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Vasomotor dysfunction in patients with angina and nonobstructive coronary artery disease is dominated by vasospasm☆

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ABSTRACT

Background: Coronary vasomotor dysfunction, comprising endotypes of coronary spasm and/or impaired microvascular dilatation (IMD), is common in patients with angina and no obstructive coronary arteries (ANOCA). However, there are discrepant reports regarding the prevalence of these endotypes. The objective of this study was to determine the prevalence of coronary vasomotor dysfunction in patients with ANOCA, underlying endotypes, and differences in clinical characteristics.

Methods: Prospective registry of patients with ANOCA that underwent clinically indicated invasive coronary function testing (CFT), including acetylcholine spasm testing (2–200 μg) to diagnose coronary spasm, and adenosine testing (140 μg/kg/min) to diagnose IMD, defined as an index of microvascular resistance ≥25 and/or coronary flow reserve <2.0.

Results: Of the 111 patients that completed CFT (88% female, mean age 54 years), 96 (86%) showed vasomotor dysfunction. The majority 93 (97%) had coronary spasm, 63% isolated and 34% combined with IMD. Isolated IMD was rare, occurring in only 3 patients (3%). Hypertension was more prevalent in patients with vasomotor dysfunction compared to those without (39% vs. 7%, $p = 0.02$). Obesity and a higher severity of angiographic atherosclerotic disease were more prevalent in patients with coronary spasm compared to those without (61% vs. 28%; 40% vs. 0%, respectively, both $p < 0.01$). No differences in angina characteristics were observed between patients with and without vasomotor dysfunction or between endotypes.

Conclusions: Coronary vasomotor dysfunction is highly prevalent in patients with ANOCA, especially epicardial or microvascular vasospasm, whereas isolated IMD was rare. Performing a CFT without acetylcholine testing should be strongly discouraged.

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1. Introduction

Around half of the patients with signs or symptoms of ischaemic heart disease that undergo coronary angiography (CAG), have no obstructive coronary artery disease (CAD). (1) This large and undifferentiated group of patients with Angina and No Obstructive CAD (ANOCA) has an increased cardiovascular risk, high morbidity, impaired quality of life, and considerable health resource utilisation. (2–5) The majority of these patients have some type of underlying coronary vasomotor dysfunction. (2–4) This encompasses a variety of endotypes, including epicardial or microvascular vasospasm, impaired microvascular dilatation (IMD) including impaired vasodilatory capacity and increased microvascular resistance), or patients with a combination of both. (2,3,6)

Defining these different endotypes of vasomotor dysfunction is important for risk stratification. Patients with coronary spasm mainly have an increased risk for future hospitalisations for angina. (7) Patients with IMD have an increased risk of future cardiovascular events including cardiovascular death, myocardial infarction and heart failure. (1,8,9) As has been emphasized by the recently published expert consensus document, it is pivotal to distinguishing these different endotypes so that tailored treatment can be initiated in patients with ANOCA. (10) Tailored treatment improves symptoms and quality of life. (11,12)

Endotypes can be distinguished by an invasive coronary function test (CFT), using acetylcholine (ACH) (or equivalent) to evaluate coronary spasm and adenosine to evaluate IMD. (6) The most recent

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European Society of Cardiology guideline for chronic coronary syndromes as well as the latest expert consensus document, recommend to consider a CFT in all patients with ANOCA with persistent anginal symptoms. (6,10) Still, a complete CFT including both ACH and adenosine vasoreactivity testing is rarely performed in clinical practice. Consequently, our knowledge of the different endotypes of coronary vascular dysfunction is limited. Furthermore, to date it is unclear whether endotypes can be distinguished by clinical characteristics, which might assist in triaging patients for CFT.

We aimed to determine the prevalence of coronary vasomotor dysfunction, and the different pathophysiological endotypes, in patients with ANOCA that underwent a clinically indicated CFT. Furthermore, we assessed the differences in clinical characteristics between the different endotypes.

2. Methods

2.1. Study population

In this prospective registry, all consecutive patients who underwent a CFT between February 2019 and February 2020 were included. This single-centre study was conducted at the Radboud University Medical Center in Nijmegen, the Netherlands, a large tertiary referral centre specialized in patients with persistent angina in the absence of obstructive CAD. All patients were referred for CFT for suspected coronary vasomotor dysfunction by their treating cardiologist. In line with current guideline recommendations, we did not exclude patients with previous PCI. (6) In general, obstructive CAD was ruled out pre-CFT by CAG or Coronary Computed Tomography Angiography (CCTA). Written informed consent was obtained before the CFT and the study was approved by the local medical ethics committee.

