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ORIGINAL PAPER

Heterogeneity of coronary vascular function and myocardial oxygenation in women with angina and non-obstructive coronary artery disease

Elizabeth Hillier[1,2†], Malik Elharram[2†], James A. White[3], Todd Anderson[3], Judy Luu[1], Dina Labib [3], Muhammad Alhussein[3], Matthias G. Friedrich[1], and Louise Pilote [1,4*]

[1]Faculty of Medicine and Health Sciences, McGill University, 3605 de la Montagne, Montreal, QC H3G 2M1, Canada; [2]Faculty of Medicine and Dentistry, University of Alberta, 2J2.00 Walter C. MacKenzie Health Sciences Centre, Edmonton, AB T6G 2R7, Canada; [3]Faculty of Medicine, University of Calgary, 2500 University Drive NW, Calgary, AB T2N 1N4, Canada; and [4]Centre for Outcomes Research and Evaluation, Research Institute of the McGill University Health Centre, 5252 boulevard de Maisonneuve West, Montreal, QC H3A 1A1, Canada

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Aims

Women with angina and non-obstructive coronary artery disease (ANOCA) have a heightened risk for cardiovascular events, and the pathophysiology for ischaemic symptoms may be related to alterations in microvascular structure and function. We examined the use of breathing-enhanced oxygenation-sensitive cardiac magnetic resonance imaging (OS-CMR) using vasoactive breathing manoeuvres to assess myocardial oxygenation in women with ANOCA.

Methods and results

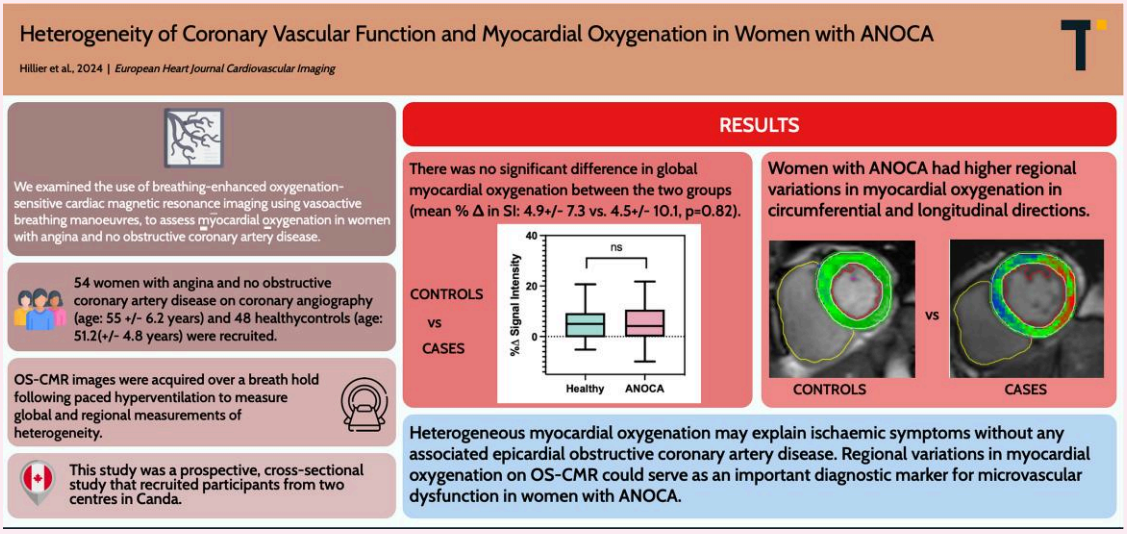
We recruited women (aged 40–65 years) from two sites in Canada who presented to healthcare with persistent retrosternal chest pain and found to have ANOCA, or without a history of cardiovascular disease. All participants were scanned using a clinical 3T MRI scanner, and OS-CMR images were acquired over a breath hold following paced hyperventilation to measure global and regional measurements of heterogeneity. Fifty-four women with ANOCA (age: 55 ± 6.2 years) and 48 healthy controls (age: 51.2 ± 4.8 years) were recruited. There was no significant difference in volume, function, mass, or global myocardial oxygenation between the two groups [mean %Δ in signal intensity (SI): 4.9 (±7.3) vs. 4.5 (±10.1), $P = 0.82$]. Women with ANOCA had higher regional variations in myocardial oxygenation in circumferential [median %Δ in SI: 5.1 (2.0–7.6) vs. 2.2 (1.4–3.5), $P = 0.0004$] and longitudinal directions [median %Δ in SI: 11.4 (5.4–16.7) vs. 6.0 (3.0–7.0), $P = 0.001$], which remained present in a multivariate model.

Conclusion

Heterogeneous myocardial oxygenation may explain ischaemic symptoms without any associated epicardial obstructive coronary artery disease. Regional variations in myocardial oxygenation on OS-CMR could serve as an important diagnostic marker for microvascular dysfunction in women with ANOCA.

