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Cardiovascular risk is associated with a transmural gradient of myocardial oxygenation during adenosine infusion

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Aims In patients with coronary artery disease (CAD), a transmural gradient of myocardial perfusion has been repeatedly observed, with the subendocardial layer showing more pronounced perfusion deficits. Oxygenation-sensitive cardiovascular magnetic resonance (OS-CMR) allows for monitoring transmural changes of myocardial oxygenation *in vivo*. We hypothesized that OS-CMR could help identify a transmural oxygenation gradient as a disease marker in patients at risk for CAD.

Methods and results We assessed 34 patients with known CAD and 28 subjects with coronary risk factors but no evidence of significant CAD. Results were compared with 11 healthy volunteers. OS-CMR was performed at 1.5 T, applying a T2*-weighted cine steady state free precession sequence at baseline and during infusion of adenosine. A reader blinded to patient data quantified the relative change of myocardial oxygenation in OS-CMR, defined by the change of signal intensity (ΔSI%) between baseline and during adenosine infusion in the entire myocardium, the subepicardial layer, and the subendocardial layer. SI changes were homogenous throughout the myocardium in healthy subjects, whereas both, patients with risk factors only and patients with CAD, had a significantly smaller ΔSI% in the subendocardial layer than in the subendocardial layer. Both patient groups had an overall decreased ΔSI% across all layers when compared with healthy subjects ($P < 0.05$).

Conclusion Even in the absence of overt CAD, cardiovascular risk factors are associated with a transmural gradient of the myocardial oxygenation response to adenosine as assessed by OS-CMR. An inducible transmural oxygenation gradient may serve as a non-invasive marker for cardiovascular risk.

Keywords transmural • regional myocardial gradient • coronary risk factors • ischaemic heart disease • oxygenation-sensitive • cardiovascular magnetic resonance imaging

Introduction

With the increasing prevalence of cardiovascular disease, significant research efforts have been devoted to the development of non-invasive cardiac imaging for the evaluation and timely diagnosis of ischaemic heart disease. This specifically includes parameters for coronary vascular function and related pathophysiology in the absence of acute infarction. It has long been known that myocardial ischaemia more severely affects the subendocardial layer,[1] caused by an increased intramyocardial pressure that competes with the prefusion pressure, and an elevated vascular resistance. The inhomogenus distribution of perfusion in patients with macro- or microvascular coronary disease has recently been demonstrated by first-pass perfusion imaging.[2] Importantly, this transmural gradient is already apparent in the absence of myocardial injury and may also be found in patients without overt ischaemia.[3,4]

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Oxygenation-sensitive cardiovascular magnetic resonance (OS-CMR) exploits the phenomenon that deoxygenated haemoglobin accelerates T2 relaxation and reduces the signal intensity (SI) in so-called OS-CMR images, acquired by specific cardiovascular magnetic resonance (CMR) sequences. The observed SI changes reflect tissue oxygenation in the myocardium[5,6] through a linear correlation with changes of myocardial blood oxygenation.[7] Recently, it has been shown that in patients with ischaemic heart disease, the microvascular response to pharmacological vasodilation is correlated with the severity of coronary artery stenosis,[8] postulating the spatial resolution of OS-CMR images can provide useful diagnostic information for patients at increased risk of microvascular ischaemia. We hypothesized that in patients with coronary risk factors, a transmural gradient of myocardial oxygenation is more pronounced than in a population without risk factors.

Methods

Study population

We prospectively recruited participants aged 18–70 into three study cohorts: (i) coronary artery disease (CAD) group: patients with known CAD confirmed by clinically-indicated diagnostic quantitative coronary angiography (QCA) but without previous coronary bypass surgery; (ii) RF (risk factors) group: individuals with no history or evidence of ischaemic heart disease, valvular heart disease, or cardiomyopathy but with coronary risk factors including diabetes type II, current or previous smoker, dyslipidaemia, family history, or hypertension (defined as systolic blood pressure >140, diastolic blood pressure >90 or effectively controlled with usage of oral anti-hypertensives); (iii) control group: healthy individuals <40 years old, with no significant previous medical history and no history of ischaemic heart disease or risk factors. In participants of the RF group, significant ischaemic heart disease was ruled out by the absence of a clinical history of typical symptoms and by a negative CMR scan including first-pass perfusion and late gadolinium enhancement imaging. Clinical readers with level 3 CMR training, blinded to the patient information, qualitatively evaluated the myocardial perfusion images for presence of subendocardial abnormalities at rest and during adenosine infusion to rule out regional perfusion deficits. Qualitative assessment of late gadolinium enhancement images were also used to rule out presence of fibrosis or scar. Qualitative assessment of CMR myocardial perfusion and late gadolinium enhancement were also performed in patients with known CAD, but not in the healthy volunteers. We also excluded participants with known contraindications to MRI (morbid obesity, implanted metallic devices, and severe claustrophobia), adenosine, or gadolinium-based contrast agents (renal dysfunction indicated by glomerular filtration rate < 60 mL/min, known intolerance or allergy). Participants were asked to refrain from ingestion of coffee, tea, or chocolate during the 12 h before the scan procedure. We furthermore verified that no vasoactive medication had been taken within 24 h prior to the CMR scan. Ethics approval was obtained from the University of Calgary Conjoint Health Research Ethics Board and full written informed consent was obtained from all subjects.