2.2. Clinical characteristics

Clinical data, including medical history, risk factors and symptom characteristics, were obtained from both the electronic patient file and an online patient questionnaire. We gathered information on traditional cardiovascular risk factors (e.g. hypertension, dyslipidaemia, diabetes, premature CAD in first-degree relatives), and non-traditional risk variables associated with vasomotor dysfunction (i.e. migraine, rheumatic diseases, female reproductive disorders). (13,14) In the questionnaire, patients were also asked to report angina characteristics, including the nature of angina (e.g. chest pain or dyspnoea, radiation), the severity, provoking factor or initiating moment (at rest, during exercise, after exercise, during emotions/stress, at night).

2.3. Coronary angiography

Patients were instructed to withhold all vasoactive medication (e.g. calcium channel blockers (CCBs), long-acting nitrates) and methylxanthine-containing substances (including caffeine) for 24–48 h before the procedure, depending on half-life time. Administration of nitroglycerin was avoided during the procedure if possible. First, a diagnostic CAG was performed to confirm the absence of obstructive CAD, defined as a visual stenosis of more than 50% in combination with a measured Resting Full-Cycle Ratio (RFR) ≤ 0.89 and/or Fractional Flow Reserve (FFR) ≤ 0.80. (15) If no or non-obstructive coronary artery disease was present, the procedure continued with the assessment of the coronary vasoreactivity in the CFT.

2.4. Coronary function test

2.4.1. Coronary spasm test with acetylcholine (ACH)

To reduce the influence of any vasoactive substances, we initiated the CFT with ACH provocation testing to assess coronary spasm. This was performed in accordance with the standardized protocol by Ong et al. (16) Heart rate, blood pressure and a 12-lead ECG were continuously monitored. Incremental doses of 2, 20, 100 and 200 μg of ACH were manually infused over a period of 1–3 min into the left coronary artery (LCA) through a guiding catheter. After each infusion, cine-images were obtained to assess the change in coronary diameter. After the 200 μg dose or if significant epicardial or microvascular spasm was present, 0.2 mg nitroglycerin was injected into the LCA. In case of persistent coronary spasm or hemodynamically significant atrioventricular conduction disorders, intravenous atropine was administered (0.5 mg i.v.).

2.4.2. Pressure indices

Second, a guidewire with distal pressure and temperature sensors (PressureWire X, Abbott Vascular, Santa Clara, CA, USA) was used to measure the RFR, a novel non-hyperaemic pressure ratio that evaluates the entire cardiac cycle. (15) With the sensor positioned at the tip of the catheter, the pressure measurement from the wire was equalized with that of the guiding catheter. The sensor was then positioned in the distal LAD coronary artery. A minimum of five steady-state cardiac cycles was used to calculate RFR. FFR was measured during the subsequent adenosine tests.

2.4.3. Impaired microvascular dilatation with adenosine (ADE)

Subsequently, using the same guidewire already in place, the mainly endothelium-independent (hyperaemic) vasoreactivity was assessed with the thermodilution method. (17) The aortic pressure at the guiding catheter (Pa) and the distal coronary pressure at the tip of the guidewire (Pd) were recorded simultaneously throughout the measurement. The resting mean transit time (Tmn) was determined by injections of 3–5 mL room temperature saline into the LAD artery, averaging at least three consecutive overlapping measurements. Next, adenosine (typically 140 μg/kg/min) was administered via a large peripheral or central vein to induce steady state maximal hyperaemia - and thereby minimal microvascular resistance – and at least 3 more injections of room temperature saline were recorded and averaged to determine the hyperaemic Tmn. Measurements of Tmn were only accepted if the variability between the three measurements of Tmn was <20%. A drift check was performed at the end of the procedure. In case of significant drift (more than 2 mmHg), measurements were repeated.

FFR was calculated by the ratio of mean Pd and mean Pa at maximal hyperaemia. Microvascular resistance, measured as the index of microvascular resistance (IMR), was calculated as the Pd at maximal hyperaemia divided by the inverse of the hyperaemic Tmn. (18,19) The coronary flow reserve (CFR) was determined by dividing the average resting Tmn by the average hyperaemic Tmn. (20) All measurements were automatically analysed by dedicated software (Coroventis Coroflow, Uppsala, Sweden).