* Corresponding author. E-mail: louise.pilote@mcgill.ca
† These authors are co-first authors on publication.

Graphical Abstract



Keywords ANOCA • OS-CMR • B-MORE • angina with no obstructive coronary artery disease • oxygenation sensitive • myocardial oxygenation • vasoactive breathing manoeuvres • cardiac MRI • CMR

Introduction

Angina with ischaemic symptoms and non-obstructive coronary artery disease (ANOCA) comprise a large proportion of poorly diagnosed and treated patients.[1,2] Although more women than men die annually of cardiovascular disease, women presenting with symptoms and signs of myocardial ischaemia are more likely to have non-obstructive coronary artery disease (CAD) on coronary angiography.[1] In fact, about 50% of women presenting with symptoms of angina have normal or minimal CAD on coronary angiography, compared with 7–17% of men.[2] Evidence has shown that a subpopulation of women with coronary vasomotor dysfunction (CVDys) are at a heightened risk for future cardiovascular events.[3–5] Data from the Women's Ischemia Syndrome Evaluation (WISE) study have shown that nearly 50% of women who present with ANOCA have evidence of coronary microvascular dysfunction on coronary function testing with reportedly higher rates of cardiovascular events.[6,7] Additionally, data from the British Heart Foundation Coronary Microvascular Angina (CorMicA) trial showed that 89% of those with ischaemia and no obstructive CAD demonstrated either microvascular or vasospastic angina on invasive coronary artery function testing.[7]

Oxygenation-sensitive cardiac magnetic resonance imaging (OS-CMR) is a novel technique that, in contrast to first-pass perfusion imaging, directly determines myocardial oxygenation without using contrast agents.[8,9] In studies performed on patients with hypertension, hypertrophic cardiomyopathy, and heart failure with preserved ejection fraction, OS-CMR could detect microcirculatory changes, suggesting it may be a useful surrogate marker for CVDys.[10–12] Recently, breathing manoeuvres have been shown to be powerful vasoactive stimulus, potentially impacting myocardial oxygenation more than an intravenous adenosine administration.[13] While the role of OS-CMR has been well studied in CAD,[14,15] its clinical utility in the diagnostic workup of patients with ANOCA has only been investigated in a small sample by our group.[16] We therefore aimed to assess the coronary vascular response to a vasoactive breathing manoeuvre assessed by OS-CMR in female patients with ANOCA compared with age-controlled healthy volunteers.

Methods

Cohort selection

Women with ANOCA

A cohort of women aged 40–65 years with persistent retrosternal chest pain who underwent cardiac catheterization were recruited and were found to have non-obstructive CAD on angiography (defined as <50% luminal diameter stenosis in an epicardial coronary artery). These patients have a clinical diagnosis of exercise-inducible chest pain responsive to nitroglycerine, with non-ischaemic causes of chest pain excluded by clinical history and physical exam. Women were excluded from the study if they had obstructive CAD with ≥50% luminal diameter stenosis in any epicardial coronary artery, acute coronary syndrome, Prinzmetal's angina, primary valvular heart disease, cardiogenic shock, prior non-cardiac illness with estimated life expectancy <4 years, chest pain with known non-ischaemic aetiology (e.g. pericarditis, pneumonia, and oesophageal spasm), contraindications to magnetic resonance imaging (MRI; pacemaker, other electronic device, and severe claustrophobia), or renal impairment with an estimated glomerular filtration rate of <45 mL/min/1.73 m^2.

Women without a history of cardiovascular disease

A cohort of women aged 40–65 without a history of cardiovascular disease were recruited as healthy volunteers. Women were excluded if they had a known clinical history of vascular disease, hypertension, diabetes mellitus, cancer, or other end-stage diseases that may compromise life expectancy, or contraindications to MRI (MRI-incompatible implants or severe claustrophobia).

Baseline clinical characteristics

Baseline clinical characteristics were obtained from each patient at the time of enrolment, including previous medical comorbidities, medication use, cardiovascular risk factors, and a health status assessment using the Seattle Angina Questionnaire (SAQ) and the Hospital Anxiety and Depression Scale (HADS). The score for each clinical domain of the SAQ was examined on a scale of 0–100, with higher scores indicating fewer

symptoms and improved clinical functioning.[17] Underlying psychiatric co-morbidities were examined using the HADS. The HADS aims to measure symptoms of anxiety and depression in a general medical population and consists of 14 items, with 7 items for the anxiety subscale and 7 for the depression subscale. Each item is scored on a response scale with four alternatives ranging between 0 and 3. All response items are summed to obtain two scales (range 0–15). Recommended cut-offs for anxiety and depression are 8–10 for doubtful cases and ≥11 for definitive cases.[18]

