Is subendocardial ischaemia present in patients with chest pain and normal coronary angiograms? A cardiovascular MR study

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Aims On the basis of an MRI study it has been suggested that subendocardial hypoperfusion is present in patients with cardiac syndrome X. However, further work is required to test whether these findings can be generalized.

Methods and results MRI was used to visually and semi-quantitatively assess subendocardial and subepicardial perfusion, at rest and during an infusion of adenosine, in 20 patients with angina pectoris and normal coronary angiograms. A myocardial perfusion index (MPI) was calculated using the normalized upslope of myocardial signal enhancement. An index for myocardial perfusion reserve (MPRI) was calculated by dividing the MPI values at maximal vasodilatation by the values at rest. The MPI in our study population increased significantly during adenosine infusion in both the subendocardium (from 0.091 ± 0.020 to 0.143 ± 0.030; P < 0.001) and the subepicardium (from 0.074 ± 0.017 to 0.135 ± 0.03; P < 0.001). The overall MPRI was 1.83 ± 0.50.

Conclusion The results show that patients with chest pain and normal coronary angiograms had significant perfusion responses to adenosine in both the subendocardium and subepicardium. In the present study we found no evidence for subendocardial hypoperfusion in these patients.

KEYWORDS
Angina pectoris with normal coronary arteries; Cardiac syndrome X; Cardiovascular MR; Microvascular angina

Introduction
About 20% of patients with anginal chest pain have normal coronary angiograms.1–5 The term 'cardiac syndrome X' was introduced to describe these patients.6,7 However, a subgroup of these patients has objective signs of ischaemia, such as the classic downsloping ST-segment depression on exercise testing and/or a reversible defect detected by myocardial single-photon emission computed tomography (SPECT).8,9

The pathogenesis of syndrome X is unclear. Physiological mechanisms such as the existence of myocardial ischaemia have been proposed, which might be caused by coronary microvascular dysfunction or an abnormal pain perception.10,11 Several studies found abnormalities consistent with ischaemia in patients with syndrome X using positron emission tomography (PET),11 scintigraphic myocardial perfusion imaging,8,11,13 thermodilution,15 nuclear magnetic resonance spectroscopy,16 intracoronary acetylcholine,17,18 and atrial pacing.19 However, other investigators have questioned the proposed role of coronary microvascular dysfunction in syndrome X. Rosen et al.20 found no differences in myocardial blood flow between syndrome X patients and healthy controls. Furthermore, in studies using stress echocardiography and myocardial metabolic measurements no evidence of ischaemia was found in patients with syndrome X.4,5,20–24

High resolution imaging with MRI offers the possibility to study subendocardial and subepicardial myocardial blood flow.25,26 An interesting MRI study suggested the presence of subendocardial hypoperfusion in patients with syndrome X.27 The authors suggested that further work is required to test whether these findings can be generalized. To our knowledge the results of this study have not been confirmed. Therefore, we employed MRI to visually and semi-quantitatively assess subendocardial and subepicardial perfusion, at rest and under stress during adenosine infusion in

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20 patients with angina pectoris, objective signs of ischaemia (ST-segment depression during exercise test and/or reversible defect on SPECT) and normal coronary angiograms.

Methods

Patient characteristics and inclusion/exclusion criteria

We identified 34 patients with typical chest pain and normal coronary angiograms: 22 women and 12 men. All had established (1999–2004) exertional angina; an abnormal exercise electrocardiogram suggesting ischaemia (0.1 mV horizontal or downsloping ST-segment depression of 80 ms after the J point), and/or a reversible perfusion defect on a myocardial SPECT; and completely normal results from coronary angiography, which was independently confirmed by two cardiologists in separate viewing sessions and without clinical information. The mean time between coronary angiography and cardiovascular MR (CMR) was 11.6 months. Furthermore, the time between myocardial perfusion scintigraphy and coronary angiography was 2.5 months, and the time between SPECT and CMR was 12.4 months.

The exclusion criteria were: a percutaneous transluminal coronary angioplasty (PTCA); coronary artery bypass grafting (CABG) or prior myocardial infarction; coronary spasm during the coronary angiography; absence of pain without medication; pregnancy; hypertension (defined as blood pressure over 140/90 mmHg); diabetes (defined by a fasting glucose level above 7.8 mmol/L or a random-sample glucose level above 11.1 mmol/L); arrhythmias such as paroxysmal atrial fibrillation (PAF); left bundle branch block (LBBB); valve dysfunction (other than mitral valve insufficiency grade 1); abnormal left ventricle ejection fraction (LVEF <50%); or other structural abnormalities of the heart. Furthermore, patients having general contra-indications for MRI according to the MR safe practice guidelines were also excluded.28 None of the patients had electrographic signs of LV hypertrophy (defined as a value above 35 mm for the sum of the height of the S wave in lead V1 and the height of the R wave in lead V5),29 or any change in clinical condition between the investigations.