2.5. Definitions

We defined coronary vasomotor dysfunction according to the underlying pathophysiological endotype into patients with or without coronary spasm (ACH+ vs. ACH-), and patients with or without IMD as measured with adenosine (ADE+ vs. ADE-). The endotype of IMD (ADE+) was present when measurements showed an abnormal CFR < 2.0 and/or an abnormal IMR ≥ 25, as defined by current consensus documents. (21) The definitions of epicardial or microvascular spasm (ACH+) were in line with these guidelines as well (10,21,22): epicardial spasm was defined as a focal or diffuse epicardial coronary diameter reduction ≥90% in response to ACH, compared to the relaxed state after intracoronary nitroglycerin infusion, with a reproduction of (recognizable) symptoms and ischaemic ECG changes. Microvascular spasm was diagnosed when the patient experienced the reproduction of recognizable symptoms with ischaemic ECG changes, in the absence of ≥90% epicardial diameter reduction during ACH infusion. (21) Ischaemic ECG changes were defined as transient ST-segment elevation or depression of ≥0.1 mV, or ischaemic T-wave changes, in at least 2 contiguous

leads. Any inconclusive result in response to ACH (e.g. only reproduction of symptoms) was considered negative. No coronary vasomotor dysfunction was concluded when both ACH and adenosine tests were normal (ACH- and ADE-).

In exploratory analyses, we divided patients into groups based on their endotype of vasomotor dysfunction: isolated ACH+ (only epicardial or microvascular spasm), isolated ADE+ (only abnormal CFR/IMR), or both ACH+ and ADE+ (combined vasomotor dysfunction). (11)

2.6. Statistical analyses

Continuous data are presented as mean ± standard deviation (SD), or median and interquartile interval, as appropriate. We used the Kolmogorov-Smirnov test to check for normal distribution of data. Categorical data are presented as numbers (%). Differences between groups were assessed by an independent sample *t*-test for continuous data with a normal distribution. Otherwise, the nonparametric Mann-Whitney *U* test was used. Categorical data were compared with the use of Fisher's exact test. A two-sided *P*-value <0.05 was considered statistically significant. All analyses were performed using SPSS Statistics version 25 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Clinical and procedural characteristics

As shown in Fig. 1, 121 patients underwent CFT. Ten patients were excluded because of obstructive CAD. ACH tests were completed in all 111 patients; Adenosine tests were completed in 103 patients. The mean age of all patients was 54 ± 8 years and most patients were female (88%), as shown in Table 1. Patients with coronary vasomotor dysfunction were older than those without (55 ± 8 vs. 50 ± 8 years, $p = 0.02$), and had a higher prevalence of hypertension (39% vs. 7%, $p = 0.02$). We observed no differences in symptom characteristics between the groups. All patients had angina with a median duration of 44 months before CFT. Both chest pain with radiation to the arms, back or throat, and/or dyspnoea were prevalent forms of angina in all patients (79% and 64% respectively). Resting angina was reported in 91% of patients, angina during exercise in 74% of patients.

Most CAGs were performed using a radial access site (without the use of nitroglycerin); in 5 patients a conversion to femoral access was necessary because of radial spasm. About half of the patients (52%) had no visual angiographic stenosis. In only 2 patients with a visual focal angiographic coronary stenosis/narrowing, nitroglycerine was administered first, followed by ADE testing, including FFR measurements. In both cases this resulted in vasodilation and no significant CAD. In both cases, ACH testing showed epicardial focal spasm at the site of the initial focal narrowing. Overall, 13 patients had an abnormal RFR or FFR value (measured after ACH testing), most of these patients had evidence of either LAD bridging or diffuse atherosclerotic disease.

Overall, there were no fatal or serious nonfatal complications (e.g., sustained ventricular tachycardia, ventricular fibrillation, or myocardial infarction due to prolonged coronary spasm) related to the CFT. During ACH infusions, 14 patients (13%) showed temporary AV-conduction disorders; intravenous injection of atropine was necessary to stabilize heart rate and blood pressure in 2 of them. In the patients that experienced vasospasm, 3 needed the administration of

