Continuous thermodilution and microvascular resistance reserve during the index procedure in acute coronary syndrome without obstructive coronary artery disease

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Continuous thermodilution and microvascular resistance reserve during the index procedure in acute coronary syndrome without obstructive coronary artery disease: A pilot study

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Abstract

Background: In 5%–25% of non-ST-elevation acute coronary syndrome (NSTE-ACS) patients, coronary angiography reveals no obstructive coronary arteries (MINOCA). Coronary microvascular disease (CMD) is a potential causal pathophysiological mechanism in these patients and can be diagnosed by continuous thermodilution assessment. Recently, the microvascular resistance reserve (MRR) has been introduced as a novel index to assess the vasodilatory capacity of the microcirculation. However, continuous thermodilution and MRR have never been investigated in the acute setting in MINOCA patients and invasive assessment of the microcirculation in these patients are currently lacking.

Aims: The objectives of the study were to investigate the incidence of CMD (MRR ≤ 2.7) in patients with MINOCA and to evaluate the feasibility and safety of continuous thermodilution-based assessment during index coronary angiography in the acute setting.

Methods: This study was a prospective, observational, pilot study investigating coronary physiology in the acute setting in MINOCA patients. Patients admitted with a diagnosis of NSTE-ACS were eligible for inclusion.

Results: In total, 19 MINOCA patients were included in this analysis; the mean age was 70 ± 9 years, and 79% were females. CMD was present in 6 patients (32%). Q_{rest} was significantly higher in the MRR ≤ 2.7 group compared to the MRR > 2.7 group (0.076 [0.057–0.100] vs. 0.049 [0.044–0.071] L/min, $p = 0.03$). $R_{\mu,rest}$ was significantly lower in the MRR ≤ 2.7 group compared to the MRR > 2.7 group (1083 [710–1510] vs. 1563 [1298–1970] WU, $p = 0.04$). No periprocedural complications or hemodynamic instability have occurred during continuous thermodilution assessment during the index coronary angiography.

Conclusion: In patients admitted for MINOCA undergoing immediate coronary angiography, continuous thermodilution assessment and MRR are feasible and safe in the acute setting, and evidence of functional CMD could be observed in one-third of the MINOCA patients.

KEYWORDS
continuous thermodilution, coronary microvascular dysfunction, coronary physiology, MINOCA, MRR, NSTE-ACS

1 | INTRODUCTION

In 5%–25% of non-ST-elevation acute coronary syndrome (NSTE-ACS) patients, coronary angiography reveals no obstructive coronary arteries (MINOCA).[1–3] Such MINOCA patients represent a heterogeneous group with varying underlying causes that involve both coronary and non-coronary pathological conditions.[4,5] Coronary microvascular disease (CMD) is a potential causal pathophysiological mechanism in these patients and can be diagnosed by continuous thermodilution assessment.[6]

The vasodilatory capacity of the coronary microcirculation has traditionally been assessed using the coronary flow reserve (CFR).[7] However, CFR is influenced by epicardial disease and not specific for CMD.[8] Whereas certain extent, even in MINOCA patients epicardial disease is present in approximately half of the patients.[1] Recently, the microvascular resistance reserve (MRR) has been introduced as a novel index to assess the vasodilatory capacity of the microcirculation.[9] In contrast to CFR, MRR is not influenced by epicardial disease. The prognostic value of MRR has been demonstrated in patients with ST-elevation myocardial infarction and stable coronary artery disease (CAD) in a staged procedure.[10,11]

Continuous thermodilution and MRR have never been investigated in the acute setting and invasive assessment of the microcirculation in MINOCA patients are currently lacking.[12] The aim of this pilot study was to investigate the incidence of CMD and to evaluate the safety of continuous thermodilution-based assessment during index coronary angiography in the acute setting in patients with MINOCA.

2 | METHODS

2.1 | Study design and population

This study was a prospective, observational, pilot study investigating coronary physiology in the acute setting in MINOCA patients. The study was performed in the Catharina Hospital (Eindhoven, the Netherlands). The study protocol was approved by the ethics committee and was conducted in accordance with the Declaration of Helsinki. All patients provided informed consent before the procedure. Patients admitted with a diagnosis of NSTE-ACS who underwent coronary angiography during office hours (Monday until Friday, between 08.00 and 16.00 h) were eligible for inclusion. Exclusion criteria were significant CAD, reduced left ventricular ejection fraction <50%, previous percutaneous coronary intervention, previous cardiac surgery (coronary artery bypass grafting or cardiac valve surgery), or prior ACS. Significant CAD was defined as an epicardial stenosis of ≥50% and/or fractional flow reserve (FFR) ≤ 0.80.