MRI protocol

All patients were scanned using a clinical 3T MRI scanner (Prisma or Skyra; Siemens Medical Systems, Germany) with a standardized CMR imaging protocol inclusive of cine imaging, T_2-weighted imaging, native T_1 mapping, rest, and stress oxygenation-sensitive imaging. Care was taken to ensure euvolaemia during imaging by way of oral hydration and blood sampled immediately before imaging to obtain haematocrit. All vasoactive medication was held 12 h prior to the MRI scan. Cine imaging was performed using a standard steady-state free precession (SSFP)–based pulse sequence in sequential short-axis slices at 8 mm intervals, three long-axis views, and in the four-, three-, and two-chamber orientations (slice thickness 6 mm, gap 2 mm, matrix 256 × 205, echo time 1.5 ms, and temporal resolution 35–40 ms). Native T_1 mapping was performed using a modified look-locker inversion recovery (MOLLI) pulse sequence in the basal, mid, and apical short-axis views. OS-CMR imaging was acquired in two short-axis slices (basal and mid-ventricular views) and performed during a prolonged end-expiratory breath hold of 30–60 s executed following a 60-s period of paced hyperventilation, as previously described and validated by our group.[19] End-systolic OS-CMR signal intensity (SI) was measured at the time points closest to 0 and 30 s of the post-hyperventilation breath hold (*Figure 1*).

A total of 25 women with ANOCA agreed to and successfully completed additional imaging during adenosine infusion for comparison of OS-CMR and first-pass stress perfusion imaging with contrast administration. Adenosine was infused infusion at a rate of 140 μg/kg/min for 3 min during which first-pass perfusion imaging was acquired during bolus infusion of 0.05 mmol/kg gadolinium contrast (Gadovist®, Bayer Inc., Canada) at a rate of 3.5 mL/s (followed by a 30 mL saline flush at same rate). Perfusion images were obtained for two short-axis slices (basal, mid, and apical) of the left ventricle using a saturation recovery turbo-FLASH pulse sequence. Typical imaging parameters were as follows: voxel size, 1.9 × 1.9 × 6 mm; TE, 1.51 ms; and duration, 100 cardiac cycles. Rest perfusion imaging was then performed 10 min later using the same bolus and slice profile.

Image analysis

All CMR analyses were performed in a blinded fashion at the McGill University Health Center Research Institute CMR Core Lab and at the Stephenson Cardiac Imaging Center using software certified for CMR image analysis (cvi,[42] Version 5.13, Circle Cardiovascular Imaging Inc., Calgary, AB, Canada). All OS-CMR images were analysed by two individual readers trained in OS-CMR analysis who were blinded to participant type.

For volumetric parameters, the endo- and epicardial borders of the cine images were manually contoured, and standard function parameters were calculated, including ejection fraction, stroke volume, diastolic volume, cardiac output, and myocardial mass indexed to the body surface area. T_1 and T_2 images were analysed using manually defined epicardial and endocardial contours. Segments were entirely excluded if >33% of the segment area was removed during analysis due to artefact.

For first-pass stress perfusion imaging, time–SI curves were generated for each myocardial segment using semi-automated tracking of the endocardial and epicardial borders. This analysis was repeated for rest perfusion imaging, and a myocardial perfusion reserve index (MPRI) was calculated as the maximum upslope of the first-pass myocardial time–intensity curve for the myocardium divided by the left ventricular cavity for stress divided by rest. MRPI values for the global myocardium, endocardium, and epicardium were calculated.

Myocardial oxygenation changes were assessed by measuring global SI changes in OS-CMR images. The mean global and segmental myocardial SI change in breathing-enhanced myocardial oxygenation reserve (B-MORE) on OS-CMR images was automatically calculated after manual tracing of the endocardial and epicardial contours and further segmented automatically according to the American Heart Association definition.[20] SI change was expressed as a % [change in SI (%)] using the first image of the breath hold (0 s) compared with the time point closest to 30 s of the breath hold.

Regional differences in myocardial oxygenation were measured as inter-segmental differences in myocardial oxygenation along radial, circumferential, and longitudinal directions, as previously described.[16] Each slice was divided into six myocardial segments analysed according to an endocardial and epicardial zone, resulting in 12 analysed segments per slice. Radial differences were defined as the sum of the absolute differences between the endocardial and epicardial zone for each of the myocardial segments, circumferential differences were the sum of the absolute differences between myocardial segments within the same endocardial or epicardial zone, longitudinal differences were the sum of the absolute differences between the endocardial and epicardial segments between the two myocardial slices, and combined differences were the sum of the absolute radial and circumferential differences.