CMR imaging protocol

CMR was performed with the participants in supine position using 1.5 T MRI System (Magnetom Avanto®, Siemens Healthcare, Erlangen, Germany) with a 32-channel cardiac coil. Image acquisition was performed during breath-holds, using retrospective electrocardiogram (ECG)-gated sequences. Steady state free precession (SSFP) cine images were initially acquired for left ventricular (LV) volume and functional scanning. OS-CMR images were acquired for the entire cardiac cycle in the short-axis view at one regional slice (mid-ventricular) using a T2* oxygenation-sensitive, ECG-triggered SSFP sequence with a long repetition time, as previously reported.[8] Scan parameters were: field of view 400 × 400 mm; matrix size 128 × 128, bandwidth 273 Hz/Pixel, TR/TE = 5.4/2.7 ms, flip angle 90°, slice thickness 15 mm. Typical breath-hold length was 10–15 s. The data acquisition of OS-CMR images was repeated during intravenous administration of 140 mcg/kg/min adenosine (at least 2 min of infusion and after verifying an increase of the heart rate by at least 10%).

Analysis of OS-CMR images

OS-CMR images acquired were analysed offline by a blinded reader using certified software (cvi[42], Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada) and performed at end-systole to allow for the greatest contouring area. Epicardial and endocardial contours were manually drawn with careful attention to avoid the blood pool, papillary muscles, or artefact. To define the subepicardial region for evaluation, a 50% offset was applied which automatically moved the endocardial border contour towards the epicardial border (cvi[42] User Manual, Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada). The same was done to define the subendocardium, where a 50% offset from the epicardium was applied using the CMR software. An approximate 10% margin was also excluded on both sides to limit the risk of partial volume effect from blood and myocardium. The computer software then divided the ventricular slice into six equal segments after the anterior right ventricular insertion point was selected according to the American Heart Association guidelines.[8,9] The SI was computed for the whole (global) myocardium, subepicardium, and subendocardium in each segment (*Figure 1*). The average (mean) of the segments at baseline and during vasodilation was used to determine the change in mean SI in percent (ΔSI%) as per the equation below. The images were also analysed according to the major coronary territory assignment outlined by the American Heart Association [(left anterior descending coronary artery (LAD), left circumflex coronary artery (LCx), or right coronary artery (RCA)].[10] Segments were excluded if there was (i) a partial volume effect causing a loss of signal intensity to a substantial area of myocardium, (ii) a severe SI inhomogeneity not related to anatomy, (iii) a significant discordance in slice position between baseline and vasodilation due to extensive respiratory motion during a breathhold, or (iv) if there was presence of LGE suggestive of scar or fibrosis.

$$\Delta\% = \frac{\text{mean SI (vasodilation)} - \text{mean SI (baseline)}}{\text{mean SI (baseline)}} \times 100$$

Statistical analysis

Data analysis was performed using statistical software (IBM SPSS Statistics for Mac version 23.0. Armonk, NY, USA: IBM Corp). Continuous variables were presented as mean ± 95% confidence intervals and categorical variables as percentages. Differences in the myocardial layers between cohorts were calculated using ANOVA (analysis of variance). Paired-sample *t*-test was used for differences within groups for the myocardial layers. The interclass correlation coefficient (ICC) was used to measure intra- and interobserver variability between two blinded

