ORIGINAL ARTICLE

Myocardial perfusion by CMR coronary sinus flow shows sex differences and lowered perfusion at stress in patients with suspected microvascular angina

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Abstract

Background: Patients with chest pain may have normal coronary arteries and suffer from microvascular angina (MVA). The aim of this study was to determine if patients with suspected MVA have lower global myocardial perfusion (global MP) during adenosine stress compared with healthy controls and coronary artery disease (CAD) patients and to determine if there are sex differences in global MP.

Methods: Twenty-three patients with suspected MVA (66 ± 11 years), 19 CAD patients (69 ± 5 years) with stress-induced ischaemia and 24 healthy controls (61 ± 10 years) underwent cardiac magnetic resonance (CMR) including coronary sinus flow measurements and first-pass perfusion at rest and during adenosine stress. Global MP was quantified as coronary sinus flow normalized to left ventricular mass.

Results: Global perfusion was lower during stress in patients with suspected MVA (2.9 ± 1.0 ml/min/g) compared with healthy volunteers (3.7 ± 1.1 ml/min/g, $p = 0.018$), but higher compared with CAD patients (2.0 ± 0.9 ml/min/g, $p = 0.019$). Female controls had higher global MP than male controls both at rest (1.0 ± 0.3 vs. 0.7 ± 0.2 ml/min/g, $p = 0.003$) and during stress (4.4 ± 1.0 vs. 3.1 ± 0.6 ml/min/g, $p = 0.001$). Furthermore, females with suspected MVA showed higher global MP than males with suspected MVA (3.3 ± 1.0 vs. 2.4 ± 0.7, $p = 0.04$).

Conclusions: Patients with suspected MVA have lower global MP at stress than healthy volunteers but higher than patients with CAD. Furthermore, there seems to be a sex difference in global MP at stress both in healthy volunteers and in patients with suspected MVA, with higher global MP in females, which implies a need for sex-specific normal limits when assessing quantitative MP.

KEYWORDS
cardiac syndrome X, CMR, coronary sinus flow, global myocardial perfusion, INOCA, microvascular angina

1 | INTRODUCTION

Angina pectoris can be caused by stress-induced regional myocardial ischaemia due to obstructive coronary artery disease (CAD) with significant stenosis in one or more of the main coronary arteries (Jespersen et al., 2012). However, angina pectoris may also be experienced in the absence of obstructive CAD (Della Rocca & Pepine, 2014), especially in females (Jespersen et al., 2012). This condition is referred to as 'microvascular angina' (MVA) (Suzuki, 2015), 'ischaemia and no obstructive coronary artery disease' (INOCA) (Knuuti et al., 2020; Kunadian et al. 2021), or 'cardiac syndrome x'. Some of these patients have low global left ventricular myocardial perfusion (global MP) at stress when examined with invasive coronary sinus flow reserve measurements (Thomson et al., 2015). Furthermore, low myocardial perfusion reserve (MPR), even in the absence of obstructive CAD, has been shown to be a prognostic marker for cardiac events (Gulati et al., 2009).

The current clinical diagnostic practice is primarily focused on identifying obstructive CAD suitable for elective revascularization either by percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG). However, there is emerging evidence that coronary microvascular dysfunction exists in the majority of patients with angina without significant CAD (<40% stenosis) on angiography (Sara et al., 2015). This highlights the importance of focusing not only on epicardial coronary artery stenoses but also coronary microcirculation. Cardiac magnetic resonance (CMR) can be used to quantify global MP using quantitative coronary sinus flow measurements (Schwitter et al., 2000), providing both diagnostic (Shomanova et al., 2017) and prognostic value (Indorkar et al., 2018; Kato et al., 2017). The latest guidelines for evaluation and diagnosis of patients with chest pain state that quantitative perfusion assessment with CMR may be used in the evaluation of patients with suspected MVA (Gulati et al., 2021).

Thus, we aimed to determine if patients with suspected MVA, defined as angina pectoris and stress-induced ST-segment changes on bicycle exercise test, with normal findings on MP single-photon emission computed tomography (MPS), have different global MP during adenosine stress compared with healthy volunteers and patients with regional stress-induced ischaemia. A second aim was to determine sex differences in global MP at stress in these groups.

2 | METHODS

2.1 | Study population and design

The study was approved by the regional ethics committee in Lund, Sweden. Written informed consent was obtained from all participants. Participants were recruited between 2010 and 2021 both retrospectively from a previous observational cohort (the MYOMER study) (Akil et al., 2018,2019; 2019) and prospectively with patients clinically referred to a bicycle exercise test followed by an MPS examination. Participants were divided into three groups using the following criteria.

2.1.1 | Patients with suspected MVA

Patients with clinically suspected MVA defined as a history of angina pectoris and pathological ST-T reaction on the bicycle exercise test, but normal findings on MPS, normal first-pass perfusion CMR during adenosine stress, and no infarction on late gadolinium enhancement (LGE) CMR (Knuuti et al., 2020; Kunadian et al., 2021).