Finally 20 of the 34 identified patients were selected for first-pass contrast cardiovascular MR. These patients’ characteristics are given in Table 1. The reasons for excluding the other 14 patients from the MRI study were: absence of pain without medication (n = 2); claustrophobia (n = 8); one patient did not fit into the MRI scanner owing to obesity (height, 167 cm; weight, 120 kg); one patient cancelled due to negative advice from his physician; one patient had moved to an unknown address; and one patient’s original coronary angiogram data were unavailable for the independent evaluation by two cardiologists.

In addition to the characteristics in Table 1, the selected patients were examined in more detail as follows, the SPECT results showed reversible perfusion defects in 16 patients, one patient had a reversed perfusion pattern, one patient showed normal perfusion, and a mild fixed defect was seen in two patients. An abnormal exercise electrocardiogram suggesting ischaemia (0.1 mV horizontal or downsloping ST-segment depression of 80 ms after the J point) was present in five patients, eight patients developed chest pain without significant ST-segment depression. The patients received hormone replacement therapy (one patient), calcium-channel blockers (seven patients), nitrates (four patients), beta-blockers (six patients), ACE-inhibitors (one patient), or no treatment (five patients). These numbers reflect the fact that some patients received a combination of these drugs.

The study complies with the Declaration of Helsinki, Institutional Ethics Committee approved this study, and all patients gave written informed consent.

Magnetic resonance imaging scan protocol

The patients were instructed to stop all cardiac medication, to refrain from caffeine-containing beverages 24 h before cardiovascular MRI and to eat light breakfast on the day of the test. Patients receiving beta-blocking drugs stopped their medication for at least three half-life times. Before testing, an intravenous line of normal saline solution, with a 20-gauge cannula was positioned in the antecubal veins in both arms. We used a single cannula for administration of contrast and a separate cannula for the administration of adenosine.

Imaging was performed with a 1.5T whole body MRI scanner (Magnetom Sonata, Siemens, Erlangen, Germany) using a four-element phased array cardiac receiver coil, and with the patient in a supine position. Scout images were acquired in the long-axis and short-axis orientations in order to specify the final short-axis views.

To obtain the first-pass contrast-enhanced images a saturation prepared single shot fast spoiled gradient echo pulse sequence was applied (repetition time 2.0 ms, echo time 1.0 ms, flip angle 12°, receiver bandwidth 770 Hz/pixel, saturation delay 120 ms). The spatial resolution was 3 × 3 × 2.3 –2.7 × 8 mm3, with an image matrix of 128 × 73 –93.

Perfusion scans were performed during the last minute of a 3 min adenosine infusion (140 µg/kg/min) and 15 min later, at rest. Three short-axis slices from apex to base at 25%, 50%, and 75% of the end-systolic ventricular length were imaged. Both rest and stress perfusion images were acquired during breath-holding for 50 heartbeats and during the first-pass of 0.05 mmol/kg gadolinium-based contrast agent (Magnevist, Schering AG, Berlin, Germany) flushed with 15 mL of 0.9% NaCl (flow rate, 5 mL/s; Medrad, Spectris).

During the waiting period between the stress and rest perfusion scans, ECG gated cine images were acquired using a breath-hold segmented steady-state free precession sequence. Cine bSSFP sequence parameters were a temporal resolution of 47 ms, excitation angle of 60°, receiver bandwidth 930 Hz/pixel, TR/TE of 3.1/1.6 ms, matrix 256 × 138 –161, and voxel size of 1.3 –1.4 × 1.8 –2.0 × 5.0 –6.0 mm3.

Each patient obtained eight to ten short-axis views every 10 mm, starting from the mitral valve insertion and covering the entire left ventricle.

Late contrast-enhanced images, in order to definitely exclude myocardial scar tissue, were acquired 10 min after the last contrast injection in the same orientation as the first-pass contrast-enhanced images, using a 2D segmented inversion recovery spoiled gradient-echo pulse sequence triggered to end-diastole (repetition time/echo time = 9.6/4.4 ms, flip angle 25°, number of excitations = 1, matrix 208 × 256, typical voxel size of 1.6 × 1.3 × 5.0 mm3, receiver bandwidth 130 Hz/pixel). The inversion time was set to null the signal of normal myocardium, and was typically in the range of 220–290 ms.