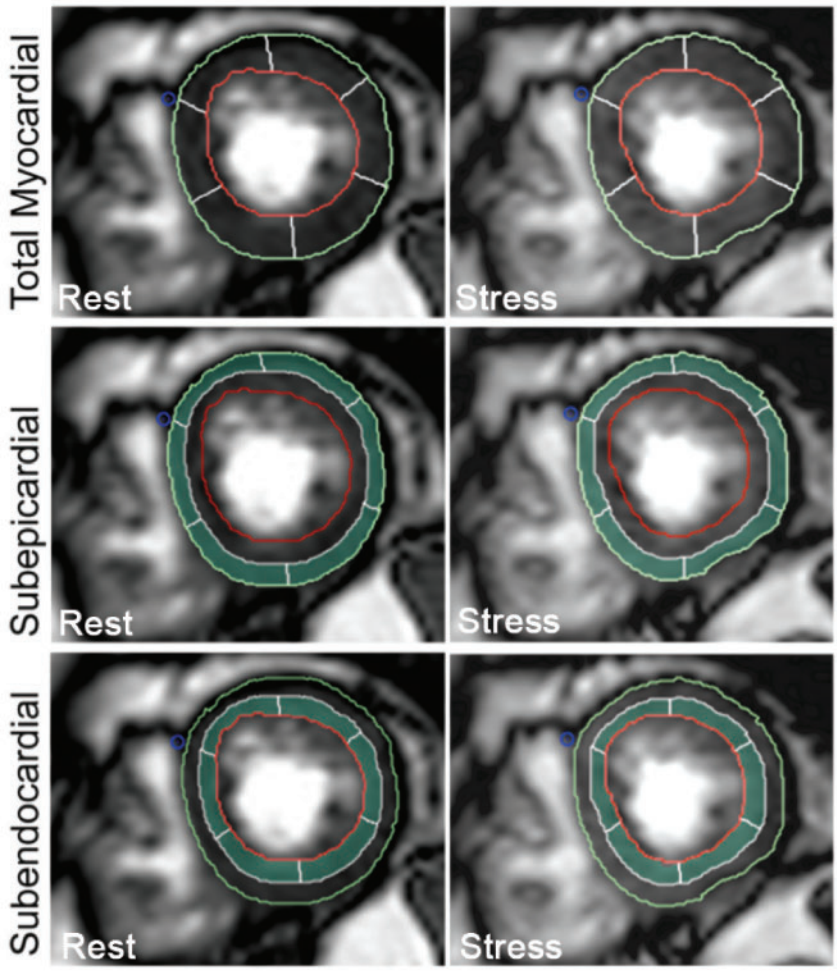

Figure 1 Manual tracing of contours for automatic computer generated signal intensity extraction. Representative OS-CMR images (short-axis orientation) from a patient to represent the method used for image analysis. Contours were drawn for both, baseline and vasodilation images. Contours were drawn along the epicardial (green) and endocardial (red) borders to define the myocardium, excluding trabeculations. The signal intensity was measured for the region isolated within the red and green borders. Careful consideration was taken to avoid artefacts and the LV cavity. Segments were automatically assigned by setting the location of the anterior right ventricular insertion (blue dot). At 50% from the endocardium, the subepicardial region was marked and at 50% from the epicardium, the subendocardial region was marked.

readers and a Bland–Altman analysis was performed to determine the variability of the segmental analyses (six segments per slice per patient) of 10 randomly selected patients with known CAD. Inter-reader reliability based on ICC values less than 0.40 was considered poor, between 0.40 and 0.59 fair. Values between 0.60 and 0.74 were considered good and any values above 0.75 were considered excellent.[11]

Results

In total, 62 patients—34 with known CAD group, and 28 with coronary risk factors but no clinical evidence of ischaemic heart disease (RF group), completed the study protocol. Eleven healthy volunteers served as control subjects. Good image quality was achieved in the majority of participants, with the exception of two patients in the CAD group that were excluded due to poor image quality. No segments were excluded from images in the controls and the RF group. Of the 32 patients with known CAD, 13 (44%) had multivessel disease, 8 (24%) had single vessel disease (6, LAD disease; 2, RCA disease), and 11 (32%) had minimal coronary disease with stenoses <50%). Nine patients (28%) had prior myocardial infarctions with evidence of LGE. Approximately 17% of segments were excluded from the patients with known CAD (35/204 segments) due to the presence of predefined artefacts. Patient demographics and baseline characteristics are listed in *Table 1*. In the RF group, the proportion with 1, 2, or 3+ risk factors were 32%, 39%, and 29%, respectively. As well, for the RF group, blood pressure values at the time of enrolment were controlled (systolic pressue <140 mmHg and diastolic pressure <90 mmHg). Observed coronary risk factors and medications are listed in *Tables 2* and *3*.