2.1.2 | CAD patients

Patients with verified CAD diagnosed with significant coronary artery stenosis on angiography, and/or stress-induced ischaemia on MPS, or stress-induced ischaemia on CMR. The presence of myocardial infarction was assessed by LGE CMR.

2.1.3 | Healthy volunteers

Healthy volunteers were recruited from the general population without a history of cardiac disease and within the same age range as the patients with suspected MVA. Exclusion criteria for the healthy volunteers were history of hypertension, smoking, cardiovascular disease, systemic disease, metabolic disease or treatment with medication other than oral contraceptives.

2.2 | Bicycle exercise test

A bicycle exercise test was performed using a bicycle ergometer according to clinical routine. Starting load and increment was based on age, sex and self-estimated work capacity, typically starting at 30–60 W with a 10–20 W/min incremental protocol exercising to exhaustion (Jorfeldt & Pahlm, 2013). Two expert readers analysed the data from the bicycle exercise test. ST-T response was considered pathologic if there was no ST depression at rest, followed by >1.0 mm stress-induced ST depression with a horizontal or negative slope or ST changes after 4 min of recovery in lateral chest leads (V4–6).

2.3 | MPS

The bicycle exercise test was followed by an MPS which was performed using a 1- or 2-day rest/stress protocol with ^{99m}Tc-tetrofosmin stress/rest protocol using either a bicycle ergometer or adenosine stress test (Table 1) following the American Society of Nuclear Cardiology recommendations (Brindis et al., 2005). 2.5–4 MBq/kg of isotope was injected 1 min before the end of the exercise or after 3 min of adenosine infusion with the rest of the examination performed after at least 2 h in patients with abnormal stress MPS. Patients were instructed to refrain from caffeine and nitrates 24 h before the investigation.

TABLE 1 Patient characteristics

	Healthy volunteers	Suspected MVA	CAD patients
Number of patients	24	23	19
Age (years)	61 ± 10	66 ± 11*	69 ± 5*
Sex (N, %)			
Female	12 (50)	12 (52)	8 (42)
Male	12 (50)	11 (48)	11 (58)
LVM/BSA (g/m^2)	66 ± 11	68 ± 14	75 ± 18
EDV/BSA (ml/m^2)	82 ± 12	76 ± 14	84 ± 19
ESV/BSA (ml/m^2)	32 ± 7	25 ± 5	35 ± 20
EF (%)	62 ± 6	69 ± 4*	61 ± 13
CI (L/min/m^2)	3.2 ± 0.5	3.4 ± 0.8	3.4 ± 0.7
Medication			
Oral nitrates	0	6	13
Acetyl salicylic acid	0	8	16
Clopidogrel	0	0	4
Ticagrelor	0	1	4
β-blockers	0	10	11
Ca-channel antagonists	0	7	9
Statins	0	10	17
ACE-inhibitors	0	8	12
Diagnoses		14	11
Hypertension		14	11
Hypercholesterolaemia		10	11
Diabetes		3	5
Adenosine/bicycle exercise MPS		7/16	16/3
Philips/Siemens CMR	11/13	5/18	14/5

Note: Data are presented as mean ± SD.

Abbreviations: BSA, body surface area; CAD, coronary artery disease; CI, cardiac index; CMR, cardiac magnetic resonance; EDV, end diastolic volume; ESV, end systolic volume; LVM, left ventricular mass; MPS, myocardial perfusion single photon emission computed tomography; suspected MVA, patients with suspected microvascular angina.

*$p < 0.05$ compared with healthy volunteers.

One of two gamma cameras was used due to a change of MPS camera at the clinic:

1. A dual-headed camera (Ventri; GE Healthcare) with the patient in supine and prone position if attenuation correction was needed; iterative reconstruction was performed using maximum likelihood expectation maximization.
2. A cadmium zinc telluride camera (Discovery NM 530c; GE Healthcare) with an iterative reconstruction of gated images using ordered subset expectation maximization.

For both cameras, ECG-gated images were acquired in 8 bins per cardiac cycle allowing evaluation of myocardial function.

2.4 | CMR imaging

Due to a scanner exchange during the duration of the study, CMR was performed on either of two 1.5 T MR scanners (Philips Achieva; Philips Healthcare) with a 32-channel coil or Siemens Magnetom Aera (Siemens Healthcare GmbH) with a 30-channel coil. Typical image parameters are shown in Table 2. All patients were instructed to refrain from caffeine and nitrates 24 h before the investigation.

Left ventricular function and mass were obtained from short-axis cine imaging covering the left ventricle, acquired with a steady-state free precession (SSFP) sequence during end-expiratory breath-hold.