Magnetic resonance imaging analysis

Analysis of the MR images was done both visually and semi-quantitatively. An 18-segment model was used, dividing the left ventricle into six basal, six midventricular, and six distal segments.
Qualitative assessment was by visual interpretation of the MR images by two observers. The SPECT and CMR analysis was performed separately. Observers of the SPECT and the observer of the CMR were blinded for the results of other diagnostic procedures.

First-pass perfusion contrast-enhanced MR images were assessed for the presence or absence of regions of reduced contrast uptake. Delayed contrast-enhanced images were assessed for the presence of any hyper-enhancement. The degree of myocardial wall thickening was assessed from functional cine images.

Global function was assessed by calculating left ventricular end-diastolic and end-systolic volumes (LVEDV and LVESV, respectively) using planimetry of all short-axis images in each patient. LVEF (%) was calculated as (LVEDV – LVESV)/LVEDV.

Semi-quantitative analysis was performed using a dedicated software package (Mass 5.0, Medis, Leiden, The Netherlands). The endocardial and epicardial contours on perfusion images were traced, and corrected manually for cardiac motion. Each slice was divided into six equiangular segments, starting from the inferior septal insertion of the right ventricle. These segments were further subdivided into subendocardial and subepicardial regions, which were traced with their outer borders close to the endocardial and epicardial surfaces and inner borders adjacent to each other in the mid-wall. To obtain information about the input function, an additional region was drawn in the left ventricular cavity.

For each of the defined regions a curve was generated showing relative signal intensity plotted against time. The maximum up-slopes of the myocardium and the left ventricular blood pool were determined using five- and three-point linear fits, respectively. The results for the myocardial regions were corrected for differences in the arterial input function of the contrast agent bolus by dividing the myocardial up-slope with the left ventricular blood pool up-slope. An index for myocardial perfusion reserve (MPRI) was calculated by dividing the values at maximal vasodilatation by the values at rest.

Statistics
There was no sample size calculation. Due to the limited CMR capacity it was decided prior to the start of the study, to include 20 patients. For statistical analysis we used mean values of perfusion parameters of the subendocardial and subepicardial regions. In this section the summary values are presented as means ± SD. Differences between means in MPI and MPRI subendocardial and subepicardial of each patient were tested using paired student test (two-sided). A P-value of less than 0.05 was considered to be significant.

Results
Heart rates, blood pressure, and chest pain
The baseline heart rate was 71 ± 11 b.p.m., increasing to 94 ± 14 b.p.m. during adenosine infusion. The baseline systolic blood pressure was 139 ± 20 mmHg and diastolic was 80 ± 9 mmHg. During maximum vasodilatation, the systolic blood pressure was 140 ± 18 mmHg and diastolic was 73 ± 10 mmHg. Furthermore, 14 of the 20 patients experienced severe chest pain during adenosine infusion. The remaining six patients did not experience any chest pain.

Magnetic resonance imaging visual analysis
All patients showed initial subendocardial signal reductions on the first-pass cardiovascular MR images, which disappeared after approximately five heartbeats (Figure 1). This temporary signal loss is considered to be an artefact related to the first-pass sequence and is not typical for an ischaemia-related defect, which shows a more sustained signal loss. These so-called dark rim artefacts were present in 93% of all the slice series, and in 44% of the slice series it was visible around the whole subendocardium.

In addition there were visual signs of ischaemia in two patients (in one patient a mid-anterior/mid-anteroskeletal sustained transmural defect, and in the other a basal anterolateral and basal posterolateral sustained transmural defect). These signs were present in four segments out of a total of 360. In other words, only 1.1% of the segments had visual signs of ischaemia. No hyper-enhancement was seen on late contrast-enhanced images.

Global ventricular function
The mean LVEDV was 159 ± 35 mL, mean LVESV was 70 ± 17 mL, and the mean EF was 57 ± 3%.

Magnetic resonance imaging semi-quantitative analysis
The MPI in our study population increased significantly during adenosine infusion in both the subendocardium and subepicardium: from 0.091 ± 0.020 to 0.143 ± 0.030 (P < 0.001), and from 0.074 ± 0.017 to 0.135 ± 0.03 (P < 0.001), respectively. Note that in both the resting and stressed states, the subendocardial MPI was higher than the subepicardial MPI, respectively, 0.091 ± 0.020 vs. 0.074 ± 0.017 (P < 0.001) and 0.143 ± 0.030 vs. 0.135 ± 0.03 (P = 0.021).

An index for myocardial perfusion reserve was calculated as the ratio of the MPI during stress to the MPI at rest. The MPRI for the entire transmural extent of the myocardium was 1.83 ± 0.50. However, there was a significant difference between the MPRI in the subendocardium, 1.67 ± 0.38 and the subepicardium, 1.98 ± 0.64 (P = 0.001).