Statistical analysis

Descriptive analyses compared baseline clinical and MRI values between patients with ANOCA and healthy volunteers using mean and standard deviation for continuous variables and frequency distributions for categorical variables. An independent *t*-test or Mann–Whitney *U* test was used to compare data between groups for continuous variables and χ^2 statistic or Fisher's exact test for categorical variables, as appropriate for the sample size of the comparison. The multiple regression analysis was conducted to determine the explanatory variables most significant in predicting heterogeneity between the two groups. The adjusted R^2 selection method was then used. The model with the highest adjusted R^2 value was considered for the selection variables used in the final regression.

A subset of 20 patients was re-analysed by a second independent reader, and inter-observer reliability was assessed using a two-way intraclass correlation test. Inter-observer reliability in a subset of 20 patients was 0.92, signifying a high degree of consistency in the image analysis between the two readers. SAS version 9.4 (SAS Institute) was used for all statistical analysis.

Results

Participant demographics

Fifty-four women with ANOCA and 48 women without a history of cardiovascular disease were recruited between April 2018 and September 2022. Women with ANOCA were older (55 ± 6.2 vs. 51.2 ± 4.8, $P = 0.0008$) with a higher body mass index (29.3 ± 6.4 vs. 25.8 ± 5.7, $P = 0.0034$) than women without a history of cardiovascular disease, respectively. Additionally, women with ANOCA had a higher proportion of cardiovascular risk factors, including dyslipidaemia (46%), hypertension (44%), obesity (35%), and type II diabetes mellitus (13%; *Table 1*). A diagnosis of depression was more prevalent in women with ANOCA compared to women without a history of cardiovascular disease (23% vs. 11%).

Close to half of women with ANOCA were on cardioprotective medications, including cholesterol-lowering medication (52%), aspirin (57%), calcium channel blockers (56%), nitrates (59%), and beta-blockers (28%).

Angiography

Most women with ANOCA had normal coronary arteries on coronary angiography (defined as <10% stenosis; 71%), with 15 (29%) having <50% stenosis on angiography (*Table 2*). Notably, no participant was