2.2 | Study objectives

The primary objective of the study was to investigate the incidence of CMD (MRR ≤ 2.7) in patients with MINOCA. In patients with ANOCA, an MRR value of >2.7 is considered normal and rules out CMD with a high probability.[13] The secondary objective was to evaluate the feasibility and safety of continuous thermodilution-based assessment during index coronary angiography in the acute setting in patients with MINOCA. Safety was defined as the occurrence of periprocedural complications (coronary dissection, bleeding complications, death, ventricular arrhythmias, or atrioventricular block) and hemodynamic instability (systolic blood pressure <90 mmHg and need of inotropics/vasopressive agents).

2.3 | Coronary catheterization and physiologic indices

A 6 Fr guiding catheter was positioned in the ostium of the left coronary artery. Intracoronary nitroglycerin (200 μg) was admitted before starting the physiologic assessment. A pressure-temperature wire (Pressurewire X; Abbott Vascular) was advanced to the left main coronary artery, where the pressure was equalized to the aortic pressure. Hereafter, the Pressurewire X was advanced to the distal LAD. The mean distal coronary pressure (P_d) and mean aortic pressure (P_a) were measured during rest ($P_{d,rest}$ and $P_{a,rest}$) and during maximal hyperemia ($P_{d,hyper}$ and $P_{a,hyper}$) by intravenous adenosine infusion at 140 mg/kg/min. FFR, defined as $P_{d,hyper}$ divided by $P_{a,hyper}$, was measured to confirm a value ≥0.80.[14]

Next, the RayFlow catheter (Hexacath) was advanced to the proximal LAD and saline infusion was started at a rate of 10 mL/min for measuring coronary blood flow at rest (Q_{rest}) and resistance measurement in rest ($R_{\mu,rest}$). Saline infusion at a rate of 20 mL/min was used for measuring maximum coronary blood blow (Q_{max}) and resistance measurement ($R_{\mu,hyp}$) during maximal hyperemia. Computation of flow and resistance

measurements was performed using the software of Coroflow (Coroventis Research). Absolute CFR was calculated by the ratio of Q_{max} and Q_{rest}. MRR was calculated using the following formula: $(Q_{max}/Q_{rest}) \times (P_{a,rest}/P_{d,hyper})$.[9]

2.4 | Statistical analysis

Continuous variables were expressed as mean ± SD or median [interquartile ranges]. Categorical variables were reported as frequencies and percentages. Differences in continuous variables between groups were compared using an unpaired *t*-test or Mann–Whitney *U* test, depending on the distribution. Categorical variables were compared using the χ^2 test or Fisher's exact test. Statistical significance was defined as a *p*-value < 0.05. All analyses were performed with SPSS V.29.0.

3 | RESULTS

Between February 2021 and 2023, 178 NSTE-ACS patients undergoing coronary angiography were screened for eligibility. A total of 110 patients were excluded due to significant epicardial CAD. In total, 19 MINOCA patients were included in this analysis (Figure 1). No patients were lost to follow-up.

The mean age was 70 ± 9 years and 79% were females. The most common risk factors were hypertension (53%) and hypercholesterolemia (47%). Myocardial injury, as suggested by the maximal hs-troponin T level, was limited in this population (28 [10–56] ng/L). Patients with MRR ≤ 2.7 were older compared to patients with MRR > 2.7 (78 ± 4 vs. 66 ± 8 years, $p < 0.001$). A trend toward higher incidence of hypertension and hypercholesterolemia was observed in patients with MRR ≤ 2.7. Baseline characteristics are presented in Table 1.

Overall, median FFR was 0.89 [0.86–0.92], CFR was 2.4 [2.0–3.6], and Q_{max} was 0.149 [0.120–0.223] L/min. The median MRR was 2.9 [2.3–4.8] (Table 2).

MRR was ≤2.7 in 6 patients (32%) and MRR was >2.7 in 13 patients (68%). CFR was significantly lower in the MRR ≤ 2.7 group than in the MRR > 2.7 group, 1.9 [1.7–2.3] versus 2.8 [2.2–3.9], $p = 0.005$, respectively (Table 2). No differences in Q_{max} and $R_{\mu,hyp}$ were observed between both groups. In contrast, Q_{rest} was significantly higher in the MRR ≤ 2.7 group compared to the MRR > 2.7 group (0.076 [0.057–0.100] vs. 0.049 [0.044–0.071] L/min, $p = 0.03$). $R_{\mu,rest}$ was significantly lower in the MRR ≤ 2.7 group compared to the MRR > 2.7 group (1083 [710–1510] vs. 1563 [1298–1970] WU, $p = 0.04$), indicative of functional CMD. No periprocedural complications or hemodynamic instability were observed during continuous thermodilution assessment throughout the index coronary angiography (Table 2).

