
38 microcirculation-specific coronary physiologic parameter^{3,4}; however, the diagnostic and
39 therapeutic thresholds in patients with angina and nonobstructive coronary arteries (ANOCA)
40 are yet to be established.

41

42 We assessed the diagnostic accuracy of MRR at predicting abnormal exercise physiology,
43 inducible ischemia and response to anti-ischemic therapy in patients with ANOCA. We have
44 previously published the inclusion criteria and study protocols^{1,2} but in brief, we recruited
45 patients with ANOCA who underwent simultaneous measurement of intracoronary pressure
46 and Doppler flow velocity at rest and during hyperemia. The first cohort (n=85) underwent
47 stress perfusion cardiac magnetic resonance (CMR) imaging and invasive coronary physiology
48 assessment during supine bicycle exercise. Maladaptive exercise physiology was defined as
49 impaired coronary perfusion efficiency during exercise, and myocardial ischemia was defined
50 as endocardial-to-epicardial perfusion ratio <1.0 during hyperemia on CMR¹. The second
51 cohort (n=87) underwent blinded coronary physiology assessment and were randomized into a
52 crossover anti-ischemic therapy trial; response to therapy was defined as ≥ 60 seconds
53 increment in exercise time from baseline². This study was approved by the National Health
54 Service Research Ethics Committee (references 20/LO/1294 and 17/LO/0203) and written
55 informed consent was obtained from all patients prior to enrolment. The data that support the
56 findings of this study are available from the corresponding author upon reasonable request.

57

58 MRR was derived as $(CFR/FFR) \times (Pa_{rest}/Pa_{hyper})$

59 *CFR: ratio of average peak velocity at hyperemia and rest*

60 *FFR: ratio of distal coronary pressure to aortic pressure during hyperemia*

61 *Pa_{rest}/Pa_{hyper}: ratio of aortic pressure during rest and hyperemia*

62

63 Binary logistic regression was performed to test if MRR was associated with exercise
64 physiology, inducible ischemia and response to anti-ischemic therapy using univariable
65 analysis and reported as odds ratio (95% CI). The Youden's index in receiver operating
66 characteristic curves was used to identify the optimal MRR threshold. The accuracy of optimal
67 CFR and MRR thresholds was calculated as $[(\text{true positives} + \text{true negatives}) \div (\text{true positives}$
68 $+ \text{true negatives} + \text{false positives} + \text{false negatives})] \times 100$.

69

70 Of the 85 patients enrolled in the first cohort (age 57 ± 10 , females 78%), 45 had a $CFR < 2.5$ and
71 40 had a $CFR \geq 2.5$. FFR was 0.92 ± 0.05 and MRR was 3.0 ± 0.9 . MRR was independently
72 associated with maladaptive exercise physiology (odds ratio (95% CI) 0.85 (0.78, 0.93),
73 $p < 0.01$) and ischemia on CMR (odds ratio (95% CI) 0.94 (0.88, 1.00), $p = 0.04$) (per 0.1 unit
74 increase in MRR). The optimal MRR threshold was 3.0 to predict maladaptive exercise
75 physiology (sensitivity 75% (95% CI 60%, 86%) and specificity 95% (95% CI 77%, 100%))
76 and 3.2 to predict ischemia on CMR (sensitivity 83% (95% CI 70%, 93%) and specificity 56%
77 (95% CI 35%, 76%)). CFR was numerically better than MRR at predicting maladaptive
78 exercise physiology (AUC 0.90 (95% CI 0.82, 0.98) vs 0.86 (95% CI 0.77, 0.94), $p = 0.07$), with
79 diagnostic accuracies of 86% (95% CI 75%, 93%) and 80% (95% CI 68%, 88%) of the
80 $CFR < 2.5$ and $MRR < 3.0$ thresholds, respectively. CFR and MRR predicted ischemia on CMR
81 with similar accuracy (AUC 0.70 (95% CI 0.56, 0.84) vs 0.70 (95% CI 0.57, 0.84), $p = 0.85$),

82 with diagnostic accuracies of 70% (95% CI 57%, 80%) and 71% (95% CI 59%, 82%) of the
83 CFR<2.5 and MRR<3.2 thresholds, respectively (**Figure 1**).

84

85 Of the 87 patients enrolled in the second cohort (age 61 ± 8 , females 62%), 57 had a CFR<2.5
86 and 30 had a CFR \geq 2.5. FFR was 0.92 ± 0.05 and MRR was 2.7 ± 0.7 . MRR was independently
87 associated with a response to anti-ischemic therapy (odds ratio (95% CI) 0.93 (0.87, 1.00),
88 $p=0.04$) (per 0.1 unit increase in MRR). The optimal MRR threshold to predict a response was
89 2.9 (sensitivity 77% (95% CI 61%, 89%) and specificity 50% (95% CI 33%, 67%)). CFR was
90 numerically better at predicting response to anti-ischemic therapy than MRR (AUC 0.68 (95%
91 CI 0.56, 0.81) vs 0.62 (95% CI 0.50, 0.75), $p=0.07$), with diagnostic accuracies of 68% (95%
92 CI 57%, 78%) and 64% (95% CI 52%, 75%) of the CFR<2.5 and MRR<2.9 thresholds,
93 respectively (**Figure 1**).

94

95 Our study demonstrates, for the first time, that MRR predicts maladaptive exercise physiology,
96 inducible ischemia and response to anti-ischemic therapy in patients with ANOCA.
97 Notwithstanding the fact that MRR is a continuous variable, the diagnostic and therapeutic
98 thresholds we have found could be adopted in clinical practice and future research studies.
99 These thresholds are very similar to that which was recently reported as predictive of adverse
100 outcomes in allcomers with ischemic heart disease (including epicardial and/or microvascular
101 disease)⁵. MRR was not superior to CFR in patients with ANOCA but, as MRR is proportional
102 to CFR and inversely proportional to FFR, the most impactful utility of MRR may be in patients
103 with concomitant epicardial and microvascular disease⁴. MRR is a metric that relies on
104 measurement of coronary flow as well as pressure; whilst we used Doppler to estimate flow in
105 our study, continuous intracoronary thermodilution may be an attractive alternative technique,

106 especially as it has less inter-operator variability and can be performed without
107 pharmacological hyperemia.

108

109 **Acknowledgements**

110 The authors offer appreciation to all study investigators, clinical site staff, and study
111 participants.

112

113 **Sources of funding**

114 The trial was funded by grants from the Medical Research Council (MR/T029390/1) and
115 British Heart Foundation (FS/16/49/32320).

116

117 **Conflict of interest**

118 None of the authors have any conflict of interest or relationships with industry that could have
119 influenced this manuscript.

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143

144 **Figure legend**

145 **Figure 1.** Receiver operating characteristic curves comparing the ability of coronary flow
146 reserve and microvascular resistance reserve at predicting maladaptive exercise physiology,
147 ischemia and response to therapy.

148 AUC: area under the curve; CFR: coronary flow reserve; CMR: cardiac magnetic resonance;

149 MRR: microvascular resistance reserve