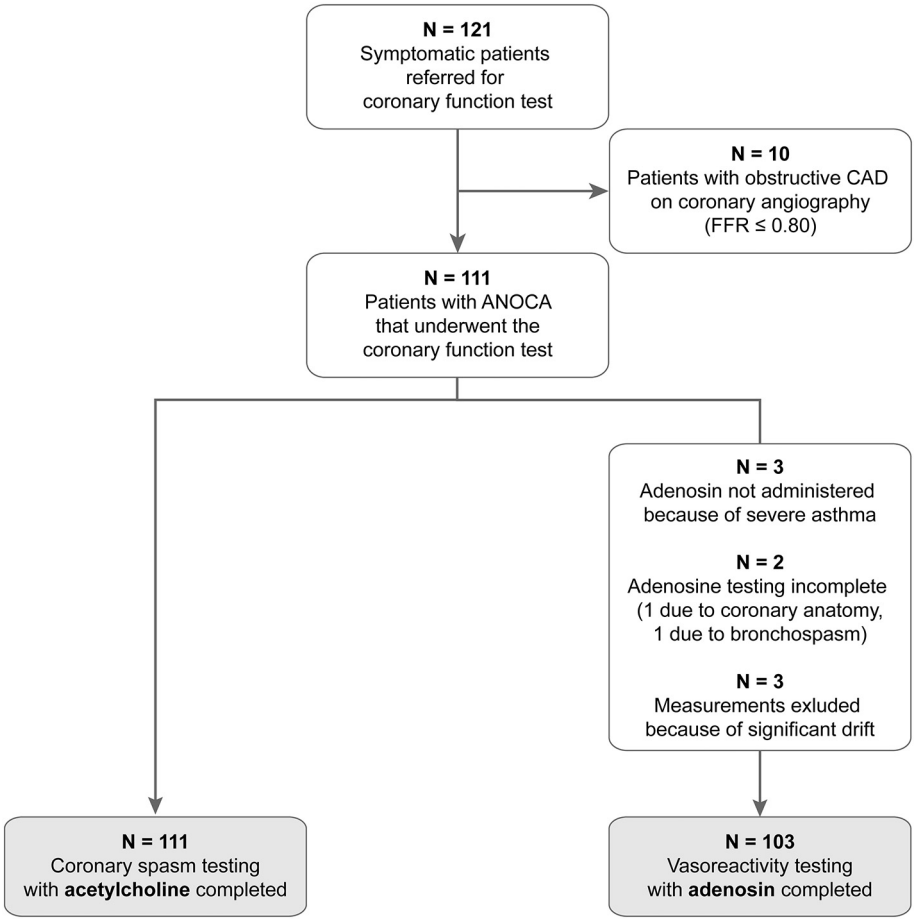

Fig. 1. Study flowchart. CAD = coronary artery disease; FFR = fractional flow reserve; ANOCA = angina and no obstructive coronary arteries.

Table 1
patient characteristics according to presence or absence of vasomotor dysfunction.

	All patients		Vasomotor dysfunction		No vasomotor dysfunction		P-value
	N = 111		*N* = 96		*N* = 15		
Age, years	**54**	**± 8**	55	± 8	50	± 8	0.02
Female	**98**	**(88%)**	84	(88%)	14	(93%)	0.52
Relevant medical history							
History of MI	**20**	**(18%)**	17	(18%)	3	(20%)	0.83
MINOCA	**7**	**(6%)**	5	(5%)	2	(13%)	0.23
History of PCI	**21**	**(19%)**	20	(21%)	1	(7%)	0.20
History of CVA/TIA/PAD	**4**	**(4%)**	6	(6%)	0	(0%)	0.42
Non-invasive ischaemia detection test performed[a]	**80**	**(72%)**	70	(73%)	10	(67%)	0.62
Positive non-invasive ischaemia detection test result	**24**	**(30%)**	22	(23%)	2	(20%)	0.68
Cardiovascular risk factors							
≥ 3 cardiovascular risk factors	**48**	**(43%)**	43	(45%)	5	(33%)	0.41
Obese (BMI ≥ 25)	**62**	**(56%)**	57	(59%)	5	(33%)	0.06
Hypertension	**38**	**(34%)**	37	(39%)	1	(7%)	0.02
Dyslipidaemia	**31**	**(28%)**	28	(29%)	3	(20%)	0.46
Diabetes	**12**	**(11%)**	11	(11%)	1	(7%)	0.58
Current/former smoker	**61**	**(55%)**	51	(53%)	10	(67%)	0.33
Premature CAD in first-degree relative	**55**	**(50%)**	48	(50%)	7	(47%)	0.81
Other risk variables							
Migraine	**45**	**(41%)**	34	(35%)	11	(73%)	< 0.01
Rheumatic disorder	**20**	**(18%)**	17	(18%)	3	(20%)	0.83
Reproductive disorders ($n = 90$[b])	**33**	**(37%)**	31	(40%)	2	(17%)	0.13
Angina characteristics							
Angina duration in months	**44**	**[19–98]**	15	[46–98]	39	[20–94]	0.96
Angina CCS III/IV	**72**	**(67%)**	62	(67%)	10	(71%)	0.73
Angina radiates	**102**	**(95%)**	88	(95%)	14	(100%)	0.38
Angina is nitroglycerin-responsive	**69**	**(64%)**	62	(67%)	7	(50%)	0.30
Symptoms							
Chest pain	**84**	**(79%)**	75	(81%)	9	(64%)	0.17
Dyspnoea	**69**	**(64%)**	62	(67%)	7	(50%)	0.23
Moment of symptoms							
Resting	**97**	**(91%)**	85	(91%)	12	(86%)	0.50
During exercise	**79**	**(74%)**	68	(73%)	11	(79%)	0.67
After exercise	**74**	**(69%)**	64	(69%)	10	(71%)	0.84
Emotion/stress	**69**	**(64%)**	60	(65%)	9	(64%)	0.99
Between 4 and 6 am	**41**	**(38%)**	35	(38%)	6	(43%)	0.71