Table 1 Patient demographics and baseline CMR parameters

	Controls ($n = 11$)	RF group ($n = 28$)	CAD group ($n = 34$)
Age (years)	29 ± 4	51 ± 9	60 ± 7
Male	6 (55%)	21 (75%)	26 (76%)
BMI	22.8 ± 2.6	27.5 ± 4.0	29.1 ± 5.7
Systolic BP (mmHg)	119 ± 7	122 ± 22	128 ± 12
Diastolic BP (mmHg)	88 ± 9	80 ± 10	77 ± 9
CMR baseline parameters			
LVSVI (mL/m^2)	49 ± 6	44 ± 7	45 ± 7
LVEDVI (mL/m^2)	74.5 ± 9	85 ± 17	88 ± 17
LVESVI (mL/m^2)	32 ± 9	31 ± 7	32 ± 11
LVEF (%)	64 ± 4	59 ± 4	59 ± 8
LVMI (g/m^2)	76 ± 13	61 ± 12	66 ± 15

BMI, body mass index; LVEDVI, LV end-diastolic volume index; LVEF, LV ejection fraction; LVESVI, LV end-systolic volume index; LVSVI, LV stroke volume index
Values are presented as *n* (%) or mean ± SD.

Table 2 Participant risk factors for coronary artery disease

Cardiovascular risk factors, *n* (%)	Controls ($n = 11$)	RF group ($n = 28$)	CAD group ($n = 34$)
Past/present smoker	0	9 (32%)	18 (53%)
Hypertension	0	9 (32%)	16 (47%)
Dyslipidaemia	0	11 (39%)	26 (76%)
Diabetes mellitus	0	12 (43%)	7 (21%)
Family history	2 (18.2%)	16 (57%)	27 (79%)
Prior CAD	0	0	8 (24%)

Table 3 Patient baseline medications

Medication, *n* (%)	Controls ($n = 11$)	RF group ($n = 28$)	CAD group ($n = 34$)
Antiplatelets	0	7 (25%)	33 (97%)
Beta-blockers	0	1 (4%)	21 (54%)
Calcium channel blockers	0	1 (4%)	1 (3%)
Statins	0	11 (39%)	33 (97%)
ACE inhibitors or ARBs	0	8 (26%)	18 (53%)
Diuretics	0	2 (7%)	6 (18%)

ACE inhibitors, angiotensin-converting-enzyme; ARBS, angiotensin II receptor blockers.

Myocardial oxygenation in different myocardial layers

The change of myocardial oxygenation as defined by ΔSI% for each cohort is illustrated in *Figure 2*. The global mean myocardial ΔSI% myocardium of the control group was 21.2% [confidence interval (CI) 14.5–27.9%], which was significantly different from the RF group (9.9%, CI 6.2–13.4%; $P < 0.05$) and the CAD group (4.5%, CI 2.1–6.9%; $P < 0.001$). This was also the case between the RF group and the CAD group ($P < 0.05$).

When comparing the mean ΔSI% for the subepicardial layers, there was significant difference between controls (21.0%, CI 14.8–27.1%) and CAD patients (8.16%, CI 5.1–11.2%; $P < 0.05$). However, there was no difference between the subepicardium of the RF group (12.9% CI 8.8–16.9%) and CAD patients (8.1%, CI 5.1–11.2%; $P = 0.168$). There was significant difference ($P < 0.05$) between the subendocardial values in controls (21.9% CI 14.4–29.3%), the RF group (6.8% CI 3.4–10.2%), and the CAD group (1.1% CI 1.0–3.3%). Overall, in participants with coronary risk factors only and CAD patients, there was a nearly 50% reduction of the SI response following adenosine-induced hyperaemia across the entire myocardium, subepicardium, and subendocardium when compared with controls ($P < 0.05$).

The ΔSI% was homogenous throughout the different myocardial layers in controls ($P = 0.510$), whereas CAD patients had reduced signal intensities within the subendocardium compared with the subepicardial segments ($P < 0.001$). An exemplary case is shown in *Figure 4* of OS-CMR signal intensities compared with coronary angiograpy and CMR myocardial perfusion imaging. A similar finding of reduced ΔSI% in the subendocardium compared with the subepicardium was also seen in the RF group ($P < 0.001$). While not statistically significant, this effect was also more pronounced when comparing females to males in the RF groups. Females had a trend towards a greater decrease in myocardial oxygenation following vasodilation across all layers. This was most evident in the subendocardium ($P > 0.05$).

Myocardial oxygenation as a function of vascular status

When comparing the OS-CMR ΔSI% across the different coronary territories, the CAD group had a trend towards increased mean ΔSI% in myocardium subtended by the LAD, when compared with the LCx or RCA ($P > 0.05$). In contrast, the mean ΔSI% across the entire myocardium, subepicardium, and subendocardium were similar and not statistically significant for different the coronary territories in the RF group ($P > 0.05$; *Table 4*).