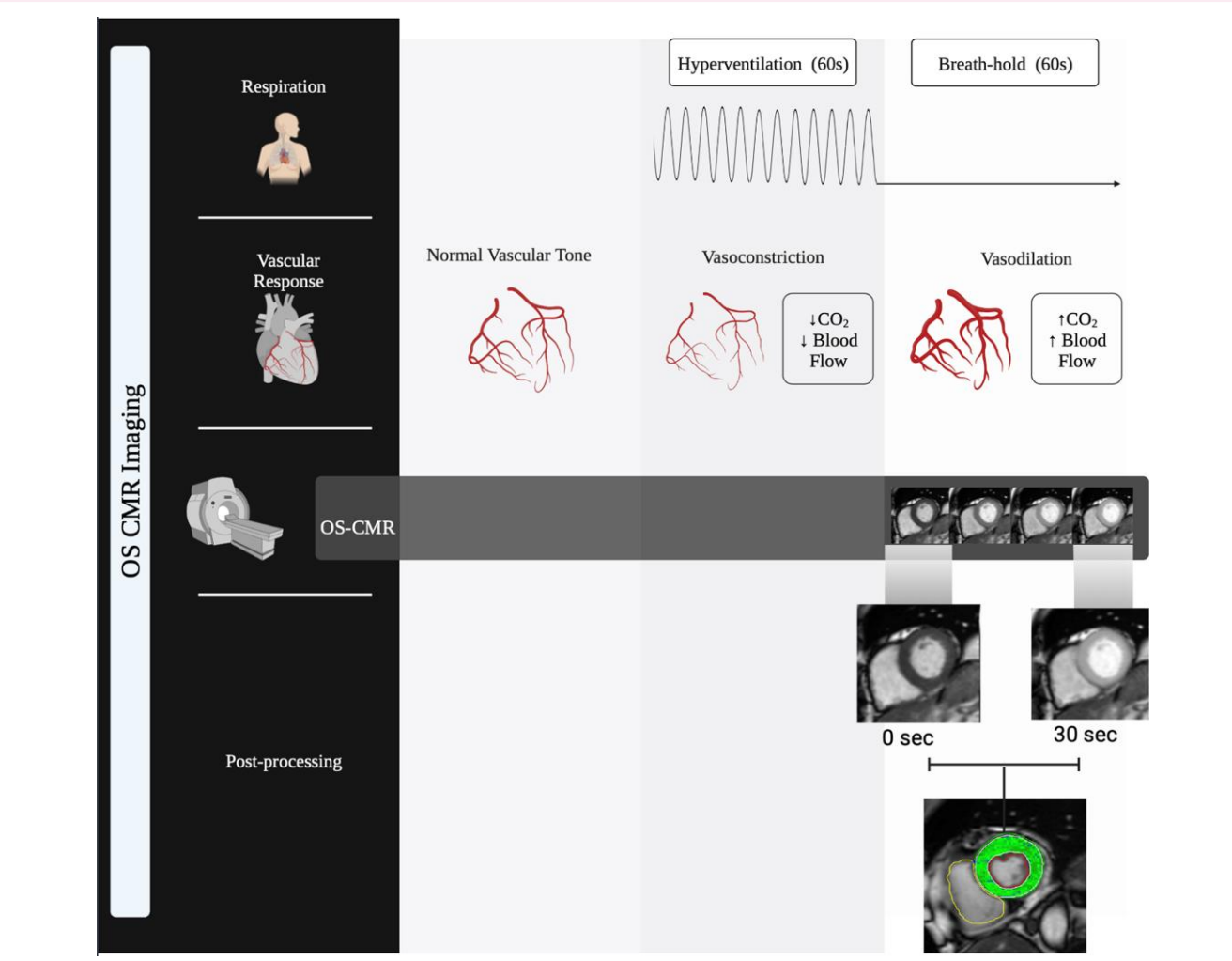


Figure 1 The acquisition of OS-CMR with vasoactive breathing manoeuvres. The workflow and physiologic effects of OS-CMR with vasoactive breathing manoeuvres of 1 min of paced hyperventilation followed by a maximal voluntary breath hold (~60 s). Hyperventilation induces vasoconstriction through a reduction in the local concentration of carbon dioxide, and breath hold induces vasodilation as a result of an increase in the concentration of carbon dioxide. The B-MORE is calculated as the per cent difference in SI between the 0- and 30-s time points of the post-hyperventilation breath hold.

identified as having high-risk calcifications or plaques, and only three participants were noted to have any calcification on coronary angiography.

Anginal scores

At study entry, the median anginal summary score of patients with ANOCA was 64 (54–76). Study patients reported moderate limitation in their physical function [median physical limitation: 68 (55–90)], and most reported symptoms monthly [median angina frequency score: 80 (60–90)]. Finally, these women reported poor to fair perceptions of their quality of life [median disease perception/quality of life: 50 (42–67)]. There was reasonable satisfaction among women with ANOCA with regard to treatment [median treatment satisfaction score: 69 (58–81); *Table 2*].

Cardiac MRI functional parameters

Comparisons of cardiac function and native T_1 and T_2 mapping between healthy volunteers and women with ANOCA are reported in *Table 3*. There was no difference in indexed left ventricular end-systolic volume, stroke volume, myocardial mass, left ventricular ejection fraction, or cardiac index. Healthy volunteers had a slightly higher left ventricular end-diastolic volume (66.1 mL/m^2 ± 10.9 vs. 60.1 mL/m^2 ± 10.3, $P = 0.007$) than healthy volunteers. There was no significant difference in native mid-ventricular T_1 and T_2 values (mid T_1: 1222 ± 43 vs. 1228 ± 42, $P = 0.046$; mid T_2 41.3 ± 2.6 vs. 40.9 ± 2.3, $P = 0.35$).

No participant had elevated T_2 signal suggestive of myocardial oedema, and no evidence of local fat deposition was visually identified on SSFP imaging within studied portions of the myocardium.

OS-CMR

Four women with ANOCA did not undergo OS-CMR imaging due to scanner technical ECG gating issues ($n = 2$) and claustrophobia when practising the breathing manoeuvre ($n = 2$). Among women undergoing OS-CMR, seven ANOCAs and four controls were not able to hold their breath for longer than 15 s and were excluded from this analysis. A further six participants ($n = 4$ ANOCA, $n = 2$ controls) were

Table 1 Baseline clinical characteristics of the total sample

Variable	Women with ANOCA ($n = 54$), N (%)	Women without a history of cardiovascular disease ($n = 48$), N (%)	P value
Cardiac risk factors			
Dyslipidaemia	25 (46.3)	0 (0)	<0.0001
Hypertension	24 (44.4)	0 (0)	<0.0001
Diabetes type 2	7 (13.0)	0 (0)	0.01
Obesity	19 (35.2)	9 (18.7)	0.06
Cardiac medications			
Cholesterol-lowering medication	28 (51.9)	1 (2.1)	<0.0001
Aspirin	31 (57.4)	1 (2.1)	<0.0001
Calcium channel blockers	30 (55.6)	0 (0)	<0.0001
Nitrates	32 (59.3)	0 (0)	<0.0001
Beta-blockers	15 (27.8)	1 (2.1)	0.0003
Angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB)	14 (25.9)	0 (0)	<0.0001
Diuretics	6 (11.1)	0 (0)	0.028
Other variables	Mean (SD)	Mean (SD)	
Age (years)	55.1 (6.2)	51.2 (4.9)	0.0008
Body mass index (kg/m^2)	29.37 (6.35)	25.76 (5.68)	0.0034
Anxiety score (HADS)	8.7 (3.7)	4.9 (3.0)	<0.0001
Depression score (HADS)	5.5 (3.2)	2.9 (2.9)	<0.0001

Comparison of the presence of cardiac risk factors, demographics, anxiety, and depression scores between women with ANOCA and women with no history of cardiovascular disease.