Values are mean ± SD, n (%), or median [interquartile interval].
MI = myocardial infarction; MINOCA = myocardial infarction and no obstructive coronary arteries; PCI = percutaneous coronary intervention; CVA = cerebrovascular accident; TIA = transient ischaemic attack; PAD = peripheral artery disease; ECG = electrocardiogram; BMI = body mass index; CAD = coronary artery disease; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; CCB = calcium channel blocker; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCS = Canadian Cardiovascular Society.
[a] In the absence of significant obstructive CAD.
[b] Not applicable in male patients or female patients that were never pregnant. Reproductive disorders include pregnancy-related hypertension, HELLP syndrome, preeclampsia or repeated spontaneous abortions.

atropine to establish coronary vasodilation, in all other cases intracoronary nitroglycerin was sufficient. During ADE infusion, one patient developed a bronchospasm that was reversed with the administration of bronchodilators.

Three patients experienced a complication related to the access site: one patients developed a distal femoral artery stenosis after angioseal placement, one patient developed a radial hematoma that resolved spontaneously (Bleeding Academic Research Consortium (BARC) type 1), one patient experienced a hemodynamically significant bleeding from the femoral access site (BARC type 3) that was resolved with thrombin injections into the bleeding site.

3.2. Results of CFT

Of the 111 patients that completed CFT, 96 (86%) had coronary vasomotor dysfunction. The CFT was negative in 15 patients (14%). Of the patients with coronary vasomotor dysfunction, coronary spasm (ACH+) was present in 93 (97%), IMD (ADE+) in 36 (38%).

3.3. Coronary spasm (ACH+)

Of the 93 patients with coronary spasm (ACH+), 60 (63%) had isolated epicardial or microvascular spasm (ACH+/ADE-), 33 (34%) had a combination of spasm and IMD (ACH+/ADE+). Supplemental Fig. 1 shows the number and percentage of patients with spasm at the various ACH dosages. Microvascular spasm was observed in 45 patients. Epicardial spasm was observed in 48 patients: 33 patients with diffuse epicardial spasm, 15 patients with focal epicardial spasm. To investigate if there was a progression from microvascular to epicardial spasm, we examined if these 48 patients with epicardial spasm showed microvascular spasm at the previous ACH step (e.g. if a patient with an epicardial spasm at the 100 μg ACH dose, we examined if microvascular spasm was present at the previously administered 20 μg dose). Two patients already demonstrated epicardial spasm at the 2 μg dose and were therefore not included. Of the remaining 46 patients, 15 patients (33%) showed microvascular spasm at the previously administered dose.

3.4. Impaired microvascular dilatation (ADE+)

Of the 36 patients (38%) with abnormalities on adenosine testing, only 3 had isolated IMD (ACH-/ADE+), 33 had a combination of spasm and IMD (ACH+/ADE+). Of all patients with ADE+, a CFR < 2.0 was present in 10 patients, an IMR ≥ 25 in 28 patients, as shown in Supplemental Fig. 2.

3.5. Characteristics associated with coronary spasm (ACH+)

Patients with coronary spasm (ACH+) had a higher rate of obesity compared to those without (ACH-) (61% vs. 28%, $p < 0.01$) (Table 2). A history of PCI was more often seen in patients with coronary spasm, although this difference was not significant (22% vs 6%, $p = 0.12$). There were no clear differences in angina characteristics between patients with and without coronary spasm, both resting and exercise-induced angina were prevalent. Patients with coronary spasm had more extensive coronary atherosclerotic disease compared to those with no coronary spasm (ACH-), as shown in Table 3 ($p = 0.001$).

3.6. Characteristics associated with IMD (ADE+)

A history of cerebrovascular accident (CVA), transient ischaemic attack (TIA) and/or peripheral arterial disease (PAD) was more prevalent in patients with versus without IMD, (11% vs. 0%, $p < 0.01$), as shown in Table 2. There were no clear differences in cardiovascular risk factors between the two groups. Similar to patients with the endotype of coronary spasm, no differences were observed in angina characteristics between patients with and without the endotype of IMD. Patients with or without IMD showed no differences in atherosclerotic disease severity (Table 3).

3.7. Characteristics in patients with isolated or combined vasomotor dysfunction

When we divided patients into either isolated coronary spasm (ACH+) ($n = 60$) or combined vasomotor dysfunction (ACH+ and ADE+)

Table 2
Patient characteristics according to pathophysiological endotype of vasomotor dysfunction.