The coronary sinus (CS) flow image plane was planned with guidance from a basal short-axis image of the left ventricle (LV), as shown in Figure 1. The image plane was prescribed as a cross-section of the coronary sinus as close as possible to the orifice in the right atrium to ensure inclusion of the middle cardiac vein, enabling assessment of total left ventricular venous flow. CS flow was measured at rest and after 4–5 min of adenosine (Life Medical) infusion (140 mg/kg/min) using phase-encoded breath-hold turbo field echo velocity mapping sequence as previously described (Arheden et al., 2001; Bloch et al., 2009; Carlsson et al., 2015; Schwitter et al., 2000). The VENC was set to 80 cm/s at rest and 120 cm/s during adenosine stress. Typical CS flow curves are shown in Figure 2. Background correction was applied when using the Siemens Magnetom Aera as recommended by the vendor. Global MP values at rest were also presented with adjustment to rate pressure product using the formula 10 000 × global MP/systolic blood pressure × heart rate (Gobel et al., 1978). Inter-vendor variability for CS flow at rest was measured in five individuals, otherwise not included in this study, on both the Philips Achieva and a Siemens Magnetom Aera at the time of the scanner change.

First-pass perfusion images were acquired for assessment of regional perfusion using an SSFP-based perfusion sequence during a bolus injection of 0.05 mmol/kg gadolinium-based contrast agent (gadoteric acid, Dotarem, Guerbet, Gothia Medical AB, Billdal or Clariscan, GE Healthcare AB). Perfusion images were obtained in three short-axis slices (base, mid-ventricular and apical) during adenosine (140 mg/kg/min) hyperaemia and at rest 10 min after adenosine infusion. Heart rate and blood pressure were monitored during adenosine infusion.

LGE imaging was performed with a 3D-inversion recovery gradient-echo sequence (Philips), or 2D phase-sensitive inversion recovery gradient-echo sequence (Siemens) acquired during end-expiratory breath-hold. Short-axis slices (8-mm slice thickness) covering the entire left ventricle from base to apex and three long-axis projections (2-, 3-, and 4-chamber views) were acquired 10–20 min after an intravenous administration of an additional 0.1 mmol/kg of contrast agent after the resting perfusion.

TABLE 2 Typical CMR image parameters

Sequence parameters	Coronary sinus flow		Cine imaging		Regional perfusion		LGE	
	Philips	Siemens	Philips	Siemens	Philips	Siemens	Philips	Siemens
Repetition time (ms)	5.0	5.0	2.9	2.5	2.7	2.3	4.2	8.3
Echo time (ms)	2.6	2.8	1.5	1.1	1.4	1.0	1.3	3.2
Flip angle (degrees)	15	20	60	69	50	50	15	25
Inversion/saturation time (ms)	n/a	n/a	n/a	n/a	220–280	110	220–280	300
Segmentation factor	4	4	17	17	n/a	69	49	20
Acquired spatial res. (mm)	2.1 × 2.1 × 7.0	1.7 × 1.9 × 8.0	2.0 × 2.0 × 8.0	2.2 × 2.2 × 6.0–8.0	2.0 × 2.0 × 10.0	2.4 × 2.8 × 8.0	1.5 × 1.5 × 8.0	1.3 × 1.8 × 8.0
Reconstructed spatial res. (mm)	1.2 × 1.2 × 7.0	1.6 × 1.6 × 8.0	1.3 × 1.3 × 8.0	2.2 × 2.2 × 6.0–8.0	1.4 × 1.4 × 10.0	2.4 × 2.4 × 8.0	1.5 × 1.5 × 8.0	1.3 × 1.3 × 8.0
Acquired temporal res. (ms)	34	40	50	40	n/a	159	n/a	n/a
Reconstructed time phases	20	20	30	25	n/a	n/a	n/a	n/a
SENSE/GRAPPA factor	2	2	2	2	3	2	0	2
VENC (cm/s)	80–120	80–120	n/a	n/a	n/a	n/a	n/a	n/a
Number of slices/heartbeat	1	1	n/a	n/a	5	3	n/a	n/a
Slice gap (mm)	n/a	n/a	0	0–2	Individual	Individual	0	2

Abbreviations: CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement.
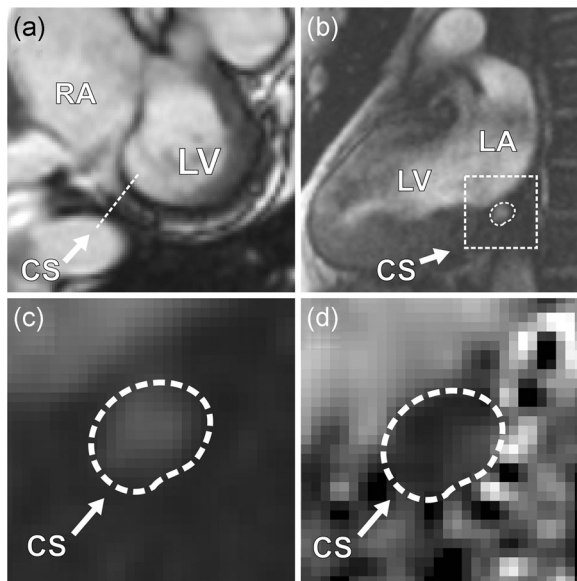
FIGURE 1 (a) Short axis view of the right atrium and coronary sinus ostium with a line that marks the placement of the coronary sinus plane in (b). (b) Magnitude image of the coronary sinus marked with a square. (c) Magnification of the same coronary sinus, panel with manual delineation. (d) Corresponding flow velocity encoded image of the same coronary sinus. CS, coronary sinus; LV, left ventricle; RA, right atrium.