Table 5 lists the mean OS-CMR ΔSI% in the subepicardium and subendocardium according to the coronary supply territory and QCA reported stenosis grade.

Inter- and intra-observer variability

The interobserver variability of the OS-CMR measurements was small, with an ICC for single measurements of 0.875 (CI 0.800–0.926). The intraobserver variability was also small, with an ICC for single measurements of 0.903 (CI 0.843–0.941). *Figure 3* shows the Bland–Altman graph with the mean difference lines representing the estimated bias between the two readers/readings.

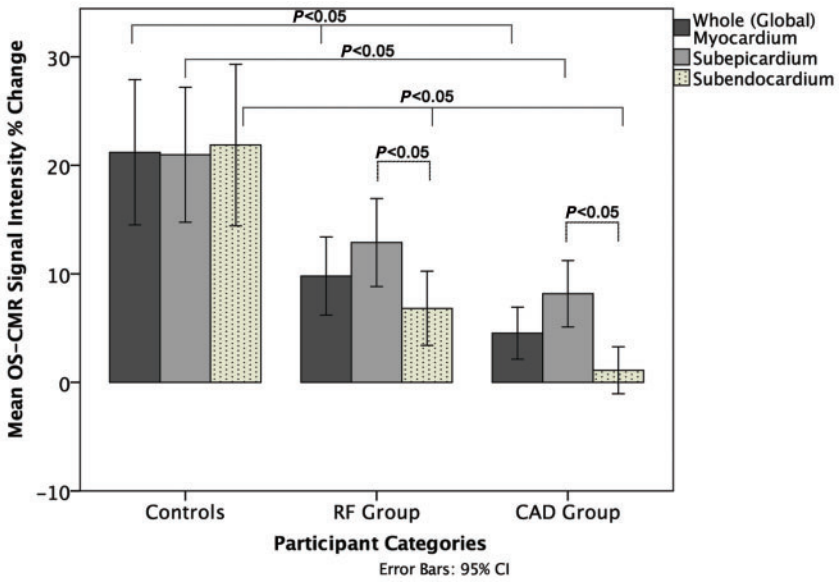

Figure 2 Mean myocardial % change of OS-CMR signal intensity for the whole myocardium (global), compared with subepicardial and subendocardial layers with indicated areas of statistical significance ($P < 0.05$). Not shown on the figure, ΔSI% for the subepicardium of the RF group and the CAD group were not significant, P = NS. CAD, coronary artery disease; RF, risk factors; OS-CMR, oxygenation-sensitive cardiovascular magnetic resonance imaging.

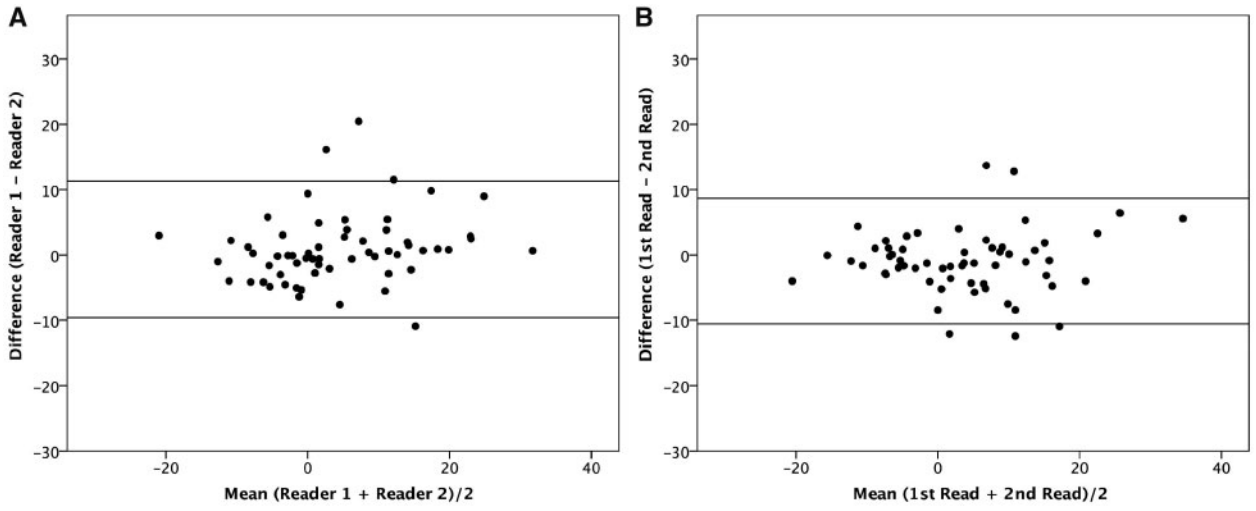

Figure 3 Bland–Altman graphs for intra-observer and inter-observer variability: (*A*) inter-observer variability between two readers and (*B*) intra-observer variability of two readings (1st read and 2nd read), with *Y*-axis lines representing mean differences ±1.96 SD.