	Coronary spasm ACH+		No coronary spasm ACH-		P-value ACH+ vs. ACH-	IMD ADE+		No IMD ADE-		P-value ADE+ vs. ADE-
	N = 93		*N* = 18			*N* = 36		*N* = 67		
Age, years	55	± 8	52	± 9	0.18	56	± 8	53	± 8	0.11
Female	81	(87%)	17	(94%)	0.38	33	(92%)	58	(87%)	0.44
Relevant medical history										
MI	17	(18%)	3	(17%)	0.87	4	(11%)	15	(22%)	0.16
MINOCA	5	(5%)	2	(11%)	0.36	1	(3%)	6	(9%)	0.24
PCI	20	(22%)	1	(6%)	0.12	7	(19%)	13	(19%)	1.00
CVA/TIA/PAD	5	(5%)	1	(6%)	0.15	4	(11%)	0	(0%)	< 0.01
Non-invasive ischaemia detection test performed[a]	68	(73%)	12	(67%)	0.58	29	(81%)	45	(67%)	0.15
Positive non-invasive ischaemia detection test result	22	(32%)	2	(17%)	0.98	7	(24%)	14	(31%)	0.45
Cardiovascular risk factors										
≥ 3 cardiovascular risk factors	42	(45%)	6	(33%)	0.36	17	(47%)	27	(40%)	0.50
Obese (BMI ≥ 25)	57	(61%)	5	(28%)	< 0.01	20	(56%)	37	(55%)	0.97
Hypertension	34	(37%)	4	(22%)	0.24	14	(39%)	22	(33%)	0.54
Dyslipidaemia	27	(29%)	4	(22%)	0.56	13	(36%)	18	(27%)	0.33
Diabetes	11	(12%)	1	(6%)	0.44	3	(8%)	9	(13%)	0.44
Current/former smoker	48	(52%)	13	(72%)	0.11	22	(61%)	34	(51%)	0.32
Premature CAD in first-degree relative	48	(52%)	7	(39%)	0.33	14	(39%)	36	(54%)	0.15
Other risk variables										
Migraine	33	(35%)	12	(67%)	0.01	15	(42%)	28	(42%)	0.99
Rheumatic disorder	16	(17%)	4	(22%)	0.61	7	(19%)	12	(18%)	0.85
Reproductive disorders (n = 90[b])	30	(40%)	3	(20%)	0.15	13	(43%)	16	(30%)	0.23
Angina characteristics										
Angina duration in months	44	[15–92]	42	[20–149]	0.64	62	[23–104]	40	[17–88]	0.25
Angina CCS III/IV	60	(66%)	12	(75%)	0.48	22	(63%)	48	(72%)	0.37
Angina radiates	87	(96%)	15	(94%)	0.75	32	(91%)	65	(97%)	0.22
Angina is nitroglycerin-responsive	62	(68%)	7	(44%)	0.39	23	(66%)	41	(61%)	0.41
Symptoms										
Chest pain	73	(80%)	11	(69%)	0.31	30	(86%)	50	(75%)	0.20
Dyspnoea	60	(66%)	9	(56%)	0.46	23	(66%)	43	(64%)	0.88
Moment of symptoms										
Resting	83	(91%)	14	(88%)	0.64	33	(94%)	59	(88%)	0.32
During exercise	67	(74%)	12	(75%)	0.91	25	(71%)	49	(73%)	0.86
After exercise	63	(69%)	11	(69%)	0.97	26	(74%)	44	(66%)	0.38
Emotion/stress	59	(65%)	10	(63%)	0.86	22	(63%)	44	(66%)	0.78
Between 4 and 6 am	33	(36%)	8	(50%)	0.30	13	(37%)	26	(39%)	0.87

Values are mean ± SD, n (%), or median [interquartile interval].
ACH+ = acetylcholine-induced spasm; ACH- = no acetylcholine-induced spasm; ADE+ = impaired microvascular dilation; ADE- = no impaired microvascular dilation. Other abbreviations are similar to those used in Table 1.
[a] In the absence of significant obstructive CAD.
[b] Not applicable in male patients or female patients that were never pregnant. Reproductive disorders include pregnancy-related hypertension, HELLP syndrome, preeclampsia or repeated spontaneous abortions.

($n = 33$), we found no major differences in clinical characteristics, cardiovascular risk factors or angina characteristics, as shown in Supplemental Table 1. We were unable to include the patients with isolated ADE+ in these analyses because only 3 patients had isolated IMD.

4. Discussion

In this study of ANOCA patients undergoing clinically indicated CFT, we have three major findings. First, coronary vasomotor dysfunction

Table 3
Procedural characteristics according to pathophysiological endotype of vasomotor dysfunction.