2.5 | CMR image analysis

All MRI images were analysed using the image analysis software Segment v3.0 (Medviso) (Heiberg et al., 2010). Left ventricular mass (LVM) was obtained from manual delineations of the endocardium and epicardium of the left ventricle in the short-axis SSFP cine images at both end-systole and end-diastole. Papillary muscles and trabeculations were included for LVM calculation, but not included for calculation of LV dimensions and function. The LVM was calculated as the mean end-systolic/end-diastolic myocardial volume multiplied by 1.05 g/ml (myocardial density). Global MP (ml/min/g) was calculated as CS flow stroke volume/LVM both at rest and during adenosine stress. MPR was calculated as the ratio between stress and rest global MP. Splenic switch-off as a sign of adequate response to adenosine was visually assessed (Hosking et al., 2017).

The assessment of regional perfusion was done by visual analysis of the first-pass perfusion images in six basal, six mid-ventricular, and four apical segments, as previously described (Gyllenhammar et al., 2014). Each segment was graded regarding the transmural extent of the deficit in each segment (<50% or >50%). The severity of the perfusion deficit was graded as mild/moderate or severe based on the observer's visually estimated degree of hypo-enhancement, taking potential dark rim artefacts into consideration. The distinction between the dark rim and subendocardial ischaemia was done by
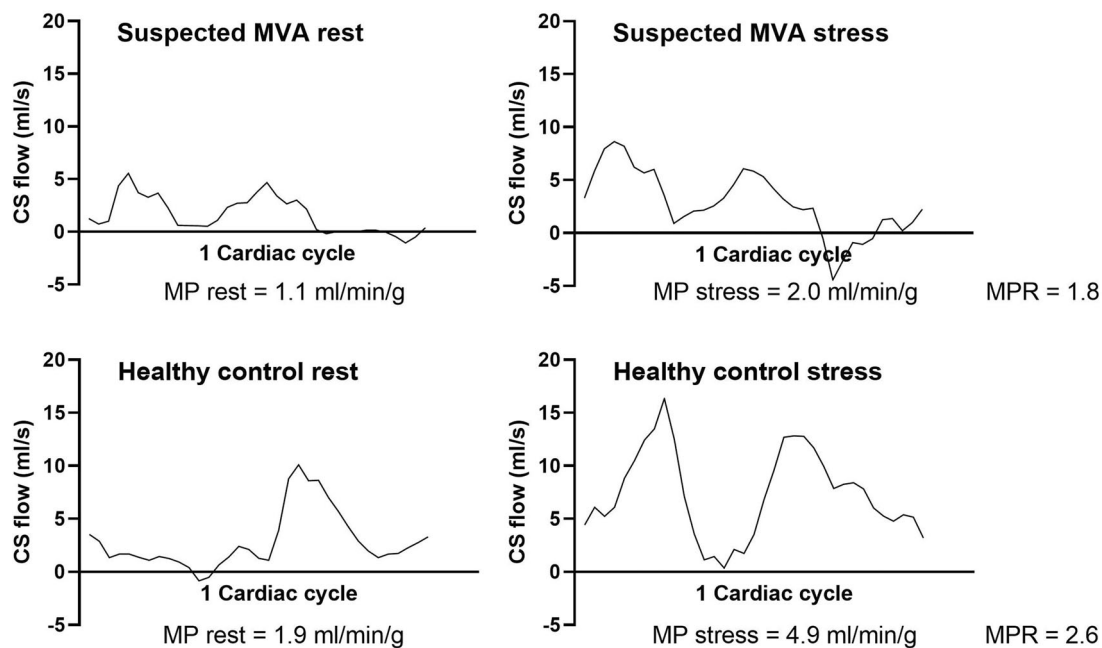

FIGURE 2 Typical coronary sinus (CS) flow measurements at rest and during stress for one healthy control and one patient with suspected microvascular angina (MVA) respectively. For these individuals, global myocardial perfusion (MP) and myocardial perfusion reserve (MPR) are indicated in the figure. The high MP at rest in the healthy volunteer yields an MPR that is even lower than that of the patient with suspected MVA, insidiously suggesting that there is no haemodynamic difference between the patient with suspected MVA and the healthy volunteer. However, the global MP is substantially lower in the patient with suspected MVA, which indicates the potential of using MP as a marker of coronary microvascular dysfunction.