Discussion

Our data indicate cardiovascular risk factors are associated with a transmural gradient of the response of the myocardial oxygenation to pharmacologic vasodilation. While previous animal and clinical studies have shown that this increase reflects changes of capillary blood oxygenation,[7,12] our study is the first to demonstrate a transmural gradient, consistent with known vascular pathophysiology. Importantly, compared with young and healthy individuals, there was a nearly 50% reduction of the response to adenosine in both the CAD cohort and patients with risk factors, but no clinical evidence of CAD. These results indicate that a gradient could serve as an early tissue marker for atherosclerotic risk. *Figure 4* illustrates

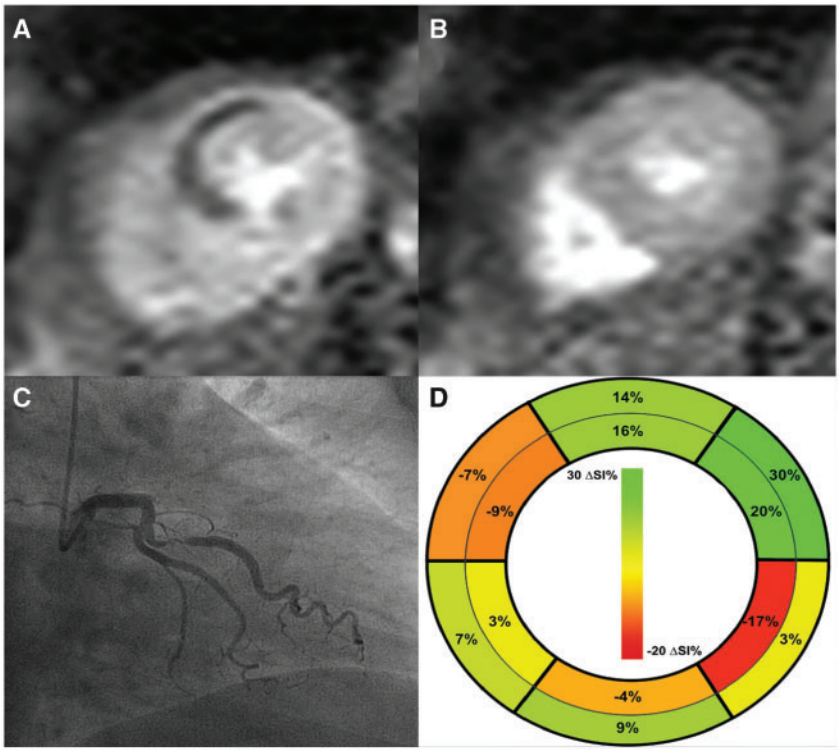

Figure 4 Example of a patient with significant CAD. CMR myocardial perfusion imaging showed an anterior defect on stress (*A*) that is not present on rest (*B*). Coronary angiogram revealed multivessel disease with CTO of the LAD and a significant 90% lesion in the obtuse marginal branch (*C*). There was also a significant lesion in the mid RCA (not shown). A segmented colour map corresponding to OS-CMR signal intensity percent changes in the subepicardium and subendocardium is depicted with multiple areas of reduced myocardial oxygenation (*D*). There was no evidence of late gadolinium enhancement (not shown).

Table 4 Mean OS-CMR signal intensity % change (with 95% confidence intervals) for the whole myocardium (global), compared with subepicardial and subendocardial layers as per coronary territory

		LAD	LCx	RCA
RF group (controls)	Whole (global) myocardium	7.3 (4.0–10.7)	11.1 (8.3–13.9)	10.0 (6.8–13.2)
	Subepicardium	9.6 (6.1–13.1)	14.9 (11.9–18.0)	12.6 (9.1–16.0)
	Subendocardium	5.6 (2.5–8.9)	8.3 (5.4–11.1)	6.8 (5.0–8.7)
CAD group	Whole (global) myocardium	5.4 (2.5–8.3)	3.9 (0.7–7.1)	3.1 (0.6–5.6)
	Subepicardium	8.7 (5.3–12.1)	7.6 (3.5–11.7)	4.8 (2.4–7.3)
	Subendocardium	1.8 (-1.1 to 4.8)	0.7 (-2.1 to 3.4)	1.4 (-1.4 to 4.3)

an exemplary case of concordance between OS-CMR images with CMR myocardial perfusion imaging and coronary angiography.