Table 2 Angiographic and clinical characteristics of the total sample

Characteristic	Women with ANOCA
Coronary angiography	
Normal coronary arteries (%)	37 (71%)
Minimal coronary artery disease (<50%; %)	15 (29%)
Seattle Angina Questionnaire	
Summary score	64 (54–76)
Physical limitation, median (range)	68 (55–90)
Angina stability, median (range)	50 (50–75)
Angina frequency, median (range)	80 (60–90)
Treatment Satisfaction, median (range)	69 (58–81)
Disease perception/quality of life, median (range)	50 (42–67)

A summary of the angiographic findings in women with no obstructive coronary artery disease (ANOCA). Normal coronary arteries were defined as having 0% stenosis in all epicardial coronary arteries, and minimal coronary artery disease was defined as having </50% stenosis in any epicardial coronary artery as assessed by quantitative coronary angiography. A summary of the SAQ scores in women with ANOCA.

excluded from analysis due to significant artefacts ($n = 4$) or ECG gating issues ($n = 2$). Therefore, 39 women with ANOCA and 40 women without a history of cardiovascular disease were included in the OS-CMR analysis.

Overall, there was no significant difference in global B-MORE after breathing manoeuvres in women with ANOCA compared to women without a history of cardiovascular disease [%Δ in SI: 4.94 (7.3) vs. 4.49 (10.1), $P = 0.82$].

Women with ANOCA had statistically significantly higher regional variations in myocardial oxygenation in circumferential [median % change in SI: 5.1 (2.0–7.6) vs. 2.2 (1.4–3.5), $P = 0.004$; visually depicted in *Figure 2*] and longitudinal directions [median % change in SI: 11.4 (5.4–16.7) vs. 6.0 (3.0–7.0), $P = 0.001$] when compared to women without a history of cardiovascular disease. There were no significant differences in radial heterogeneity [median % change in SI: 2.4 (1.4–4.1) vs. 1.9 (0.7–3.1), $P = 0.22$] between the two groups (*Table 3*).

First-pass perfusion CMR

Of the 25 ANOCA patients incrementally undergoing first-pass adenosine stress perfusion imaging, their mean global MPRI was 2.1 (0.5; *Table 3*). There was no significant correlation between MPRI and global B-MORE ($r = -0.4$, $P = 0.064$) or OS-CMR-derived values of regional heterogeneity (longitudinal: −0.2, $P = 0.29$; circumferential: −0.3, $P = 0.15$; radial: −0.04, $P = 0.86$).

Multivariate analysis

In the multivariate model (including all independent variables listed in *Table 1*), significant differences in heterogeneity persisted between women with and without ANOCA. Women with ANOCA showed a mean % change significantly higher in longitudinal heterogeneity (beta = 14.24, 95% CI = 7.83, 20.66, $P < 0.0001$), circumferential heterogeneity (beta = 3.17, 95% CI = 0.71, 5.63, $P = 0.0125$), and B-MORE (beta = 6.16, 95% CI = 0.28, 12.04, $P = 0.0404$).

Table 3 Functional and tissue characteristics of the total sample

	Women with ANOCA ($n = 39$)	Women without a history of cardiovascular disease ($n = 40$)	*P* value
Left ventricular end-diastolic volume, mean (SD), mL/m^2	60.1(10.3)	66.0 (10.9)	0.0069
Left ventricular end-systolic volume, mean (SD), mL/m^2	16.4 (5.7)	17.6 (5.4)	0.28
Stroke volume, mean (SD), mL/m^2	80.9 (15.2)	84.4 (14.9)	0.26
Cardiac output, mean (SD), L/min	5.4 (1.3)	5.4 (1.1)	0.94
Cardiac index, mean (SD), L/min/m^2	2.9 (0.7)	3.09 (0.5)	0.11
Myocardial mass systole, mean (SD), g	117.6 (28.1)	114.2 (20.4)	0.50
Left ventricular ejection fraction (%), mean (SD)	72.8 (8.7)	73.4 (5.1)	0.69
MRI mapping			
Native mid T_1 (ms), mean (SD)	1221.52 (42.8)	1228.1 (42.3)	0.46
Mid T_2 (ms), mean (SD)	41.3 (2.6)	40.9 (2.3)	0.35
First-pass perfusion CMR			
Global myocardial perfusion index, SD	2.1 (0.5)		
Epicardial myocardial perfusion index, SD	2.3 (0.6)		
Endocardial myocardial perfusion index, SD	1.8 (0.4)		
Oxygenation-sensitive CMR			
Basal slice (median %ΔSI)	7.5 (11.7)	6.4 (19.2)	0.77
Mid slice (median %ΔSI)	3.6 (8.1)	3.1 (5.9)	0.77
Global (median %ΔSI)	4.9 (7.3)	4.5 (10.1)	0.82
Radial heterogeneity (median %Δ in SI)	2.4 (1.4–4.1)	1.9 (0.7–3.1)	0.22
Circumferential heterogeneity (median %Δ in SI)	5.1 (2.0–7.6)	2.2 (1.4–3.5)	0.0010
Longitudinal heterogeneity (median %Δ in SI)	11.4 (5.4–16.7)	6.0 (3.0- 7.0)	0.0004