TABLE 3 Haemodynamic response

	Healthy volunteers	Suspected MVA	CAD patients
Rest			
HR (bpm)	67 ± 10	67 ± 11	68 ± 10
Systolic BP (mmHg)	123 ± 13	131 ± 20	136 ± 26
Diastolic BP (mmHg)	75 ± 9	76 ± 11	81 ± 12
Global MP (ml/min/g)	0.9 ± 0.3	0.9 ± 0.6	0.7 ± 0.2
Corr global MP (ml/min/g)	1.3 ± 0.5	1.3 ± 0.8	1.1 ± 0.4
Adenosine stress			
HR (bpm)	88 ± 13	91 ± 13	86 ± 16
Systolic BP (mmHg)	125 ± 17	129 ± 19	132 ± 19
Diastolic BP (mmHg)	72 ± 11	72 ± 12	74 ± 14
Global MP (ml/min/g)	3.7 ± 1.1	2.9 ± 1.0*[†]	2.0 ± 0.9*
MPR	4.6 ± 1.2	4.6 ± 2.8[†]	2.9 ± 1.8*

Note: Patients with suspected microvascular angina (suspected MVA) and coronary artery disease patients (CAD) showed lower global myocardial perfusion (MP) than healthy volunteers during adenosine stress. However, there was no difference between patients with suspected MVA and CAD patients. Data are presented as mean ± SD.

Abbreviations: BP, blood pressure; Corr, rate pressure product corrected; HR, heart rate; MPR, myocardial perfusion reserve.

*$p < 0.05$ compared with healthy volunteers.

[†]$p < 0.05$ compared with CAD patients.

evaluating the images both before contrast entered the left ventricle and comparing the stress and rest images. A dark rim artefact was defined as a distinct dark subendocardial rim that existed already when contrast entered the left ventricle before reaching the myocardium also present at rest perfusion. Ischaemia was defined as hypointense myocardium during stress when myocardium and blood pool reached isointensity and that was not present at rest.

The amount of myocardial infarction was quantified using the LGE short-axis images, employing a previously described semi-automatic method taking partial volume effects into account (Engblom et al., 2016). The amount of myocardial infarction was expressed as a percentage of the LVM.

2.6 | Statistics

Statistical analysis was performed using IBM SPSS Version 25. Results are presented as mean ± SD unless otherwise stated. The Kruskal–Wallis test with Dunn's test post hoc was used to compare groups. Differences with a $p < .05$ were considered statistically significant.

3 | RESULTS

The study population characteristics are shown in Table 1. In total, 23 patients with suspected MVA (66 ± 11 years), 19 CAD patients (69 ± 5 years) and 24 healthy volunteers (62 ± 10 years) were included in the study. All patients with suspected MVA and healthy volunteers (except one) had normal cardiac volumes and function as assessed by CMR (Maceira et al., 2006). One healthy volunteer had an EF of 50%, thus below the age- and gender lower normal limits (Maceira et al., 2006). No regional myocardial dysfunction was seen. Furthermore, this volunteer had previously undergone a CT angiography and an exercise stress test with gas analysis with normal findings as a part of another study. Therefore, this individual was included as a healthy volunteer.

Thirteen patients were included as CAD patients due to stress-induced ischaemia on MPS. Four CAD patients were included due to obstructive coronary artery stenosis on angiography. Two patients with ST-depressions on exercise test but no stress-induced ischaemia on MPS were included as CAD patients due to regional hypoperfusion on stress first-pass perfusion CMR, and one of these was later found to suffer from the balanced three-vessel disease. For one patient with suspected MVA, the global MP at rest could not be determined due to poor image quality.

To get an estimate of the frequency of patients fulfilling the criteria for suspected MVA used in the present study, a 3-week inventory at the beginning of summer 2021 of all patients referred for MPS at the department where inclusion took place was performed. During the inventory, 178 patients were examined with MPS of which 8 (4.5%) had suspected MVA as defined by a history of angina pectoris and pathological ST-T reaction on the bicycle exercise test, but normal findings on MPS, normal first-pass perfusion CMR during adenosine stress, and no signs of infarction on LGE CMR.

3.1 | MP by CMR

Haemodynamic parameters are reported in Table 3. Two patients with suspected MVA did not have an increase in heart rate above 10 beats/minute during adenosine. However, both showed signs of splenic switch-off on first-pass perfusion indicating an adenosine effect.

Patients with suspected MVA had lower global MP (2.9 ± 1.0 ml/min/g) during adenosine stress compared with healthy volunteers (3.7 ± 1.1 ml/min/g, $p = 0.018$). Subgroup analysis based on sex (Figure 3) showed significantly lower global MP during adenosine stress in female patients with suspected MVA than female controls (3.3 ± 1.0 vs. 4.3 ± 1.0 ml/min/g, $p = 0.03$). The global MP at stress was, however, not significantly lower in male patients with suspected MVA compared with male controls (2.4 ± 0.7 vs. 3.1 ± 0.6 ml/min/g, $p = 0.07$).