Figure 2 provides an illustration of a continuous thermodilution assessment (incorporating MRR and CFR measurement) conducted on a patient diagnosed with MINOCA.

4 | DISCUSSION

This is the first study to evaluate CMD in patients with MINOCA during the index coronary angiography in the acute setting using continuous thermodilution assessment and MRR and should serve as hypothesis generating for future research. We found that CMD was present in one-third of MINOCA patients in this way as a potential causal mechanism for myocardial injury. Furthermore, we demonstrate that it is safe and feasible to perform absolute flow measurements in the acute setting in such patients. This pilot study should serve as a hypothesis generating for future research.

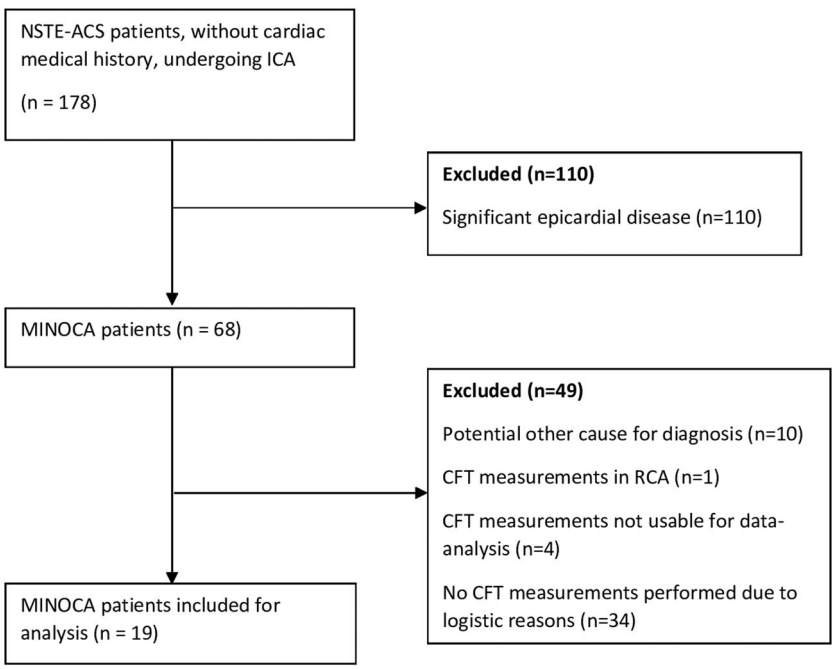

FIGURE 1 Flowchart. NSTE-ACS, non-ST-elevation acute coronary syndrome.

TABLE 1 Baseline characteristics.

	Total cohort ($n = 19$)	MRR ≤ 2.7 ($n = 6$)	MRR > 2.7 ($n = 13$)	p Value
Age (years), mean ± SD	70 ± 9	78 ± 4	66 ± 8	<0.001
Female sex, *n* (%)	15 (79)	6 (100)	9 (69)	0.26
Hypertension, *n* (%)	10 (53)	5 (83)	5 (39)	0.07
Diabetes mellitus, *n* (%)	1 (5)	1 (17)	0	0.32
Current smoker, *n* (%)	4 (21)	0	4 (31)	0.28
Hypercholesterolemia, *n* (%)	9 (47)	5 (83)	4 (31)	0.06
PAD, *n* (%)	1 (5)	0	1 (8)	1.00
BMI ≥30 kg/m^2, *n* (%)	4 (21)	2 (33)	2 (17)	0.56
Chronic kidney injury (<GFR 30 mL/min), *n* (%)	0	0	0	NA
Auto-immune disease, *n* (%)	1 (5)	0	1 (8)	1.00
Systolic blood pressure (mmHg), mean ± SD	153 ± 25	160 ± 30	150 ± 23	0.46
Diastolic blood pressure (mmHg), mean ± SD	73 ± 13	73 ± 13	73 ± 13	0.96
Heart rate (bpm), mean ± SD	70 ± 17	75 ± 9	67 ± 19	0.34
Hb (mmol/L), mean ± SD	8.2 ± 0.9	7.8 ± 9	8.4 ± 1.0	0.19
Creatinine (μmol/L), mean ± SD	72 ± 12	76 ± 14	70 ± 12	0.36
CRP (mg/L), median [IQR]	5.0 [5.0–6.0]	5.0 [4.0–11.0]	5.0 [5.0–6.5]	0.84
First hs-troponin[a] (ng/L), median[IQR]	16 [7–63]	18 [12–190]	11 [7–104]	0.43
Second hs-troponin (ng/L), median[IQR]	28 [11–38]	32 [25–257]	19 [10–39]	0.14
Maximal hs-troponin (ng/L), median[IQR]	28 [10–56]	36 [17–173]	23 [10–120]	0.63