Using OS-CMR, Egred *et al.*[13] showed that an impairment of vasodilation following dipyridamole infusion resulted in a decreased ΔSI% from a concomitant increase of deoxyhaemoglobin and reduced coronary perfusion in CAD patients with established three-vessel disease. We also found a globally decreased response by over 50% following adenosine-induced vasodilation in our CAD population with a global myocardial ΔSI of 4.5% and notably an even more decreased ΔSI (1.1%) in the subendocardium. Previous data from our research group using the cine SSFP sequence demonstrated a ΔSI of 4.8% or less is associated with functionally significant stenoses defined by a fractional flow reserve (FFR) of <0.80.[8] Therefore, a mean ΔSI of 1.1% in tissue oxygenation of the subendocardium may better reflect disease severity in patients with CAD. While a mean difference of 1.1% may be small, previous researchers have found small differences

Table 5 Mean OS-CMR signal intensity % change as a function of vascular territory and stenosis grade

		Coronary territory					
		LAD		LCx		RCA	
		Subepicardial	Subendocardial	Subepicardial	Subendocardial	Subepicardial	Subendocardial
QCA	>70%	11.2	6.0	11.4	0.3	0.9	-0.9
	40–70%	7.8	0.09	2.7	-3.0	3.2	-1.6
	<40%	9.4	3.6	13.5	5.5	7.5	5.2

can adequately predict coronary disease. Walcher *et al.*[14] found that mean signal intensities ranging from 1.50% to 1.54% can predict segments supplied by normally perfused coronary arteries and mean signal intensities ranging as low as 0.90–1.08% can predict coronaries supplied by functionally significant stenosis.

In territories corresponding to epicardial stenosis greater than 40%, such as the dominant LAD, there appeared to be a compensatory increase in myocardial oxygenation in response to adenosine vasodilation, suggestive of the potential effect of collateralization to LAD from the other coronary vascular territories. In contrast, in the control patients with only risk factors for CAD, the myocardial oxygenation following adenosine vasodilation is more homogenous. This finding was also alluded to in previously published work by our research group, whereby the development of ischaemia in response to pharmacological vasodilatory stress may be hypothesized to be secondary to transmural steal phenomenon and/or horizontal steal phenomenon.[8] For a more widespread clinical application, however, the accuracy and reproducibility require further research.

Oxygen-sensitive CMR for the evaluation of microvascular dysfunction

Coronary microvascular dysfunction (CMD) presents as a reduced vasodilator capacity of the small arterial network. Previous studies demonstrated the ability of CMR to assess oxygenation changes in the peripheral circulation,[15] as well as in the microcirculation of the renal cortex and in skeletal muscle of rabbits,[16] indicating a strong potential of OS-CMR for evaluating microvascular disease. In canine studies, Vohringer *et al.*[7] also showed that OS-CMR is susceptible to changes induced by endothelial-dependent vasodilation using acetylcholine, in which an abnormal response to acetylcholine was shown in patients with endothelial dysfunction of the coronary microvasculature.[17] In our study, we demonstrated a nearly 50% weaker response in participants without CAD but with atherosclerotic risk factors. This is consistent with studies that demonstrated a correlation of coronary risk factors with a blunted response to endothelium-dependent vasodilation, indicating that there may be abnormalities in the microvasculature that are not detectable on conventional imaging modalities for CAD,[18] which may be suggested in *Figure 5* of an exemplary case of a patient with no evidence of significant obstructive CAD on coronary angiography or CMR perfusion imaging, but discordant area of reduced myocardial oxygenation on OS-CMR images.

Interestingly, while microvascular disease affects the entire myocardium, we demonstrated a greater decrease in ΔSI% in the subendocardium compared with the subepicardium. This is consistent with previous studies, whereby Lanza *et al.* provided evidence to support the presence of CMD in patients with cardiac syndrome X by using dobutamine CMR perfusion imaging and transthoracic echo-Doppler recording. These researchers confirmed the evidence of perfusion defects localized to the subendocardium. The perfusion defects detected by CMR were accompanied by impaired coronary microvascular dilatory function following adenosine, as assessed by echo-Doppler.[3] Similarly, recent data in patients with aortic valve steonsis showed that oxygenation maybe more affected than perfusion.[19] The observation that the subendocardium was more preferentially affected than the subepicardium could be explained by different limits of autoregulation of blood flow between the endocardium and the epicardium. While the heart can autoregulate over a wide range of perfusion pressures, differential compressive forces result in more constrained blood flow during systole in the endocardium. Thus, the resistance vessels (arterioles) have a higher vasodilatory capacity in diastole to compensate for the reduced blood flow in systole. The lower limit of perfusion pressure for maximal vasodilation in the endocardium is 70 mmHg, whereas it is 40 mmHg in the epicardium.[20] Therefore, in cases where blood flow to the heart is severely limited, the endocardium is more prone to cardiac injury, with areas of necrosis generally larger in the endocardium than epicardium.[20]