Female controls had higher global MP than male controls both at rest (1.0 ± 0.3 vs. 0.7 ± 0.2 ml/min/g, $p = 0.003$) and during stress (4.4 ± 1.0 vs. 3.1 ± 0.6 ml/min/g, $p = 0.001$). During stress, female patients with suspected MVA showed higher global MP than male patients (3.3 ± 1.0 vs. 2.4 ± 0.7, $p = 0.04$). In patients with suspected MVA, global MP at rest was significantly higher in patients with hypertension ($n = 15$) compared with those without ($n = 8$; 1.0 ± 0.6 vs 0.6 ± 0.4 ml/min/g, $p = 0.04$) but not during stress (3.0 ± 1.1 vs. 2.6 ± 0.7 ml/min/g, $p = 0.4$). In the same patient group there was no significant difference in global MP comparing patients with ($n = 4$) and without ($n = 19$) diabetes neither at rest (0.9 ± 0.6 vs. 0.8 ± 0.6 ml/min/g, $p = 1.0$) nor during stress (2.8 ± 1.0 vs. 2.9 ± 1.0 ml/min/g, $p = 0.1$).

Interobserver agreement for coronary sinus flow measurements was assessed in a subset of 11 cases (rest and stress). The difference in global MP between the two observers was 0.2 ± 1.2 ml/min/g. The inter-vendor variability assessed in five individuals examined at rest on both scanners was 0.05 ± 0.28 ml/min (mean difference ± SD).

3.2 | Viability

No patient with suspected MVA had signs of previous myocardial infarction or other fibrosis on LGE. Eight patients in the CAD group had myocardial infarction with an average infarct size of 8% of LVM (range 2%–26%).

4 | DISCUSSION

The findings in the present study show that patients presenting with suspected MVA have lower global MP at stress than healthy volunteers but higher than patients with CAD. Furthermore, there seems to be a sex difference in global MP at stress both in healthy volunteers and in patients with suspected MVA, with higher global MP in females.

4.1 | Causes of low global MP

Decreased global MP at stress may be caused either by regional hypoperfusion due to obstructive CAD, or coronary microvascular
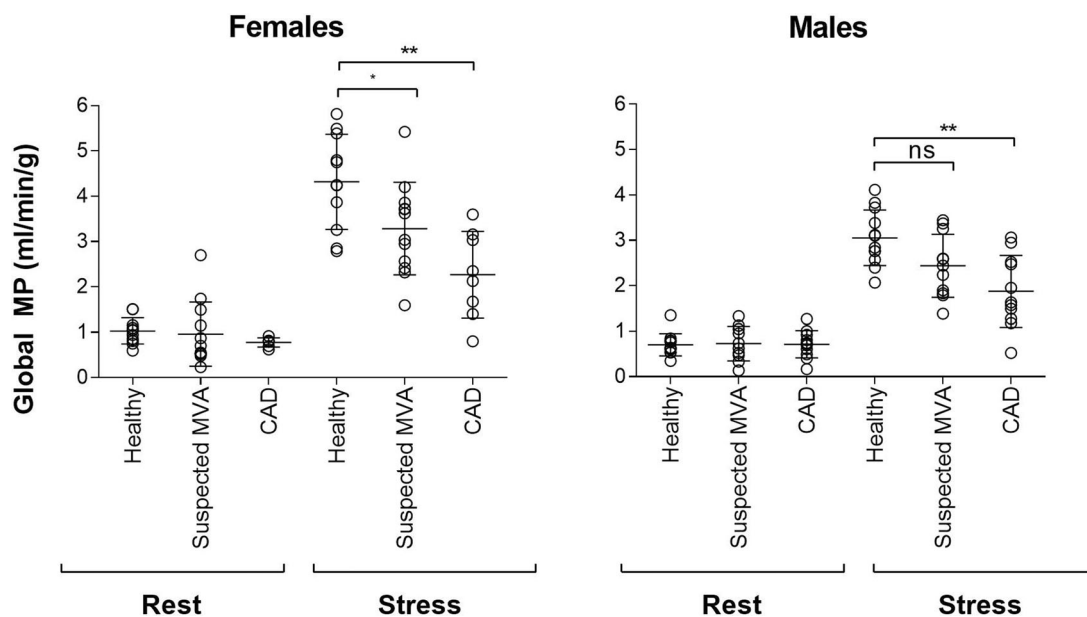

FIGURE 3 Global left ventricular myocardial perfusion (global MP) at rest and during adenosine stress. Patients with suspected microvascular angina (MVA) and coronary artery disease patients (CAD) showed lower global MP than healthy volunteers (Healthy), but there was no difference between patients with suspected MVA and CAD patients. Global MP increased from rest to stress in both males and females (significance values not shown). Error bars denote mean ± SD. *$p < 0.05$, **$p < 0.01$.

dysfunction, or a combination of both. Since we excluded patients with regional stress-induced ischaemia from the group with suspected MVA, coronary microvascular dysfunction is suspected to be the cause of the low global MP at stress in these patients.