The mean subendocardial:subepicardial MPRI ratio was 0.91 ± 0.11. None of the patients had a subendocardial: subepicardial MPRI ratio less than 0.72, which has been proposed as the optimal cut-off for distinguishing between normal controls and subendocardial hypoperfusion in patients with syndrome X.

Discussion
This study has shown that patients with chest pain and normal coronary angiograms had significant perfusion...
responses to adenosine in both the subendocardium and the subepicardium. Hence, we found no evidence for subendocardial ischaemia in our group of patients.

The adenosine-induced significant increases in subendocardium MPI, from 0.091 to 0.143, contrast with an earlier MRI study, where the MPI did not change significantly.27

These MPI values found in our patient group at rest and under stress agree with the results from the control group in the study by Panting et al.27 Both studies found significant MPI increases in the subepicardium in response to adenosine. The selection of both patient populations is not exactly equal, this difference in selection may partially explain the different results we have found in patients with syndrome X (although the mean age and male/female distribution were similar). In our study, more patients with syndrome X had an abnormal myocardial SPECT result, while in the study of Panting et al. more patients showed an abnormal ECG during exercise. However, the selection of syndrome X patients using both exercise-ECG and SPECT is an accepted method.27 As Lanza stated in an overview, exercise-induced ST-segment depression is not required. In patients with obstructive CAD, exercise electrocardiogram may be negative in patients with coronary microvascular disease, whereas findings compatible with myocardial ischaemia could be detected by other diagnostic techniques (e.g. stress myocardial scintigraphy).12

In our study we found dark rim artefacts during the peak gadolinium concentration in the left ventricular blood-pool MRI images in all patients. This temporary signal loss is considered to be an artefact related to the first-pass sequence and is not typical for an ischaemia-related defect, which shows a more sustained signal loss. These dark rims along parts of the subendocardial border of the left ventricle and the myocardium has been noticed in dynamic contrast-enhanced MR perfusion studies.31,32 Several causes have been proposed for this so-called dark rim artefact, such as cardiac motion, Gibbs ringing due to limited spatial resolution and susceptibility. Considering the spatial resolution and the cardiac acquisition window applied in this study is not to be expected that we experienced more artefacts compared to the study of Panting et al.27

We found no evidence for microvascular dysfunction in the subendocardium or subepicardium since both regions showed a clear increase in MPI during adenosine infusion.

This is in accordance with the previous work with PET, which failed to show absolute myocardial perfusion abnormalities during pharmacological stress in syndrome X patients when compared with normal controls.6,20 Although absolute flow determination is difficult with MRI, we found small differences in the MPI between the subendocardial and subepicardial region of the left ventricle. In the resting state there was a 21% higher MPI in the subendocardium when compared with the subepicardium. This result might be explained by the higher workload of the subendocardial part of the left ventricle wall, which is in agreement with an experimental study of dogs by Hittinger et al., who observed a 31 ± 7% higher blood flow in the LV subendocardium when compared with the subepicardial region for normal dogs in the resting state.33

The pathogenesis of cardiac syndrome X is unclear. The main hypotheses for its occurrence are microvascular dysfunction or abnormal pain perception.2–4,34 There have been conflicting data concerning the possible role of myocardial ischaemia in syndrome X. Several studies of patients with syndrome X demonstrated ischaemia,1,15–19 whereas other investigations found no confirmatory evidence of ischaemia during stress in these patients.5,20–22 Alternative non-ischaemic mechanisms of chest pain have been proposed in patients with cardiac syndrome X. In one study an abnormal pain perception has been reported, using pain provocation by catheter movement within the right atrium or ventricle.35 Another study showed specific cortical activation in the right anterior insula in patients with syndrome X and not in controls.36 The exact mechanism of chest pain in patients with syndrome X remains unclear since our data do not support the hypothesis of subendocardial ischaemia in this patient group.

We consider the relatively small number of patients and the frequent occurrence of subendocardial artefacts with CMR as the major study limitations.

Larger studies with newer CMR sequences and independent coronary flow measurements may increase the insight of subendocardial perfusion in syndrome X patients. Further studies are needed to reveal the cause of chest pain in this specific patient group.

Concluding remarks

We conclude that our cardiovascular MRI study of patients with chest pain, positive exercise ECG stress testing, and/or positive myocardial perfusion SPECT and normal coronary angiography, demonstrated significant adenosine-induced increases in both subendocardial and subepicardial MPIs. We found no evidence for specific subendocardial ischaemia with MRI in this group of patients.

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