A comparison of cardiac MRI–derived volumetric, functional, and tissue characterization parameters (T_1, T_2 mapping) between women with a history of ANOCA and women without a history of cardiovascular disease. A comparison of the B-MORE global and regional parameters, as calculated by the regional changes in myocardial SI, derived from OS-CMR in women with ANOCA compared to women with no history of cardiovascular disease.
CMR, cardiac magnetic resonance imaging; MRI, magnetic resonance imaging; SD, standard deviation; SI, signal intensity.

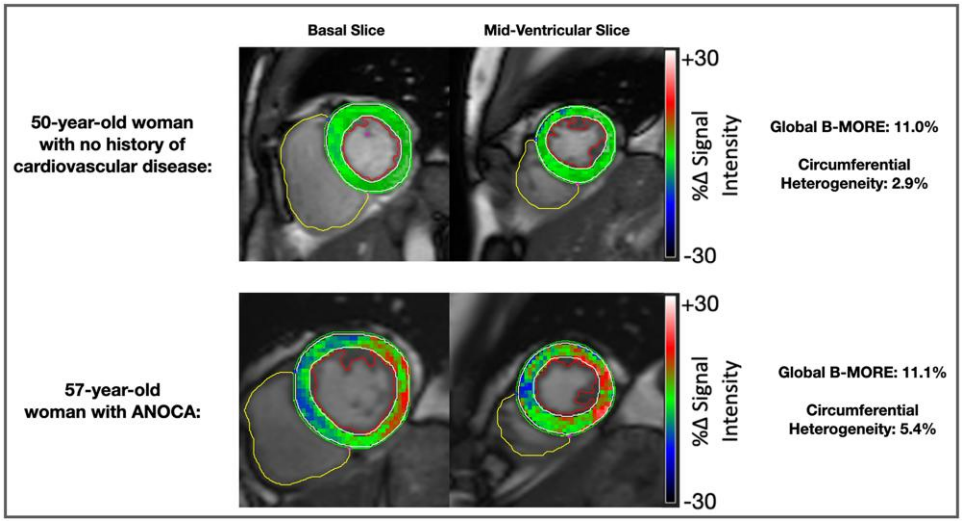


Figure 2 The B-MORE in a woman with angina and no obstructive CAD and a healthy control. A visual representation of the differences in myocardial oxygenation reserve regional heterogeneity in women with ANOCA and women with no history of cardiovascular disease. On the top is the B-MORE of a 50-year-old woman with no history of cardiovascular disease and globally preserved B-MORE (11.0%) and a low circumferential heterogeneity (2.9). On the bottom is the B-MORE of a 57-year-old woman with ANOCA with a preserved global B-MORE (11.1%), but a significant circumferential heterogeneity.

Discussion

In this prospective cohort of women with ANOCA undergoing OS-CMR with vasoactive breathing manoeuvres, there was no significant difference in global myocardial oxygenation between women with ANOCA and healthy volunteers. However, women with ANOCA were noted to have greater longitudinal and circumferential heterogeneity in myocardial oxygenation, consistent with our previous publication,[16] which persisted in a restricted multivariate model. Our findings suggest that regional heterogeneity in myocardial oxygenation may not only be an important diagnostic marker in women with ANOCA but may explain ischaemic symptoms in the absence of widespread myocardial ischaemia or obstructive coronary disease.

Women with ANOCA comprise a large group of patients referred for coronary angiography, for which limited non-invasive evidence exists to guide diagnosis or therapy.[6] While traditional risk factors, including smoking, diabetes mellitus, hypertension, and dyslipidaemia, have been associated with impairment in microvascular function,[21] recent evidence has further suggested the role of non-traditional risk factors, including inflammation,[22] psychosocial stressors,[23] or reproduction-related condition, such as preeclampsia,[24] in the pathogenesis of this disease. Furthermore, psychological stress may also contribute to CVDys through an elevation in vasomotor tone or endothelial dysfunction related to a stress-mediated response.[23] Within our cohort of ANOCA, nearly one-quarter of women experienced underlying depression or anxiety as demonstrated on the HADS scale. These psychosocial stressors may have contributed to CVDys or may be related to a higher symptom burden and poor quality of life experienced by women with ANOCA. Indeed, we noted that women with ANOCA demonstrated significant symptom limitation from angina and a poor quality of life as reflected by measures on the SAQ. Across measures, women with ANOCA reported significant physical limitations, frequent symptoms, and a poor quality of life, similar to SAQ scores in patients with obstructive CAD.[17] We further noted a significant heterogeneity in baseline cardioprotective therapies, which reflects the lack of adequate evidence-based therapies for patients with ANOCA.[25]