	ACH+		ACH-		P-value	ADE+		ADE-		P-value
	N = 93		N = 18			N = 36		N = 67		
Coronary angiography visual stenosis					0.001					0.95
0%	43	(46%)	15	(83%)		18	(50%)	36	(54%)	
1–29%	13	(14%)	3	(17%)		7	(19%)	8	(12%)	
30–49%	37	(40%)	0	(0%)		11	(31%)	23	(34%)	
Coronary angiography visual stenosis in CFT interrogated vessel	11%	(± 15%)	2%	(± 5%)	0.004	10%	(± 14%)	10%	(± 14%)	0.85
Resting indexes										
RFR	0.93	[0.91–0.94]	0.93	[0.92–0.94]	0.61	0.93	[0.92–0.96]	0.93	[0.91–0.94]	0.17
Mean resting Tmn in s	0.98	[0.65–1.28]	1.11	[0.63–1.31]	0.79	1.04	[0.69–1.33]	0.97	[0.63–1.28]	0.54
Adenosine-induced hyperaemia										
FFR	0.88	[0.84–0.92]	0.88	[0.86–0.92]	0.38	0.90	[0.86–0.94]	0.87	[0.84–0.91]	0.06
Mean hyperaemic Tmn in s	0.26	[0.18–0.38]	0.25	[0.21–0.37]	0.96	0.40	[0.29–0.43]	0.21	[0.17–0.27]	<0.001
CFR	3.5	[2.6–4.8]	3.5	[2.9–5.3]	0.67	2.6	[1.9–3.4]	4.1	[3.1–5.3]	<0.001
IMR	19.1	[14.1–25.9]	17.6	[12.0–24.0]	0.70	30.9	[25.5–37.8]	16.0	[12.6–19.7]	<0.001

Values are n (%) or median [interquartile interval].
LAD = left anterior descending coronary artery; RFR = resting full-cycle ratio; Pd = distal (coronary) pressure; Pa = aorta pressure; Tmn = mean transit time; FFR = fractional flow reserve; CFR = coronary flow reserve; IMR = index of microvascular resistance. Other abbreviations are similar to those used in Tables 1 and 2.

was present in 86% of the patients. Second, of the patients with coronary vasomotor dysfunction, the vast majority (97%) had epicardial or microvascular vasospasm: either isolated spasm (63%), or in combination with IMD (low CFR and/or high IMR) (34%). Isolated IMD was observed in a minority of patients (3%). Our results highlight the need to perform CFT, including ACH testing, in patients with ANOCA.

4.1. Diagnostic yield of CFT

Our study shows that coronary vasomotor dysfunction was present in 86% of the patients. This diagnostic yield of the CFT is greatly dependent upon the results of the ACH test, with 97% of the patients demonstrating epicardial or microvascular spasm during ACH administration.

Part of the variation in reported prevalences of coronary vasomotor dysfunction endotypes could be related to the ACH dose used. With a maximum dose of approximately 100 μg ACH, the Scottish and Japanese report coronary spasm in 78–82% and IMD in 42–44% of their tested patients with coronary vasomotor dysfunction. (5,23) American study groups report IMD in 38% of their patients, and performed endothelial function testing using intracoronary Doppler-based flow measurements instead of coronary spasm testing. (8) In our study we diagnosed similar rates of IMD (38% of the patients). The relatively higher prevalence of coronary spasm (97% of our patients) could be related to our maximum dose of 200 μg ACH. It should be stressed that this dose is consistent with other contemporary protocols (16,24), and has been shown to be safe. (25) We have yet to reach international consensus on the optimal ACH dose for the best sensitivity and specificity of the diagnosis of coronary spasm. Nevertheless, we do believe that our results support that performing a CFT without ACH testing should be strongly discouraged.

4.2. Distinct endotypes: clinical and angina characteristics

In the present study, we demonstrated a higher prevalence of obesity and CAD severity in patients with the endotype of coronary spasm compared to those with no spasm. In healthy endothelium, ACH stimulates the endothelial cells to produce of vasodilator substances such as nitric oxide, which overrules the direct vasoconstrictor effects of ACH on the vascular smooth muscle cells (VSMCs). (26) Obesity and CAD severity are related to inflammation and oxidative stress, which promote endothelial dysfunction. Among other things, this results in a nitric oxide depletion of the endothelial cells, leaving the VSMCs hyperreactive to vasoconstricting stimuli, although the exact mechanism is still unclear. (27) The Rho-kinase pathway, which is also involved in the pathogenesis of a wide range of cardiovascular diseases, has been described to play a central role in VSMC hyperreactivity. (28)

The pathophysiological mechanism of coronary spasm might be different in ANOCA patients with a previous PCI. We, as well as others (25), report a trend towards a higher rate of spasm in these patients. Stent placement might cause spasm because of direct toxic effects (either the drug-eluting or direct toxic effects from the polymer), or inadequate re-endothelialisation of the coronary artery. (29) Larger samples are needed to elucidate the differences in coronary spasm between patients with and without previous PCI.