Abbreviations: BMI, body mass index; hs, high-sensitive; MRR, microvascular resistance reserve; PAD, peripheral arterial disease.
[a]Upper limit normal: 14 ng/L.

As this is the first prospective study to measure absolute flow, CFR, and MRR during coronary angiography in the acute setting in MINOCA patients, no data determining an optimal cutoff value for MRR in this population are available. Since maximal hs-troponin levels in these patients are relatively low, myocardial injury and infarct size in these patients are limited. Using the cutoff value of 2.7, one-third of the MINOCA patients in our study could potentially be diagnosed with CMD. Using the stricter cut-off value of 2.1, established as the definitive cut-off value for CMD diagnosis, two out of 19 patients (11%) could be diagnosed with CMD with certainty in this pilot study.[13] In patients with STEMI and subsequent larger infarct size, a lower MRR cut-off value might be more appropriate to select patients with CMD.[11]

Our results show that in MINOCA patients with CMD (MRR ≤ 2.7), Q_{rest} was higher and $R_{\mu,rest}$ were lower compared to patients without CMD, while Q_{max} and $R_{\mu,hyp}$ were not different. These results are suggestive of the functional endotype of CMD in MINOCA.[15] The cause of higher resting flow is either disordered autoregulation or appropriate autoregulation but with increased myocardial oxygen demand.[15] Higher resting flow, as is the case in these CMD patients, might also be explained by the difference in age between both groups. This was already demonstrated for CFR.[16] Understanding the mechanisms of CMD in MINOCA patients could help to develop new therapies to treat CMD, whether in the context of MINOCA or in ANOCA patients.[17–19]

CMD in patients with MINOCA and, for that matter, in infarct patients in general, is known to correlate to worse clinical outcomes.[20] Patients without CMD have favorable clinical outcomes, and less strict monitoring might be safe in such patients. However, our study population is too small and follow-up is too short to analyze this.

In current clinical practice, a limited number of MINOCA patients may undergo assessment of the coronary microcirculation. If such evaluation is performed, this is mostly done during follow-up in a staged procedure. This results in a delayed diagnosis and appropriate treatment, while in some patients CMD may be transient and not detectable anymore in a staged procedure. Previous studies have shown that continuous thermodilution-based assessment of the coronary microcirculation is safe when performed in a non-acute setting.[21,22] Our results extend this position to the acute setting during the index procedure in MINOCA patients.

TABLE 2 Coronary physiology and microvascular function.

	Total cohort (*n* = 19)	MRR ≤ 2.7 (*n* = 6)	MRR > 2.7 (*n* = 13)	*p* Value
FFR, median [IQR]	0.89 [0.86–0.92]	0.88 [0.81–0.91]	0.89 [0.87–0.92]	0.49
Pd/Pa, median [IQR]	0.95 [0.93–0.96]	0.94 [0.92–0.97]	0.96 [0.93–0.97]	0.48
CFR, median [IQR]	2.4 [2.0–3.6]	1.9 [1.7–2.3]	2.8 [2.2–3.9]	0.005
MRR, median [IQR]	2.9 [2.3–4.8]	2.2 [2.1–2.4]	3.5 [2.9–5.3]	<0.001
Q,rest (L/min), median [IQR	0.056 [0.047–0.077]	0.076 [0.057–0.100]	0.049 [0.044–0.071]	0.03
Q,max (L/min), median [IQR]	0.149 [0.120–0.223]	0.147 [0.111–0.229]	0.153 [0.129–0.242]	0.73
Rμ,rest (WU), median [IQR]	1406 [1020–1820]	1083 [710–1510]	1563 [1298–1970]	0.04
Rμ, hyp (WU), median [IQR]	485 [328–635]	527 [340–756]	448 [311–602]	0.38
Procedural safety				
Periprocedural complications, *n* (%)	0			

Abbreviations: CFR, coronary flow reserve; FFR, fractional flow reserve; L/min, liters per minute; MRR, microvascular resistance reserve; Q,max, hyperemic coronary blood flow (L/min); Q,rest, resting coronary blood flow (L/min); Rμ, hyp, minimal microvascular resistance; Rμ,rest, absolute microvascular resistance; WU, wood units.