Future studies may use diastolic phases to assess myocardial oxygenation, as this is the period of maximal coronary perfusion.[21]

Limitations

Firstly, for this initial experience, we used a single-slice technique, thus the observed results may not be representative of the vascular response in other regions. Secondly, the RF group and the healthy participants were not age matched to the CAD patients. Indeed, ageing, among other coronary risk factors, has been shown to play an important role in the impairment of endothelial function in both the coronary epicardial arteries and microvasculature.[22–24] Arterial stiffness increases with age and atherosclerosis, where one hypothesis suggests that the repetitive cyclic stress over an individual's life span can lead to degradation of the elastic fibers in the smooth muscles of arteries.[25] Future studies are required to better understand the effect of age on myocardial oxygenation. Finally, our sample size was limited and to establish the clinically utility of this modality would require a much larger sample population.

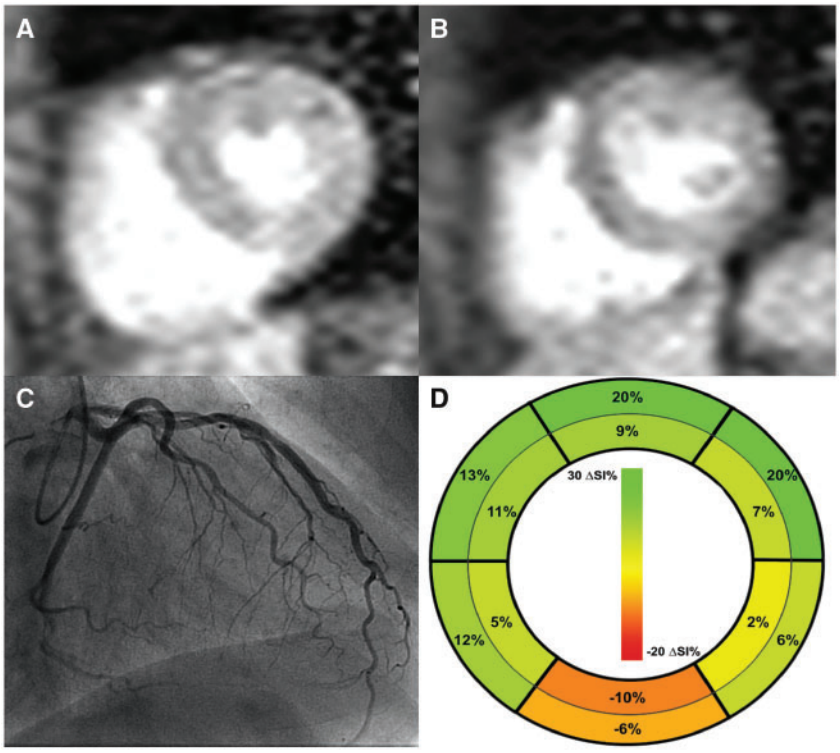

Figure 5 Example of a patient with no significant obstructive CAD. CMR myocardial perfusion imaging were normal on both stress (*A*) and rest (*B*) images, which was consistent with a coronary angiogram that showed minimal (<40%) epicardial disease in the RCA and LCx, as well a 40% lesion in the mid LAD (C). A segmented colour map of the corresponding OS-CMR signal intensity percent changes in the subepicardium and subendocardium is depicted with a discordant area of reduced myocardial oxygenation in the mid inferior wall (*D*). There was no evidence of late gadolinium enhancement (not shown).

Conclusion and clinical significance

Cardiovascular risk, even in the absence of evidence for CAD, is associated with a transmural gradient of the coronary vascular response to adenosine as assessed by oxygenation-sensitive CMR images. Further research should explore the utility of this technique as a tissue marker for coronary vascular function and risk. Moreover, with the emerging understanding of non-occlusive/obstructive CAD and the role of sex/gender on cardiovascular disease, OS-CMR may potentially play an important role in the clinical armentarium to help better diagnose and understand conditions related to the pathophysiology of microvascular disease.

Conflict of interest: M.G.F. is a board member, advisor and shareholder of Circle Cardiovascular Imaging Inc., Calgary, Alberta (Significant relationship). All remaining authors have no relevant financial, personal, or professional relationships to disclose.

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