Patients with the endotype of IMD (ADE+) had higher rates of CVA/TIA/PAD in their medical history compared to patients without (ADE-). Even though patient numbers were limited, these results are consistent with other studies that report a higher rate of cardiovascular events in patients with IMD, especially in women. (4,9)

We did not observe differences in angina characteristics between patients with or without coronary vasomotor dysfunction, or between the different endotypes. This confirms the observations made in Japanese and Scottish patients undergoing CFT. (11,23) Others did observe differences and have reported coronary spams to cause resting angina while IMD causes exercise or post-exercise complaints. (3,21,22,25,30) It is important to recognize that women might present different than men with coronary vasomotor dysfunction. (31) However, as our patient population comprised 87% women, we could not properly evaluate gender differences in symptom presentation.

In the current study, allparticipants reported high rates of angina, both resting (91%) and during exercise (74%), regardless of their endotype of vasomotor dysfunction. This might be a reflection of the high prevalence of epicardial or microvascular vasospasm. In coronary spasm, exercise can induce a dynamic occlusion of the epicardial or microvascular coronary arteries also resulting in ischaemia and angina. (3,32) While known to occur at rest as well, the mechanisms of symptoms during rest in these patients are less well understood. Hypertension and a subsequent increased shear stress, or mental stress, might play a role as a provoking factor. (26,33) Finally, the high angina rates might be explained because the CFTs were performed in a tertiary referral centre.

4.3. Endotypes of vasomotor dysfunction: different classifications

We categorized vasomotor dysfunction into pathophysiological endotypes and showed that IMD (high IMR and/or low CFR) rarely occurs in the absence of epicardial or microvascular spasm. Current consensus statements regarding vasomotor dysfunction propose to categorize patients into either macro- or microvascular dysfunction, in which macrovascular dysfunction - or vasospastic angina (VSA) - consists of epicardial spasm, and microvascular angina (MVA) is composed of microvascular spasm, high IMR, and/or low CFR. (10,21,22) From a patient perspective, complaints and prognosis are important factors in diagnosis and treatment. This especially accounts for the large proportion of women affected by these disorders. (10) In 97% of the patients with vasomotor dysfunction, the anginal complaints were reproduced by coronary spasm provoked by ACH. In the 3% with isolated IMD, no overt symptoms were reproduced. With regards to prognosis, the presence of IMD is consistently associated with worse cardiovascular outcome. (4,8,9) Therefore, from a patient perspective, and pathophysiologically, it would be more correct to characterise different endotypes based upon either mainly (epicardial or microvascular) spasm which seem to be mainly related to complaints, or mainly IMD being an important prognostic factor, or a combination of both. This categorisation might aid in investigating prognostic differences and treatment effects in future studies.

4.4. Implications

The landmark CorMicA trial has shown that CFT-guided tailored medical treatment in patients with ANOCA leads to a marked and sustained improvement in angina and quality of life. (11) These improvements are sustained up to at least a year after the procedure. (12) Our study has confirmed the feasibility and safety of performing a CFT. One of the main questions that remains is which patients to refer for CFT. Based on our results, clinical characteristics do hardly seem to assist in the triage of patients with ANOCA for CFT. However, more extensive research is warranted to elucidate the optimal referral strategy for CFT.

4.5. Study limitations

As previously mentioned, this is a single centre study performed in an ANOCA expertise centre with a selected population of patients who were referred to CFT by their treating physician. This might have influenced the high yield of abnormalities we observed. On the other hand, studies including a less selected patient population also report a high prevalence of coronary vasomotor dysfunction in patients with ANOCA. (11)

Also, we only performed invasive physiological measurements (ADE and ACH) in the left coronary artery. The added diagnostic value of structurally testing the right coronary artery is currently unclear, but would probably only have resulted in a higher prevalence of coronary

vasomotor dysfunction. Also, adenosine testing was incomplete in 7% of the patients we included. This resembles a real-life clinical scenario. In the future, implementing non-adenosine-induced hyperaemic measurements might aid in evaluating IMD in these patients. (34)

Moreover, the subgroups of the different endotypes in our study were too small to confirm smaller differences between the groups. Our data were also too recent to include follow-up data. Larger trials including prognostic data should confirm and extent our findings.

5. Conclusion

In this study including patients with ANOCA that underwent CFT, 86% of the patients was diagnosed with coronary vasomotor dysfunction. Of the patients with coronary vasomotor dysfunction, 97% had coronary epicardial of microvascular spasm; isolated IMD (high IMR and/or low CFR) was present in only 3%. Performing a CFT without ACH testing should therefore be strongly discouraged.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.02.079.

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