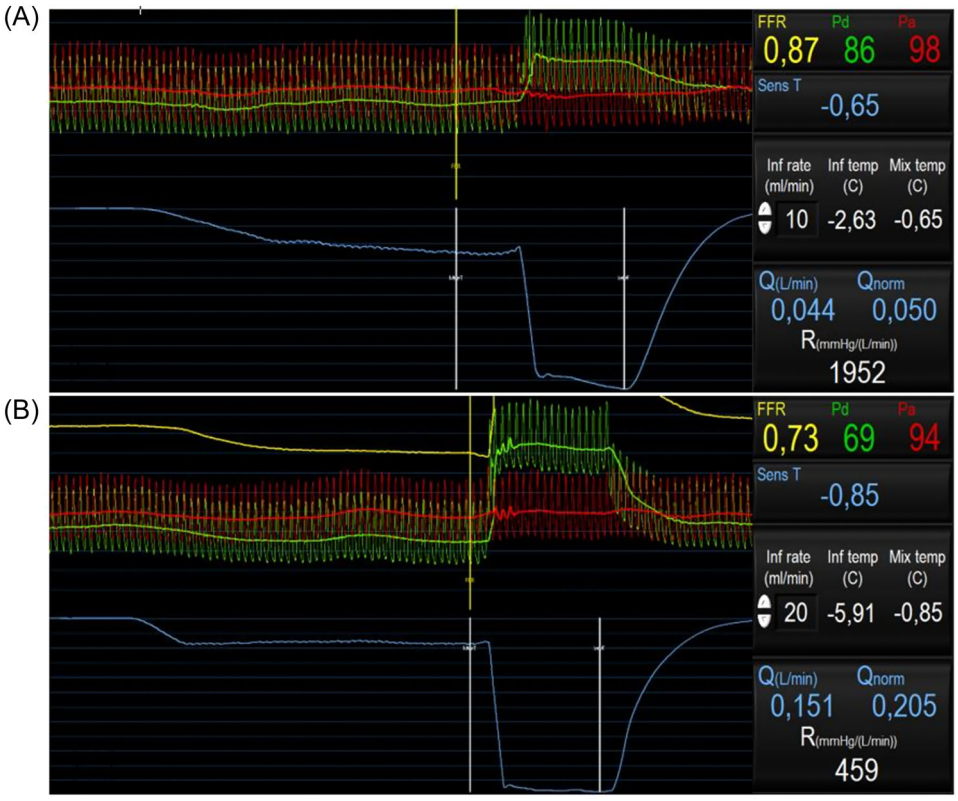

FIGURE 2 Continuous flow assessment during index coronary angiography in a MINOCA patient. (A) Illustrates a continuous thermodilution assessment in rest with a saline infusion at a rate of 10 mL/min. Notably, with this infusion rate, no hyperemia is induced. (B) Illustrates a continuous thermodilution assessment with a saline infusion at a rate of 20 mL/min. With this infusion rate, maximal hyperemia is induced. In this example: - MRR was calculated as follows: $(Q_{max}/Q_{rest}) \times (P_{a,rest}/P_{d,hyper}) = (0.151/0.044) \times (98/69) = 5.2$. CFR was calculated as follows: $Q_{max}/Q_{rest} = 0.151/0.044 = 3.4$. CFR, coronary flow reserve; MRR, microvascular resistance reserve; Q,max, hyperemic coronary blood flow (L/min); Q,rest, resting coronary blood flow (L/min). [Color figure can be viewed at wileyonlinelibrary.com]

4.1 | Limitations

This study has several limitations. First, this was a pilot study with a small sample size. This small sample size could have influenced differences in baseline characteristics (e.g. age) between patient groups. Therefore, these results should be confirmed in larger cohorts. Second, we did not perform vasoreactivity testing with acetylcholine to investigate possible underlying (micro)vascular spasms as a potential cause due to logistic reasons. It is likely that by performing vasoreactivity testing with acetylcholine, additional patients would be diagnosed as having epicardial and microvascular spasms.

5 | CONCLUSION

In patients admitted for MINOCA undergoing immediate coronary angiography, continuous thermodilution assessment and MRR are feasible and safe in the acute setting, and evidence of functional CMD could be observed in one-third of the MINOCA patients.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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