The majority of the patients with suspected MVA (15 of the 23) had either diabetes or hypertension. These conditions have been shown to be related to the development of microvascular disease in the myocardium (Kaski et al., 1995; Kibel et al., 2017; Opherk et al., 1984). In a previous study by Zorach et al. (2018) using quantitative CMR perfusion mapping, it was shown the patients suffering from angina with risk factors for coronary microvascular dysfunction (female sex or male with diabetes or metabolic syndrome) and no obstructive CAD had lower MP at stress compared with controls ($p < 0.002$). In patients with suspected MVA in the present study, global MP at stress was, however, not significantly lower in patients with hypertension or diabetes compared with those without. The lack of observed differences might be due to the limited number of patients in each subgroup.

Ten of the 23 patients with suspected MVA were treated for hypercholesterolaemia.

High plasma caffeine level is a potential confounder to low global MP during adenosine stress since caffeine is a competitive receptor antagonist to adenosine. In our study, all participants had either a heart rate increase >10 beats/min or splenic switch-off.

4.2 | Diagnostic and prognostic significance of coronary microvascular dysfunction

The 23 patients with suspected MVA included in the study would be relieved from suspicion of ischaemic heart disease due to negative findings with MPS or first-pass perfusion CMR (Task Force et al., 2013). Consequently, these patients would have been declared healthy using today's clinical routine. Given the overlap with the healthy volunteers (Figure 3), some of the patients with suspected MVA might indeed have no myocardial disease, whereas some may suffer from coronary microvascular dysfunction as an early marker of atherosclerotic CAD (Zeiher et al., 1991) or due to other etiologies (Wessel et al., 2007). Patients with coronary microvascular dysfunction have been shown to have an increased risk of major cardiovascular events (Brown et al., 2021; Gan et al., 2017; Gulati et al., 2009; Murthy et al., 2011). In contrast, other studies have not shown any increase in deaths from cardiovascular events in patients with coronary microvascular dysfunction (Kaski et al., 1995; Suzuki et al., 2002). Thus, there is a need for an increased understanding of coronary microvascular dysfunction to allow for the development of new therapeutic targets aiming to improve prognosis in MVA patients.

A large portion of the patients with suspected MVA in the present study was treated with anti-anginal drugs as reported in Table 1. Anti-anginal treatment with different combinations of calcium antagonists, ACE inhibitors, nitrates, beta-blockers and potassium channel agonists has been shown to successfully relieve patients from angina pectoris in the majority of MVA patients (Suzuki et al., 2002).

4.3 | Sex differences in coronary microvascular function

In the present study, both male patients with suspected MVA and male controls had significantly lower global MP at stress than females in their corresponding groups. These findings are coherent with previous studies reporting lower global MP in males compared with females using quantitative CMR first-pass perfusion imaging at both rest and stress (Nickander et al., 2020). A lower global MP at stress has also been reported at rest using PET (Peterson et al., 2008) and contrast-enhanced multidetector computed tomography (Byrne et al., 2013). However, our results differ from previous PET data in which there was no sex difference with regard to global MP in a cohort of 56 healthy controls at rest and dipyridamole stress (Uren et al., 1995). The observed sex difference needs to be confirmed in larger cohorts.

Previous studies based on the prospective multi-centre WISE-Coronary Vascular Dysfunction (WISE-CVD) study showing that microvascular disease, defined as a decreased MPR, is common in females with angina without significant CAD (Bairey Merz et al., 1999; Reis et al., 2001; Thomson et al., 2015).

In the present study, MPR in patients with suspected MVA was not lower than in healthy volunteers. This may partly be explained by the high variability in global MP at rest (SD = 0.6 ml/min/g) in the patients with suspected MVA, resulting in high variability in MPR (SD = 2.9). The high variability in global MP at rest remained despite adjusting for rate pressure product. A possible explanation may be a more heterogeneous aetiology in patients with MVA compared with healthy controls and patients with established CAD. In a recent study by Kato et al. (2017), the risk of major adverse cardiac events was increased in patients with a low MPR, explained by an increased global MP at rest. It has been suggested that this increase in rest perfusion would be a compensatory mechanism accounting for ischaemia caused by epicardial coronary stenosis or microvascular dysfunction (Kato et al., 2017; Lichtenberg, 2017). As previously reported in a study using cardiac PET, there is a large variability in MP at rest, resulting in difficulties to establish the lower limit of normal MP at rest (Chareonthaitawee et al., 2001). This probably also explains the wide range of regional MPR reported in healthy individuals (Verberne et al., 2015). MPR is commonly used to diagnose coronary microvascular dysfunction, as in the WISE-CVD study where about one-half of the females with angina pectoris but no significant stenosis on angiography had low MPR on first-pass perfusion CMR (Reis et al., 2001). In a recent study by Rahman et al. (2021) on patients with chest pain but no obstructive CAD, CMR quantitative first-pass perfusion MPR could detect patients with coronary microvascular dysfunction defined as a reduced MPR on invasive angiography.