Overall, we found no significant differences in cardiac MRI parameters of volume, function, mass, perfusion, or global myocardial oxygenation between women with ANOCA and healthy volunteers, which demonstrates that despite normal routine measurements, there can be cardiac remodelling abnormalities present in biomarkers not routinely assessed. Previously, one study examined the myocardial oxygenation response in 18 patients with cardiac syndrome X, defined as exercise-induced angina and abnormal exercise electrocardiography, compared to 14 healthy controls and found no significant difference in global signal change during a hyperaemic stimulus.[26] Together, our findings suggest that global measures of myocardial tissue oxygenation and perfusion are preserved in women with ANOCA. There may be several potential explanations for preserved global oxygenation in the presence of ANOCA. One possibility may be related to impairment in microvascular function in homogenizing blood flow during hyperaemia. Homogenization of capillary flow during hyperaemia is an intrinsic property of microvascular networks and critical in limiting functional shunting of blood and increasing the efficiency of oxygen extraction.[27,28]

A further explanation for the absence of significant differences in global myocardial oxygenation may be due to the heterogeneity of patients included within our cohort. ANOCA is increasingly being recognized as a heterogenous entity with multiple underlying aetiologies. ANOCA may be mediated through endothelial dysfunction, microvascular or epicardial vasospasm, and/or marked diffuse coronary disease without focal stenosis.[25] Impairment in global myocardial oxygenation may be more evident in specific endotypes of ANOCA, particularly in those with impaired global flow reserve from endothelial dysfunction, which can be present in 40–50% of these patients.[7] Along the same lines, this may also partly explain why there was no correlation between global MPRI and global B-MORE or any other measures of regional heterogeneity. The use of adenosine as a pharmacological stress agent for perfusion imaging predominately evaluates the pathway for non–endothelial-dependent vascular relaxation through direct stimulation of smooth muscle cells, limiting the assessment of other disease pathways for ANOCA.[29] Previous studies have similarly reported that microvascular perfusion may itself be uncoupled from myocardial oxygenation, whereby myocardial hypoperfusion is not necessarily commensurate with deoxygenation.[30]

Among women with ANOCA, we again noted a heterogenous coronary vasomotor response to vasoactive breathing manoeuvres as characterized by longitudinal and circumferential heterogeneity in myocardial oxygenation that persisted in a restricted multivariate model. Our findings are consistent with recent data from a large cohort of patients undergoing positron emission tomography, which demonstrated regional heterogeneity in myocardial perfusion on coronary flow reserve in patients with CVDys.[31] Microvascular dysfunction may lead to an increased heterogeneity of flow and distribution through physiologic shunting from areas of impaired microvasculature towards areas of normal microcirculatory function.[32]

Finally, the study underscores the utility of breathing-enhanced OS-CMR in clinical settings. The small logistical effort and the non-invasive short protocol confirm the globally increased interest in this modality as a very helpful addition to standard CMR protocols.

Limitations

Our study has several important limitations to note. Firstly, our novel marker of regional heterogeneity has yet to be validated in external and larger cohorts. Secondly, given the preponderance of women with ANOCA, we excluded male subjects from our study, and our findings therefore may not apply to males with ANOCA. Thirdly, a proportion of patients were excluded from the analysis due to an inability to tolerate the vasoactive breathing manoeuvres or poor image acquisition for analysis. The reasons for this phenomenon in this group are unclear but may affect the routine use of OS-CMR in patients with ANOCA. However, all exclusions due to inability to adequately perform the breathing manoeuvre were participants who were scanned in the first third of participants, potentially highlighting the importance of proper training of both research personnel and study participants. Finally, the use of coronary angiography in our study to investigate the quality and quantity of coronary atherosclerosis is suboptimal. Further studies should compare coronary computed tomography with OS-CMR and regional heterogeneity in the myocardium of patients with ANOCA.

Conclusion

Our results indicate a heterogeneous coronary vascular response to a standardized vasoactive breathing manoeuvre with a regionally diminished adaptation of myocardial oxygenation, which may explain the presence of ischaemic symptoms in the absence of epicardial CAD in women with ANOCA. Therefore, breathing-enhanced OS-CMR may provide an important diagnostic marker for CVDys in patients with ANOCA and should be validated in further studies.

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Data availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

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