Furthermore, a low MPR measured by CMR using either quantitative first-pass perfusion (Knott et al., 2020) or CS flow

measurements (Kato et al., 2017) has been shown to increase the risk for major adverse cardiac events in patients with either known or suspected CAD. A low MPR value has been shown by PET to be able to predict the long-term risk of major adverse cardiovascular events (Gebhard et al., 2018; Murthy et al., 2014). However, the risk of MACE was shown to be higher in males than in females when MPR < 2 was used as cut-off (Gebhard et al., 2018; Murthy et al., 2014). Therefore, an optimized cut-off value of MPR < 2.32 to predict MACE has been suggested for females (Pepine et al., 2010). These findings emphasize the need for sex-specific reference values of this measure.

Assessment of regional perfusion distribution with first-pass perfusion alone may be insensitive to three-vessels disease and combining the first-pass perfusion with global MP measurement at stress increases the sensitivity for detecting CAD in this clinical context (Nakamori et al., 2018). Advances in first-pass perfusion imaging with CMR have enabled fully quantitative MP measurements (Engblom et al., 2017; Kellman et al., 2017). Using this novel technique, Nickander et al. (2020) showed significant sex differences in MP among healthy volunteers. Furthermore, this technique has recently been used to show lower global MP at stress in patients with the balanced three-vessel disease compared with patients with coronary microvascular dysfunction where global perfusion at stress of 1.82 ml/min/g was suggested to discriminate between the patient groups (Kotecha et al., 2019). Notably, only one of our patients with suspected MVA had a global MP < 1.82 ml/min/g at stress.

Two different MR scanners from different vendors (Siemens Magnetom Aera and Philips Achieva) were used in this study due to a scanner upgrade at the department during the inclusion period. Since there were differences between the scanners on how phase correction for flow imaging was implemented (Siemens scanner had no built-in background phase correction and had to be performed manually whereas for the Philips scanner it was done automatically) inter-vendor variability was assessed at the time of the scanner exchange. The agreement of the coronary sinus flow measurements between the scanners was considered acceptable to allow for pooling of flow data (0.05 ± 0.28 ml/min).

4.4 | Limitations

The study population is relatively small and thereby the study has limited power in showing differences between groups. The study was exploratory by design and therefore no power calculation was performed. Current clinical guidelines do not suggest coronary angiography (CT or invasive) when MPS is normal unless the patient has severe symptoms despite medication (Knuuti et al., 2020). Since the patients with suspected MVA were included in the present study based on a negative MPS, invasive coronary angiography was not performed as a result of the examination in any of the cases. Thus, the presence of coronary stenosis in the patients with suspected MVA included in the study cannot be excluded. The likelihood of

significant CAD is, however, low given that all patients with suspected MVA included in the study also had negative first-pass perfusion imaging and no signs of myocardial infarction.

Since angiography (CT or invasive) was not performed in the healthy volunteers (nonsmoking persons without history of, or medication for, cardiovascular disease), it cannot be excluded that some of the healthy volunteers had silent CAD. It has recently been shown that there is a 5% prevalence of significant coronary artery stenosis when screening the general population with CT angiography in the SCAPIS study (Bergström et al., 2021). However, when applying similar inclusion criteria as for the present study for healthy volunteers in the SCAPIS study (excluding individuals with hypertension, diabetes and smoking habits), the prevalence of CAD decreases to 0.3%–0.6%.

In our study, we used a fixed VENC of 80 cm/s at rest and 120 cm/s at stress. Recent studies have used a lower VENC of 60 cm/s at stress (Indorkar et al., 2018), which would not have been feasible in our study due to the observation of participants with higher maximum flow velocity requiring a higher VENC to avoid aliasing.

There was a wide range of global MP at stress in the patients with suspected MVA with some patients having global MP well below the healthy volunteers and some patients within the same range as the healthy volunteers. This overlap makes it difficult to suggest diagnostic limits to be used for the classification of patients. Global MP in patients with suspected MVA should therefore be interpreted in light of other clinical variables such as risk-factor profile, age and sex.

4.5 | Conclusion

Patients presenting with suspected MVA have lower global MP at stress than healthy volunteers but higher than patients with CAD. Furthermore, there seems to be a sex difference in global MP at stress both in healthy volunteers and in patients with suspected MVA, with higher global MP in females, which implies a need for sex-specific normal limits when assessing quantitative MP.

CONFLICTS OF INTEREST

DATA AVAILABILITY STATEMENT

The datasets analysed during the current study are not publicly available due to patient integrity but anonymized datasets are available from the corresponding author on reasonable request.

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